THE FONTAN CIRCULATION: PROBLEMS AND SOLUTIONS

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THE FONTAN CIRCULATION: PROBLEMS AND SOLUTIONS

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Editorial: The fontan circulation: Problems and solutions

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Editorial on the Research Topic
The Fontan Circulation: Problems and Solutions

The Fontan circulation has been developed as a strategy for multiple, unrepairable complex cardiac malformations in which there is only one effective ventricle. Almost 50 years later, the Fontan circulation is seen as an important achievement, resulting in good hemodynamic outcome for an otherwise untreatable heart disease. At the same time, complications occur due to challenges associated with a failing circulation due to the physiological features of chronically elevated systemic pressure and decreased cardiac output, obligatory features in the absence of a sub-pulmonary ventricle. As a consequence, patients are at risk for various complications including ventricular failure, organ failure, arrhythmias, protein losing enteropathy and plastic bronchitis. Despite recent improvements in tackling these complications, patients still face a high morbidity and mortality.

This special issue focuses on analyzing these challenges in a problem and potential solution framework. Fifteen manuscripts addressed various aspects of the Fontan circulation in children and adults. The contributions in this special issue articulate for practitioners and scientists what we can do today, and what we need to develop going forward.

Problems and solutions: specifics of the Fontan pathophysiology and its failure

The Fontan operation is the palliative procedure of choice for single ventricle patients. It is achieved by connecting both caval veins directly to the pulmonary arteries without the interposition of a sub-pulmonary ventricle. This approach separates the systemic and pulmonary venous returns to the heart and markedly diminishes mixing of deoxygenated and oxygenated blood as well as reduces volume overload of the single ventricle. However, the resulting Fontan circulation, in which the systemic and pulmonary circulation are connected in series, is characterized by a distinct physiology with chronically elevated central venous pressure. Chronic preload deprivation of the single ventricle reduces cardiac output.

Currently, we are still facing a lack of comprehensive knowledge regarding Fontan circulatory physiology which translates into a lack of effective treatment options.

Van de Bruaene et al. (2022) shed light on underlying factors of Fontan failure and contributed with a comprehensive review drawing the focus on its most limiting factor: the pulmonary circulation. The systemic ventricle in a Fontan circulation lacks preload at rest and during exercise. Therefore, systemic venous return through the pulmonary circulation becomes the main determinant in the regulation of pulmonary blood flow and hence exercise capacity. Since there is no sub-pulmonary ventricle, even minimal changes in pulmonary vascular resistance cause significant changes in cardiac output. The authors suggest optimizing the Fontan conduit early in life to allow for sufficient pulmonary artery growth and later in life by stenting of the conduit to adult size. In particular, stenting of a hypoplastic left pulmonary artery if present is important. The value of physical activity-which introduces some degree of pulsatility to the pulmonary vasculature and improves filling of the ventricle with stiffness-reducing stretching- as well preventing the accumulation of risk factors for heart failure with a preserved ejection fraction phenotype (obesity, hypertension, diabetes) cannot be understated. In practice, pediatric cardiologists and congenital cardiac surgeons should always aim for the "perfect" Fontan circulation. The patient should maintain an active, healthy lifestyle avoiding weight gain and the adult congenital cardiologist should not accept suboptimal hemodynamics (i.e., AV valve regurgitation, undersized Fontan conduits, pulmonary artery hypoplasia).

Clinical presentation and hemodynamic phenotypes of Fontan failure are considerably variable. Kramer et al. (2022) developed an uncomplex yet remarkably accurate score to classify Fontan failure and late mortality in adult Fontan patients to allow a timely risk stratification. The score is based on hemodynamic, clinical and laboratory findings and is composed through analysis of a cohort of 198 adult Fontan patients with a median follow-up of about 20 years. Fifteen parameters were identified associated with Fontan failure and/or mortality. The accuracy to discriminate between patients with and without late Fontan failure as well as late mortality and survival was assessed in their cohort and patients with Fontan failure had a significantly higher median Fontan Failure Score compared to non-failing Fontan patients. Mortality associated with Fontan failure was substantial (48.1%). A prospective validation and likely refinement and calibration of the score in larger and preferably multi-institutional cohorts is still required.

Problems and solutions: the respiratory system

Respiratory function plays a crucial role in Fontan circulation by having the systemic and pulmonary circulations in series. Ventilation strongly determines pulmonary blood flow and cardiac output at rest and with exercise. Laohachai et al. (2022) reviewed the impact of impaired lung function which is characterized by restrictive ventilatory patterns and a reduced lung volume. In addition, the authors report on the reduced skeletal and respiratory muscle strength in Fontan patients. Respiratory muscle training has shown potential promise to improve exercise capacity.

While respiration influences phasic pulsatility, it has a limited effect on the effective forward flow in the Fontan circulation. Interestingly, van der Woude et al. (2021) discussed the influence of respiration on blood flow based on insights gained from imaging-based clinical evaluations. In contrast to the healthy circulation, respiration is the main source of blood flow pulsatility in the Fontan circulation, whereas cardiac contraction mostly drives the effective forward flow rate. In particular hepatic venous flow, which contributes approximately 38% to the total Fontan tunnel flow, is strongly influenced by respiration. In essence, the higher blood flow during inspiration is countered by depressed flow rates during expiration. Since MRI examination is recommended every 2 years in Fontan patients, clinicians should be aware that most conventional MRI flow sequences do not capture the pulsatility of the blood flow as a result of respiration. Therefore, authors state that conventional ECG-gated PC-MRI acquisitions can be used for the measurement of clinical parameters based on net forward flow. Inclusion of respiratory phasic pulsatility in state-of-the-art patient-specific CFD models are recommended for evaluation of detailed, time-resolved hemodynamic metrics (e.g., wall shear stress and viscous energy loss rate), continuing to provide important insights for clinicians in the function of the Fontan circulation.

Pulmonary arteriovenous fistulae (PAVF) are one of the major complications after Fontan operation. Ohuchi et al. (2022) clarified the incidence, clinical characteristics and its influence on mortality. PAVF were present in 9.2% of 391 Fontan patients investigated by pulmonary artery angiography and/or contrast echocardiography during catheterization. Most patients (83%) showed a diffuse type of PAVF, associated with a significant decrease in mean arterial blood oxygen saturation compared to the non-PAVF group. Oxygen values in these patients decreased further corresponding to the postoperative stage from 90% at 1 year to 88% in the long-term follow-up of >25 years postoperatively. Authors highlighted that discrete-PAVF had no influence on SaO2 or mortality, whereas the presence of diffuse-PAVF caused hypoxia and had an adverse impact on all-cause mortality. The incidence of PAVF increases with patient age.

Problems and solutions: lymphatic disorders

Patients with single ventricle palliation are susceptible to a variety of lymphatic abnormalities of both the thorax and

abdomen, such as protein-losing enteropathy (PLE) and plastic bronchitis (PB). Imaging the central lymphatic system by dynamic contrast MR lymphangiography allows visualization of the lumbar lymphatic networks, the cisterna chyli and the thoracic duct. Utilizing these imaging tools, Dori et al. (2022) report on the management of patients with PLE and PB, potential life-threatening diseases affecting approximately 5%–15% of single ventricle patients. Conservative management of PLE involves use of diuretics including high-dose aldactone and sildenafil. The role of low-fat high-protein diet is less clear. Cardiac catheterization must be performed to determine hemodynamics and any reversible Fontan pathway obstruction. Fenestration creation or recreation can also be attempted. Patients that remain symptomatic can be started on enteric steroids, however this treatment strategy should be finite and limited due to the risk of serious side-effects and complications. Interventions for protein-losing enteropathy include embolization of hepatoduodenal and periduodenal lymphatic networks and procedures to lower pressure in the lymphatic system such as thoracic duct decompression.

Conservative management of PB involves inhaled bronchodilators, inhaled steroids and pulmonary vasodilators. If symptoms persist, medications aimed at breaking down the casts are used including inhaled tissue plasminogen activator. However, if active lymph leaking into the airway is present, lymphatic imaging and selective lymphatic duct embolization are needed. If symptoms in both entities, PLE and PB, persist despite lymphatic intervention, then thoracic duct decompression (interventional or surgical) or orthotopic heart transplant should be considered.

Problems and solutions: the hepatic system

Hepatic dysfunction after Fontan operation can occur as a postoperative complication and might also develop long term. In a retrospective case control study of 409 patients after TCPC, Luo et al. (2022) identified an increased central venous pressure and intraoperative aortic cross-clamping as risk factors for postoperative and persistent liver dysfunction after day 7 postoperatively. Special attention to this patient group is suggested by the authors to prevent liver impairment.

Schleiger et al. (2021) reported on Fontan-associated liver disease in the adult population. They investigated the metabolic liver function with the liver maximum function capacity test (LiMAx®) in 39 patients and compared it to laboratory testing, elastography and ultrasound. The authors found preserved metabolic hepatic function in about 80% of the patients. Results of metabolic testing did not correlate to the severity of abnormal hepatic findings evaluated by sonography or laboratory analysis, indicating that while abnormalities are present, hepatic functionality remains relatively intact.

Both studies indicate that the development and progression of liver dysfunction in Fontan patients is not a linear or uniform process. Therefore, Schleiger and colleagues suggest that the diagnostic approach during follow-up should encompass a variety of modalities in order to obtain the most comprehensive picture. More work is necessary to determine the most valuable surveillance strategy in this domain.

Problems and solutions: extra-cardiac systems

Organ dysfunction occurs beyond the heart, lungs, liver and gut in those with Fontan circulation. Ritmeester et al. (2022) present an interesting review on this subject and report on abnormalities in the nervous system, pituitary, kidneys, and musculoskeletal system. The thyroid axis may be affected by pituitary edema which is related to its unique vasculature. Therefore, awareness for potential hypothyroidism is important. Renal dysfunction is frequent and might be underestimated by creatinine based renal function testing due to myopenia as both lean muscle mass and bone mineral density are decreased in most of the Fontan patients. The assessment of cystatin C for renal function is recommended by the authors.

Little is known about the sexual health in patients after Fontan operation. Rubenis et al. (2021) assessed the sexual function of men with a Fontan circulation by performing a prospective, cross-sectional study based on the data from the Australian and New Zealand Fontan registry. Self-reported erectile function of 54 men with Fontan circulation was not significantly impaired when compared with historical controls, however sexual desire and overall satisfaction were reduced. The presence of erectile dysfunction was not correlated to the Fontan type or the New York Heart classification and the proportion of the cohort who had a prior pregnancy was congruent with population data.

Problems and solutions: origins of neurodevelopmental challenges

Calderon et al. (2022) reviewed the findings that many Fontan patients present with impaired neurodevelopmental and mental health outcomes. Patients experience difficulties in areas of cognition related to attention and executive functioning, visual spatial reasoning and psychosocial development. A high risk for mental health morbidities, particularly anxiety disorders and depression, is present. Underlying alterations in brain processes may occur during fetal development which may be further influenced by hemodynamic parameters and perioperative factors. Variables such as multiple interventions requiring a prolonged hospital stay, is shown to be associated with adverse long-term neurodevelopmental outcome. The authors emphasize

the benefit of early screening for neurodevelopmental deficits to initiate adequate support, thus allowing for early interventions and support to achieve the best potential outcomes.

Problems and solutions: thromboembolic risk factors

The Fontan circulation is associated with an increased risk of thromboembolism. To prevent patients from pulmonary embolism or ischemic stroke Fontan patients are commonly treated with anti-platelet agents and/or anti-coagulants. Van Den Helm et al. (2022) addressed this topic and reviewed the nature of thromboembolism post Fontan surgery and the evidence for thromboprophylaxis management using anti-platelet and anti-coagulant agents. The authors highlight that the complex pathophysiology of the highly thrombogenic environment in a Fontan circulation is based on all 3 elements of Virchow's triad: endothelial cell dysfunction, abnormal blood flow and a hypercoagulable state caused by coagulation factor abnormalities. Further dysregulation of hemostasis can be caused by a tendency towards liver function abnormalities and associated serum protein imbalances. Subclinical cerebrovascular thromboembolic events are still underdiagnosed. Importantly, authors stated that the risk of thromboembolic events, mainly occurring in the venous system, is the highest in the first year post Fontan operation with a second peak 10 years post Fontan. Furthermore, the authors focus on the needs for an emerging consensus on prophylaxis. Fontan patients with no clinical complexities should receive life-long aspirin as thromboprophylaxis, whereas further anti-coagulation with vitamin K antagonists can be reserved for patients with special risk factors like previous thrombotic events or in the older Fontan patient. A comprehensive follow-up including monitoring and attention for bone mineral density should be provided. Currently, the use of new classes of oral anti-coagulants may hold promise but is not yet recommended as primary prevention due to the lack of evidence. Despite prophylaxis, a significant risk of thromboembolic disease post Fontan surgery remains.

Problems and solutions: exercise tolerance

A markedly reduced exercise performance affects most Fontan patients. Reduced exercise capacity influences long-term quality of life and is associated with worse prognosis, although a subset of patients have high physical performance ("Super-Fontan"), which may represent a unique low-risk phenotype. Typical cardiopulmonary exercise testing response in Fontan patients includes a depressed peak heart rate (HR), elevated minute ventilation /carbon dioxide production slope (ventilatory inefficiency), reduced peak work rate and an increased breathing frequency.

Stating that patients with the best clinical outcome might provide important insights, Tran et al. (2021) studied 60 patients from the Australian and New Zealand registry with the "Super Fontan" phenotype defined as having a normal exercise tolerance. When compared to a Fontan group with impaired exercise capacity, the "Super-Fontan" phenotype is associated with a healthy weight, lower age at Fontan completion, better exercise self-efficacy and higher overall levels of sport and physical activity participation during physical development. This said, exercise capacity has significant implications on clinical outcome and survival. As the mechanisms underlying improvements in aerobic exercise capacity and the effects of exercise training on circulatory and end-organ function remain incompletely understood, Tran et al. (2022) focused on the need for developing adapted exercise programs. In this second manuscript, the authors present the planning of a large well designed, multi-center randomized controlled trial: The Fontan Fitness Intervention Trial which will investigate as a primary outcome the change in aerobic exercise capacity after a 4-month supervised aerobic and resistance exercise training program of moderate-to-vigorous intensity followed by an 8-month maintenance phase in children and adults. Results of this study are pending and have the potential to strongly impact clinical practice.

In line with this therapeutic strategy, Dirks et al. (2022) report on their innovative prospective study of home-based bicycle-ergometer and inspiratory muscle training for children and adults with Fontan circulation. After performing 90 min of endurance training per week in addition to inspiratory muscle training (30 breaths per day) for 10 months the authors observed significant increases in maximum relative workload and in maximum inspiratory and expiratory pressures. Peak VO2 values did increase significantly as compared to baseline in a subgroup analysis of teenage/adult patients while the subjective quality of life remained unchanged under a potential influence of COVID times. This study confirms that an individually adapted home-based training program is safe and is associated with improvements in exercise test variables.

Future directions

The contributions of research efforts and reviews in this special issue on the Fontan circulation teach us to focus on principles of management and the identification of risk factors to improve patient outcomes. There is a great need for advancing multidisciplinary health care for this unique group. Special focus should be given to optimization of cardiovascular parameters pre-Fontan e.g., the pulmonary vasculature and the lymphatic vasculature. A comprehensive follow-up surveillance program post Fontan needs to pay

attention to early discovery of organ dysfunctions. An important measure to prevent or reverse negative outcome and the development of complications appears to be the maintenance of a good exercise capacity with encouragement of physical activity and regular exercise training. According to Van de Bruaene et al. (2022) the areas in need of innovation to improve the Fontan circulation include:

- retraining of the pulmonary vasculature and ventricle
- using right-sided assist devices prior to transplant
- performing further research on implantable right-sided assist devices
- reducing the risk of AV valve surgery
- determining novel pathways to improve the thrombo-inflammatory state in Fontan patients.

In this issue, perspectives are highlighted to improve long-term risk stratification and the implementation of new tools for future care to effectively improve the quality and duration of life of individuals with a Fontan circulation.

Author contributions

RH conceptualized and wrote the original draft. All authors reviewed the submitted version. JR edited the final version. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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The Influence of Respiration on Blood Flow in the Fontan Circulation: Insights for Imaging-Based Clinical Evaluation of the Total Cavopulmonary Connection

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Congenital heart disease is the most common birth defect and functionally univentricular heart defects represent the most severe end of this spectrum. The Fontan circulation provides an unique solution for single ventricle patients, by connecting both caval veins directly to the pulmonary arteries. As a result, the pulmonary circulation in Fontan palliated patients is characterized by a passive, low-energy circulation that depends on increased systemic venous pressure to drive blood toward the lungs. The absence of a subpulmonary ventricle led to the widely believed concept that respiration, by sucking blood to the pulmonary circulation during inspiration, is of great importance as a driving force for antegrade blood flow in Fontan patients. However, recent studies show that respiration influences pulsatility, but has a limited effect on net forward flow in the Fontan circulation. Importantly, since MRI examination is recommended every 2 years in Fontan patients, clinicians should be aware that most conventional MRI flow sequences do not capture the pulsatility of the blood flow as a result of the respiration. In this review, the unique flow dynamics influenced by the cardiac and respiratory cycle at multiple locations within the Fontan circulation is discussed. The impact of (not) incorporating respiration in different MRI flow sequences on the interpretation of clinical flow parameters will be covered. Finally, the influence of incorporating respiration in advanced computational fluid dynamic modeling will be outlined.

Keywords: Fontan, total cavopulmonary connection, respiration - physiology, flow imaging, MRI, hepatic veins, blood flow, extracardiac conduit Fontan

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INTRODUCTION

Congenital heart disease is the most common birth defect with an estimated incidence of 1 in 100 live births (1). Functionally univentricular heart defects represent the most severe end of the spectrum of congenital heart disease, characterized by a severely underdeveloped ventricle that is unable to drive the systemic or pulmonary circulation. Many underlying diagnoses can be present, including patients with an underdeveloped right ventricle (e.g., tricuspid atresia) or an underdeveloped left ventricle (e.g., hypoplastic left heart syndrome). The Fontan operation is the palliative treatment of choice for single ventricle patients, by connecting both caval veins directly to the pulmonary arteries (PAs), also called the total cavopulmonary connection (TCPC) (2). Via this procedure, the venous inflow connections to the heart are rerouted, excluding the hypoplastic ventricle from the circulation, whereas the other ventricle will serve as systemic ventricle. Without the interposition of a subpulmonary ventricle, the pulmonary circulation in Fontan patients is a low-energy, passive circulation that is dependent on elevated systemic venous pressure to drive pulmonary blood flow toward the single ventricle. The Fontan circulation is thus characterized by chronically elevated central venous pressure with reduced cardiac output due to chronic preload deprivation of the single ventricle (3). Although the Fontan circulation has led to survival into adulthood >90%, significant morbidity is present including a reduced quality of life, exercise capacity and the occurrence of liver fibrosis/cirrhosis or protein losing enteropathy (4).

Because of the vulnerable state of the Fontan physiology and its dependence on favorable hemodynamics, regular evaluation of flow within the Fontan circulation is recommended for early detection of (subclinical) complications (4). Currently, echocardiography and magnetic resonance imaging (MRI) are the imaging modalities of choice to evaluate TCPC flow, but differently incorporate the effect of respiration on flow rates. Since respiration importantly influences TCPC flow (5–7), knowledge about the effect of respiration on blood flow and how flow measurements and flow-related clinical parameters are affected by different MRI protocols is therefore important for clinicians taking care of Fontan patients.

In this review, blood flow characteristics as influenced by the cardiac and respiratory cycle at multiple locations within the TCPC are discussed. The effect of not/partially incorporating the influence of the respiratory cycle in conventional MRI flow imaging will be described. Finally, the importance of including respiration-resolved flow measurements in advanced computational fluid dynamic (CFD) modeling of TCPC hemodynamics (e.g., wall shear stress, energy loss) is outlined.

THE TOTAL CAVOPULMONARY CONNECTION: DEFINITION OF THE DIFFERENT VESSELS

Nowadays, the Fontan circulation is created using two techniques. The lateral tunnel technique connects the IVC to the PA via an intra-atrial patch (thus including part of the right atrium in the Fontan tunnel) (2). The extracardiac conduit technique (8) connects the IVC with the PA via a rigid Goretex conduit outside the heart. Conventionally, the term "TCPC" is considered to cover the area consisting of the Fontan tunnel (both the lateral tunnel and extracardiac conduit technique, above the entry of the HVs), the SVC, and both right- and left PAs. Thus, most papers use the terminology "IVC" when assessing flow in the Fontan tunnel (9–11). In this review, as depicted in **Figure 1**, the term "IVC" is used for the subhepatic IVC (below the entry of the HVs), and "Fontan tunnel" for the suprahepatic IVC (above the entry of the HVs) to make a clear distinction between these locations within the TCPC.

PHYSIOLOGY OF TCPC FLOW

In the normal biventricular circulation, systemic venous return toward the right atrium is determined by the ratio of the pressure gradient between (1) the mean systemic filling pressure and right atrial pressure and (2) the venous vascular resistance (12). Consequently, a change in one of these parameters is needed to affect venous return and, as a consequence of the Frank-Starling mechanism, thereby affects preload leading to altered cardiac output. For example, factors that increase systemic filling pressure (e.g., augmented blood volume or vasomotor tone) can alter systemic venous return by increasing the pressure gradient promoting venous return (12, 13).

In the Fontan circulation, systemic venous return and thus pulmonary blood flow to the single ventricle is therefore determined by the ratio of (1) the pressure gradient between the mean systemic filling pressure and the atrium, and (2) the venous vascular resistance and the total resistance in the Fontan circuit, constituting of the serial TCPC resistance and pulmonary vascular resistance (3, 14). In general, four components have been described in literature that can affect flow rates in the TCPC, including alterations in blood flow along the cardiac cycle (15), the respiratory cycle, flow alterations because of peripheral muscular pump activity during lower-leg exercise (14, 16), and by gravitational forces, leading to decreased inferior systemic venous flow rates at the upright vs. the supine position (17). All these factors influence TCPC flow by altering the venous pressure gradient from the systemic veins toward the atrium. For example, central venous pressure has been shown to be raised to 20–30 mmHg during lower-leg exercise by the contribution of the peripheral muscle pump, thereby effectively raising the pressure gradient and thus pulmonary blood flow in Fontan patients (3, 18).

Unique to the Fontan circulation where the systemic venous return and pulmonary circulation are fully bypassed from the single ventricle, only minor alterations in blood flow occur along the cardiac cycle, with in general increased flow during systole and early diastole (early filling), with decreased flow during late diastole (atrial contraction) (15). In Fontan patients, however, the effect of respiration on venous return and pulmonary blood flow pulsatility is much more pronounced. This is predominantly caused by a change in intrathoracic pressures (i.e., intrapleural and pericardial pressures), leading to a change in atrial pressures,

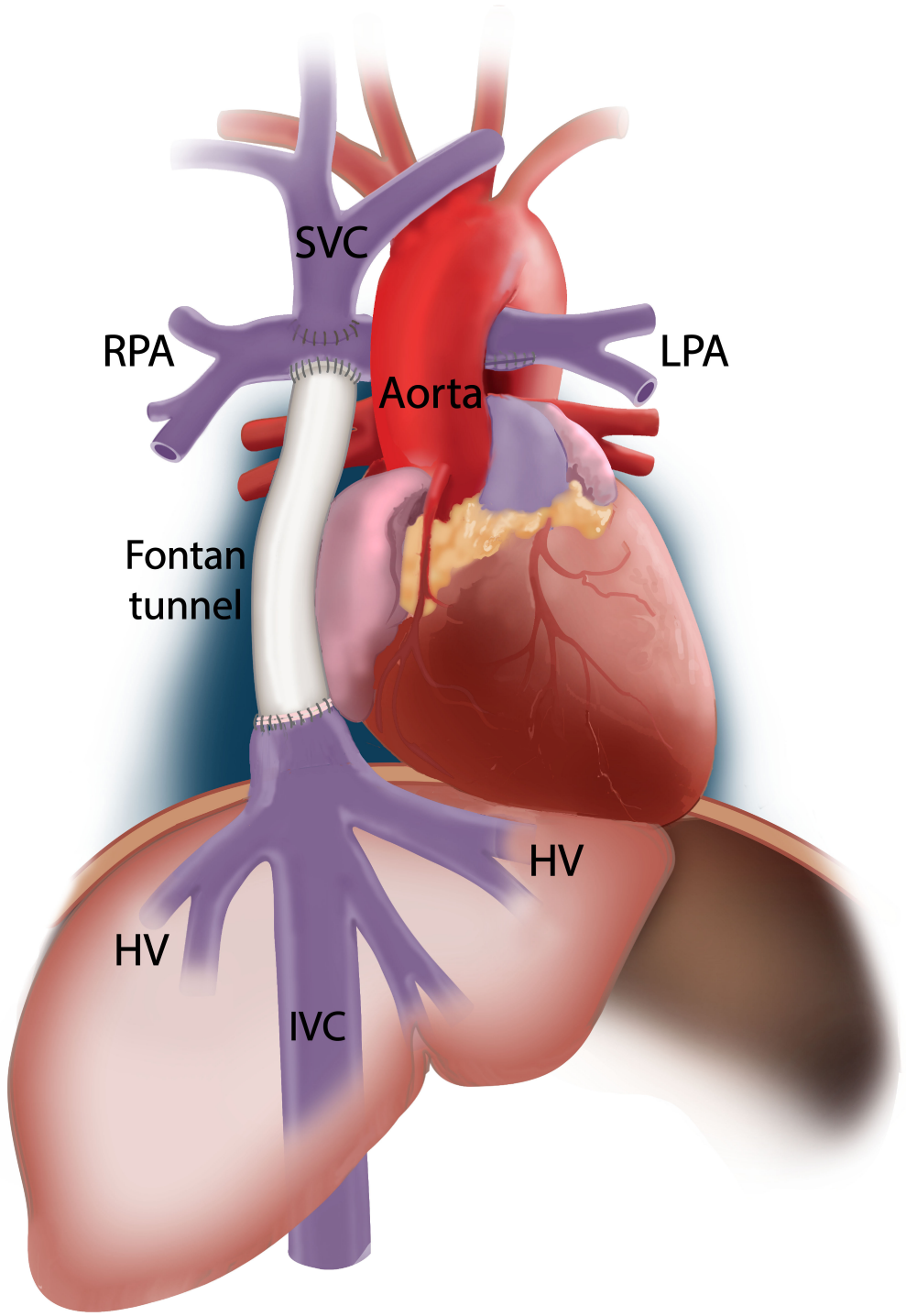

FIGURE 1 | A schematic representation of the TCPC is shown. In this example, an extracardiac conduit Fontan circulation is shown. The IVC represents the part inferior to the entry of the hepatic veins. The suprahepatic part of the IVC is indicated as the Fontan tunnel, representing either the extracardiac conduit or lateral intraatrial tunnel.

and a change in abdominal pressure, thereby effectively changing the pressure gradient from the inferior vena cava and hepatic veins, via the pulmonary arteries and pulmonary vascular bed, to the atrium. For this reason, mechanical ventilation using positive end-expiratory pressure has been shown to reduce cardiac output in Fontan patients (19), with significantly increased pulmonary

blood flow and cardiac output when negative pressure ventilation is applied (19, 20). Additionally, it also explains reduced caval flow rates during the Valsalva maneuver, as increased intrathoracic pressures during Valsalva lead to a decreased pressure gradient and thus venous return (21).

Of note, it is currently not known if changes in PVR during respiration also have effect on the change in blood flow during respiration. In healthy persons, PVR is lowest around functional residual capacity, with an increase in PVR at total lung capacity or residual volume (22). To date, no studies have studied possible changes in PVR during normal respiration in Fontan patients.

The minor effect of the cardiac cycle on blood flow pulsatility is in contrast to a normal biventricular circulation, where a rise in pulmonary artery pressure during systole results in significant pulmonary blood flow alterations during the cardiac cycle, with a much less pronounced influence of respiration. Because of its relevance to blood flow imaging, flow dynamics along the cardiac and respiratory cycle are the subject of this review.

IMAGING MODALITIES FOR ASSESSMENT OF TCPC BLOOD FLOW ALONG CARDIAC AND RESPIRATORY CYCLE

Doppler Echocardiography

Doppler echocardiography allows for real-time measurement of one-directional blood flow velocity along the direction of the ultrasound beam. Simultaneous recording of the respiratory and electrocardiography (ECG) signal provides insight into the timing of the velocity measurements with respect to the cardiac and respiratory cycle.

Phase Contrast-MRI

Flow quantification using phase contrast MRI (PC-MRI) is based on the fact that changes in the phase of the MR signal along a magnetic field gradient are proportional to the velocity of the blood flow (23). Subsequently, flow rates can be calculated by multiplying the mean velocity over a cross section with the vessel cross-sectional area. For most PC-MRI techniques, however, the time to acquire these phase (i.e., velocity) images exceeds the length of a single heartbeat. Therefore, to obtain dynamic flow information along an entire cardiac cycle, it requires data acquisition over multiple heartbeats, gated to the ECG signal (ECG-gating). Subsequently, the data from multiple heartbeats is synchronized and retrospectively reconstructed into one single cardiac cycle. Importantly, flow imaging using ECG-gating will therefore not take respiratory effects on flow rates into account, as data from multiple different heartbeats are acquired irrespective of the phase of the respiratory cycle.

Respiratory Motion Compensation

PC-MRI can be performed under breath hold (2D flow MRI only) or free-breathing conditions. Since breathing motion can lead to image artifacts with poor image quality, PC-MRI acquired during free-breathing usually requires some form of respiratory movement compensation. Most commonly, a respiratory abdominal belt or navigator is used to track the level of the diaphragm. Only data acquired within a predefined range around the end-expiratory diaphragm position is accepted to minimize breathing artifacts. Thus, only flow data acquired around the end-expiratory phase of the respiratory cycle will be captured when a respiratory navigator is used, similar to the breath-hold condition (24). Knowledge about the effect of respiration on blood flow and how flow measurements and flow-related clinical parameters are affected by the different PC-MRI sequences and respiratory compensation strategies is therefore important for clinicians taking care of Fontan patients.

Currently, multiple PC-MRI sequences are used that are mainly focused on flow dynamics during the cardiac cycle with variable degrees of incorporation of the respiratory component.

2D Flow MRI

2D flow MRI obtains ECG-gated, one-directional (through-plane) velocity at a predefined 2D plane at a vessel of interest, and is the current clinical standard for flow quantification (25). Scan durations are in the order of 10–15 s. 2D flow can be acquired using free-breathing, with or without respiratory motion compensation, or under breath-hold conditions. Thus, 2D flow MRI does not capture respiration induced flow variations.

2D Real-Time Flow MRI

Advances in MRI acquisition strategies nowadays allow for 2D real-time (ungated) flow acquisitions without the need for respiratory motion compensation, allowing for assessment of dynamic flow variations (typical temporal resolution 15–20 measurements per second) along both the cardiac and respiratory cycle (26). The respiratory and electrocardiography (ECG) signals are simultaneously recorded, allowing to synchronize the timing of the flow rate measurements with the phase of the cardiac and respiratory cycle.

3D Flow MRI

Recently, 3D flow MRI has been introduced for assessment of flow and flow-related parameters in the TCPC in Fontan patients, exploiting the negligible TCPC blood flow pulsatility along the cardiac cycle (27). With 3D flow MRI, three-directional velocities within a 3D volume of interest are acquired for a single, cardiac-cycle averaged (no ECG-gating) phase. It allows for quantification of cardiac-cycle averaged flow rates and flow related clinical parameters (e.g., pulmonary flow distribution), within a 1.5 min scan. 3D flow MRI does not incorporate the effect of respiration on flow characteristics (27).

4D Flow MRI

4D flow MRI allows for the acquisition of ECG-gated (usually 20–30 phases along the cardiac cycle), three-directional velocities within a 3D volume of interest. Flow rates can be retrospectively quantified at any vessel of interest within the scanned volume. Furthermore, it allows for visualization of three-dimensional flow patterns within the TCPC and quantification of advanced hemodynamic parameters (e.g., viscous energy loss rate). Scan durations are in the order of 8–16 min, depending on the application, sequence and use of respiratory motion compensation (28). Due to the long scan times, 4D flow MRI can only be acquired using free-breathing with or without

the use of respiratory motion compensation. Consequently, conventional 4D flow MRI sequences do not incorporate the effect of respiration on flow dynamics.

5D Flow MRI

Most recently, 5D flow MRI has been used to quantify blood flow by obtaining ECG- and respiratory-gated, three-directional velocities within a 3D volume (i.e., 4D flow MRI + respiratory-gating = 5D flow MRI). 5D flow MRI allows for obtaining cardiac-cycle resolved (ECG-gated) flow information from data acquired in four different respiration phases: inspiration, end-inspiration, expiration and end-expiration (29).

THE INFLUENCE OF THE CARDIAC AND RESPIRATORY CYCLE ON NET FORWARD FLOW IN THE TCPC

An important differentiation must be made between net forward flow and flow pulsatility within the TCPC. It is a common belief that part of the venous return in Fontan patients is dependent on energy provided by respiration (9, 17). Hsia et al. (17) used doppler echocardiography to define the percentage of respiration-dependent flow as follows: $\frac{Qinsp-Q\,\exp}{Qinsp+Qexp}$, where Q_{insp} and Q_{exp} are the flow rates during inspiration and expiration, respectively. Based on this parameter, ∼30, 14, and 55% of Fontan tunnel flow, subhepatic IVC and HV flow is respiration-dependent, respectively (30). In comparison, in healthy controls respiration-dependent flow in the subhepatic IVC, HVs, and suprahepatic IVC were 11, 25, and 15%, respectively. Therefore, it has been suggested that a significant percentage of specifically Fontan tunnel and HV net forward flow is dependent on respiration as a driving force. However, although inspiration does actively *increase* flow rates compared to breath-holding conditions due to a decrease in intrathoracic pressure and atrial pressure augmenting the transpulmonary pressure gradient, it must be emphasized that expiration also leads to *decreased* flow rates, thereby mostly countering the effect of inspiration. Consequently, defining the respiration-dependency of flow using inspiration and expiration flow rates is not ideal. In fact, respiration has only a significant influence on the net forward flow if the increased flow volume during inspiration (i.e., inspiratory flow rate * duration of inspiration) outweighs the decreased flow volume during expiration, compared to a breath-hold condition. Indeed, Wei et al. (11) demonstrated that respiration did not significantly affect net forward flow rates (difference on average <0.1 L/min/m^2) by comparing 2D real-time MRI acquired under both free-breathing and breath-hold conditions in the SVC, Fontan tunnel and aorta. Recently, Gabbert et al. also stressed the limited influence of respiration on net forward flow in the Fontan tunnel (7). In line with these findings, net forward flow was not affected by forced breathing conditions or after a 6 week inspiratory muscle training program (5, 31). Initiation of hyperventilation (representing the ventilatory pump) in addition to zero resistance exercise (representing the muscle pump) did also not result in significantly higher blood flow rates (16). Thus, it must be concluded that respiration is not an important driving force for net forward flow in the TCPC.

THE INFLUENCE OF THE CARDIAC AND RESPIRATORY CYCLE ON BLOOD FLOW PULSATILITY IN THE TCPC

However, these studies clearly showed a significant increase in *pulsatility* (flow variations along the cardiac and/or respiratory cycle) caused by respiration, with high variability between the different vessels of the TCPC (5, 7, 11). Various parameters have been used to assess blood flow pulsatility along the respiratory cycle, of which the *inspiratory-to-expiratory flow ratio* (mean inspiratory flow rate divided by mean expiratory flow rate, Q_{insp}/Q_{exp}) is most commonly used.

Fontan tunnel flow represents ∼65–70% of total systemic venous return (9, 32). Many studies consistently show the pronounced effect of respiration on Fontan tunnel flow rates (5, 9–11, 30, 33), with a 70–90% higher flow rate during inspiration compared to the entire respiratory cycle, significantly more pronounced compared to a 20% increase observed in healthy controls (5, 9). Other studies demonstrate similar findings by reporting a Q_{insp}/Q_{exp} of 1.6–3.0 (11, 34, 35). By dividing 2D real-time flow MRI measurements of the Fontan tunnel into components along the respiratory and cardiac cycle, it was shown that respiration-derived pulsatility was 2.8-times the pulsatility along the cardiac cycle. This was the opposite in healthy controls, where pulsatility along the cardiac cycle was 2.5-times the pulsatility along the respiratory cycle at the level of the suprahepatic IVC (**Figure 2**) (7). As opposed to its effect on net forward flow, normal and forced breathing significantly increases blood flow pulsatility in Fontan patients, further illustrating that respiration rather than the cardiac cycle is the major contributor of flow pulsatility in the Fontan tunnel (**Figure 2**) (5, 7, 11).

The Fontan tunnel receives blood from both the subhepatic IVC and HVs, which contribute on average 62 and 38%, respectively, to total Fontan tunnel flow (6, 17, 35–38). The study of flow dynamics in this area is of great importance, as the splanchnic venous return plays an important role in the pathophysiology of liver cirrhosis and protein-losing enteropathy. Using (invasive) doppler echocardiography, Q_{insp}/Q_{exp} in the subhepatic IVC was 1.3–1.6 (17, 35), not significantly different from healthy controls (Q_{insp}/Q_{exp} 1.2) (6, 17, 36, 37). Thus, respiration has a much less pronounced influence at the subhepatic IVC compared to the Fontan tunnel, indicating that most of the respiratory-derived pulsatilty in the Fontan tunnel must be explained by the HV flow contribution.

Respiration indeed strongly influenced HV flow in Fontan patients (Q_{insp}/Q_{exp} 2.9–4.4), significantly higher compared to healthy controls (Q_{insp}/Q_{exp} 1.7) (17, 35). The important increase in HV flow during inspiration is explained by the liver acting as a reservoir of blood with high venous capacitance, from which both the increased extra- to intra-thoracic venous pressure gradient, as well as the direct pressure of the diaphragmatic descent on the liver, can draw blood toward the Fontan tunnel during inspiration (39). Presence of a fenestration was associated

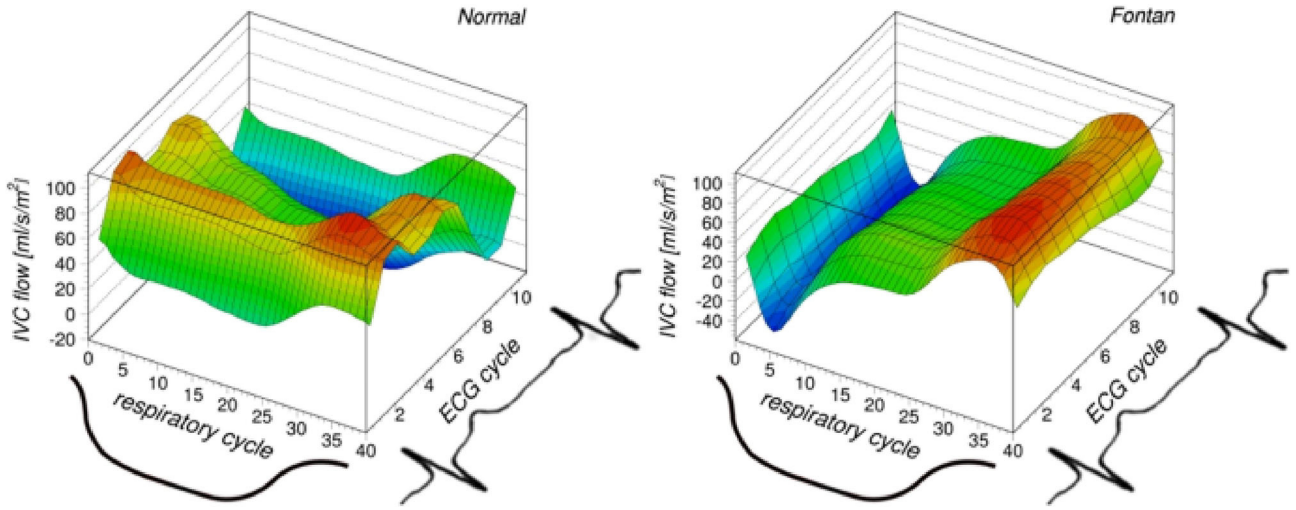

FIGURE 2 | Reproduced from Gabbert et al. (7) https://www.nature.com/articles/s41598-019-38848-5/figures/2. This figure shows the blood flow profile in the suprahepatic IVC (healthy control, left image) and Fontan tunnel (right image), separated along the respiratory and cardiac cycle. Flow rates are indicated in color, with red indicating higher flow rates and blue indicating lower/negative flow rates. In healthy controls, pulsatility is almost exclusively observed along the cardiac cycle with retrograde flow observed during atrial contraction. In complete contrast, in Fontan patients pulsatility is almost exclusively observed along the respiratory cycle, with minimal or negative flow rates observed during expiration and maximal flow rates during inspiration. Along the cardiac cycle, negligible pulsatility is present.

with a significantly higher inspiratory-to-expiratory fraction; 4.4 vs. 3.0 (36). Since central venous pressure is lowered by the presence of a fenestration between the Fontan tunnel and the atrium, the decreased afterload for HV flow likely causes the increased flow rates during inspiration. Importantly, plication of the diaphragm in Fontan patients with a diaphragm paresis does not fully restore normal respiratory mechanics, evidenced by a significantly smaller inspiratory-to-expiratory ratio of HV flow; 2.3 vs. 3.2 (37). However, respiration likely also does not affect net forward HV flow, in line with observations in the Fontan tunnel. This might explain why Fontan patients with a diaphragm paresis have similar cardiac index and exercise capacity compared to patients with a normal functioning diaphragm (40).

Studies on the influence of respiration on SVC flow, contributing ∼35% of total systemic venous return, have been conflicting (Q_{insp}/Q_{exp} 1.0–1.9) (5, 9, 11, 35). Wei et al. reported an inspiratory-to-expiratory ratio of 1.9 in the SVC, higher compared to the fraction of 1.6 they observed in the Fontan tunnel (11). This is in strong contrast to a previous study using 2D real-time flow MRI, which did not find an effect of breathing on SVC flow rates, in line with observations in healthy controls (5, 9). It remains the question from which vascular region with high venous capacitance (analog to the HVs providing most of the pulsatility observed in the Fontan tunnel) blood would be drawn toward the SVC during inspiration.

In normal subjects, aortic flow rate or ventricular stroke volume only slightly increase during expiration and decreases during inspiration, opposite to systemic venous return. Compared to mean aortic flow rates, flow rates are 0–6% higher at (end)-expiration and 1–6% lower at (end)-inspiration (5). A similar, modest effect of respiration on aortic flow has been observed in Fontan patients, ranging from a 7% increase during expiration, to a 4% decrease during inspiration (5, 9). Therefore, since systemic venous flow (predominantly HV and Fontan tunnel flow) rates are markedly raised during inspiration while aortic flow rates are not, the pulmonary circulation and lungs act as a reservoir with a large inspiratory capacity, releasing blood toward the single ventricle during expiration (9). In contrast to the systemic venous part of the Fontan circulation, respiration thus has a minimal influence on pulsatility in the aorta, which is primarily caused by the cardiac contraction. An example of flow rates during free breathing and under breath-hold conditions in the subhepatic IVC, HVs, Fontan tunnel and aorta are shown in **Figure 3**. An overview of the influence of respiration on flow rates and a schematic representation are presented in **Table 1** and **Figure 4**.

Clinical Relevance of Pulsatility

It is currently not known if respiratory derived pulsatility plays an important role in maintaining low pulmonary vascular resistance. The negligible blood flow pulsatility along the cardiac cycle has been thought to negatively influence pulmonary vascular resistance and endothelial function in Fontan patients, by altering the passive recruitment of capillaries and shear stress-mediated nitric oxide release (41). In turn, the respiratory derived pulsatility in the Fontan tunnel is profoundly different in amplitude and frequency compared to the cardiac pulsatility (**Figure 3B**). Recently, no significant difference was found in pulmonary vascular resistance between Fontan patients with or without diaphragm paresis, indicating that respiration derived pulsatility might not be important for healthy pulmonary vasculature (40).

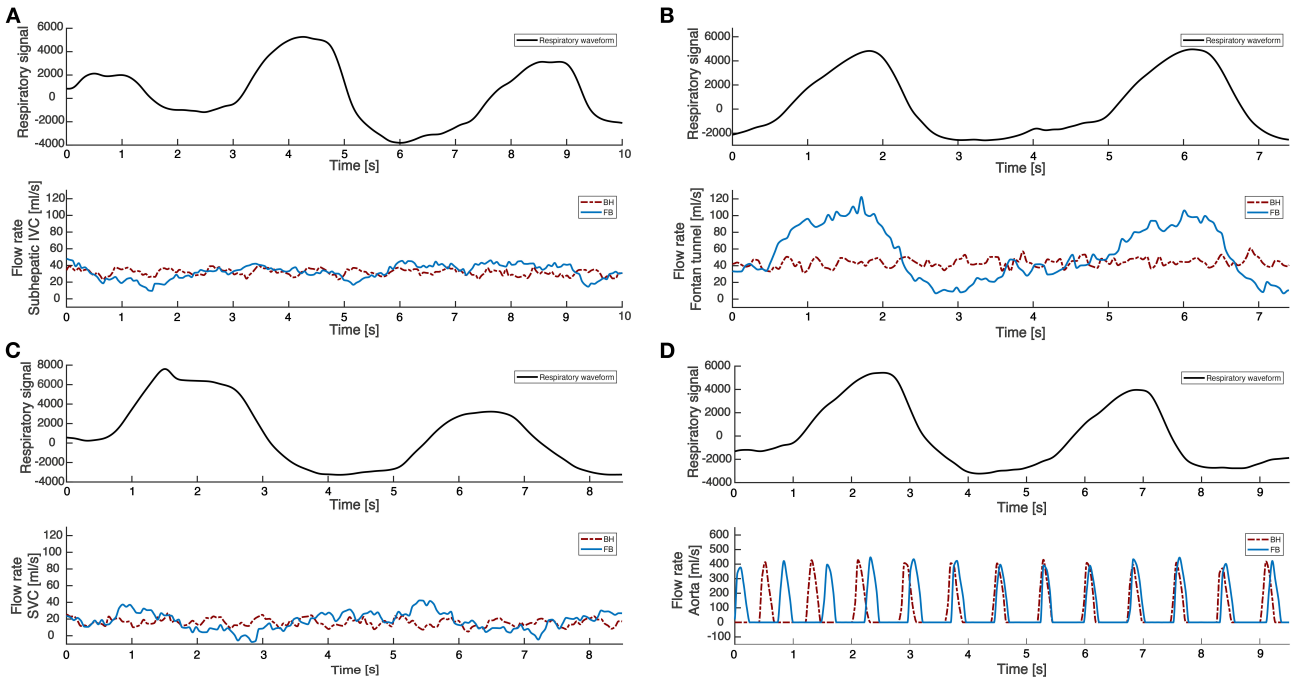

FIGURE 3 | 2D real-time flow MRI measurements in the IVC, Fontan tunnel, SVC and aorta. 2D real-time flow MRI measurements are shown under both free breathing (FB, blue line) and breath-hold (BH, red line) conditions for the subhepatic IVC **(A)**, Fontan tunnel **(B)**, SVC **(C)**, and ascending aorta **(D)**. Under breath-hold conditions, negligible cardiac-cycle related pulsatility is present in all venous vessels due to the absence of a subpulmonary ventricle in Fontan patients. During free breathing conditions, predominantly the Fontan tunnel flow is influenced by respiration, with a significant augmentation of flow rates during inspiration compared to expiration. Since the effect of respiration on subhepatic IVC flow is only minimal, most respiratory pulsatility in the Fontan tunnel originates from the hepatic veins. The influence of respiration on flow rates in the SVC and aorta is also minimal, although studies have reported conflicting results regarding respiratory pulsatility in the SVC.

TABLE 1 | Influence of respiration on blood flow at multiple locations within the Fontan circulation.

Parameter	Fontan					Healthy				
	Fontan tunnel	Subhepatic IVC	HV	SVC	Aorta	Suprahepatic IVC	Subhepatic IVC	HV	SVC	Aorta
Inspiratory-to-expiratory flow ratio: Q_{insp}/Q_{exp}	1.6–3.0	1.3–1.6	2.9–4.4	1.0–1.9			1.2	1.7	1.2	
Inspiratory flow fraction: Q_{insp}/Q_{avg}	1.7–1.9	–	–	–	0.96	1.2	–	–	–	0.94–0.99
Respiratory-dependent flow fraction: $(Q_{insp}-Q_{exp})/(Q_{insp}+Q_{exp})$	30%	14%	55%	–	–	15%	11%	25%	–	–

IVC/SVC, inferior/superior vena cava; HV, hepatic veins; Q_{insp}, inspiratory flow rate; Q_{exp}, expiratory flow rate; Q_{avg}, flow rate during the entire respiratory cycle.

Retrograde Flow

While flow rates increase during inspiration, flow rates in the Fontan tunnel strongly decrease during expiration with potential back flow during the early expiratory phase. On average, backflow represents ∼5–11% (range 0–30%) of mean forward flow volume in the Fontan tunnel (7, 9, 10), reducing to only 2.9% under exercise conditions (9). Similar percentages are observed in the suprahepatic IVC in healthy controls with a mean backflow of 6% (range 0–20%). Other studies used the retrograde-to-forward flow rate ratio to express back flow, but this parameter does not represent retrograde-to-antegrade flow *volume*, as the duration of antegrade and retrograde flow are not taken into account. In the subhepatic IVC and HVs, a retrograde-to-forward flow rate ratio of 0.06–0.07 and 0.27, respectively, were observed (17, 34, 36). Importantly, backflow is also observed in healthy persons as a result of the atrial contraction and is not related to respiration, while backflow in Fontan patients is related to the expiratory phase (7, 38). Retrograde flow is usually negligible in the SVC, accounting for only 0–1% of mean forward flow volume (9).

THE INFLUENCE OF RESPIRATION ON BLOOD FLOW DURING EXERCISE

Currently, the influence of respiration on flow rates under exercise conditions in Fontan patients has only been investigated

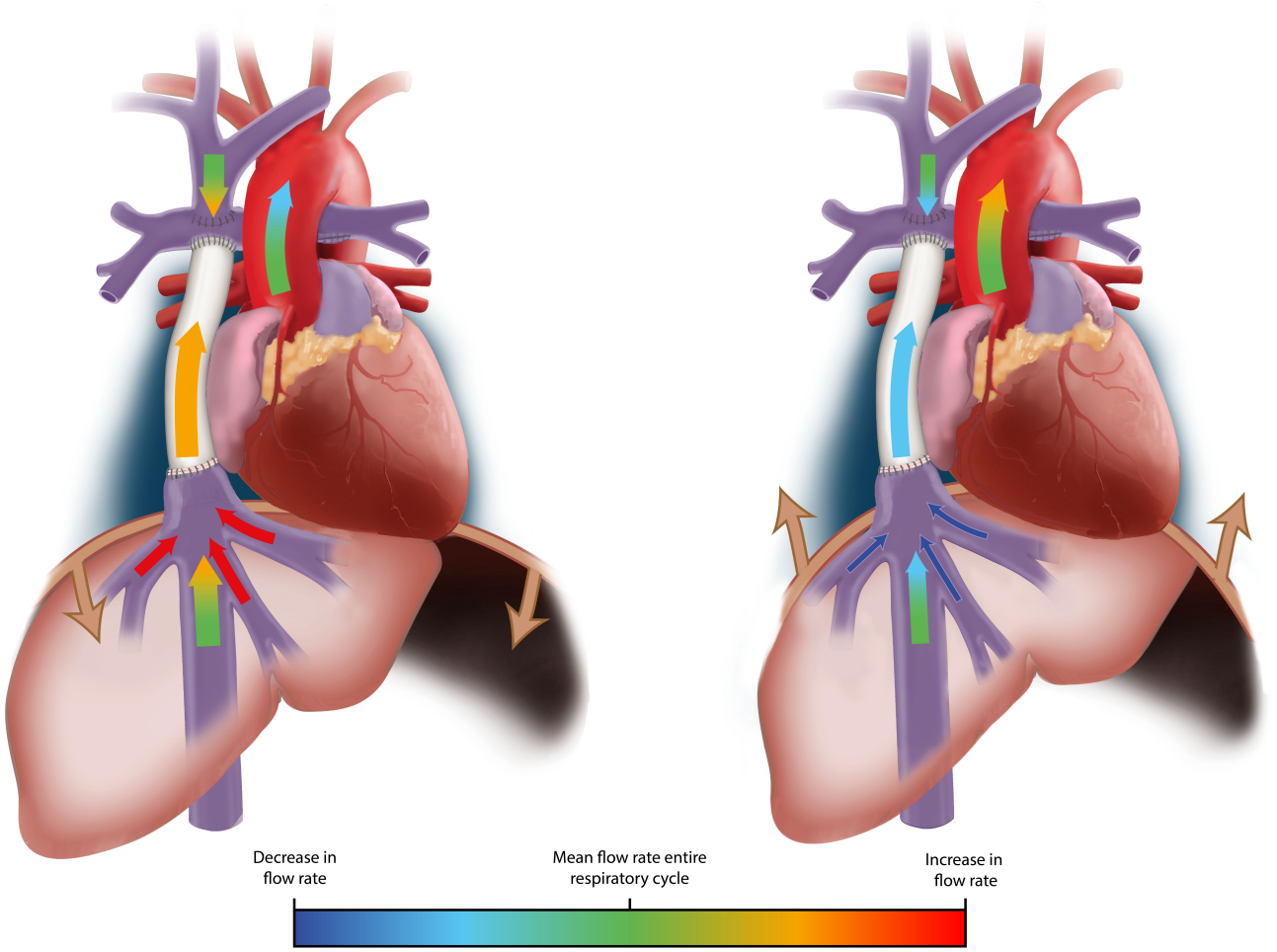

FIGURE 4 | Schematic representation of the influence of respiration on flow rates in the TCPC and aorta. A schematic representation of flow rates in the TCPC and aorta is shown during inspiration (left image) and expiration (right image). Arrows are color-coded by the change in flow rate in each vessel during inspiration and expiration using a linear gradient toward red (strong increase) or dark blue (strong decrease), compared to the average flow rate during the entire respiratory cycle (light green). Change in width of the arrows for each vessel schematically represent the change in flow rates between inspiration and expiration. Flow rates in the subhepatic IVC, SVC* and aorta are only minimally influenced by respiration. Predominantly HV flow is strongly influenced by respiration, with a significant increase in flow rate during inspiration and decrease during expiration. Therefore, Fontan tunnel flow rates also show a considerable increase in flow rate during inspiration and decrease during expiration, primarily caused by the contribution from the HVs. *Of note, studies report conflicting results regarding respiratory pulsatility in the SVC, ranging from only minimal to considerable pulsatility. SVC/IVC, superior/inferior vena cava; HV, hepatic veins.

in the Fontan tunnel, SVC and aorta. During lower-leg exercise conditions, the predominance of inspiratory flow augmentation in the Fontan tunnel seems to become less pronounced. Hjortdal et al. found a mean inspiratory fraction ($Q_{insp}/Q_{average\ respiratory\ cycle}$) decrease from 1.9 in rest, to 1.4 under 1 W/kg lower-leg exercise conditions. Peripheral muscle contractions were responsible for an almost 3-fold increase in expiratory flow rates, while inspiratory flow rates only increased by 1.6-fold (10). Of interest, Cordina et al. also showed predominantly increased expiratory flow rates in rest in patients after 20 weeks of peripheral muscle resistance training. The increased flow rates are explained by the presence of increased peripheral muscle mass leading to reduced venous compliance, thereby presumably increasing systemic filling pressures leading to increased preload and cardiac output (21). The reason why the muscle pump predominantly increases expiratory flow rates compared to inspiratory flow rates, thereby leading to reduced "respiratory dependence," remains incompletely understood. Although speculative, there may be a limit in the venous capacity in the inspiratory phase, leading to a diminished response to increased filling pressures caused by the muscle pump.

EFFECT OF RESPIRATION ON CLINICALLY USED FLOW PARAMETERS

PC-MRI Derived Clinical Flow Parameters

Previous paragraphs have shown the variable influence of respiration on flow rates observed at multiple locations in the

TCPC. Most conventional PC-MRI sequences are focused to capture flow changes during the cardiac contraction (ECG-gating) only and do not take respiration into account. Therefore, knowledge about the effect of (not) incorporating respiration on flow and flow-related clinical measurements are important for the correct interpretation of MRI examinations in Fontan patients.

Net Forward Flow vs. Pulsatility

Since respiration predominantly affects pulsatility but not net forward flow (7, 11), conventional ECG-gated 2D flow MRI sequences did not show significantly different net forward flow rates between patients scanned under free-breathing vs. breath-hold conditions (42). However, dynamic flow characteristics specific to part of the respiratory cycle, such as retrograde flow during expiration, or peak velocities during inspiration will not be captured (7, 43). The same likely applies for ECG-gated sequences using a respiratory navigator (as the acceptance window contains the last part of expiration, the end-expiratory phase and the first part of inspiration), although no studies exist in Fontan patients comparing free-breathing navigator-gated PC-MRI with PC-MRI acquisitions during breath-hold conditions.

Net Forward Flow-Derived Flow Parameters

Clinical parameters derived from net forward flow rates can thus most likely be accurately determined using ECG-gated sequences, since respiration minimally affects net forward flow rates. Only limited data exist of studies that have evaluated the effect of respiration on these parameters. Using a 4D flow MRI sequence able to provide cardiac-cycle resolved flow data based on inspiratory or expiratory data only, Rutkowski et al. showed a non-significant difference in pulmonary flow distribution (52 vs. 64% based on expiratory and inspiratory data, respectively) (44). Modeling studies using computational fluid dynamics (CFD) found similar results, with differences <5% in right-to-left pulmonary flow distribution along the respiratory cycle (45, 46).

Hepatic Flow Distribution

Fontan patients require a certain amount of hepatic venous flow toward both lungs in order to prevent the formation of pulmonary arteriovenous malformations (47). The hepatic flow distribution (HFD) can be determined by tracking particles from the Fontan tunnel toward the PAs based on time-resolved, three-dimensional velocity fields acquired with 4D- (48, 49) or 5D flow MRI (29), or derived from computational fluid dynamic (CFD) models (39, 50, 51). Bastkowski et al. used a novel 5D flow MRI sequence to reconstruct four ECG-gated flow fields using data from 4 respiratory phases: inspiration, end-inspiration, expiration and end-expiration. On average, the maximum differences in HFD between the four respiratory-phases was 20% (range 9–30%). Hence, the contribution of hepatic flow toward the PA changes during the respiratory cycle because of the flow pulsatility in the Fontan tunnel associated with respiration. However, the necessity of including respiration for accurate average HFD quantification was not investigated (29). A recent study using patient-specific CFD models with both 2D real-time MRI acquired under free-breathing and breath-hold as boundary conditions, showed that respiration has negligible influence on average HFD with mean differences of 1% (range −3 to 7%) (43).

CFD-Derived Hemodynamic Metrics of the TCPC

CFD models are increasingly used to study flow dynamics in the TCPC in Fontan patients, and can now be performed using patient-specific 3D TCPC reconstructions and patient-specific physiological data. It allows not only for the visualization of time-resolved 3D flow patterns within the TCPC, but also for quantification of advanced velocity and pressure-related hemodynamic parameters, including power loss, viscous energy loss rate, wall shear stress and stagnation volume (52–54).

Importance of Including Respiration-Derived Pulsatility in CFD Simulations

Flow Patterns

Previous studies using CFD, *in vitro* models or 4D flow MRI have shown the presence of adverse secondary flow patterns, including helical, swirling flow patterns at the IVC-to-conduit junction (55) and in the PAs (56, 57) or caval flow collision leading to chaotic flow disturbances at the central Fontan confluence (58, 59). The appearance of adverse, energy-consuming flow patterns increase blood flow resistance that may lead to an increased risk of complications (14). Importantly, these dynamic, 3D flow patterns change when respiration is included (43, 60). Furthermore, potential deleterious effects of backflow on the splanchnic circulation and its association with liver fibrosis can only be studied by incorporating respiration into the models, as backflow is exclusively observed during (early) expiration. In addition, incorporation of respiration may also be important to study whether the pulsatile HV hemodynamics effect the presence and magnitude of local secondary flow patterns observed in the IVC-to-conduit junction using 4D flow MRI (55).

Energy Loss

Power loss and viscous energy loss describe the flow efficiency in the TCPC in Fontan patients which is related to the presence of adverse flow patterns and geometries (e.g., PA stenosis or undersized extracardiac conduit) (61, 62). Increased power loss and TCPC resistance have been associated with reduced exercise capacity (63) and increased levels of liver fibrosis (64). Inclusion of respiration is important for accurate power loss measurements, as incorporation of respiration resulted in a 1.4–3.1-fold increase in power loss, consistently higher compared to simulations incorporating the cardiac cycle only (43, 45, 60, 65).

Importantly, although not incorporating respiration in CFD models leads to an underestimation of power loss, it did not affect the ranking of multiple surgical TCPC options created using "virtual surgery" CFD platforms (66). Virtual surgery platforms allow for the pre-operative determination of the optimal TCPC geometry by evaluating the flow efficiency and HFD within the proposed TCPC using patient-specific CFD simulations (67).

Thrombosis Markers

Thrombosis can occur in some Fontan patients within the TCPC. Although no clear markers can currently predict thrombosis risk, regions with low wall shear stress and/or high stagnation volumes have been reported as potential markers. Stagnation volume (blood volume with a velocity <0.01 m/s) can be specifically high during expiration in large conduits with significantly reduced flow stagnation during inspiration (53). Thus, it is emphasized that incorporation of respiration is important when local hemodynamic metrics are of interest, including wall shear stress and stagnation volume, due to the high temporal variation of such metrics during the respiratory cycle (45, 53, 65). As a result, inclusion of pulsatile boundary conditions acquired under free-breathing in patient-specific CFD models is recommended (11, 60, 68).

CONCLUSION

In conclusion, in contrast to the healthy circulation, respiration is the main source of blood flow pulsatility in the TCPC, whereas cardiac contraction mostly drives the net forward flow rate. Consequently, conventional ECG-gated PC-MRI acquisitions (i.e., 2D flow MRI and 4D flow MRI) can be used for measurements of clinical parameters based on net forward flow.

Inclusion of respiratory pulsatility in state-of-the-art patient-specific CFD models are recommended for evaluation of detailed, time-resolved hemodynamic metrics (e.g., wall shear stress and viscous energy loss rate), continuing to provide important insights for clinicians in the functioning of the TCPC.

AUTHOR CONTRIBUTIONS

SW performed the initial literature review. FR drafted the first manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Sexual Function in Men Living With a Fontan Circulation

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Introduction: It is unknown if the Fontan circulation has an impact on sexual health in men. This study assessed self-reported sexual health and fertility in men with a Fontan circulation.

Aims: In this prospective, cross-sectional study, Australian men ≥18 years enrolled in the Fontan Registry of Australia and New Zealand were invited to complete the International Index of Erectile Function (IIEF), alongside questions assessing fertility. These data were compared to historical, age-matched controls.

Results: Of 227 eligible men, 54 completed the survey; of those 37 were sexually active and included in the final analysis. Mean age was 28 ± 3 years, age at Fontan was 5 ± 3 years. Fontan type was extra-cardiac conduit in 15 (41%), lateral tunnel in 12 (32%), and atriopulmonary connection (APC) in 10 (27%). Ventricular function was normal in 24 (83%), and all were New York Heart Association Class I (23 patients, 79%) and II (six patients, 21%). Nine participants (24%) had erectile dysfunction (IIEF-EF score ≤25). The severity was mild (IIEF 22–24) in six (16%), mild–moderate (IIEF 17–21) in two (5%), and moderate (IIEF 11–16) in one (3%). Baseline characteristics and current medication usage were similar in those with and without erectile dysfunction. Compared with historical control values, erectile function was not significantly impaired in the Fontan population ($p = 0.76$). Men with a Fontan circulation had decreased levels of sexual desire and overall satisfaction ($p < 0.001$). There was no correlation between the presence of erectile dysfunction and any assessed parameter. Eleven (30%) of the cohort reported a pregnancy with a prior partner.

Conclusion: In our cohort, overall erectile function was comparable between men with a Fontan circulation and historical controls, however sexual desire and overall satisfaction were reduced. There was no correlation between study parameters and the presence of erectile dysfunction. The proportion of the cohort who had a prior pregnancy was congruent with population data.

Keywords: congenital heart disease, Fontan, sexual health, fertility, erectile dysfunction

INTRODUCTION

Since its initial development almost 50 years ago, the Fontan procedure has been increasingly implemented for children who have complex single ventricle cardiac anatomy (1–4). Over this time the technique has undergone multiple advancements, including the lateral tunnel (LT) and extracardiac conduit (EC) modifications (2–4). These new techniques, along with improved critical and medical care, have contributed to improved long-term survival for people living with a Fontan circulation—the majority of whom now reach adulthood (5–7).

There are numerous long-term morbidities which are well documented complications of a Fontan circulation due to the altered physiological state characterized by systemic venous hypertension, reduced cardiac output, endothelial dysfunction, neurohormonal activation and chronic cyanosis in many (8). Late complications include increased propensity to thromboembolic events, arrhythmia, and cyanosis as well as Fontan-associated liver disease, protein losing enteropathy and plastic bronchitis (5, 8). The impact that a Fontan circulation has upon sexual function, satisfaction and fertility is less well established. A proportion of women with a Fontan can conceive and carry a pregnancy safely through to delivery but fertility is reduced (9–11). The effect that Fontan physiology has upon sexual function in either sex is not well characterized and fertility within the male population is not established. We sought to investigate male sexual function in young adult men from the Australia and New Zealand Fontan Registry.

METHODS

For this prospective, cross-sectional study, men over the age of 18 years who had consented to involvement in research were contacted *via* the Fontan Registry of Australia and New Zealand. A total of 227 patients across all Australian states were identified and contacted between March 2019 and July 2020. A mailed questionnaire was sent to eligible men. If no response was received, they were contacted via telephone and given the opportunity to complete the questionnaire online. The study was approved by the Human Research Ethics Committee at all involved institutions (HREC2019.042).

The survey utilized the International Index of Erectile Function (IIEF), an internationally validated sexual health questionnaire. The IIEF examines the domains of erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. Questions were also included to provide a qualitative assessment of fertility. Patients self-reported appropriate scores for each domain based on their experience in the preceding 4 weeks. The IIEF defines a diagnosis of erectile dysfunction (ED) as an erectile function score of $\leq$26 (out of a possible 30). Mild ED is defined as an IIEF-EF score of 22–25, mild-moderate 17–21, moderate 12–16, and severe $<$11. These data were compared with historical control data with mean age of 35 years (12).

Men were excluded if they had a history of significant mental health disorder, or if they were not sexually active prior to the study period. Baseline characteristics were obtained from records of the Fontan Registry of Australia and New Zealand.

Erectile function score and the presence of erectile dysfunction were analyzed according to patient age, age at Fontan, years since Fontan, type of type of Fontan, NYHA class, oxygen saturations and ventricular function, and prior pregnancy in a partner. Clinical variables were used if collected within 12 months of questionnaire completion. Continuous variables were compared utilizing Student's independent or one sample T test and reported as mean $\pm$ standard deviation. Proportions were analyzed using a Chi-square test and reported as number (%). Correlations were completed using Spearman rank correlation and Pearson correlation coefficient. All statistical analysis was completed via SPSS v26 for Windows. Statistical significance was based on a p value of $<$0.05.

RESULTS

Of 227 eligible men, 135 were unable to be contacted or did not complete the survey, 22 were excluded due to a history of mental disorder, 17 refused to complete the survey upon contact, 13 did not have sexual activity during the study period, two declined to have their registry data accessed, and one person died during the study period, leaving 37 men included in the final analysis.

Baseline characteristics are shown in **Table 1** and were evenly matched between those without and with erectile dysfunction. Four men in total had implantable cardiac devices, all of which were in the group without ED ($p = 0.23$). Fourteen patients in total had a history of arrhythmia, eight in the cohort without ED and six in the cohort with ED ($p = 0.75$). All arrhythmias were atrial in origin.

Patients with a Fontan circulation had significantly decreased levels of sexual desire at 8.1 $\pm$ 1.2 compared to 9.1 $\pm$ 1.0 ($p <$ 0.001) and overall satisfaction at 8.3 $\pm$ 1.9 compared to 9.5 $\pm$ 0.8 in controls (both out of 10) ($p < 0.001$).

As demonstrated in **Figure 1**, the average IIEF erectile function score was 27.1 $\pm$ 3.9 (out of 30) for the Fontan cohort, compared to 27.2 $\pm$ 3.2 for historical control data ($p = 0.76$). **Table 2** outlines the results for the IIEF domains for those with ED compared to those without ED. As expected, those with ED had significantly reduced levels of erectile function ($p < 0.001$). Patients with ED also had significantly decreased scores in the domains of orgasmic function ($p = 0.05$), intercourse satisfaction ($p = 0.01$), and overall satisfaction ($p = 0.01$). There was no difference between groups in sexual desire ($p = 0.29$).

The range of IIEF-EF scores are demonstrated in **Figure 2**. Nine participants in the study (24%) reported an IIEF-EF score consistent with a diagnosis of erectile dysfunction. Of these, severity was mild (IIEF-EF 22–25) in six (16%), mild-moderate (IIEF-EF 17–21) in two (5%), and moderate (IIEF-EF 11–16) in one (3%).

Abbreviations: ED, erectile dysfunction; EF, erectile function; IIEF, International Index of Erectile Function; NYHA, New York Heart Association; CHD, congenital heart disease; APC, atriopulmonary connection; LT, lateral tunnel; ECC, extracardiac conduit.

TABLE 1 | Baseline characteristics.

	n	No ED	*n*	ED	*p*
Age, years (±SD)	28	29.4 ± 6.2	9	27.4 ± 4.3	0.39
Fontan type, *n* (%) (APC vs. TCPC)					0.62
AP		7 (25%)		3 (33.3%)	
LT		9 (32.1%)		3 (33.3%)	
ECC		12 (42.1%)		3 (33.3%)	
Age at Fontan, years (±SD)	28	5.2 ± 3.0	9	5.6 ± 2.8	0.67
Years since Fontan (±SD)	28	24.2 ± 6.6	9	21.9 ± 4.6	0.34
Ventricular function, *n* (%)[a]	23		6		0.24
Normal/mild		20 (87%)		4 (66.7%)	
Moderate/severe		3 (13%)		2 (33.3%)	
NYHA class, *n* (%)[a]	24		5		0.97
Class I		19 (79.2%)		4 (80%)	
Class II		5 (20.8%)		1 (20%)	
Implantable cardiac device, *n* (%)	28	4 (14.3%)	9	0 (0%)	0.23
Resting oxygen saturations, % (±SD)[b]	20	92.4 ± 5.0	6	93.0 ± 3.3	0.72
History of arrhythmia, *n* (%)		8		6	0.75
Medications, *n* (%)					
Warfarin		16 (57.1%)		3 (33.3%)	0.21
Aspirin		10 (35.7%)		2 (22.2%)	0.45
ACEI		10 (35.7%)		2 (22.2%)	0.45
DOAC		0		2 (22.2%)	0.01
Spironolactone		2 (7.1%)		0	0.41
Sildenafil		1 (3.6%)		0	0.57
Digoxin		2 (7.1%)		1 (11.1%)	0.70
Sotalol		4 (14.3%)		2 (22.2%)	0.57

Continuous data analyzed utilizing Student's Independent T Test. Continuous variables reported as mean ± standard deviation, categorical data reported as number and percentage (%) and analyzed using Chi-square test.

[a]*Data unavailable for 8 patients.*

[b]*Data unavailable for 11 patients.*

AP, atriopulmonary connection; LT, lateral tunnel; ECC, extracardiac conduit; NYHA, New York Heart Association Functional Class; ACEI, angiotensin converting enzyme inhibitor; DOAC, direct oral anticoagulant.

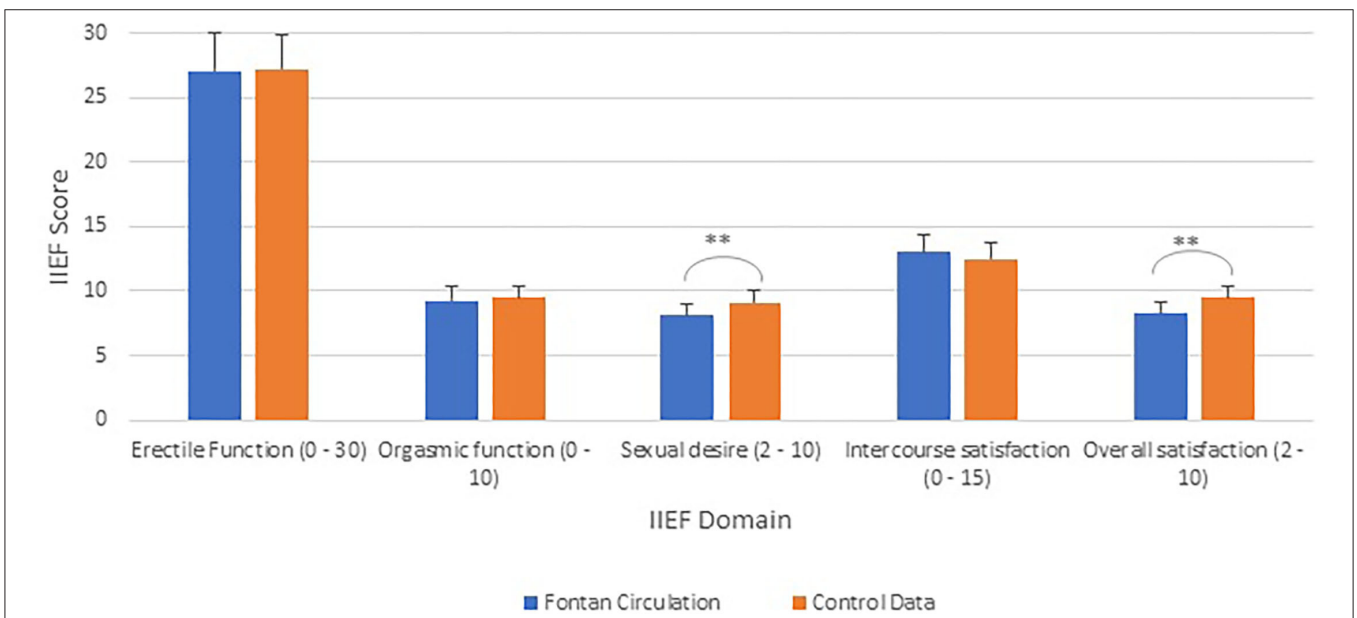

FIGURE 1 | International Index of Erectile Function scores (IIEF) (range) for men with a Fontan compared to reference control data (12). $^{**}p < 0.001$.

TABLE 2 | IIEF results comparing those with ED to those without.

IIEF Domain (range) (m ± SD)	No ED ($n = 28$)	ED ($n = 9$)	p
Erectile function (0–30)	28.8 ± 1.4	21.4 ± 4.3	<0.001
Orgasmic function (2–10)	9.8 ± 0.6	7.8 ± 2.6	0.05
Sexual desire (0–10)	8.2 ± 1.3	7.6 ± 1.1	0.29
Intercourse satisfaction (0–15)	13.6 ± 1.7	11.1 ± 2.4	0.01
Overall satisfaction (2–10)	8.6 ± 1.5	7.1 ± 1.2	0.01

Continuous data analyzed using Student's independent sample T test. All variables reported as mean ± standard deviation.
ED, erectile dysfunction.

There was no difference in orgasmic function ($p = 0.44$) and intercourse satisfaction ($p = 0.14$). There was no association between clinical indices and IIEF-EF (**Table 3**; $p > 0.1$ for all). There was no difference in IIEF-EF score between those with APC compared to those with total cavopulmonary connection (TCPC; $p = 0.65$).

A total of 11 men (30%) in the cohort reported a pregnancy in a prior sexual partner. There was no significant difference in the proportion of those with and without ED who reported a prior pregnancy ($p = 0.85$). Of those who did not report a pregnancy, 19 (51%) reported they had only ever used contraception. Four men (11%) reported they had been trying to conceive with a partner for greater than 6 months. There was no difference in IIEF-EF score between the patients who had and those who had not reported a prior pregnancy ($p = 0.41$). Patients who had an APC Fontan procedure were more likely to report a pregnancy compared to those who underwent a TCPC procedure ($p < 0.001$).

DISCUSSION

As Fontan-specific management has refined, an ever-greater proportion of the population are surviving well into adulthood. Consequently, important issues are arising that were not contemplated in an earlier era focused on early life (13, 14). Holistic care should include guidance for adults regarding the impact that their unique physiology may have on sexual function, and the ability to have children.

In this cross-sectional study we present the largest prospective report of the subjective sexual health and self-reported fertility of men with a Fontan circulation to date. We utilized the IIEF tool. We found that almost one quarter of men studied within our cohort had IIEF-EF scores consistent with a diagnosis of erectile dysfunction. We compared the IIEF-EF scores of our cohort to those of historical age-matched controls. Even though 24% of our population had IIEF-EF scores indicating ED, overall, the EF score for the cohort not significantly different to that of the control data. Our data demonstrated that most of the cohort had well preserved erectile function, and that those with ED did not suffer from a severe phenotype. This is congruent with reports more broadly in congenital heart disease (CHD) literature that ED is typically of mild severity (15). Prior studies which have utilized the IIEF in the setting of (CHD) reported rates of ED to be between 10–14% (15, 16). However, when including studies that have included different assessment tools, rates of ED ranged from 10% up to 38% (17, 18), with reported risk varying from the same as expected "normal" population rates to two times higher (19, 20). In Australia, ED rates in young men have been reported to be lower than the rates we recorded in young men living with a Fontan circulation; Chew et al. (21) found that in a cohort of men aged 20–29 years the background rate of ED in the community was 16 and 8.7% in 30–39 year olds using the IIEF-5 questionnaire (a truncated version of the IIEF utilized in this study, with similar sensitivity and specificity).

Most studies that have examined sexuality in the setting of CHD have included heterogenous CHD types without distinction as to the underlying pathology or anatomy; this is an important consideration for the Fontan population who are affected by unique physiological problems including chronic venous hypertension and reduced cardiac output, especially during exertion. Elevated systemic vascular resistance, chronic cyanosis and cardiovascular drugs including anti-arrhythmics and some diuretics (spironolactone in particular) may also contribute to dysfunction (18, 22).

Wolff et al. (10) are the only group who have examined sexual wellbeing in a small group of men ($n = 7$) with a Fontan circulation. This study included a questionnaire and interview assessing sexual satisfaction and fertility (10). The issues reported included avoidance of sexual activity, that may in part be related to symptoms during exertion (17, 23). Consistent with the results of our study, there was no significant difference in the presence of erectile dysfunction when patients with a Fontan were compared to controls (10). Two out of seven (29%) of patients in their cohort reported erectile dysfunction, a result congruent to the 24% in our cohort (10).

Completion of the IIEF allowed assessment of sexual health across multiple domains. Our results demonstrated that when compared with healthy controls, men with a Fontan circulation had decreased levels of sexual desire and overall satisfaction. The domains of sexual health, such as desire and satisfaction, are less well studied than erectile function, though have been identified to potentially be reduced in patients with cardiac disease (16, 24). Deficiencies in these areas are likely multifactorial in nature. Patients with CHD have reported the fear of developing cardiac symptoms during sexual intercourse as detrimental to overall sexual health (15, 25). Many CHD patients develop health concerns from a young age. It has been theorized that the presence of significant illness during adolescence may be detrimental to sexual development, and indeed may lead to avoidance of sexual activity (15, 23). Our results are congruent with a prior study which demonstrated men with CHD had a decreased level of overall satisfaction and orgasmic function (16). However, this study of pooled, predominantly simple CHD did not demonstrate any difference in level of sexual desire. In contrast, other research did not find a significant difference in sexual satisfaction in a heterogenous group of men with CHD compared to healthy controls (23)—clearly, more well-designed data are needed. Of the prior CHD studies

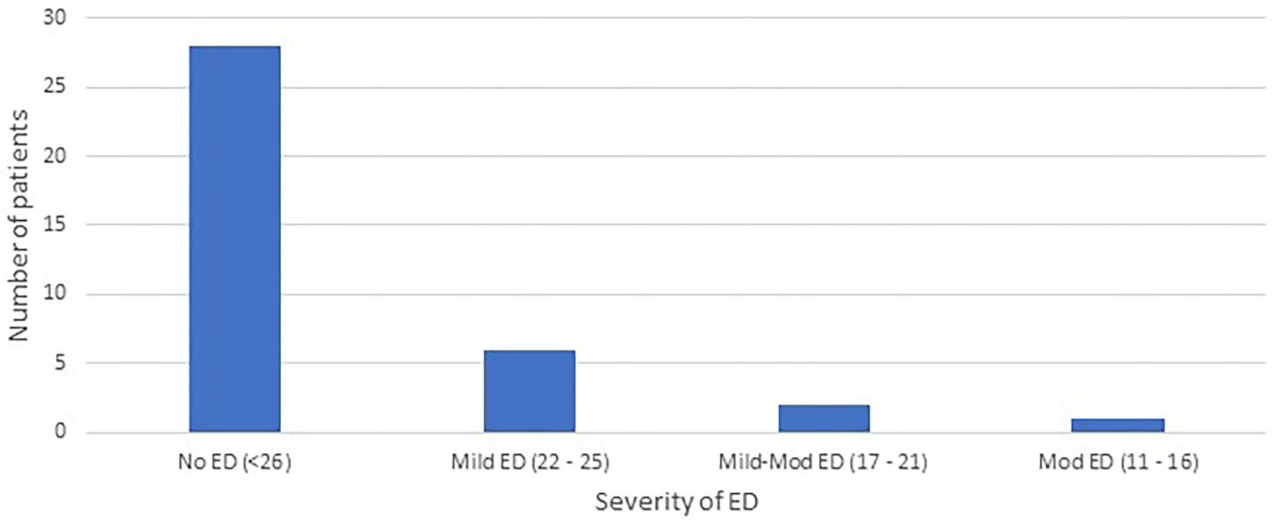

FIGURE 2 | Number of patients with, and severity of erectile dysfunction (ED) *via* the International Index of Erectile Function.

in this field, men with a Fontan circulation were infrequently included (15, 17, 26).

Long-term medical therapy is frequently required for the management of a person with a Fontan circulation. The effect that this has on sexual health of men has not been clearly delineated. Men with CHD have previously been found to attribute ED to prescribed medical therapy (17). Spironolactone is often cited as being contributory due to its known androgen-suppressing properties, and it has been theorized that prescription of spironolactone may lead to impaired sexual functioning for men with CHD (10, 15, 18). In a cohort of adult male patients aged in their 40s with mixed CHD, the use of spironolactone and digoxin were associated with sexual dysfunction (18). In our cohort spironolactone was only prescribed in two men (5%) and so, although we did not note an association with erectile dysfunction our data in that regard are limited. Beyond the field of CHD, the exact impact that spironolactone has on the sexual health of men with acquired cardiac disease has not been conclusively defined (27). Beta-blockers and ACE inhibitors are classes of medication which have previously been associated with sexual dysfunction in men with CHD in some (17, 23) but not all studies, in keeping with our findings (16, 18).

Our study demonstrated that approximately 30% of surveyed men reported a pregnancy in a partner and there was no association between IIEF-EF score and prior pregnancy. We did note that patients with an APC were more likely to have reported a prior pregnancy, a finding which must be interpreted with caution given the limited numbers involved. Four patients reported unsuccessful conception with a partner for longer than 6 months. Census data have demonstrated that between 17 and 35% of the population at a comparative age have fathered children (28). A single prior study examined fertility in the setting of a Fontan circulation (10). Of seven surveyed men in this study, two had previously fathered children (10). Based on limited data, there is currently no evidence that the Fontan circulation has an impact on the male ability to father children.

TABLE 3 | Correlation of IIEF Erectile Function Score and presence of ED against type of Fontan, NYHA FC, ventricular function, and prior pregnancy.

Variable	*n*	*r*	*p*
Age, years	37	0.16	0.34
Age at Fontan, years	37	0.01	0.96
Years since procedure	37	0.15	0.38
Type of Fontan procedure (APC vs. TCPC)	37	−0.08	0.64
NYHA FC	29	−0.01	0.97
Ventricular function	29	0.22	0.26
Resting oxygen saturations	26	−0.11	0.60
Prior pregnancy	11	0.70	0.68

Non-parametric data analyzed using presence of ED via Spearman rank correlation. Continuous data analyzed using Pearson correlation coefficient with EF score. TCPC, total cardiopulmonary connection.

There are limitations to our study. Of the 227 eligible patients, 135 (60%) were either unable to be contacted or did not complete the survey. A number of these had outdated contact details. Others never returned the survey despite repeated contact. Thus, selection bias is an important consideration. It is feasible that due to the personal nature of the questioning, men with erectile dysfunction may have been less inclined to complete the survey. Men with more significant erectile dysfunction may also have a propensity to avoid sexual intercourse, and thus have been excluded from final analysis once the survey was completed. The overall small number of patients within both cohorts makes it important to consider that the study was underpowered to detect true differences in baseline characteristics between those with and without erectile dysfunction. It is theorized however, that chronic venous hypertension may be implicated in the pathogenesis of sexual dysfunction in men with a Fontan circulation. As our study

did not incorporate invasive haemodynamic assessment, we have been unable to assess whether this is contributory.

A further limitation to research in sexual health is the reliance on self-reported questionnaires. It is also noted that several different research tools have been used in this area. We utilized the IIEF, as it has a broad base of supporting literature and has been used previously in the field of adult congenital heart disease (15, 16). Other studies have been performed utilizing other tools for assessment of erectile dysfunction or sexual dysfunction. These include the Golombock-Rust Instrument of Sexual Satisfaction, or the IIEF-5. The diversity in assessment tools utilized is a hinderance to researchers attempting to draw direct comparisons between results of different studies.

CONCLUSION

In our cohort, erectile function was comparable in men with a Fontan circulation compared with age-matched historical controls, though they did report decreased levels of sexual desire and overall satisfaction. Overall, men with a Fontan circulation reported levels of fertility congruent with that of the general population. Clinicians should be aware that erectile dysfunction may occur in this population and consider asking appropriate questions to ensure that concerns regarding sexual health and fertility are not overlooked.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by HREC Royal Children's Hospital, Parkville, Victoria. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RC: concept design, project supervision, and data analysis. IR: assistance with concept design, survey implementation, and data analysis. DT, AB, VW, DB, Yd'U, KP, DK, ML, DZ, and DC: assistance with project design, data interpretation, and manuscript preparation. All authors contributed to the article and approved the submitted version.

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The "Super-Fontan" Phenotype: Characterizing Factors Associated With High Physical Performance

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Background: People with a Fontan circulation usually have moderately impaired exercise performance, although a subset have high physical performance ("Super-Fontan"), which may represent a low-risk phenotype.

Methods: People with a "Super-Fontan" phenotype were defined as achieving normal exercise performance [≥80% predicted peak oxygen uptake (VO_2) and work rate] during cardiopulmonary exercise testing (CPET) and were identified from the Australian and New Zealand Fontan Registry. A Fontan control group that included people with impaired exercise performance (<80% predicted VO_2 or work rate) was also identified based on a 1:3 allocation ratio. A subset of participants were prospectively recruited and completed a series of physical activity, exercise self-efficacy, and health-related quality of life questionnaires.

Results: Sixty CPETs ("Super-Fontan", $n = 15$; control, $n = 45$) were included. A subset ("Super-Fontan", $n = 10$; control, $n = 13$) completed a series of questionnaires. Average age was 29 ± 8 years; 48% were males. Exercise capacity reflected by percent predicted VO_2 was 67 ± 17% in the entire cohort. Compared to the "Super-Fontan" phenotype, age at Fontan completion was higher in controls (4.0 ± 2.9 vs. 7.2 ± 5.3 years, $p = 0.002$). Only one (7%) person in the "Super-Fontan" group had a dominant right ventricle compared to 15 (33%) controls ($p = 0.043$). None of those in the "Super-Fontan" group were obese, while almost a quarter (22%) of controls were obese based on body mass index ($p = 0.046$). Lung function abnormalities were less prevalent in the "Super-Fontan" group (20 vs. 70%, $p = 0.006$). Exercise self-efficacy was greater in the "Super-Fontan" group (34.2 ± 3.6 vs. 27.9 ± 7.2, $p = 0.02$). Self-reported sports participation and physical activity levels during childhood and early adulthood were higher in the "Super-Fontan" group ($p < 0.05$). The total average time spent participating

in structured sports and physical activity was 4.3 ± 2.6 h/wk in the "Super-Fontan" group compared to 2.0 ± 3.0 h/wk in controls, $p = 0.003$. There were no differences in self-reported current total physical activity score or health-related quality of life between groups ($p \geq 0.05$).

Conclusions: The "Super-Fontan" phenotype is associated with a healthy weight, lower age at Fontan completion, better exercise self-efficacy, and higher overall levels of sport and physical activity participation during physical development.

Keywords: physical activity, congenital heart disease, exercise training, cardiac rehabilitation, exercise capacity

INTRODUCTION

Francis Fontan first described the Fontan procedure in 1971 as a surgical method to treat babies born with tricuspid atresia (1). The procedure involves redirecting venous return directly into the pulmonary arteries resulting in no subpulmonary pump. The Fontan procedure has evolved with the advancement of medicine and surgical techniques in an attempt to optimize long-term outcomes, and although clinical outcomes have improved significantly, rates of morbidity and premature death are still high.

Exercise intolerance is common in people living with a Fontan circulation. Peak oxygen uptake (VO_2) is the primary index of exercise tolerance (i.e., exercise capacity) and has significant prognostic value in patients with congenital heart disease (2). People with a Fontan circulation have reduced percent predicted peak VO_2, which on average ranges from 60 to 65% (3, 4). However, there is extensive variability between patients, and it is acknowledged that a subgroup—"Super-Fontans"—have superior exercise performance (exercise and work capacity) compared to the majority of the Fontan population (5).

Currently, there is limited information about this subset of people who have superior physical performance. Since we originally described this unique phenotype (5), other centers have also characterized a similar subset of Fontan patients with normal exercise capacity (6, 7). Importantly, higher exercise capacity in people with a Fontan circulation appears to be associated with better prognosis and end-organ function (7–9). Understanding the factors associated with normal exercise capacity in this unique subset of patients can potentially aid in risk stratification and the identification of therapeutic targets. The aim of this study was to characterize factors associated with superior exercise performance in people with the "Super-Fontan" phenotype.

METHODS

People in the Australian and New Zealand Fontan Registry with recorded cardiopulmonary exercise testing (CPET) results and a "Super-Fontan" phenotype were identified and included in this study. People with impaired exercise capacity were also identified as controls based on a 1:3 allocation. Exercise and work capacity was measured by peak VO_2 and work rate, respectively. To account for sex, height, and weight differences, peak VO_2 and work rate are expressed as a percentage of predicted normal values (10, 11). Participants were categorized into a "Super-Fontan" (5) or a control group. The "Super-Fontan" group was defined as achieving normal exercise and work capacity (≥80% predicted) (5, 6, 12–15). The control group consisted of Fontan subjects who had reduced exercise or work capacity (<80% predicted).

We decided to include work capacity as a criterion as obese patients may have normal exercise capacity but present with limited work capacity and exercise intolerance. Participants were excluded if their CPET was conducted on a treadmill or if results were considered to be submaximal effort defined as a peak respiratory exchange ratio <1.0 (16). A subset of participants (study group) completed a series of health-related quality of life, physical activity, and exercise self-efficacy questionnaires. Clinical and demographic information, including dominant ventricular morphology, type of Fontan procedure, patent fenestration, sex, and age at Fontan completion, were obtained from the Australian and New Zealand Fontan Registry database and medical records when available. This study was approved by the Royal Children's Hospital Melbourne Human Research Ethics Committee (38,172).

Exercise Self-Efficacy and Quality of Life

Exercise self-efficacy was assessed using the Exercise Self-Efficacy Scale (17). The total score was calculated as the sum of all questions, with a higher score reflecting greater exercise self-efficacy, which assesses an individual's beliefs in their ability to continue exercising regularly.

Health-related quality of life was measured using the PedsQL Adult Quality of Life Inventory Version 4. The items of each question were reversed scored, and linearly transformed in accordance with the scoring guidelines. In addition to the total score, the physical health summary score and psychosocial health summary score were also calculated, with higher scores suggesting better health-related quality of life.

Cardiopulmonary Exercise Testing and Spirometry

Center specific CPET protocols were performed on an electronically braked cycle ergometer as part of routine clinical care. In addition to measures of peak VO_2, work rate, and pre-exercise spirometry, CPET parameters including minute ventilation (VE), carbon dioxide production (VCO_2), blood pressure, VO_2 at the anaerobic threshold, heart rate (HR),

and arterial oxygen saturation indicated by pulse oximetry were obtained when available. Predicted maximal oxygen pulse (ml/beat)—a surrogate for stroke volume—was calculated by dividing predicted maximal VO_2 by predicted maximal HR (220–age) (18). A cardiovascular limitation to exercise performance was indicated by a chronotropic index (cardiovascular index) above the upper limit of normal (19) or a reduced peak oxygen pulse (<80% predicted). Chronotropic index was calculated as ΔHR (beats/min)/ΔVO_2 (L/min) (19, 20). Maximal voluntary ventilation (MVV) was estimated as forced expiratory volume in 1 s (FEV_1) x 40, and breathing reserve was calculated as MVV–peak VE or (MVV–peak VE)/MVV x 100. A mechanical ventilatory limitation to exercise was suggested by a breathing reserve of <15% or <11 L/min (18, 21). Peak circulatory power was calculated as peak VO_2 (mL/kg/min) x peak systolic blood pressure (mm Hg). Ventilatory inefficiency was suggested by a peak VE/VCO_2 ratio of >40. A significant fall in oxygen saturation was considered as a decrease of ≥5%.

Spirometry parameters were considered as abnormal if values were below the lower limit of normal calculated from the Global Lung Initiative regression equations (22). Lung function was defined as normal, obstruction, restriction, or mixed defect in accordance with the American Thoracic Society/European Respiratory Society algorithm (23). In the absence of total lung capacity measured by plethysmography, ventilatory restriction was suggested if forced vital capacity (FVC) was below the lower limit of normal. Mixed defect was suggested if the FEV_1/FVC ratio and FVC were below the lower limit of normal.

Physical Activity Across the Lifespan

To assess structured sport and physical activity participation across the lifespan, we used a modified version of the Kriska long-term recall physical activity questionnaire (24). Participants were asked to recall the sports and physical activities they participated in across multiple age ranges. For each sport and physical activity reported, the years in each age range, duration (hours) per month, and months per year were recorded. Sports and physical activities were categorized as childhood (ages 4–12 years), high school and early adulthood (ages 13–21 years), older adulthood (ages 22+ years), and physical activity across the lifespan (four to the age at questionnaire completion). The total hours of sport or physical activity participation were summated for each category and indexed as an average per week (h/wk).

Current Level of Physical Activity

Self-reported current levels of physical activity and sedentary time were assessed using the International Physical Activity Questionnaire (IPAQ) Long-Form. The IPAQ scores were not truncated, and metabolic minutes per week (MET-min/week) were calculated in accordance with the IPAQ Scoring Manual. Sedentary activity was reflected by sitting time (minutes) per day.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 26 software (IBM Corp, Armonk, NY, USA). Data are presented as mean ± standard deviation or number (%) unless specified otherwise. The Shapiro-Wilk test or visual inspection of histograms and Q-Q plots were conducted to assess for normal distribution. An independent *t*-test or Mann–Whitney U was used as appropriate to compare differences between the "Super-Fontan" group and the control group. Proportions were compared using Pearson Chi-Square. A *p*-value of <0.05 was considered as statistically significant.

RESULTS

Participant Demographics

Detailed participant demographics and characteristics are shown in **Table 1**. Of the 60 people with a Fontan circulation included in the CPET analysis, 15 had a "Super-Fontan" phenotype, and 35 had impaired exercise performance. The average age was 28.7 ± 7.6 years, and 48% were males.

The average body mass index (BMI) was 25.9 kg/m^2, and 20 people (33%) were overweight or obese. None who had the "Super-Fontan" phenotype were obese based on BMI compared to 22% in the control group ($p = 0.046$). The majority (70%) had a total cavopulmonary connection, and the average age at Fontan procedure was 6.4 ± 5.0 years. The age at Fontan procedure was lower in the "Super-Fontan" group compared to the control group (4.0 ± 2.9 vs. 7.2 ± 5.3 years, $p = 0.002$). Thirty-seven (62%) had a dominant left ventricle, 16 (27%) had a dominant right ventricle, 3 (5%) had biventricular morphology, and 4 (7%) had indeterminate ventricles. A dominant right ventricle was associated with impaired exercise performance ($p = 0.043$). One person (7%) in the "Super-Fontan" group had a Fontan conversion from an atriopulmonary connection to an extracardiac conduit type circulation. There were no statistically significant differences in age, sex, BMI, type of Fontan procedure, or patent fenestration between groups ($p \geq 0.05$ for all).

Twenty-three Fontan participants completed the questionnaires. Of the 23 Fontan study group participants, 10 (43%) were in the "Super-Fontan" group, and 13 (57%) were in the control group. There were no differences between groups in baseline demographics for the subset of study participants who completed the questionnaires ($p \geq 0.05$ for all).

Exercise Self-Efficacy and Health-Related Quality of Life

The average total exercise self-efficacy score was higher in the "Super-Fontan" group compared to the control group (34.2 ± 3.6 vs. 27.9 ± 7.2, $p = 0.02$).

There was no statistically significant difference in total health-related quality of life score between the "Super-Fontan" group and the control group (78.9 ± 13.0 vs. 68.2 ± 18.8, $p = 0.14$). There was also no statistically significant difference between the "Super-Fontan" and control groups in the physical health summary score (80.3 ± 11.7 vs. 67.1 ± 21.9, $p = 0.1$) or psychosocial health summary score (78.2 ± 15.4 vs. 68.8 ± 19.6, $p = 0.23$).

Cardiopulmonary Exercise Testing and Spirometry

Detailed CPET and spirometry results are shown in **Tables 2**, **3**. In the study group, the average time from the CPET to the

TABLE 1 | Participant demographics.

	All Fontan Participants		"Super-Fontan"		Control		*p*-value
	n		***n***		***n***		
Sex (males), *n* (%)	60	29 (48.3%)	15	5 (33.3%)	45	24 (53.3%)	0.18
Age, years	60	28.7 ± 7.6	15	27.9 ± 5.7	45	28.9 ± 8.2	0.53
BMI, kg/m^2	60	25.9 ± 4.7	15	24.4 ± 2.7	45	26.3 ± 5.1	0.34
Obese, *n* (%)	60	10 (16.7%)	15	0 (0%)	45	10 (22.2%)	**0.046**
Type of Fontan, *n* (%)	60		15		45		0.75[a]
APC		18 (30.0%)		4 (26.7%)		14 (31.1%)	
LT		23 (38.3%)		8 (53.3%)		15 (33.3%)	
ECC		19 (31.7%)		3 (20.0%)		16 (35.6%)	
Dominant ventricle, *n* (%)	60		15		45		**0.043**[b]
Left		37 (61.7%)		13 (86.7%)		24 (53.3%)	
Biventricular		3 (5%)		1 (6.7%)		2 (4.4%)	
Indeterminant		4 (6.7%)		0 (0%)		4 (8.9%)	
Right		16 (26.7%)		1 (6.7%)		15 (33.3%)	
Age at Fontan palliation, years	60	6.4 ± 5.0	15	4.0 ± 2.9	45	7.2 ± 5.3	**0.002**
Patent fenestration, *n* (%)	60	10 (16.7%)	15	1 (6.7%)	45	9 (20%)	0.23
Time since Fontan palliation, years	60	22.2 ± 5.6	15	23.9 ± 4.2	45	21.7 ± 6.0	0.19

APC, atriopulmonary connection; BMI, body mass index; ECC, extra cardiac conduit; LT, lateral tunnel.

[a]*APC vs. total cavopulmonary connection.*

[b]*Dominant left ventricle, biventricular, or indeterminant ventricle vs. dominant right ventricle. Bold values denote statistical significance ($p < 0.05$).*

questionnaires was 2.1 ± 1.9 years, and there was no difference between groups ($p = 0.5$).

The average percent predicted peak VO_2 and work rate for the entire cohort was 67 ± 17% and 72 ± 22%, respectively. There was no statistically significant difference in percent predicted maximum HR between the "Super-Fontan" and control groups (83 ± 9% vs. 76 ± 15%, $p = 0.09$). Peak circulatory power, HR reserve (HRR), peak VE, and VO_2 at anaerobic threshold (percentage of predicted VO_2) were higher in the "Super-Fontan" group ($p < 0.05$ for all). There was no difference in exercise-induced desaturation between groups ($p = 0.5$).

Of the 40 participants ("Super-Fontan," $n = 11$; control, $n = 29$) where the chronotropic index could be calculated, 7 (18%) participants had values outside the normal range. All participants in the "Super-Fontan" group had a chronotropic index within the normal range. In the control group, 4 (14%) participants had a high chronotropic index, and 3 (10%) had a low chronotropic index suggesting cardiovascular limitation and chronotropic insufficiency as inhibitors to exercise performance, respectively. The "Super-Fontan" group also had a higher percent predicted oxygen pulse compared to the control group (109 ± 16% vs. 80 ± 20%, $p < 0.001$). When markers of cardiovascular limitation were combined [low peak oxygen pulse (<80% predicted) or a high chronotropic index], no patient with the "Super-Fontan" phenotype had evidence of a cardiovascular limitation to exercise capacity compared to 62% in the control group ($p < 0.001$).

Thirty-seven people with a Fontan circulation ("Super-Fontan," $n = 10$; control, $n = 27$) had baseline spirometry recorded, 16 (43%) had normal spirometry function, 20 (54%) had evidence of ventilatory restriction, and 1 (3%) had a pattern suggestive of mixed defect. The "Super-Fontan" group tended to have higher percent predicted FVC compared to the control group (85 ± 8% vs. 78 ± 10%, $p = 0.05$). Lung function abnormalities at rest were associated with impaired exercise performance; 2 (20%) patients in the "Super-Fontan" group had ventilatory or mixed defect compared to 19 (70%) in the control group ($p = 0.006$).

The average breathing reserve was 36 ± 18%, and five out of the 37 patients had a mechanical ventilatory limitation to exercise performance. The majority (80%) who had a mechanical ventilatory limitation also had evidence of ventilatory restriction at rest.

Physical Activity Across the Lifespan

One of the participants in the control group had an incomplete questionnaire and was excluded from the analysis. Results for the Kriska physical activity questionnaire are shown in **Table 4**; **Figure 1**. Childhood physical activity was higher in the "Super-Fontan" group compared to the control group (3.9 ± 3.3 h/wk vs. 2.0 ± 3.4 h/wk, $p = 0.04$). The average h/wk of sports and physical activity participation during high school and early adulthood was 5.2 ± 4.4 h/wk in the "Super-Fontan" group and 2.1 ± 3.1 h/wk in the control group, $p = 0.04$. There was no statistically significant difference in sport and physical activity participation during older adulthood. The overall average duration of sport and physical activity participation indexed per week was higher in the "Super-Fontan" group compared to the control group (4.3 ± 2.6 h/wk vs. 2.0 ± 3.0 h/wk, $p = 0.003$).

TABLE 2 | Lung function and cardiopulmonary exercise testing results.

	All Fontan Participants		"Super-Fontan"		Control		*p*-value
	n		*n*		*n*		
FEV_1, percent predicted	37	80.6 ± 11.7	10	85.7 ± 10.4	27	78.7 ± 11.7	0.11
FVC, percent predicted	37	79.9 ± 9.8	10	85.0 ± 7.8	27	78.0 ± 9.9	0.05
FEV_1/FVC ratio	37	0.85 ± 0.06	10	0.85 ± 0.06	27	0.85 ± 0.06	0.93
Peak VO_2, percent predicted	60	66.8 ± 17.1	15	89.4 ± 7.1	45	59.3 ± 12.0	**<0.001**
Peak work rate, percent predicted	60	71.7 ± 21.5	15	98.0 ± 9.7	45	63.0 ± 16.6	**<0.001**
VO_2 at AT, percentage of predicted VO_2	58	44.4 ± 14.9	14	60.2 ± 16.2	44	39.4 ± 10.3	**<0.001**
Oxygen pulse, percent predicted	60	87.0 ± 23.0	15	108.7 ± 15.6	45	79.7 ± 20.4	**<0.001**
Maximal HR, percent predicted	60	78.1 ± 13.7	15	83.3 ± 9.2	45	76.4 ± 14.6	0.09
HRR, bpm	60	65.7 ± 27	15	83.2 ± 20.4	45	59.9 ± 26.6	**0.003**
Chronotropic index, percent predicted	40	109.2 ± 36.9	11	99.1 ± 23.1	29	113.0 ± 40.6	0.19
Peak SpO_2, percent	56	90.4 ± 7.2	13	91.2 ± 6.9	43	90.2 ± 7.4	0.57
ΔSpO_2, percent	56	3.6 ± 4.6	13	4.3 ± 5.2	43	3.4 ± 4.5	0.56
Peak RER	60	1.21 ± 0.11	15	1.12 ± 0.07	45	1.22 ± 0.11	**0.04**
Peak circulatory power, mm Hg × mL/kg/min	53	3,425 ± 1,454	13	4,739 ± 1,519	40	2,998 ± 1,161	**<0.001**
Peak VE, L/min	60	72.1 ± 21.8	15	85.6 ± 21.7	45	67.7 ± 20.1	**0.01**
Peak VE/VCO_2	60	37.3 ± 8.6	15	35.9 ± 8.3	45	37.7 ± 8.7	0.54
Breathing reserve, percent	37	35.5 ± 17.8	10	28.6 ± 23.6	27	38.1 ± 14.8	0.15

AT, anerobic threshold; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, heart rate; HRR, heart rate reserve; RER, respiratory exchange ratio; SpO_2, arterial oxygen saturation measured by pulse oximetry; VE, minute ventilation; VO_2, oxygen uptake; VCO_2, carbon dioxide production. Bold values denote statistical significance ($p < 0.05$).

TABLE 3 | Lung function and cardiopulmonary exercise testing result categories.

	All Fontan Participants		"Super-Fontan"		Control		*p*-value
	n		*n*		*n*		
Lung function, *n* (%)	37		10		27		**0.006**[a]
Normal		16 (43.2%)		8 (80%)		8 (29.6%)	
Restriction		20 (54.1%)		2 (20%)		18 (66.7%)	
Obstruction		0 (0%)		0 (0%)		0 (0%)	
Mixed defect		1 (2.7%)		0 (0%)		1 (3.7%)	
Mechanical ventilatory limitation (yes), *n* (%)	37	5 (13.5%)	10	2 (20%)	27	3 (11.1%)	0.48
Peak VE/VCO_2 ratio, *n* (%)	60		15		45		0.53
≤40		40 (66.7%)		11 (73.3%)		29 (64.4%)	
>40		20 (33.3%)		4 (26.7%)		16 (35.6%)	
Chronotropic index, *n* (%)	40		11		29		0.073[b]
Low		3 (7.5%)		0 (0%)		3 (10.3%)	
Low-normal		3 (7.5%)		0 (0%)		3 (10.3%)	
Normal		22 (55%)		10 (90.9%)		12 (41.4%)	
High-normal		8 (20%)		1 (9.1%)		7 (24.1%)	
High		4 (10%)		0 (0%)		4 (13.8%)	
Oxygen pulse, *n* (%)	60		15		45		**<0.001**
≥80% predicted		32 (53.3%)		15 (100%)		17 (37.8%)	
<80% predicted		28 (46.7%)		0 (0%)		28 (62.2%)	
Cardiovascular limitation (yes), *n* (%)	60	28 (46.7%)	15	0 (0%)	45	28 (62.2%)	**<0.001**
ΔSpO_2 >5% (yes), *n* (%)	56	17 (30.4%)	13	5 (38.5%)	43	12 (27.9%)	0.47

SpO_2, arterial oxygen saturation measured by pulse oximetry; VCO_2, carbon dioxide production; VE, minute ventilation.

[a]*Normal lung function vs. restriction, obstruction or mixed defect.*

[b]*Normal range chronotropic index vs. low or high chronotropic index. A mechanical ventilatory limitation to exercise performance was suggested by a breathing reserve of <15% or <11 L/min. A cardiovascular limitation to exercise performance was suggested by a peak oxygen pulse <80% of predicted or a high chronotropic index. Bold values denote statistical significance ($p < 0.05$).*

Current Physical Activity Levels

The detailed IPAQ results are shown in **Table 4**. The average self-reported MET-min/wk was higher at all physical activity intensities and sub-domains, except for the transport domain in the "Super-Fontan" group, although this did not achieve statistical significance (**Figure 2**). Sitting time tended to be lower in the "Super-Fontan" group compared to the control group (308 $\pm$ 123 vs. 453 $\pm$ 175 min/day, $p = 0.07$).

DISCUSSION

Despite an absent subpulmonary ventricle in the Fontan circulation, a subset of the population ("Super-Fontans") can still achieve normal exercise performance, which is associated with increased levels of physical activity early in life, a healthy weight, and earlier age at Fontan completion.

Factors Associated With Superior Physical Performance

In this study, the age at Fontan completion was lower in those with a "Super-Fontan" phenotype, and the absence of obesity or a dominant right ventricle were associated with normal exercise performance. This contrasts with previous findings that showed no differences between exercise performance Fontan phenotypes with these factors (6, 7). Our study describes an older Fontan cohort compared to previous series, and the conflicting findings might be attributed to an era effect. Alternatively, later age at Fontan completion, dominant right ventricular morphology, and obesity may manifest as important factors that impair the ability to achieve "normal" exercise performance later in life when circulatory function is more susceptible to compromise and maladaptation.

Similar to our findings, a review by Daley et al. found that earlier age at Fontan completion is associated with preserved long-term exercise capacity (25). A large multi-center series in a contemporary Fontan cohort also corroborates this; each year Fontan completion was delayed, percent predicted VO_2 and HRR decreased by 1.5 percentage points and 4.1 beats/min, respectively (26). This association may be explained by enhanced reversal of adverse cardiac remodeling and offsetting volume overload with earlier age at Fontan completion (27, 28). Indeed, patients with a later age at Fontan completion present with evidence of greater ventricular dysfunction and atrioventricular valve insufficiency (29). Conversely, one study found a positive correlation between age at Fontan completion, and percent predicted peak VO_2 (30). Although later age at Fontan completion is accompanied by an extended period of volume overload and cyanosis, it may allow for pulmonary artery catch-up growth and a larger conduit to optimize flow (31, 32); however, this theory requires verification.

We have previously reported increased adiposity is associated with a higher risk of adverse outcomes in people with a Fontan circulation (33). None of the people with the "Super-Fontan" phenotype were obese based on BMI compared to 22% in the comparator group with impaired exercise performance. The latest Pediatric Heart Network results also support this finding (34). This may be related to the impact of excess adiposity on respiratory muscle pump function and increased mechanical loading, which may impair exercise performance. In addition, the importance of maintaining a healthy body weight to preserve low pulmonary vascular resistance is increasingly recognized (32). Importantly, higher BMI often co-exists with increased visceral adiposity (epicardial and intra-abdominal fat), which may be particularly pathological—visceral adiposity is positively associated with pulmonary vascular resistance and inversely associated with ejection fraction and cardiac index in the Fontan circulation (35, 36). Of course, BMI may not be a robust measure of adiposity in the setting of complex congenital heart disease, where myopenia is common (33, 37, 38). The association between adiposity and pulmonary vascular resistance may be attributed to the adverse effects of pro-inflammatory adipokines (39), co-existing obstructive sleep apnea (40, 41), or decreased adiponectin (39, 42). The mechanisms underlying the association between adiposity and Fontan hemodynamics warrant further investigation.

We showed that an absence of a dominant right ventricle was associated with the "Super-Fontan" phenotype. A linear association between ventricular morphology and exercise capacity has previously been reported (43, 44). However, when categorized into exercise performance phenotypes (i.e., normal exercise performance vs. impaired exercise performance), series from Cincinnati Children's Hospital and the Children's Hospital in Philadelphia (a younger population than ours) found no association between ventricular morphology and a superior exercise performance phenotype (6, 7). It would seem plausible that a systemic right ventricle (compared to a systemic left ventricle) would be less likely to adapt to progressive hemodynamic perturbations over time and become more susceptible to circulatory demise and exercise intolerance. Long-term follow-up studies show dominant right ventricular morphology to be associated with worse clinical outcomes (45, 46).

We did not find any differences with regard to type of Fontan circulation, fenestration patency, or sex between the "Super-Fontan" phenotype and those with impaired exercise performance. However, although not statistically significant, there was a higher percentage of females in the "Super-Fontan" group compared to those with impaired exercise performance. Previous studies have also shown that a higher proportion of females are able to achieve better exercise performance (6, 7, 34), and have superior long term-outcomes (47, 48). The mechanisms underlying these sex differences are unclear and warrant further investigation.

Of note, while not statistically significant, and there were no differences in oxygen saturation, 20% of people with impaired exercise performance had a patent fenestration. It is unknown if this is associated with institutional bias toward fenestration or if these patients reflect a higher risk cohort requiring a fenestration at Fontan completion.

There were also no statistically significant differences in health-related quality of life measures between the "Super-Fontan" and control group in this study. However, the

TABLE 4 | The international physical activity questionnaire (IPAQ) and modified Kirska questionnaire results.

	"Super-Fontan"		Control		*p*-value
	n		*n*		
IPAQ					
Work, MET-min/wk	10	2,002 ± 2,399	13	372 ± 889	0.06
Transport, MET-min/wk	10	306 ± 488	13	592 ± 721	0.10
Domestic and garden, MET-min/wk	10	1,519 ± 1,285	13	999 ± 1,483	0.23
Leisure time, MET-min/wk	10	1,214 ± 1,456	13	966 ± 1,141	0.83
Walking, MET-min/wk	10	2,015 ± 2,320	13	1,161 ± 1,419	0.78
Moderate activity, MET-min/wk	10	2,393 ± 1,794	13	1,294 ± 1,485	0.13
Vigorous activity, MET-min/wk	10	632 ± 584	13	474 ± 1,043	0.21
Total physical activity score, MET-min/wk	10	5,040 ± 2,209	13	2,929 ± 2,186	0.10
Sitting time, min/day	10	308 ± 123	13	453 ± 175	0.07
Modified Kriska physical activity questionnaire					
Childhood activity (ages 4–12), h/wk	10	3.9 ± 3.3	12	2.0 ± 3.4	**0.04**
High school and early adulthood (ages 13–21), h/wk	10	5.2 ± 4.4	12	2.1 ± 3.1	**0.04**
Older adulthood (22+), h/wk	10	4.6 ± 3.8	10	2.4 ± 3.5	0.11
Physical activity across the lifespan, h/wk	10	4.3 ± 2.6	12	2.0 ± 3.0	**0.003**

Hours per week, h/wk; Metabolic minutes per week, MET-min/wk; Minutes per day, min/day. Bold values denote statistical significance ($p < 0.05$).

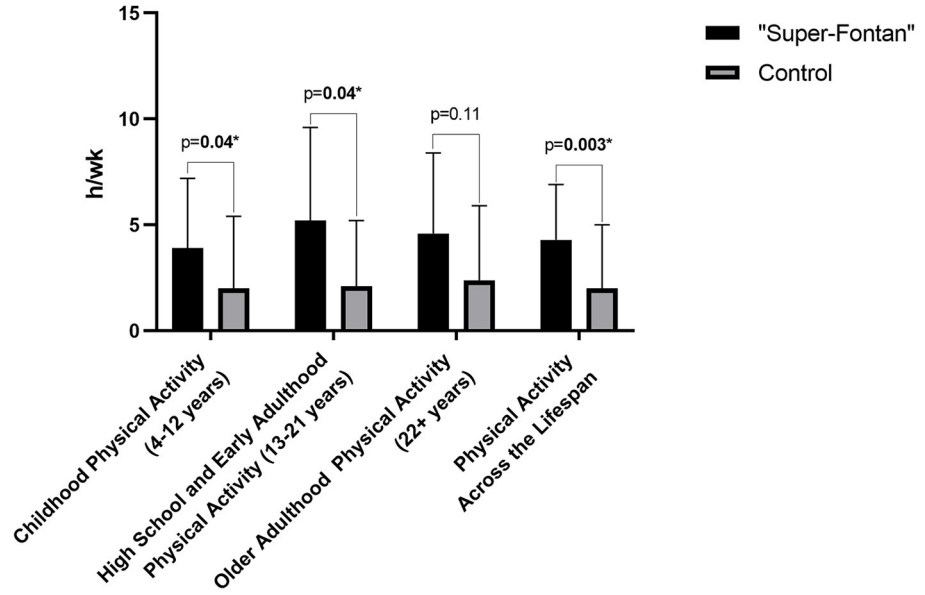

FIGURE 1 | Hours per week (h/wk) spent participating in sports and physical activity.

associations between quality of life and exercise performance are inconsistent across studies and warrant further investigation (49–51). This may be related to adults with a Fontan circulation accommodating to exercise intolerance over time. Supporting this notion, even asymptomatic people with congenital heart disease (New York Heart Association Functional Class I) have objectively impaired exercise capacity (2). Furthermore, the benefits of physical activity and exercise training on quality of life (particularly in the psychosocial domains) are potentially related to the social engagement that accompanies participation rather than better physical function.

Exercise Response and Lung Function

HRR was greater in those with the "Super-Fontan" phenotype compared to the control group. Importantly, diminished HRR may be associated with arrhythmia-related mortality (9). This may explain why the combination of peak VO_2 and HRR has a more substantial prognostic value for 5-year survival (52), with peak VO_2 likely associated with heart-failure-related mortality.

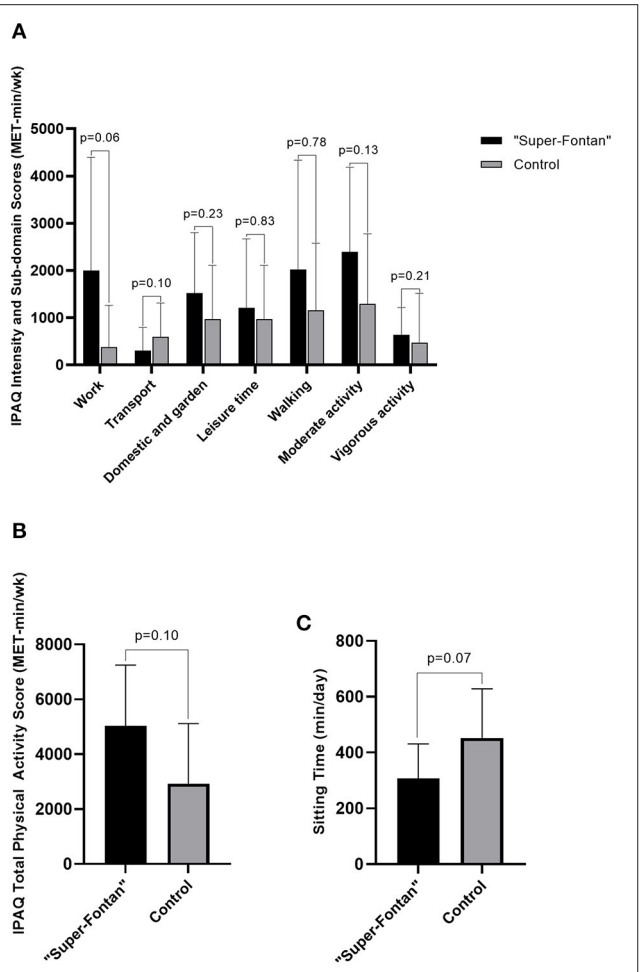

FIGURE 2 | International physical activity questionnaire (IPAQ) scores. **(A)** IPAQ intensity and sub-domain scores, **(B)** IPAQ total physical activity score, **(C)** Sitting time. Metabolic minutes per week (MET-min/wk); minutes per day (min/day).

We also found higher peak circulatory power on average in people with the "Super-Fontan" phenotype, which is associated with better outcomes (53, 54). Collectively, the "Super-Fontan" exercise response reflects a low-risk Fontan phenotype.

Overall, most of our Fontan cohort had normal range chronotropic index implying an appropriate HR response relative to the metabolic load. Only three patients had a low chronotropic index with impaired exercise capacity indicating chronotropic insufficiency—It has been postulated that an inappropriate HR response is not a primary limiting factor to exercise performance unless severe chronotropic incompetence is present (55, 56). Exercise performance in the Fontan circulation appears predominately limited by preload deprivation that inhibits stroke volume augmentation. Over half of our Fontan patients with impaired peak VO_2 show evidence of a cardiovascular (stroke volume) limitation to exercise performance denoted by an elevated chronotropic response or low peak oxygen pulse. Of course, the reduced oxygen pulse and elevated chronotropic index can also reflect impaired peripheral muscle oxygen extraction, which is also present in the Fontan circulation (57).

Lung function is commonly impaired in people with a Fontan circulation and is associated with prognosis and exercise capacity (58–60). The majority of our Fontan cohort with baseline spirometry results recorded had evidence of ventilatory restriction or mixed defect. Baseline spirometry abnormalities were less prevalent in the "Super-Fontan" phenotype compared to those with impaired exercise performance. However, despite abnormal lung function at rest, most patients in this study had ample breathing reserve, potentially because exercise performance in Fontan patients is predominantly impaired by cardiovascular limitations prior to encroaching upon ventilatory constraints. Only five people had evidence of mechanical ventilatory limitation during exercise, with no difference between the "Super-Fontan" and control groups. Of note, it is likely ventilatory limitations to exercise performance is underappreciated using breathing reserve in isolation as a surrogate. The addition of exercise flow-volume loops will perhaps reveal more Fontan patients with ventilatory limitations to exercise performance.

Exercise Self-Efficacy and Physical Activity

Although self-reported physical activity levels were higher and sedentary (sitting) time was lower in the "Super-Fontan" group compared to the controls, this did not achieve statistical significance. This may be attributed to the duration between CPET and the administration of the questionnaires (∼2 years), which likely does not truly reflect their current levels of physical activity. Furthermore, while the IPAQ shows moderate validity compared to accelerometers (61), in the setting of congenital heart disease, patients often overestimate their physical activity levels using the IPAQ long-form (62).

Indeed, Powell et al. reported that 77% of patients with the "Super-Fontan" phenotype participated in regular physical activity compared to 10% in those with impaired exercise performance (6). This is in accordance with our previous reports that show many of those with a "Super-Fontan" phenotype or positive exercise capacity trajectory regularly participate in moderate-to-vigorous sports and physical activity (5, 63). Importantly, increased physical activity levels could be attributed to higher exercise self-efficacy in the "Super-Fontan" cohort. Preceding studies have shown an association between physical activity levels and exercise self-efficacy (64).

We found that participation in regular structured sports and physical activity from childhood to early adulthood was significantly higher in those with a "Super-Fontan" phenotype compared to those with impaired exercise performance. Total overall participation in sports and physical activity was also higher in the "Super-Fontan" group. While exercise training interventions can increase peak VO_2 (65, 66), it appears that participation in regular sports and physical activity from a younger age lays the foundation to achieve a low-risk "Super-Fontan" phenotype. This is consistent with the findings of Ohuchi et al. who showed that increased physical activity levels during childhood—reflected by a positive exercise capacity trajectory—were associated with better adult Fontan physiology,

hepatic function, and prognosis (67). In another series, children and adolescents with a Fontan circulation who participated in sports during middle and high school had better lung function and exercise capacity (68). Regular sports, exercise training, or physical activity may be particularly crucial during childhood when organs, and especially the pulmonary vasculature, are likely more sensitive to adaptation in this period of rapid growth and development (67).

The association with regular moderate-to-vigorous physical activity participation and the "Super-Fontan"—superior exercise performance and low-risk—phenotypical expression may be attributed to multiple mechanisms. Regular participation in moderate-to-vigorous intensity sports and physical activity is important for the development of skeletal muscle mass and prevention of Fontan-associated myopenia (37). Deficiencies in skeletal muscle mass have important implications for ventricular function (37), and exercise capacity (57, 69). Higher appendicular muscle mass provides structural support to reduce venous compliance and enhances skeletal muscle pump function, facilitating preload and ventricular filling (70, 71). Indeed, increasing skeletal muscle mass through resistance exercise training improves ventricular filling, cardiac output, peak VO_2, and reduces respiratory dependence in people with a Fontan circulation (72).

A primary constraint to ventricular filling appears to be elevated pulmonary vascular resistance. To maintain low pulmonary vascular resistance, there must be an adequately developed pulmonary circulation. However, pulmonary artery growth essentially ceases after Fontan completion (73), likely due to the combination of reduced pulsatility and pulmonary flow. We have previously shown that lower limb exercise can transiently increase (pulsatile) pulmonary flow (74). It is likely that engaging in regular long-term physical activity or exercise training (particularly during childhood), which transiently increases pulmonary flow (and may also alter the flow profile), facilitates pulmonary vascular development. Furthermore, periodic increases in ventricular filling associated with exercise may augment volume load to the chronically preload deprived ventricle and attenuate progressive "disuse hypofunction". This phenomenon is observed when volume load is restored following atrial septal defect closure in adults, reversing diastolic dysfunction (31).

Of course, the association between the "Super-Fontan" phenotype and physical activity during childhood, and early adulthood, may simply reflect that those with superior exercise performance are more capable of participating in regular sports and physical activity, especially from an earlier age.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

While there appear to be common characteristics associated with the "Super-Fontan" phenotype, some patients in this subset still have features—such as a dominant right ventricle, atriopulmonary connection, or patent fenestration—that are expected to impede exercise performance. This suggests that extracardiac and potentially modifiable factors contribute to the expression of the "Super-Fontan" phenotype.

A key finding of our study is that exercise-self efficacy and regular participation in structured sports and physical activity from a young age is significantly higher in those with the "Super-Fontan" phenotype. This highlights the need to promote exercise training, sports, and physical activity in people with a Fontan circulation from early in life. Those who participated in sports from a young age probably also have higher exercise self-efficacy, which establishes a foundation for life-long physical activity habits. To date, exercise training is the most effective therapy for improving peak VO_2 in people who have a Fontan circulation (70). While exercise training recommendations are now available for people with a Fontan circulation (65, 66, 75), they are predominantly based on clinical experience and expert opinion.

The forthcoming multi-center randomized controlled Fontan Fitness Intervention Trial (F-FIT) will hopefully provide more conclusive evidence to aid the development of future exercise training recommendations for people living with a Fontan circulation.

LIMITATIONS

It is important to note that the retrospective design of this study can only show association and not causation. A key limitation in this study is the reliability of long-term physical activity questionnaires, which is subject to recall error. However, the reliability of long-term physical activity recall appears to be reasonable, with a previous study reporting an intraclass correlation coefficient of ∼0.4 (76).

CPET is a specialized assessment that requires a high degree of clinical expertise to perform and interpret. This may restrict the results of this study to patients in the care of expert centers, which are predominately located in major cities. Indeed, we previously reported that <8% of people in the Australian and New Zealand Fontan Registry had recorded serial CPET documented (63). Therefore, our sample may be subjected to selection bias. The spirometry and CPET data were also derived from the tabulated reports available, and we had limited access to the flow-volume curves or primary CPET data. This restricted our ability to visually inspect the acceptability and repeatability of spirometry maneuvers, verify anaerobic threshold selection, or standardize the processing of CPET parameters. However, the spirometry and CPET studies were predominantly performed in "expert" experienced centers, and our results reflect the available reports used in clinical practice.

Our study is also limited in sample size, which increases the risk of a type II error, and we may not be able to detect some important associations.

Ideally, the function of the single ventricle and "Super-Fontan" status should be evaluated during upright exercise with invasive haemodynamic measures, but this is technically challenging. Currently, we and others have defined the "Super-Fontan" phenotype as achieving ≥80% predicted VO_2

and/or work rate (5–7, 15), which can be influenced by the regression prediction equation selected and remains an arbitrary threshold.

CONCLUSIONS

The "Super-Fontan" phenotype is associated with a healthy weight, younger age of Fontan completion (around 4 years), and higher overall levels of sport and physical activity participation during childhood and early adulthood. The "Super-Fontan" phenotype exercise response was accompanied by a higher HRR, oxygen pulse, peak circulatory power, and a later anaerobic threshold onset.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Royal Children's Hospital Melbourne Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DT, Yd'U, DC, and RC contributed to the conception and design of the study. DT drafted the manuscript and acquired and analyzed the data. All authors critically reviewed the manuscript, contributed to the interpretation of the results, and approved the submission of the manuscript.

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Morphologic Alterations Precede Functional Hepatic Impairment as Determined by ^{13}C-Methacetin Liver Function Breath Test in Adult Fontan Patients

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Objectives: Fontan-associated liver disease (FALD) is the most common end-organ dysfunction affecting up to 70–80% of the Fontan population. The clinical significance of FALD is incompletely understood and no unambiguous correlation between hepatic function and FALD severity has been established. In this study, we sought to evaluate maximal liver function capacity with liver maximum function capacity test (LiMAx®) in adult Fontan patients.

Methods: Thirty-nine adult Fontan patients (median age: 29.4 years [IQR 23.4; 37.4], median follow-up after Fontan operation: 23.9 years [IQR 17.8;26.4]) were analyzed in a cross-sectional observational study using LiMAx® test (Humedics GmbH, Berlin, Germany), laboratory testing, transient elastography (TE) and hepatic ultrasound. The LiMAx® test is based on the metabolism of ^{13}C-methacetin, which is administered intravenously and cleaved by the hepatic cytochrome P4501A2 to paracetamol and $^{13}CO_2$, which is measured in exhaled air and correlates with maximal liver function capacity.

Results: Maximal liver function capacity assessed by LiMAx® test was normal in 28 patients (>315 μg/h*kg) and mildly to moderately impaired in 11 patients (140–314 μg/h*kg), while no patient displayed severe hepatic impairment (<139 μg/kg*h). No correlation was found between maximal liver function capacity and hepatic stiffness by TE ($r^2 = -0.151$; $p = 0.388$) or the presence of sonographic abnormalities associated with FALD ($r^2 = -0.204$, $p = 0.24$). There was, however, an association between maximal liver function capacity and the laboratory parameters bilirubin ($r^2 = -0.333$, $p = 0.009$)

and γ-glutamyl transferase ($r^2 = -0.367$; $p = 0.021$). No correlation was detected between maximal liver function capacity and the severity of FALD ($r^2 = -0.235$; $p = 0.152$).

Conclusion: To the best of our knowledge, this is the first study to evaluate maximal liver function capacity using LiMAx® test in Fontan patients, which is a useful complementary diagnostic instrument to assess chronic hepatic injury. Maximal liver function capacity was preserved in most of our adult Fontan patients despite morphologic evidence of FALD. Moreover, maximal liver function capacity does not correlate with the extent of FALD severity evaluated by sonography or laboratory analysis. Thus, the development and progression of FALD in Fontan patients is not a uniform process and diagnostics of chronic hepatic injury during follow-up should encompass various modalities.

Keywords: Fontan-associated liver disease, enzymatic liver function, hepatic assessment, second-organ dysfunction, Fontan failure

INTRODUCTION

Over the past decades, survival of Fontan-palliated patients significantly improved with the majority of patients now reaching adulthood (1, 2). Nevertheless, the unphysiological Fontan circulation leads to progressive end-organ damage in the long-term (3–5). Fontan-associated liver disease (FALD) is the most common end-organ dysfunction and affects up to 70–80% of the adult Fontan population (5, 6). FALD manifestations vary from slightly elevated serum liver enzymes and mild hepatic parenchymal changes to end-stage liver cirrhosis (5, 6). The clinical significance of FALD is incompletely understood, and its diverse manifestations need to be put into clinical context when making therapeutic decisions. In a previous study, we proposed a scoring system (FALD score) to grade FALD severity based on a combination of laboratory parameters, hepatic ultrasound and transient elastography (TE). Our results revealed that the FALD score significantly correlated with Fontan hemodynamics and reliably discriminated between patients with and without Fontan failure (7). Liver-associated morbidity and mortality are well-described in the adult Fontan population and constitute major risk factors limiting survival after cardiac transplantation (8, 9). Therefore, reliable diagnostic modalities are indispensable to monitor hepatic end-organ damage and to determine the optimal timing for cardiac transplantation.

Since conventional liver function tests are often insensitive indicators of early disease stages, Stockmann et al. introduced the liver maximum capacity test (LiMAx®) for exact determination of quantitative enzymatic liver function and prediction of outcome after hepatectomy (10). The test is based on the enzymatic function of the cytochrome P4501A2 (CYP1A2) system, which is exclusively expressed in hepatocytes and is proportional to the hepatic parenchymal volume (10). As methacetin is exclusively metabolized by CYP1A2, the intravenous administration of ^{13}C-methacetin and the continuous real-time breath analysis of exhaled $^{13}CO_2$ provides an exact quantification of maximal liver capacity.

The aims of this study were to determine maximal liver function capacity with the LiMAx® test in adult Fontan patients, in comparison to the results of other hepatic diagnostic modalities and to analyze its relationship with the severity of FALD.

METHODS

Study Design and Patients

From 2019 to 2021 we performed a cross-sectional observational study including 39 adult Fontan patients, who successively presented in our outpatient clinic for follow-up and received measurement of maximal liver function capacity using the LiMAx® test. Exclusion criteria consisted of patient age < 18 years and/or intolerance to paracetamol or methacetin. The study was approved by the institutional review board and ethics committee (decision number: EA2/127/18). Informed written consent was obtained from all individual participants prior to inclusion.

FALD Diagnostics

Our institutional protocol and diagnostic algorithm for hepatic assessment of Fontan palliated patients has previously been described in detail and consists of laboratory analyses, hepatic ultrasound and liver stiffness measurement by TE (5). The laboratory parameters alanine-aminotransferase (ALT), γ-glutamyltransferase (γGT), total bilirubin, α_2-macroglobulin, apolipoprotein A_1 and haptoglobin were required to calculate a biomarker fibrosis score with FibroTest®. FibroTest® was computed on Biopredictive website (Paris, France; www.biopredictive.com). The calculated Fibrotest® score was converted into liver fibrosis stages according to METAVIR histological classification for liver biopsies (11). The calculation of the FALD score has previously been described in detail (7). Briefly, scoring points assigned for each hepatic abnormality detected in the diagnostics mentioned above were summed up for the final FALD score (7). In addition, patients received a standardized LiMAx® test as described by Stockmann et al. (10). Briefly, after 4 h of fasting, patients were placed in a resting horizontal position. Ten minutes prior to the injection of ^{13}C-methacetin, the baseline $^{13}CO_2/^{12}CO_2$ ratio was recorded.

A solution of 2 mg/kg body weight ^{13}C-labeled methacetin was intravenously injected as a bolus over a maximum of 30 s followed by 20 mL 0.9% sodium chloride solution. ^{13}C-methacetin is metabolized by the hepatozyte-specific CYP1A2 system into paracetamol and $^{13}CO_2$, which is exhaled and measured in expired air (**Supplementary Figure 1**). Each LiMAx® test analyzed 46 breath samples per patient and the result is given in μg/kg*h (**Supplementary Figure 2**).

STATISTICAL ANALYSIS

Data were obtained from medical records of the German Heart Centre Berlin. Patients' characteristics were expressed as median and interquartile range [IQR]. Fontan follow-up duration was defined as the interval between Fontan operation and last follow-up. Correlations between maximum liver capacity and laboratory parameters, TE, the number of hepatic abnormalities detected by ultrasound and the FALD score were assessed using Spearman's correlation. Associations between FALD severity graded as mild, moderate, and severe and maximal liver function capacity was analyzed using Kuskal Wallis and Wilcoxon tests as appropriate. Statistical analyses were performed using SPSS statistical software (version 23, IBM Corp., NY, USA). A $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics of the entire cohort are listed in **Table 1**. Median patient age was 29.4 years [IQR 23.4, 37.4] and median follow-up after Fontan operation 23.9 years [IQR 17.8, 26.4]. The most common underlying cardiac morphologies were tricuspid atresia ($n = 10$), double inlet left ventricle ($n = 11$) and unbalanced atrioventricular septal defect ($n = 3$). Fontan modifications included extracardiac conduit in 13 patients, lateral tunnel in 16 patients and atriopulmonary/atrioventricular connection (APC/AVC) or other modifications in 10 patients. Systolic ventricular function was normal or mildly impaired in the majority of the cohort ($n = 33$). Atrioventricular valve regurgitation was classified as absent or mild in 30 patients, moderate in 8 patients and severe in 1 patient. In 4 patients cardiac transplantation was performed, 2 patients died after transplantation. In addition, 1 patient died on mechanic circulatory support prior to cardiac transplantation.

TABLE 1 | Patient characteristics.

Patient age (years)	29.4 [23.4;37.4]
Age at Fontan operation (years)	6.5 [3.5;12.9]
Follow-up after Fontan (years)	23.9 [17.8;26.4]
Cardiac anatomy	
Double inlet left ventricle	11 (28.2%)
Tricuspid atresia	10 (25.6%)
Unbalanced AVSD	3 (25.6%)
Complex TGA	3 (25.6%)
Hypoplastic left heart syndrome	2 (5.1%)
Other	10 (15.5%)
Left ventricular morphology	27 (69.2%)
Fontan type	
Intracardiac TCPC	16 (41.7%)
Extracardiac TCPC	13 (33.3%)
APC/AVC/other	10 (30.3%)
Impairment of systolic ventricular function	
None	12 (30.8%)
Mild	21 (53.8%)
Moderate	5 (12.8%)
Severe	1 (2.6%)
Atrioventricular valve insufficiency	
None	13 (33.3%)
Mild	17 (43.6%)
Moderate	8 (20.5%)
Severe	1 (2.6%)

Data are presented as median [IQR] or frequencies (%).
APC, Atriopulmonary connection; AVC, Atrioventricular connection; AVSD, Atrioventricular septal defect; IQR, interquartile range; TCPC, total cavopulmonary connection; TGA, Transposition of great arteries.

Hepatic Assessment

Results from laboratory analysis, TE, hepatic ultrasound and the LiMAx® test are reported in **Table 2**. According to age-adjusted institutional reference values, ALT was elevated in 6 patients, aspartate aminotransferase (AST) in 7 patients, γGT in 31 patients and bilirubin in 13 patients. Thrombocytopenia was found in 12 patients. Median Fibrotest® fibrosis score was 0.6 [IQR 0.4, 0.6]. Referring to Fibrotest® calculation, fibrosis was staged F2 in the majority of our patients ($n = 12$; **Table 2**). Ultrasound revealed hepatic parenchymal changes in all patients (**Table 2**). The most common ultrasound findings were heterogeneous echotexture ($n = 35$), liver vein dilatation ($n = 31$), altered liver vein morphology ($n = 25$) and segmental hypertrophy or atrophy ($n = 11$). Hyperechogenic lesions were present in 7 patients. In 7 patients, sonographic signs of liver cirrhosis were detectable. Median TE values were 20.0 kPA [IQR 15.0, 34.3]. FALD was graded as mild in 6, moderate in 11 and severe in 22 patients based on the FALD score (7).

Median maximal liver function capacity was 350.0 μg/kg*h [IQR 288.0; 470.0] corresponding to a normal hepatic function (≥ 315 μg/kg/h) based on previously published normative values (12). In 11 patients, a moderate hepatic impairment was detected (140–314 μg/kg*h), while none had severely impaired maximal liver function capacity (≤ 139 μg/kg*h). As shown in **Figure 1**, hepatic function as assessed by LiMax® tended to decrease with a longer follow-up after Fontan operation ($r^2 = -0.333$, $p = 0.038$). A significant correlation between maximal liver function capacity and the laboratory parameters bilirubin ($r^2 = -0.421$, $p = 0.009$) and γGT ($r^2 = -0.367$; $p = 0.021$) was detected. However, no significant correlations were found between maximal liver function capacity and Fibrotest® fibrosis score ($r^2 = -0.335$, $p = 0.052$), TE ($r^2 = -0.151$, $p = 0.388$) or the number of hepatic abnormalities detected by liver ultrasound ($r^2 = -0.204$, $p = 0.24$). Seven of thirty-nine patients were diagnosed with liver cirrhosis based on sonography, in these patients maximal liver function capacity was significantly reduced as compared to patients without liver cirrhosis (274.5 μg/kg*h [IQR 216.3; 346.0] vs. 384.0 μg/h*kg [IQR 320.0; 497.5], $p = 0.025$).

TABLE 2 | Hepatic assessment.

	Median [IQR]	Outside RR/N (%)
Laboratory parameters		
ALT (U/l)	30.0 [25.0; 38.0]	6/39 (15.4%)
AST (U/l)	30.0 [26.0; 34.0]	7/39 (17.9%)
γGT (U/l)	87.0 [54.0; 125.0]	31/39 (79.5%)
Total bilirubin (mg/dl)	0.9 [0.7; 1.6]	13/39 (33.3%)
Thrombocytes (K/μl)	159.0 [137.0; 211.0.]	12/39 (30.8%)
Fibrotest®	0.6 [0.4; 0.7]	
F0		4/34 (11.8%)
F1		6/34 (17.6%)
F2		12/34 (35.3%)
F3		8/34 (23.5%)
F4		8/34 (23.5%)
TE (kPa)	20.0 [15.0; 34.3]	
< 21.2 kPa		18/34 (52.9%)
21.3–27.6		2/34 (5.9%)
27.7–35.7		8/34 (23.5%)
> 35.8 kPa		7/34 (20.6%)
Hepatic ultrasound findings		
Hepatomegaly		9/35 (25.7%)
Splenomegaly		9/35 (25.7%)
Heterogeneous liver parenchyma		35/35 (100.0%)
Segmental atrophy/hypertrophy		11/35 (31.4%)
Hepatic vein dilatation		31/35 (88.6%)
Abnormal hepatic vein architecture		35/35 (100.0%)
Hyperechogenic lesions		7/35 (20.0%)
Surface nodularity		7/35 (20.0%)
Ascites		4/35 (11.4%)
FALD score/ FALD severity	6.0 [5, 8]	
Mild		6/39 (15.4%)
Moderate		11/39 (28.2%)
Severe		22/39 (56.5%)
Maximal liver function capacity		
LiMax® test (μg/kg*h)	350.0 [288.0; 470.0]	
Hepatic metabolic impairment		
None (> 315 μg/kg*h)		28/39 (71.8%)
Moderate (140–315 μg/kg*h)		11/39 (28.2%)
Severe (0–139 μg/kg*h)		0/39 (0.0%)

Data are presented as median [IQR] or frequencies (%).
AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; γGT, γ-Glutamyl-aminotransferase; IQR, interquartile range; kPa, Kilopascal; RR, reference range; TE, Transient elastography.

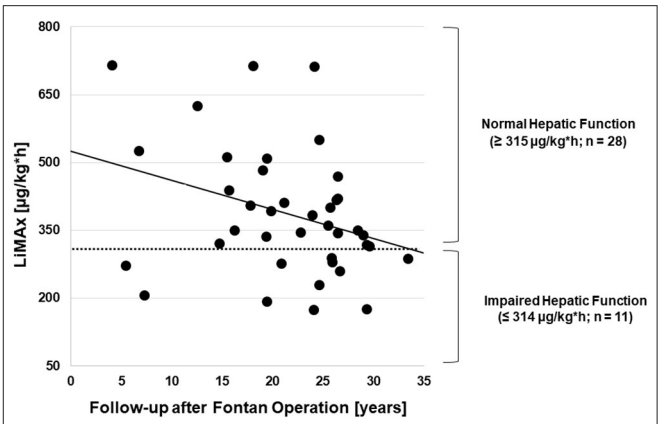

FIGURE 1 | Correlation between the follow-up time after Fontan operation and maximal liver function capacity ($n = 39$).

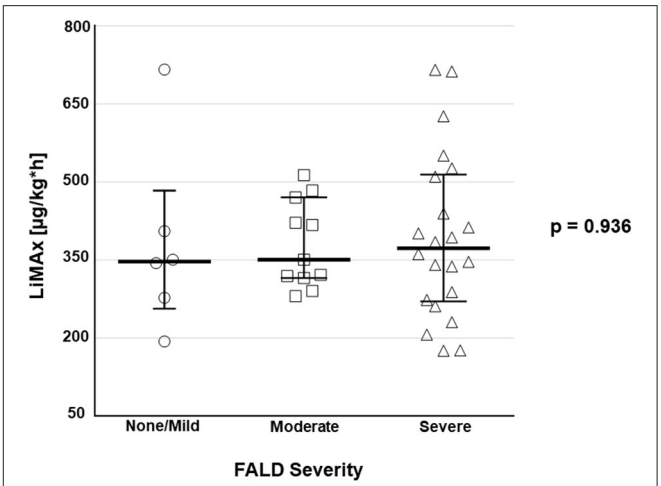

FIGURE 2 | Boxplots depict maximal liver function capacity according to the classification of FALD severity [absent/ mild ($n = 6$), moderate ($n = 11$), severe ($n = 22$)].

No correlation was observed between maximal liver function capacity and the FALD score ($r^2 = -0.237$; $p = 0.152$). Also, maximal liver function capacity did not differ significantly between varying degrees of FALD severity ($p = 0.936$; **Figure 2**).

DISCUSSION

Fontan-associated liver disease (FALD) encompasses all abnormalities in liver structure and function which are associated with the unphysiological Fontan circulation (3–6). Affecting up to 80% of the Fontan population, it is the most common second-organ disease (7–9). Various studies focused on the detection and monitoring of FALD, but its clinical significance and importance for therapeutic decision-making remains unclear. The LiMAx® test was successfully evaluated in several clinical settings such as hepatic surgery, hepatic transplantation, sepsis, and hepatic cirrhosis (10, 12–15). To the best of our knowledge, we herein provide the first results on maximal liver function capacity measured by LiMAx® in Fontan patients in comparison with other diagnostic modalities and FALD severity. Of note, maximal liver function capacity was normal in the majority of our patients although more than half of our cohort had FALD graded as severe. In addition, no clear correlation of maximal liver function capacity with TE and sonographic hepatic abnormalities was detected. We only found a relationship between the laboratory parameters bilirubin and γGT and LiMAx® values. An increase of laboratory parameters associated with cholestasis is the most common abnormality in Fontan patients as well as in patients with congestive hepatopathy (16). The degree of cholestasis is

known to be related to increases in right atrial pressure and to the severity of tricuspid valve regurgitation in patients with right heart failure (17, 18). The underlying mechanism is supposed to be the compression of bile canaliculi and small ductules by centrally congested sinusoids (16). Additionally, diminished cardiac output results in reduced vascular supply and increased oxidative stress leading to necrosis of centrilobular hepatocytes and ischemic damage of the intrasinusoidal endothelium (16), which might not only be detected by increased indicators of cholestasis but also by reduced maximal liver function capacity.

The major finding of our study is the missing correlation between FALD severity and maximal liver capacity measured by the LiMAx® test. This important result suggests that the progress of hepatocyte-specific damage is decelerated and enzymatic liver function remains preserved for a considerably long time in the majority of patients during the morphologic development and progression of FALD. This finding may have important implications for the routine hepatic follow-up of Fontan patients and for the evaluation of failing Fontan patients for cardiac transplantation. Assessing maximal liver function capacity may help to identify failing Fontan patients that require a combined cardiac and liver transplantation. In line with these findings, we previously reported remarkable hepatic remodeling in a patient with normalization of hepatic stiffness values and regression of sonographic signs of hepatic cirrhosis after cardiac transplantation (7). This observation underlines that certain FALD-specific abnormalities are potentially reversible, which might be explained by the missing or slow progression of hepatic injury revealed by our measurements of maximal liver function capacity.

Maximal Liver Function Capacity and Evaluation for Cardiac Transplantation

Cardiac transplantation is currently the only remaining treatment option for patients with refractory Fontan failure since effective evidence-based medical heart failure therapies are virtually non-existent, and mechanic circulatory support is not well-established in Fontan-palliated patients (19, 20). However, cardiac transplantation remains a high risk surgical procedure in the adult Fontan population and hepatic end-organ damage contributes to post-transplant morbidity and mortality (8, 9). Moreover, no guidelines exist for the optimal timing for cardiac transplantation in Fontan patients which may result in a delayed listing for transplantation with already advanced second-organ damage that may negatively impact transplantation outcome. In our cohort, maximal liver function capacity was significantly reduced in patients listed or evaluated for listing for cardiac transplantation ($n = 4$) compared to the remaining cohort (288.0 μg/kg*h [IQR 182.8, 331.5] vs. 361.0 μg/kg*h [IQR 302.5, 454.5], $p = 0.035$). This observation suggests that FALD was rather progressed in these patients, already resulting in functional impairment of the liver which in turn might indicate that listing for cardiac transplantation needs to be considered early. In a previous study, we emphasized on the importance of FALD monitoring to determine the optimal timing for cardiac transplantation and proposed the FALD score as a tool to grade FALD severity and facilitate surveillance of FALD progression (7). The LiMAx® test may represent a valuable complementary additional diagnostic modality in the hepatic assessment of Fontan patients since it provides a reproducible quantitative measurement of enzymatic hepatocyte function. Since a deterioration of maximal liver function capacity seems to occur relatively late during the disease course, its occurrence should trigger an evaluation for cardiac transplantation.

CONCLUSION

We herein demonstrate that maximal liver function capacity as measured by the LiMAx® test is generally well-preserved in Fontan patients despite morphologic evidence of advanced FALD. Our findings suggest that the development and progression of FALD is not a uniform process and diagnostics of chronic hepatic injury during follow-up after Fontan operation should encompass various modalities. Specifically, morphologic changes as detected by ultrasound and/or TE seem to precede functional impairment as evidenced by preserved hepatic function in several patients with significant structural anomalies.

Limitations

There are several limitations to this study. This is a cross-sectional single center trial with a comparably small patient cohort. Future studies, preferably in a multi-institutional setting, are necessary to comprehensively evaluate the assessment of hepatic function in Fontan palliated patients. Methacetin is only approved in adult patients, therefore pediatric patients could not be included in this study. After intravenous injection ^{13}C methacetin undergoes a hepatic microsomal deacylation into paracetamol and $^{13}CO_2$, which is transported to the lung as bicarbonate. Inter – and intraindividual bicarbonate kinetics might influence the respiratory $^{13}CO_2$ excretion by delayed liberation of transiently trapped $^{13}CO_2$. Moreover, although our results suggests an earlier appearance of morphologic changes as compared to functional impairments the temporal relationships of FALD progression and changes of maximal liver function capacity cannot be determined by our cross-sectional study design and requires longitudinal studies. Additional diagnostic modalities such as histological analyses from biopsies or hepatic magnetic resonance imaging were not included in our routine hepatic assessment and the relationship between Fontan hemodynamics and hepatic function was not addressed in this study and needs to be evaluated in the future. The FALD score and gradation of FALD severity have not been evaluated or validated in large patient cohorts or multicenter settings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Charité-Universitätsmedizin

Berlin (desicion number EA2/127/18). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS and SO: conceptualization. AS, NJ, and MP: data collection. AS, FD, PK, MS, HS, H-PM, and TM: investigation. AS: formal analysis and writing original draft. SO, FB, FT, MJ, and MS: supervision. SO, PK, FB, FT, HS, and TM: writing review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.764009/full#supplementary-material

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REVIEW
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Exercise Intolerance, Benefits, and Prescription for People Living With a Fontan Circulation: The Fontan Fitness Intervention Trial (F-FIT)—Rationale and Design

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Background: Despite developments in surgical techniques and medical care, people with a Fontan circulation still experience long-term complications; non-invasive therapies to optimize the circulation have not been established. Exercise intolerance affects the majority of the population and is associated with worse prognosis. Historically, people living with a Fontan circulation were advised to avoid physical activity, but a small number of heterogenous, predominantly uncontrolled studies have shown that exercise training is safe—and for unique reasons, may even be of heightened importance in the setting of Fontan physiology. The mechanisms underlying improvements in aerobic exercise capacity and the effects of exercise training on circulatory and end-organ function remain incompletely understood. Furthermore, the optimal methods of exercise prescription are poorly characterized. This highlights the need for large, well-designed, multi-center, randomized, controlled trials.

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Aims and Methods: The Fontan Fitness Intervention Trial (F-FIT)—a phase III clinical trial—aims to optimize exercise prescription and delivery in people with a Fontan circulation. In this multi-center, randomized, controlled study, eligible Fontan participants will be randomized to either a 4-month supervised aerobic and resistance exercise training program of moderate-to-vigorous intensity followed by an 8-month maintenance phase; or usual care (control group). Adolescent and adult (≥16 years) Fontan participants will be randomized to either traditional face-to-face exercise training, telehealth exercise training, or usual care in a three-arm trial with an allocation of 2:2:1 (traditional:telehealth:control). Children (<16 years) will be randomized to either a physical activity and exercise program of moderate-to-vigorous intensity or usual care in a two-arm trial with a 1:1 allocation. The primary outcome is a change in aerobic exercise capacity (peak oxygen uptake) at 4-months. Secondary outcomes include safety, and changes in cardiopulmonary exercise testing measures, peripheral venous pressure, respiratory muscle and lung function, body composition, liver stiffness, neuropsychological and neurocognitive function, physical activity levels, dietary and nutritional status, vascular function, neurohormonal activation, metabolites, cardiac function, quality of life, musculoskeletal fitness, and health care utilization. Outcome measures will be assessed at baseline, 4-months, and 12-months. This manuscript will describe the pathophysiology of exercise intolerance in the Fontan circulation and the rationale and protocol for the F-FIT.

Keywords: aerobic exercise, cardiac rehabilitation, single ventricle, congenital heart disease, telehealth, exercise intolerance, hypoplastic left heart syndrome, tricuspid atresia

BACKGROUND

Most babies who are born with single ventricle physiology and are palliated with the Fontan procedure will now survive into adulthood (1). The Fontan circulation is the result of a series of staged surgical procedures that redirect venous return to the pulmonary arteries, bypassing the heart. While establishing a Fontan circulation alleviates volume loading and cyanosis, it comes at the expense of elevated central venous pressure, reduced preload, and diminished (pulsatile) pulmonary artery flow. Chronically, these abnormal hemodynamic conditions cause long-term complications, including premature mortality, Fontan-associated liver disease, protein-losing enteropathy, thromboembolic events, arrhythmias, and heart failure (2). However, major advances in surgical techniques and medical care have dramatically improved prognosis, and the projected population of people living with a Fontan circulation in Australia and New Zealand is expected to double over the next 20 years (3). This improved prognosis highlights the need to establish adequate health care services and therapies to provide appropriate care for people living with a Fontan circulation.

Exercise training is a well-established therapy and is part of routine clinical care in people with cardiopulmonary conditions (4). In non-congenital cardiac conditions, improvements in aerobic exercise capacity—reflected by peak oxygen uptake (VO_2)—following cardiac rehabilitation or exercise training is associated with better prognosis and clinical outcomes, including potential reductions in mortality and hospitalization (5–9). While this association has yet to be directly shown in people with a Fontan circulation, it would seem plausible that increasing peak VO_2 with exercise training would yield similar benefits in this cohort, especially since the peripheral muscle pump is of heightened importance in this unique physiological environment. This is supported by studies that show an association between higher aerobic exercise capacity and better prognosis in people with a Fontan circulation (10–13).

Multiple series from tertiary centers around the world have shown the utility of peak VO_2 to identify high-risk phenotypes. People who have congenital heart disease (CHD) with a peak VO_2 below 15.5 ml/kg/min are at a 2.9-fold increased risk of hospitalization or death compared to those with greater aerobic exercise capacity (10). Higher peak VO_2 is also associated with better end-organ function in people with a Fontan circulation (14). Furthermore, deterioration in aerobic exercise capacity appears to be the strongest predictor of adverse events in people with a Fontan circulation (15, 16).

Given the apparent prognostic implications associated with higher aerobic exercise capacity, it would seem intuitive to understand the pathophysiology of exercise intolerance and optimize therapies such as exercise training that can improve peak VO_2. This manuscript will review the pathophysiology of exercise intolerance in the Fontan circulation and describe the rationale, aims, and methods for the multi-center, randomized, controlled Fontan Fitness Intervention Trial (F-FIT).

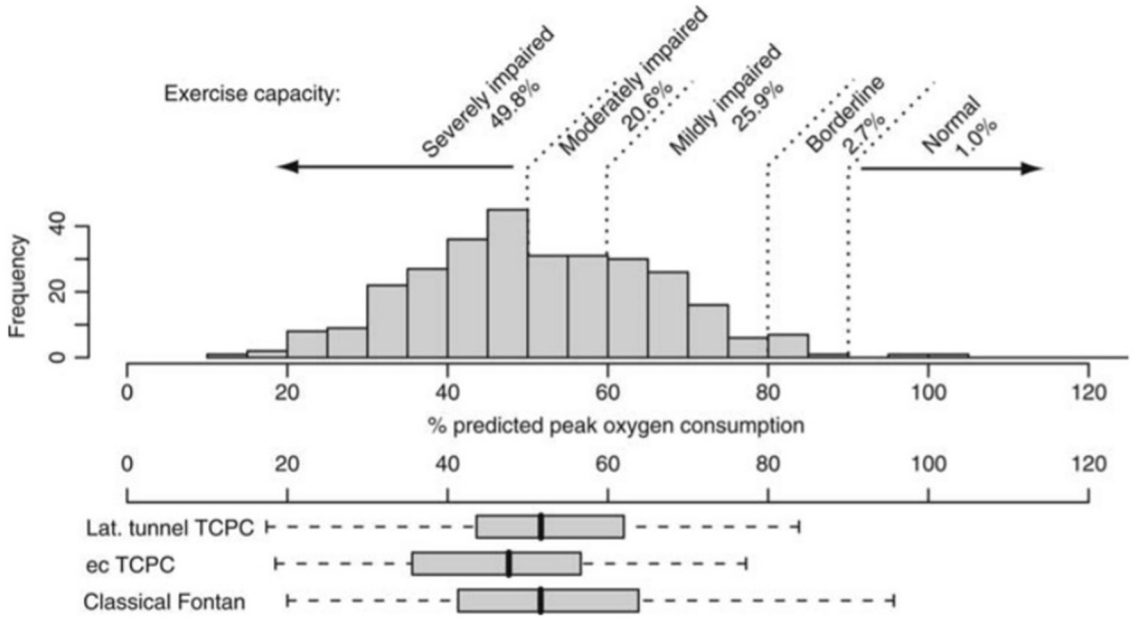

FIGURE 1 | Distribution of % predicted peak oxygen uptake (consumption) in patients after Fontan operation and its distribution in patients with different types of Fontan surgery. ec, extracardiac; lat, lateral; TCPC, total cavopulmonary connection. Reproduced from (12).

PATHOPHYSIOLOGY OF EXERCISE INTOLERANCE IN THE FONTAN CIRCULATION

Cardiopulmonary Exercise Testing Response in the Fontan Circulation

People living with a Fontan circulation usually have at least moderately impaired aerobic exercise capacity (**Figure 1**), with large series reporting an average peak VO_2 ranging from 23 to 27 ml/kg/min (52-61% predicted) (12, 13). The typical cardiopulmonary exercise testing response includes a depressed peak heart rate (HR), elevated minute ventilation (V_E)/carbon dioxide production (VCO_2) slope (ventilatory inefficiency), reduced peak work rate, and increased breathing frequency (17–19). Peak oxygen pulse—a surrogate for stroke volume and arteriovenous oxygen extraction—is impaired, with an early plateau or downsloping trajectory of the oxygen pulse curve, likely reflecting cardiogenic (preload) limitation to exercise performance and intrinsic skeletal muscle dysfunction (20, 21). Exercise ventilatory oscillation is also common (22). Furthermore, a subset of people may also have mechanical ventilatory limitations reflected by limited breathing reserve (23). Interestingly, the anaerobic threshold and other submaximal measures of exercise capacity are often better preserved compared to peak VO_2, albeit still lower than normal predicted values. Some people may also experience exercise-induced oxygen desaturation secondary to diffusion type limitation or right-to-left shunting *via* veno-venous collaterals or Fontan fenestration.

Serial Changes in Aerobic Exercise Capacity

The change in aerobic exercise capacity over time may be more prognostically significant than a single measurement (16); a decline in peak VO_2 is associated with increased risk of adverse cardiovascular events, death, and cardiac transplantation (15, 24). Some longitudinal studies have reported an average decline in aerobic exercise capacity ranging from 0.8 to 2.6 percentage points per year (15, 24–26). The accelerated rate of decline may result in a premature deterioration below the "critical" peak VO_2 threshold (16.6 ml/kg/min or 50% predicted) that significantly increases the risk of adverse events (27, 28). This may explain the high prevalence of morbidity, and premature mortality observed as early as the third or fourth decade of life. Promisingly, more recent reports have shown slower rates of decline or even an increase in aerobic exercise capacity trajectory (29). Understanding the contributors to the trajectory of aerobic exercise capacity may aid the determination of appropriate therapies and potentially identify the appropriate timing for intervention.

Surgical Factors

Age at Fontan Completion

The optimal age at Fontan completion remains controversial. It is uncertain whether prolonging the period prior to partial surgical correction (Glenn shunt) can allow for optimal pulmonary vascular development, albeit at the expense of cyanosis and volume loading. Fontan completion at a later age may also allow for a larger conduit to "optimize" flow. However, data appears to support the notion of early Fontan completion to preserve

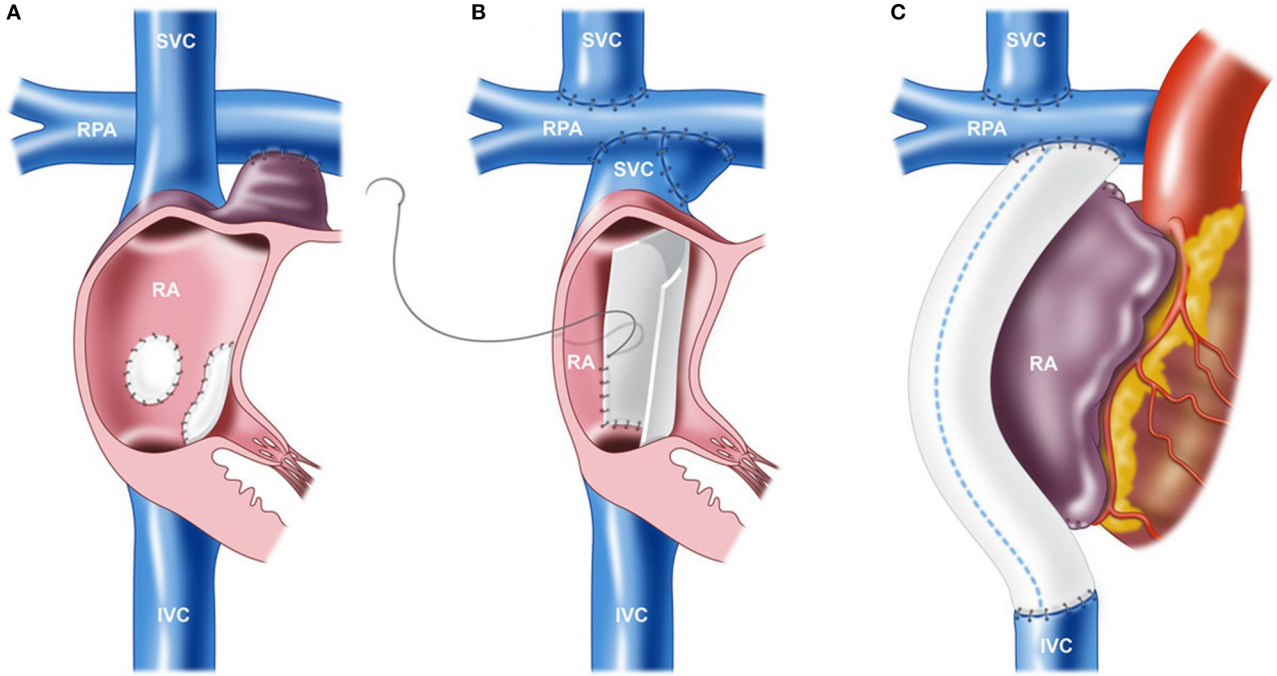

FIGURE 2 | Various techniques of the Fontan procedure. **(A)** Atriopulmonary connection. **(B)** Lateral tunnel total cavopulmonary connection (TCPC). **(C)** Extracardiac conduit TCPC. IVC, inferior vena cava; RA, right atrium; RPA, right pulmonary artery; and SVC, superior vena cava. Reproduced from (32).

long-term aerobic exercise capacity (30, 31). This association may be explained by protecting the single ventricle from excessive volume loading with earlier age at Fontan completion.

Type of Circulation

Since the original atriopulmonary connection-type Fontan procedure, there have been various modifications to this approach (**Figure 2**). While the notion of the original procedure was to "ventriculize" the right atrium to compensate as a subpulmonary pump, long-term follow-up data demonstrated poor prognostic outcomes with this surgical approach (33). The preferred approach in the current era is the total cavopulmonary connection (lateral tunnel or extracardiac conduit), which has dramatically improved long-term outcomes and survival because atriopulmonary connections are more prone to arrhythmias, cardiac maladaptation (heart failure), worse atrial and ventricular mechanics, and premature mortality (1, 33, 34). Importantly, the modification to the total cavopulmonary connection-type Fontan circulation has optimized hemodynamics and flow energetics. Indeed, those with a total cavopulmonary connection tend to have greater pulmonary flow and stroke volume compared to those with an atriopulmonary connection, but the impact on aerobic exercise capacity is unclear. In adolescents and adults, peak VO_2 and submaximal exercise measures were higher in those with a total cavopulmonary connection (35), although surprisingly, large seminal series show no difference in aerobic exercise capacity between groups (12, 26). These contradictory findings may be attributed to the vastly heterogeneous group of patients that present with extensive variations in arrhythmia burden, ventricular morphology, pulmonary vascular function, muscle mass, lung function, physical activity levels, and ventricular function. It is likely that the type of Fontan circulation is associated with aerobic exercise capacity only in a selected subset of older patients with other co-existing complications and suboptimal Fontan circuit geometry.

Cardiac Factors and Pulmonary Vascular Resistance: Implications for Cardiac Output

Cardiac Factors

Systolic Ventricular Function

At rest, cardiac output is often within the normal range or only mildly depressed in the single ventricle circulation, with relatively well-preserved systolic function (contractility). Reductions in resting cardiac output may be the consequence of "ventricular-vascular" uncoupling instead of impaired contractility (36). However, at elevated HRs, there is evidence of limited inotropic response, likely secondary to decreased preload rather than intrinsic cardiac abnormalities (37). Although some studies have reported a correlation between measures of systolic function and aerobic exercise capacity (38, 39), the degree of ventricular systolic dysfunction does not completely account for the level of exercise intolerance experienced in the majority of the cohort, most of whom have preserved systolic function. This is supported by our local data (35) and a large, multi-center series from the Pediatric Heart Network, which did not find any association between systolic ventricular function and peak VO_2 (40). Furthermore, if contractility was a significant cause of exercise intolerance, the use of inotropic agents would theoretically

improve cardiac output, and in turn, aerobic exercise capacity, which has not been demonstrated in the Fontan circulation (41). In summary, while it is probable that systolic ventricular function contributes to aerobic exercise capacity, it is unlikely to be a primary contributor to exercise intolerance unless systolic ventricular dysfunction is severe (42).

Diastolic Ventricular Function

In the Fontan circulation, preserving diastolic function is imperative to minimize pulmonary pressure and increase pulmonary blood flow. Even modest elevations in filling pressure can have significant effects on preload and aerobic exercise capacity (28). Resting diastolic dysfunction assessed by echocardiogram inversely correlates with peak VO_2 (38, 43, 44). Of note, however, studies that utilize traditional echocardiography measures of ventricular function (systolic and diastolic) should be interpreted with caution, as they are poorly validated and likely inaccurate in the setting of preload deprivation and atypical chamber geometry in the Fontan circulation (45, 46). While the ability of the ventricle to "pull" blood through the pulmonary vasculature is limited, preserving diastolic function in the single ventricle is likely an important factor to prevent the deterioration of aerobic exercise capacity by maintaining ventricular filling.

Dominant Ventricle Morphology

The myocardial architecture and coronary blood supply of the left ventricle are designed to sustain the systemic circulation (47). Unsurprisingly, the ability of the right ventricle to support the systemic circulation is often suboptimal, and adverse remodeling likely ensues over time in many patients, which theoretically should impair aerobic exercise capacity. Indeed, some studies have reported an association between left ventricular morphology and aerobic exercise capacity (25, 48).

However, series involving older cohorts were unable to detect an association between exercise intolerance and dominant ventricle morphology (26, 49–51). This is consistent with other clinical measures of exercise capacity (6-min walk distance or treadmill exercise duration), which showed no differences in exercise performance between ventricular morphology type in patients with an extracardiac conduit type circulation (52). The latest Pediatric Heart Network study also did not show an association between ventricular morphology and peak aerobic exercise capacity, although patients with a dominant left ventricle had better submaximal exercise capacity (higher VO_2 at anaerobic threshold) (26). Notably, even those with a dominant left ventricle show evidence of pathological abnormalities compared to the normal biventricular heart (53), and may in part, explain the conflicting findings reported.

Despite the association between ventricular morphology and aerobic exercise capacity previously reported, people with a systemic right ventricle can still achieve normal or even supranormal exercise capacity (14, 54), suggesting that it is not a central limiting factor. This is likely related to the somewhat limited role that contractility has on cardiac output in the setting of limited preload.

Outflow Obstruction and Valvular Regurgitation

Outflow obstruction may be attributed to valvular stenosis, aortic obstruction, subvalvular stenosis (e.g., membrane or muscle bar), or supravalvular stenosis, which may impede the augmentations of cardiac output during exercise. This can lead to increased afterload, ventricular hypertrophy, and potentially maldistribution of blood flow, with significant implications on atrial filling pressures and stroke volume. Importantly, these obstructions may progress over time and can become dynamic with exertion (55), further restricting flow and potentially resulting in a precipitous decline in cardiac output during exercise.

Regurgitation of the systemic semilunar or atrioventricular valve predisposes the heart to chamber enlargement and progressive ventricular dysfunction, which may impair aerobic exercise capacity. Ohuchi *et al.* reported that a small subset of Fontan patients with atrioventricular valve insufficiency had lower peak VO_2 (48). This reduction in aerobic exercise capacity may be associated with the deleterious consequences that accompany atrioventricular valve regurgitation (e.g., elevations in atrial pressure), which affect the transpulmonary flow gradient. However, more prospective data are required to confirm the degree to which atrioventricular valve insufficiency contributes to reduced aerobic exercise capacity.

Chronotropic Response

Chronotropic limitation is a common factor associated with impaired aerobic exercise capacity in people with cardiac conditions. In contrast to patients with a biventricular circulation, mildly-to-moderately depressed peak HR (often described as "chronotropic incompetence") may be, in part, an autoregulatory response to reduced preload. Scarring of the conduction system related to cardiac surgery, intrinsic developmental abnormalities of the conduction system, and drugs (such as beta-blockers and anti-arrhythmic medications) also impair the chronotropic response. Unless chronotropic limitation is severe, peak HR does not appear to significantly impair aerobic exercise capacity. Further supporting this notion, there is no difference in chronotropic limitation between patients who achieve "normal" aerobic exercise capacity compared to those with reduced aerobic exercise capacity (54). In addition, atrial pacing studies have shown no improvement in cardiac output. Further increases in peak exercise HR may result in a plateau or decrease in cardiac output and promote exercise intolerance (**Figure 3**). The observed diminished HR reserve (HRR) can be predominantly attributed to hemodynamic abnormalities (i.e., reduced preload) (56). However, during relative submaximal exercise intensities, the chronotropic response is appropriate or even higher compared to healthy control subjects (57).

Pulmonary Vasculature

The "Critical Bottleneck"

Gewillig et al. have usefully described the pulmonary vascular bed as the "critical bottleneck" that is predominantly responsible for impeding ventricular filling and cardiac output, which in turn impairs aerobic exercise capacity (58). Transpulmonary flow

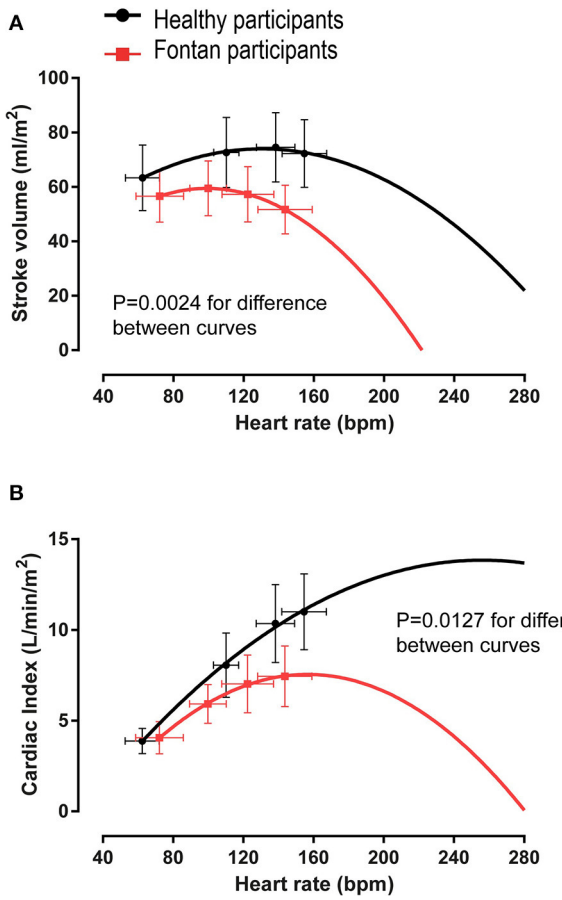

FIGURE 3 | Quadratic regression analysis of mean stroke volume and cardiac output vs. average heart rate values. In people with a Fontan circulation, an additional increase in heart rate beyond peak exercise values would result in **(A)** a disproportionate fall in stroke volume such that **(B)** cardiac output cannot increase further. Modified from (56).

restriction attributed to inadequate pulmonary artery growth and progressive pulmonary vascular disease likely ensues from the absence of pulsatile pulmonary flow; pulmonary artery growth essentially ceases after Fontan completion, potentially restricting venous return and impairing aerobic exercise capacity. Supporting this notion, pulmonary artery size is inversely correlated with New York Heart Association Functional Class and is positively associated with peak VO_2 (59). Maldistribution of pulmonary blood flow, which is common in Fontan physiology due to altered branch pulmonary artery anatomy and flow dynamics, is also associated with decreased aerobic exercise capacity (60).

The influence of the pulmonary vasculature on aerobic exercise capacity has been elegantly demonstrated in an invasive study performed by the Mayo Clinic (**Figure 4**) (61). Egbe et al. showed that people with abnormal exercise pulmonary vascular reserve (primarily reflecting pulmonary vascular dysfunction) have significantly worse aerobic exercise capacity (49% predicted peak VO_2) compared to those with a normal pulmonary vascular reserve (67% predicted peak VO_2). When interpreted with other hemodynamic data (decreased stroke volume index with increased pulmonary vascular resistance index), it is reasonable to speculate that the difference in peak VO_2 is attributed to lower pulmonary vascular resistance, resulting in enhanced ventricular filling in patients with normal pulmonary vascular reserve.

It is likely that opening the "critical bottleneck" (i.e., reducing pulmonary vascular resistance) would theoretically improve ventricular filling and aerobic exercise capacity, but therapies targeted at the pulmonary vasculature have yielded disappointing and inconsistent results; a 7% increase was the greatest improvement in peak VO_2 reported (62–64). Marginal improvements were also observed for submaximal exercise parameters (VO_2 at anaerobic threshold) with phosphodiesterase five inhibitors; the landmark FUEL (Fontan Udenafil Exercise Longitudinal) trial failed to show improvements in peak VO_2 (62). Disappointingly, the reported treatment effect (3-5%) with pulmonary vasodilator therapies for peak VO_2 is of questionable clinical benefit (65).

Despite statistically insignificant improvements in peak aerobic exercise capacity, drug therapies such as phosphodiesterase five inhibitors may still provide clinical benefits (66). Long-term use of pulmonary vasodilators may reduce systemic venous pressure and attenuate or prevent future complications or decline in aerobic exercise capacity.

The available data suggest that the pulmonary vascular characteristics are an important contributor to aerobic exercise capacity in the Fontan circulation. However, treatments that target pulmonary vasculature alone are insufficient to "normalize" aerobic exercise capacity—perhaps because the bottleneck is fixed and/or unlike pulmonary arterial hypertensive vasculopathy—or perhaps simply because trials are underpowered and more careful patient selection is required due to the vast heterogeneity of the cohort.

Extending Beyond the Heart and Pulmonary Vasculature

Lung Function

Typically, resting lung function demonstrates a mildly restrictive ventilatory pattern in people who have a Fontan circulation (67–69). The impairments in lung function parameters are associated with lesion complexity, multiple sternotomies or thoracotomies, physical activity restriction, respiratory muscle dysfunction, body mass index (BMI), and scoliosis (19, 67, 70). Reduced forced vital capacity, lung volumes, and diffusion capacity of the lung for carbon monoxide are common and associated with decreased peak VO_2 (67, 70–72). In addition to better aerobic exercise capacity, superior lung function is associated with increased handgrip strength that may reflect superior respiratory muscle strength (73).

Interestingly, despite the apparent resting lung function abnormalities, in general, patients rarely encroach upon their breathing reserve (74). However, in an extensive series of 260 young people with a Fontan circuit, 23% of those with impaired aerobic exercise capacity (<80% predicted peak VO_2) had limited breathing reserve, suggesting a mechanical ventilatory limitation to exercise (23). Assessing ventilatory limitation using

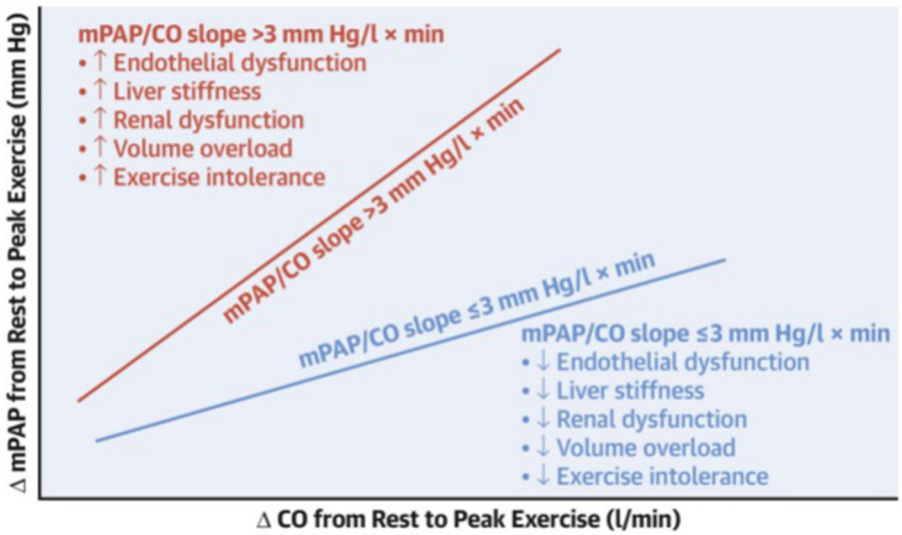

FIGURE 4 | Schematic showing the relationship between pulmonary vascular reserve (VR) and end-organ function. Pressure-flow relationship showing change in mean pulmonary artery pressure (mPAP) (Fontan pressure) per unit change in cardiac output (CO), or mPAP/CO slope, during exercise. Abnormal pulmonary VR defined as mPAP/CO slope > 3 (red) is associated with worse endothelial dysfunction and end-organ dysfunction (more liver stiffness, renal dysfunction, volume overload, and exercise intolerance) as compared to normal pulmonary VR defined as mPAP/CO slope ≤ 3 (blue). Reproduced from (61).

breathing reserve alone likely underappreciates the pulmonary contribution to exercise intolerance. The addition of tidal flow-volume loops during exercise testing may reveal further underlying ventilatory constraints. Indeed, studies that utilized inspiratory capacity maneuvers to assess dynamic operating lung volumes and expiratory flow limitations during exercise show further evidence of abnormal ventilatory responses (75). At submaximal work rates, people with Fontan physiology have lower inspiratory reserve volumes compared to controls, possibly resulting in higher elastic work of breathing. These ventilatory abnormalities during exercise may be attributed to the restrictive ventilatory impairment observed and likely contributes to the heightened dyspnea intensity reported at submaximal workloads (75).

The relationship between lung function and aerobic exercise capacity may also be explained by additional mechanisms. Reductions in forced vital capacity may be of particular importance, as it can impair the ability to compensate for ventilatory inefficiency during exercise (23). Furthermore, it has been postulated that smaller lungs have less blood volume and reduced capacitance, and in turn, diminished capacity to accommodate decreases in pulmonary vascular resistance, which has important implications for ventricular filling during exercise. While it is clear that lung function contributes to exercise intolerance in the single ventricle circulation, the extent and precise mechanisms remain poorly defined.

Systemic Vascular Resistance and Vascular Function

Vascular dysfunction (increased arterial stiffness and endothelial dysfunction) is associated with worse aerobic exercise capacity (76–78). This is likely related to impaired skeletal oxygenation and muscle blood flow rather than the contribution of endothelial dysfunction to increased systemic vascular resistance (elevated afterload) in the setting of limited preload reserve (41, 79). Elevated systemic vascular resistance is likely a secondary phenomenon required to maintain adequate blood pressure in the Fontan circulation at rest and during exercise (80).

Sex

Data from the Australian and New Zealand Fontan Registry has shown that the male sex is associated with an increased risk of premature death or transplantation (1, 81). Consistent with this observation in people with a Fontan circulation, male sex is a factor associated with lower aerobic exercise capacity (relative to age and sex) and progressive exercise intolerance (26, 49). The sex differences in aerobic exercise capacity may be related to reduced muscle mass compared to healthy controls, which is likely more pronounced in males (especially during puberty), and the inability of the single ventricle to support the increased metabolic demands of the greater absolute skeletal muscle mass in males.

Hypoxemia and Cyanosis

Cyanosis or hypoxemia is common in people with a Fontan circulation. It is unclear whether a patent fenestration is associated with improved aerobic exercise capacity as a result of increased ventricular filling or if the establishment of a right-to-left shunt and subsequent hypoxemia will impair it; data on the effects of fenestration closure are inconsistent (82–84). However, fenestration closure has been shown to improve ventilatory efficiency (83), which may decrease dyspnea perception during submaximal exercise.

Paradoxically, lower hemoglobin is associated with better aerobic exercise capacity (14). A similar relationship was reported with lean mass, which is inversely correlated with hemoglobin (85). This is probably because elevated hemoglobin reflects a compensatory erythrocytosis in the setting of low oxygen saturation. This contrasts with the findings of Kodama et al., who reported a positive correlation between peak VO_2 and hemoglobin (86). Regardless of the reported conflicting associations, the contribution of arterial desaturation to reduced aerobic exercise capacity is minimal, explaining <5% of the variance in peak VO_2 (40).

Skeletal Muscle Function

Handgrip strength, dynamic muscular strength, and muscular endurance have all been reported to be lower in people with a Fontan circulation than in healthy, age-matched controls and are associated with reduced skeletal muscle mass (85, 87–89). In a series with a heterogenous sample of CHD lesions (30% Fontan), when strength was indexed to lean mass, there was no difference in isometric strength compared with healthy controls (90). This may suggest that the reductions in muscle strength reported can largely be attributed to the reduction in lean mass that we and others have demonstrated (85, 89, 91). Beyond generalized muscle weakness (92), peripheral skeletal muscle blood flow and ergoreceptor function appear to be abnormal (89, 93), and this is likely accompanied by a shift in muscle fiber type (to type IIb), similar to the findings in acquired heart failure. Furthermore, impaired skeletal muscle oxidative capacity has been shown using MRS P^{31} spectroscopy, and delayed muscle oxygen uptake kinetics denote potential muscle metabolic abnormalities (21, 94). The combination of these skeletal muscle abnormalities likely result in the early onset of metabolic acidosis, premature fatigue during exercise, and consequently impaired aerobic exercise capacity.

Body Composition

Skeletal Muscle Mass

Even in relatively young people with a Fontan circulation, there is a high prevalence of skeletal muscle deficit compared to age-sex matched controls (21, 91). Although myopenia (low muscle mass) is prevalent across many CHD lesions, it is likely those with a Fontan circulation experience a greater degree of lean mass deficits. The causes of lean muscle deficits are poorly defined, but in the Fontan circulation, relative deconditioning, chronically elevated central venous pressure, physical inactivity, neurohormonal activation, and altered blood flow are likely contributing factors. To highlight this pathophysiological difference to sarcopenia (age-related muscle deficits) and low lean mass in other CHD lesions, Tran et al. described the term Fontan-associated myopenia (appendicular lean mass index Z-score < -2) (85). Low lean mass in the setting of Fontan physiology is particularly concerning, given the strong correlation between skeletal muscle mass and exercise stroke volume and/or aerobic exercise capacity (21, 89, 95, 96). This can be attributed, inter alia, to improved cardiac preload—greater skeletal muscle mass decreases venous compliance and squeezes a greater volume of blood back toward the pulmonary vasculature and heart (97). Leg muscle contractions may also generate a pulsatile flow profile in the pulmonary vascular bed (98).

Obesity and Adiposity

A higher BMI is associated with lower aerobic exercise capacity in people with a Fontan circulation. High levels of adiposity—particularly in the thoracic region—may impair the function of the respiratory bellows. The Pediatric Heart Network Fontan III study showed that patients in the lowest tertile, based on percent predicted peak VO_2, were more likely to be overweight or obese (26). However, defining "healthy" weight status using BMI in this cohort is problematic because the high prevalence of lean mass deficiency conceals the presence of increased fat mass when BMI is used as a surrogate of adiposity (85). Although the adverse effects of obesity will likely impair aerobic exercise capacity (14), further research using reference measures of lean and fat mass should be conducted to better characterize the implications of obesity on Fontan physiology.

Respiratory Muscle Dysfunction

Extending beyond the effects that respiratory muscle weakness may have on dynamic lung function, it also contributes to an increase in motor command output, resulting in a greater sensation of breathlessness during exercise (99). Furthermore, in the setting of limited cardiac reserve, the redirection of blood flow from the exercising skeletal muscles to the respiratory muscles ("metaboreflex") promotes premature fatigue and profound impairment in aerobic exercise capacity. These mechanisms may, in part, explain the association between respiratory muscle function and aerobic exercise capacity in Fontan patients (92).

At rest, Fontan physiology is heavily dependent on respiration to promote ventricular filling. Theoretically, it would be expected that improving inspiratory muscle strength would augment the respiratory muscle pump and ventricular filling. While inspiratory muscle training has been shown to improve ventilatory efficiency and resting cardiac output, most studies have not resulted in statistically significant increases in peak VO_2 (100–102). This may be because the skeletal muscle pump accounts for the majority of the increase in cardiac output, with only minor contributions attributed to the respiratory pump during exercise (103). Respiratory muscle training may be beneficial in patients who specifically have clinical respiratory muscle weakness. This notion was supported by a recent randomized controlled trial, where baseline measures of maximal inspiratory pressure indicated inspiratory muscle weakness in the cohort; peak VO_2 increased after 4 months of inspiratory muscle training (104).

Benefits of Exercise Training and Safety

Paradoxically, the most effective non-invasive therapy to manage exercise intolerance is exercise training (97, 105, 106). A recent review of respiratory muscle and exercise training studies in over 200 people with a Fontan circulation showed that the majority of studies resulted in improvements in peak VO_2 (107), and increases of up to 23% (treatment effect 30%) have been shown with combined aerobic exercise and light resistance

training (104). Other benefits included improvements in skeletal muscle mass, cardiac output, peripheral muscle oxygenation, and ergoreceptor function (97, 105, 106, 108–110). Importantly, some studies also show improvements in health-related quality of life (111–115).

Furthermore, long-term participation in sports, physical activity, or exercise may have direct benefits on Fontan physiology. Increasing skeletal muscle mass through resistance exercise training can enhance the function of the peripheral muscle pump and augment venous return (108). The periodic increase in volume load during exercise "stretches" the preload deprived ventricle and may attenuate the phenomenon of progressive "disuse hypofunction" (58, 116). Regular physical activity like exercise training transiently but repetitively increases pulsatile flow and recruit pulmonary vessels, which may have important implications for pulmonary vascular growth and function (97, 116). Indeed, those who participate in regular physical activity (particularly during childhood) appear to have better Fontan physiology and are more likely to exhibit a high physical performance ("Super-Fontan") phenotype (54, 117, 118). Collectively, these mechanisms may explain the association between higher peak VO_2 and better end-organ function, clinical outcomes, and prognosis (10, 13, 14). However, further research is required to confirm this hypothesis.

Safety of Physical Activity and Exercise Training

Reviews of exercise training studies in people with a Fontan circulation have not reported any serious adverse events associated with exercise training (107, 110). Undeniably, during exercise, systemic venous pressure can increase dramatically in the Fontan circulation (119). While there are some concerns related to the deleterious effects of the transient elevation of central venous pressure during exercise on end-organ function, the current evidence suggests these are unwarranted. Higher aerobic exercise capacity is associated with healthier end-organ function biomarkers, potentially reflecting decreased venous pressure, better hemodynamics, and reduced hepatic congestion (14, 54). This is further supported by a series that showed lower venous pressure and better markers of end-organ function in adult patients who increased their aerobic exercise capacity during childhood (reflecting increased physical activity levels or exercise training) (118). Together, these data should alleviate the concerns regarding safety and end-organ damage associated with chronic moderate-to-vigorous intensity exercise training, but more prospective data are needed.

ADDRESSING THE UNANSWERED QUESTIONS: RATIONALE FOR THE FONTAN FITNESS INTERVENTION TRIAL—THERAPIES AND FUTURE DIRECTION

The mechanisms underlying impaired aerobic exercise capacity in the setting of Fontan physiology differ significantly from other chronic cardiac conditions. Traditional pharmacotherapies used to manage exercise intolerance in the biventricular circulation are of limited utility in the Fontan circulation. Currently, exercise training has been shown to be the most effective, non-invasive therapy for improving aerobic exercise capacity in people who have a Fontan circulation (**Figure 5**) (105, 106, 109).

While this review identifies common factors that contribute to exercise intolerance (**Figure 6**), understanding factors associated with superior aerobic exercise capacity is also important to more deeply characterize the pathophysiology. Recent series have studied cohorts of people with Fontan physiology with normal or superior aerobic exercise capacity (14, 54, 121). We previously described a subset of young people who can achieve normal or even supranormal exercise performance ("Super-Fontan") (121). Importantly, in this series, a proportion had unfavorable Fontan features (e.g., dominant right ventricle, pacemakers, and atriopulmonary connections), suggesting extracardiac factors play a significant role in aerobic exercise capacity.

A common characteristic of a person with a Fontan circulation who has "normal" aerobic exercise capacity is regular participation in moderate-to-vigorous intensity physical activity from a young age (54, 121, 122). Some possible mechanisms for this observation may include superior development of the pulmonary vasculature (e.g., increased pulmonary artery size), increased lower limb lean mass, higher lung volumes due to stronger respiratory muscles, and adaptive remodeling of the single ventricle due to better preload (97, 98, 106). Exercise training can systemically target components that are both distal (downstream) and proximal (upstream) to the critical "bottleneck" as well as the pulmonary vasculature itself. This makes exercise training an attractive therapy and may explain the efficacy observed compared to drug therapies that may only target a single component of Fontan physiology.

However, despite the aforementioned benefits associated with exercise training and physical activity, traditionally, most people with CHD have not received formal advice (beyond restrictions) on physical activity, sports, and exercise training during their clinical consultations (123). This may be related to the paucity of quality evidence available on safety and efficacy; most studies are based on small heterogenous samples and were without a control group. While current exercise training recommendations are available to guide clinical practice (106, 109, 124, 125), these are predominantly based on clinical experience and expert opinion. Indeed, the most recent 2018 AHA/ACC and 2020 ESC guidelines suggest that there is only moderate (level B) evidence to support recommending cardiac rehabilitation or exercise training in people with CHD (4, 126). Therefore, adequately powered, multi-center, randomized, controlled trials such as the F-FIT are required to provide high-quality (level A) evidence to conclusively support recommending exercise training in clinical practice.

Furthermore, the "traditional" model of exercise training for people living with chronic diseases requires face-to-face supervision by exercise professionals (at least initially) that are often only available at expert centers. Whilst it is likely that performing exercise training in a supervised fitness facility setting is "optimal", this method of exercise training delivery requires high resource utilization and may not be economically feasible or practical for many people living with a Fontan circulation. In addition, traditional exercise training programs offered to people with CHD are usually designed for older adults with

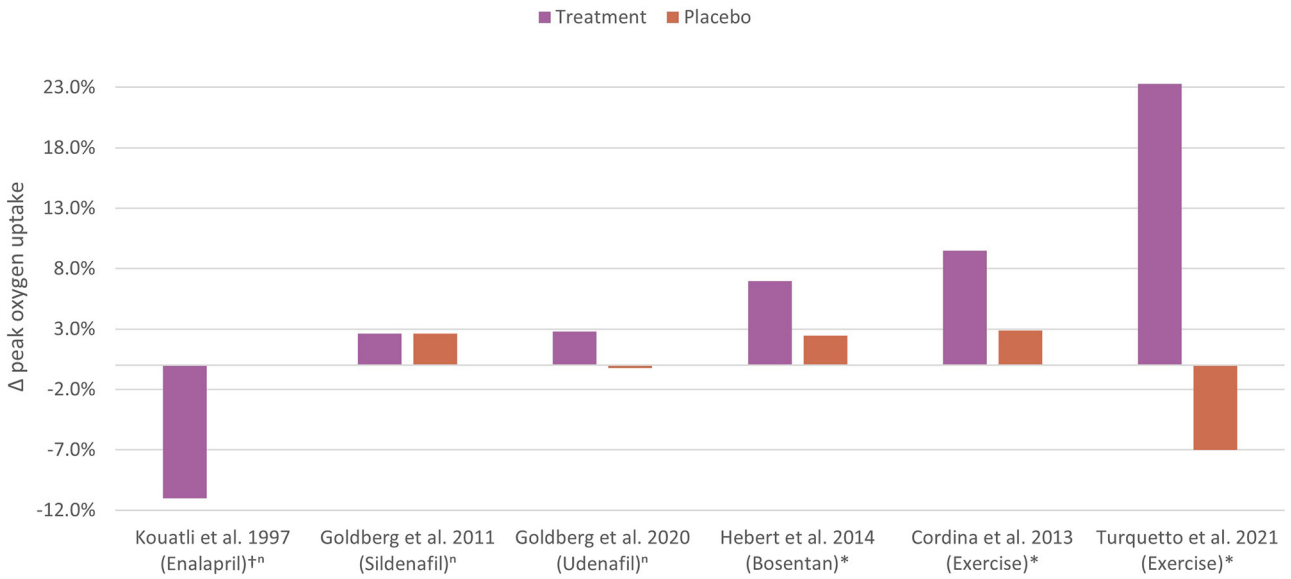

FIGURE 5 | Controlled trials of non-invasive therapy to improve aerobic exercise capacity in the Fontan circulation. The percentage change in peak oxygen uptake following non-invasive therapies or placebo in Fontan cohorts are shown. The most effective non-invasive therapy is exercise training. n, non-significant; *, statistically significant; †, percentage difference between groups. Kouatli et al. (120); Goldberg et al. (63); Goldberg et al. (62); Hebert et al. (64); Cordina et al. [high intensity resistance training] (108); Turquetto et al. [combined aerobic exercise and light resistance training] (104).

chronic conditions (e.g., cardiac rehabilitation), which may not be suitable for the relatively young adult CHD population. Indeed, previous studies have identified this as a potential barrier to participation (127, 128), and over half of those surveyed with CHD expressed interest in a technology-directed, home-based, exercise program (129).

The F-FIT will be one of the first phase III multi-center, randomized, controlled trials to provide high-quality evidence to "optimize" exercise training in people living with a Fontan circulation. The F-FIT will also investigate if a telehealth exercise training model (that requires less resources) can produce equivalent (non-inferior) results to a traditional supervised gym-facility-based approach.

The primary objectives of the F-FIT are to:

a) Establish the efficacy of a 4-month traditional supervised gym-based aerobic and resistance exercise training program of moderate-to-vigorous intensity on peak VO_2 compared to usual care in adolescents and adults.
b) Establish the efficacy of a 4-month physical activity program of moderate-to-vigorous intensity on peak VO_2 compared to usual care in children.
c) Evaluate if a 4-month telehealth exercise training program of moderate-to-vigorous intensity can produce comparable (non-inferior) improvements in peak VO_2 compared to the traditional exercise training group in adolescents and adults.

Secondary objectives include:

a) Determining if participants in the exercise intervention groups can maintain changes in peak VO_2 with remote support over an 8-month period.
b) To evaluate the health economics (cost-effectiveness) of exercise training interventions based on health-related quality of life, health care utilization, and patient costs.
c) To characterize the mechanisms that underlie changes in peak VO_2.
d) To characterize the physiological and neurocognitive changes associated with exercise training, including changes in cardiopulmonary testing measures, peripheral venous pressure, body composition (skeletal muscle mass, fat mass, and bone mineral density), endothelial function, neurohormonal activation, skeletal muscle oxygenation, respiratory muscle and lung function, neurocognitive and neuropsychological function, metabolites, nutritional and dietary status, liver stiffness, and cardiac function.

STUDY DESIGN AND METHODS

Study Population

Participants will be recruited from the Australian and New Zealand Fontan Registry (130), National CHD Database, and eight quaternary CHD centers, including Royal Prince Alfred Hospital, Sydney, Australia; The Children's Hospital at Westmead, Sydney, Australia; Royal Melbourne Hospital, Melbourne Australia; Royal Children's Hospital, Melbourne Australia; Perth Children's Hospital, Perth, Australia; Fiona Stanley Hospital, Perth, Australia; The Prince Charles Hospital, Brisbane, Australia; and Queensland Children's Hospital, Brisbane, Australia. Advertisements will also be disseminated *via* social media, websites, and flyers to facilitate recruitment.

The F-FIT will include people with a Fontan circulation aged 10-55 years. Participants will also need to be ≥6 months

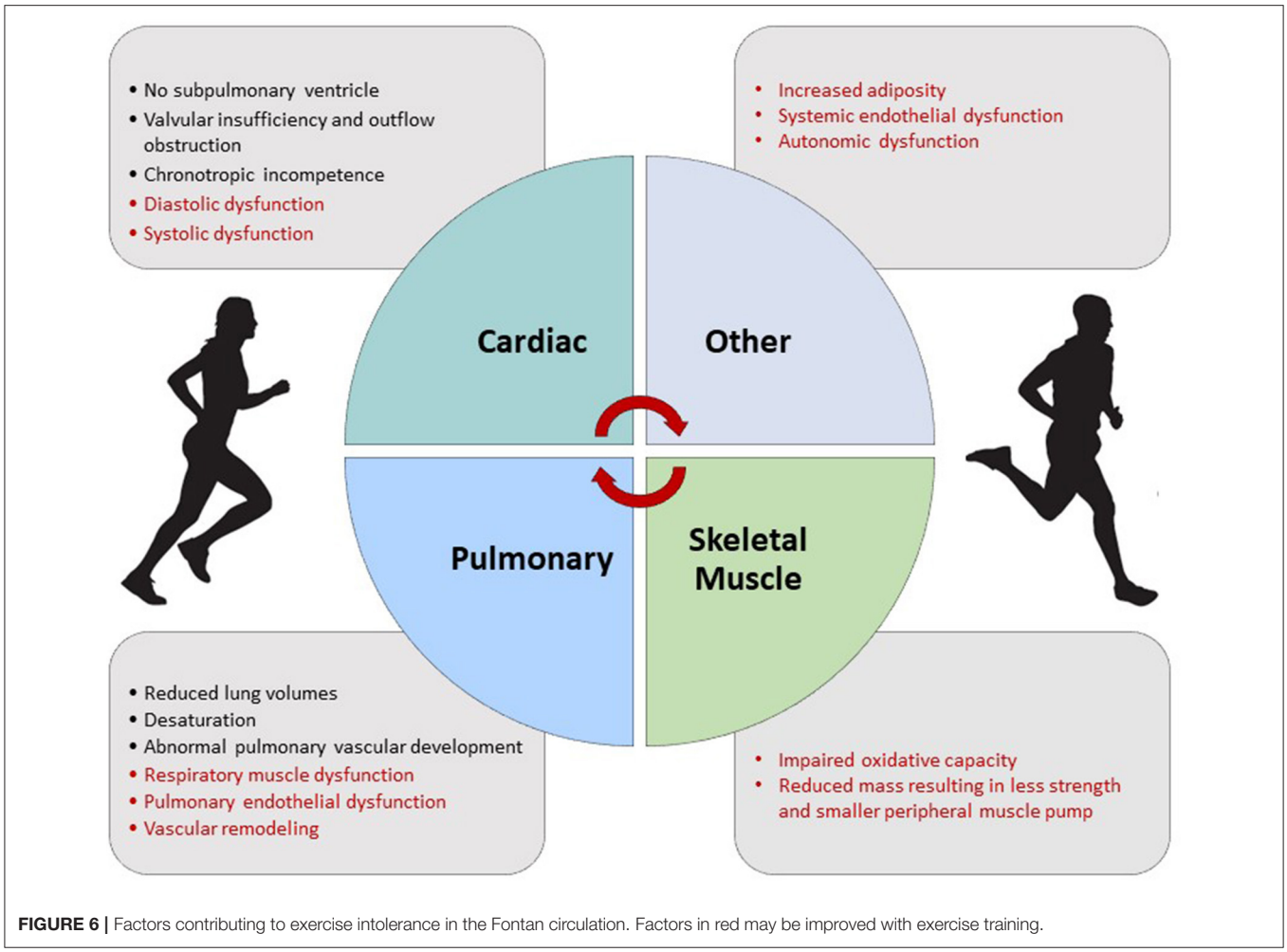

FIGURE 6 | Factors contributing to exercise intolerance in the Fontan circulation. Factors in red may be improved with exercise training.

TABLE 1 | Study inclusion and exclusion criteria.

Inclusion criteria
• People with a Fontan circulation aged 10-55 years
• Medically stable and on stable medical therapy for ≥3 months
• ≥6 months post-Fontan completion
Exclusion criteria
• Planned intervention within 2 years
• Mental or physical disability that prevents participation in exercise training
• Current or actively planned pregnancy
• Uncontrolled systemic hypertension at rest or during exercise
• Clinically unstable or recent significant change in therapy (within 3 months)
• Physiological stage D in accordance with ACC/AHA guidelines
• COVID-19 unvaccinated individuals despite being eligible according to ATAGI recommendations
• Unreliable internet connection
• Current participation in structured sports or exercise training for more than 30 min, three times a week

post-Fontan completion, clinically stable, and on stable medical therapy for ≥3 months to be eligible. The inclusion and exclusion criteria are provided in **Table 1**. A two-step exclusion process will take place:

1) Based on the patient's most recent medical records, phone screening, and approval from their treating cardiologist.
2) Following baseline testing.

Participants will be excluded prior to randomization during the two-step eligibility evaluation if any of the following are identified: categorized as physiological stage D, have a planned surgical intervention within 2 years, current pregnancy or actively planned pregnancy (within 1 year), mental or physical disability that restricts participation in exercise training, uncontrolled arrhythmias or (systemic) hypertension at rest or during exercise, a recent significant change in medical therapy (<3 months), and people who currently participate in structured sports or exercise training for more than 30 min, three times per week. People who are COVID-19 unvaccinated and are eligible for vaccination according to the Australian Technical Advisory Group on Immunization (ATAGI) recommendations will also be excluded.

Randomization and Stratification

The F-FIT will involve three arms in adolescents and adults (≥16 years), and two arms in children (<16 years). Adolescents and adults will be randomized in an allocation of 2:2:1 to

either a traditional gym-based exercise program (traditional group), a telehealth exercise training program (telehealth group), or usual care (control group), respectively. Children will be randomized to either an exercise training program or usual care (control group) based on a 1:1 allocation. Randomization will be stratified by: baseline aerobic exercise capacity (<65% or ≥65% predicted peak VO_2); sex (male or female); and age (16-34 years or 35-55 years for adolescents and adults; 10-12 years or 13-15 years for children). Computer-generated, random permuted blocks will be prepared by an independent statistician in the Clinical Epidemiology and Biostatistics Unit (CEBU) at Murdoch Children's Research Institute (MCRI) and incorporated into the REDCap randomization tool (hosted by MCRI) that will be embedded in the REDCap database created for this trial. The randomization schedules will be prepared for each recruitment site.

Study Investigations

The F-FIT will conduct a range of assessments at baseline, 4-months, and 12-months. The study design is outlined in **Figure 7**, and the assessments are summarized in **Table 2**. In brief, all participants will undergo a detailed evaluation of aerobic exercise capacity, respiratory muscle and lung function, body composition, musculoskeletal fitness, endothelial function, quality of life, neurocognitive and neuropsychological function, neurohormonal activation, liver stiffness, dietary intake and nutritional status, metabolites, habitual physical activity levels, and cardiac function. Follow-up visits will be conducted within 15 days of the scheduled reassessment date. If a testing date cannot be scheduled within 15 days, participants in the intervention groups may continue exercise training in accordance with the protocol to prevent detraining for up to 31 days.

Statistical Considerations

Power Analysis

Sample size calculations have accounted for a 10% dropout over 4-months.

Adolescents and Adults

This study will involve testing two hypotheses: the first involves demonstrating the superiority of the traditional exercise training group compared to the usual care group with regards to improvements in peak VO_2. The second involves demonstrating that telehealth exercise training is non-inferior to traditional exercise training. Using this rationale, we based the sample size calculation for a three-arm trial with a randomization allocation of 2:2:1 using the R package Three *Armed Trials* (version 1.0-3).

We will require 110 adolescent and adult Fontan participants (44 each in the traditional and telehealth training groups and 22 in the usual care group) to achieve at least 80% power (two-sided α of 5%) to detect a difference of 10% in peak VO_2 (standard deviation of 5%) between the traditional exercise training group compared to the control group. If there is a statistically significant difference between the traditional and control group (i.e., p-value < 0.05), then the test of non-inferiority will have 80% power (one-sided α of 2.5%) of showing that telehealth training retains at least 85% of the effect seen in traditional testing compared to control.

Children

A total of 70 children with a Fontan circulation (35 in the training group and 35 in the usual care group) is required to achieve >99% power (two-sided α of 5%) to detect a difference in peak VO_2 of $10 \pm 5\%$ at 4-months.

Statistical Analysis

The primary analysis will be based on intention-to-treat (ITT), including all randomized participants regardless of exposure to the allocated treatment or adherence to the trial protocol. Comparison of the primary outcome measure (change in peak VO_2 at 4-months) between the groups will be estimated using linear regression adjusted for the stratification factors used during randomization. Results will be presented as the difference of means with a corresponding 95% confidence interval (CI) and p-value. Secondary outcomes at 4-months and 12-months will be compared between the groups using linear regression with adjustment for the stratification factors for continuous outcomes and binary regression adjusted for the stratification factors used during randomization for binary outcomes where results will be presented as a risk difference and corresponding 95% CI.

For each participant cohort, if the proportion of missing data for the primary outcome is more than 5%, analysis based on multiple imputation may be performed. A sensitivity analysis to compare the results of analyses restricted to participants with complete data and analyses where those with missing data are included using multiple imputation will be performed. If used, multiple imputation models will be conducted for the outcome variable, and 50 completed data sets will be imputed by chained equations, including all the participants initially randomized. The primary outcome, randomization strata variables and variables predictive of (i) missingness and/or (ii) the change in peak VO_2 will be included in the imputation model.

Exercise Training and Physical Activity Interventions

Exercise Training Interventions for Adolescents and Adults

Traditional Fitness Facility-Based Exercise Training

Patients randomized to the traditional model of exercise training delivery will participate in moderate-to-vigorous intensity aerobic and resistance exercise training three times a week for 4-months. All sessions will be supervised by a qualified exercise professional (e.g., exercise physiologists or and physiotherapists) in small groups of 1-4 people. The sessions will be supervised in a local fitness facility near the participant's residence, where they will be provided with a complimentary membership for the duration of the study. Participants will start and conclude each session with a 5 min warm-up and cool down, which may include low-intensity exercise and dynamic or static stretching. The structure of the sessions will involve 10 min of aerobic exercise, 30 min of resistance exercises, followed by another 10 min of aerobic exercise.

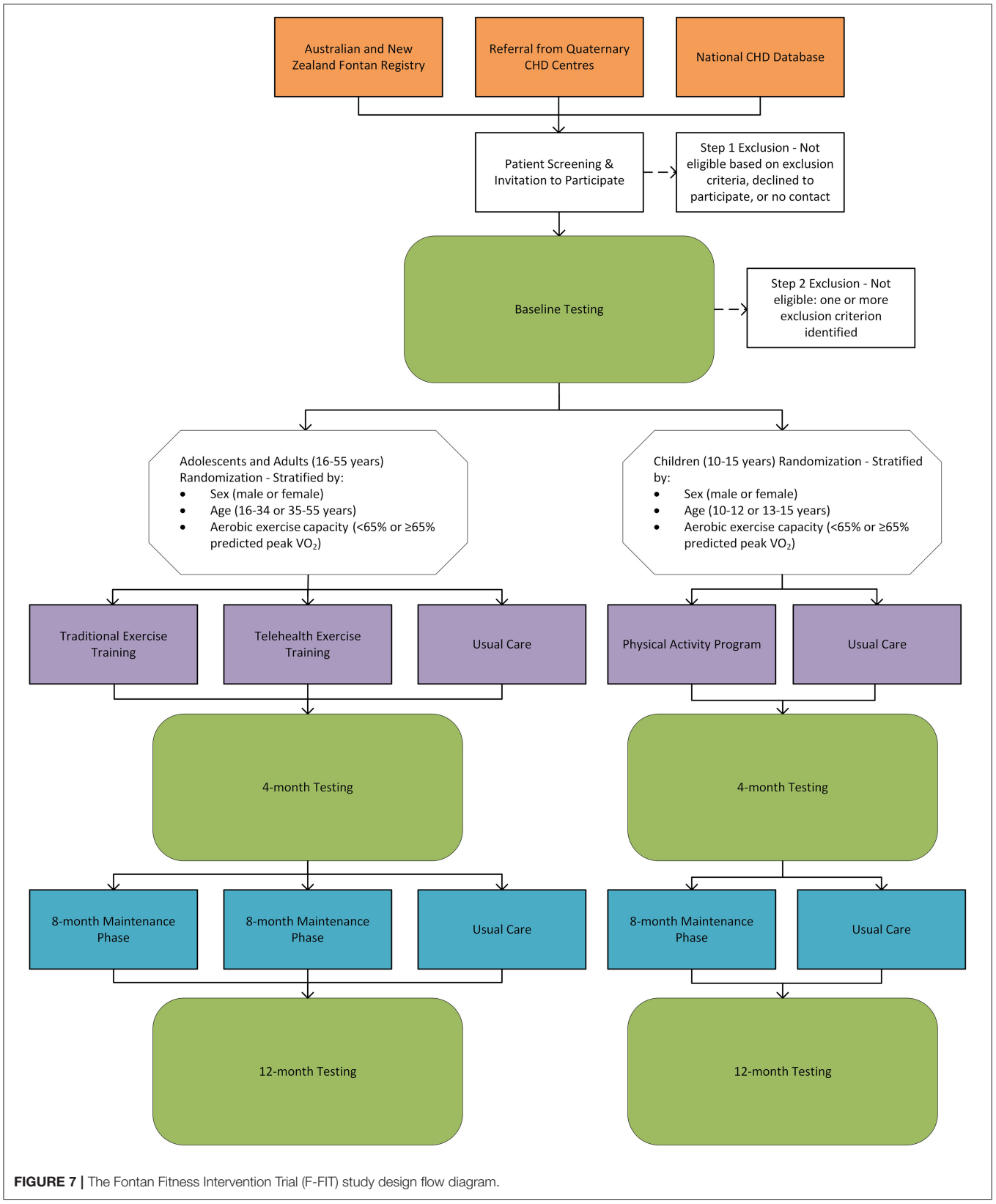

FIGURE 7 | The Fontan Fitness Intervention Trial (F-FIT) study design flow diagram.

TABLE 2 | Assessments and testing.

	Outcomes measures	
Cardiopulmonary exercise testing	Aerobic exercise capacity (peak VO_2)‡, V_E/VCO_2 ratio and slope, RER, HR, OUES, VO_2 at AT, work rate, oxygen pulse, VO_2/work rate slope, and peripheral venous pressure	
Respiratory muscle and lung function tests	FEV_1, FVC, FEV_1/FVC ratio, TLC, DL_{CO}, PImax, and PEmax	
Dual-energy x-ray absorptiometry	Lean mass, fat mass, bone mineral content, and bone mineral density†	
Liver elastography	Liver stiffness	
Near-infrared spectroscopy†	HHb, HbO_2, and skeletal muscle oxidative capacity	
Neurocognitive function assessment (Cogstate)	Psychomotor function, attention, visual learning and memory, verbal learning and memory, processing speed, social-emotional cognition, working memory, and executive function scores	
Habitual physical activity (accelerometers; Actigraph GT9X Link)	Counts per minute, steps per day; and time spent in sedentary, light, moderate, vigorous, and moderate-to-vigorous activity	
Nutrition and dietary assessments (ASA24, SGA† or SGNA†, GSRS†, and indirect calorimetry†)	SGA (in adults)/SGNA (in children) classification of nutritional status; GSRS (reflux, abdominal pain, indigestion, diarrhea, constipation scores, and total score); dietary macronutrient and micronutrient intake and composition, and REE	
Flow-mediated dilation (FMD)†	FMD% (Δ diameter), baseline diameter, peak diameter, and time to peak	
Laboratory and biochemical investigations	NT-proBNP and metabolomic analysis	
Transthoracic echocardiography	AVV S/D ratio, valvular function, VTI, annulus size, aortic flow, and ventricular function	
Resting and exercise cardiac MRI†	Ventricular volumes (end-diastolic, end-systolic, stroke volume), ejection fraction, flows (aortic, vena caval), diastolic function (feature tracking, T1 mapping E'), pulmonary artery size (Nakata index), lung water density, hepatic T1 mapping, and AV valve function	
Anthropometry and BIA	Height, weight, waist circumference, BMR, total body water, %BF, and skeletal muscle index	
Quality of life (PedsQL core and cardiac modules)	Physical functioning, emotional functioning, social functioning, school/work functioning, psychosocial functioning, heart problems and treatment, perceived physical appearance, treatment anxiety, cognitive problems, communication and total scores	
	Adolescents and adults	**Children**
Musculoskeletal fitness testing	Chest press 1RM, leg press 1RM, number of leg press repetitions at 70% 1RM (muscular endurance), and handgrip strength	Number of sit-ups, number of push-ups, standing long jump distance, and handgrip strength
Health economic analysis (EQ-5D-5L, CHU-9D, patient cost, and health care expenditure data linkage)	Health state in EQ-5D dimensions, patient cost, and health care utilization	CHU-9D scores, patient cost, and health care utilization

‡*Primary outcome,* †*Conducted in a subset of participants at selected sites. 1RM, one-repetition maximum; AT, anaerobic threshold; AV, atrioventricular; ASA24, automated self-administered dietary assessment tool; AVV S/D, atrioventricular systolic to diastolic duration; BIA, bioelectrical impedance analysis; BMR, basal metabolic rate; BF, body fat;* DL_{CO}*, diffusing capacity of the lung for carbon monoxide;* FEV_1*, forced expiratory volume in one second; FMD, flow-mediated dilation; FVC, forced vital capacity; GSRC, gastrointestinal symptom rating scale;* HbO_2*, oxyhemoglobin; HHb, deoxyhemoglobin; HR, heart rate; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro b-type natriuretic peptide; OUES, oxygen uptake efficiency slope; PEmax, maximum static expiratory pressure; PImax, maximum static inspiratory pressure; REE, resting energy expenditure; RER, respiratory exchange ratio; SGA, subjective global assessment; SGNA, subjective global nutritional assessment; TLC, total lung capacity; VTI, velocity time integral; VE/VCO2, ventilatory equivalent for CO2;* VO_2*, oxygen uptake.*

The first 10-min bout of aerobic exercise will be performed on a cycle ergometer, and the second 10-min bout is selected based on the participant's preference to allow for autonomy. Aerobic exercise training will start at a moderate intensity (40-50% HRR) and progress up to vigorous intensity (70-80% HRR) after 10 weeks, as tolerated. The aerobic exercise training work rate will be continually adjusted throughout the program to maintain the target training HR range.

Resistance training will comprise of 5 exercises, including the leg press, seated row, leg curl, chest press, and calf raise. The participant's one-repetition maximum (1RM) will be assessed for each exercise during the first session and every 4 weeks to titrate the load to the appropriate training intensity. Resistance exercise intensity will start at 3 sets of 8-12 repetitions at 60% 1RM and be progressed to 70% 1RM after 2 weeks. Participants will be provided with ∼60 s rest between sets. Consistent with clinical practice, intensity can be up titrated based on the participant's rating of perceived exertion (RPE) and observer RPE for aerobic exercise training using the OMNI scale. For resistance exercises, the two for two method, and the participant's or observer's RPE using the OMNI scale can be used to facilitate progression in between 1RM tests, which can be guided by the supervising exercise professional. An outline of the method of progression is shown in **Table 3**. The total estimated duration of each session is 60-75 min.

Telehealth Exercise Training

People in the telehealth group will participate in partially supervised moderate-to-vigorous intensity aerobic and resistance exercise training 3 times a week for 4-months. Prior to each

TABLE 3 | Exercise training progression for the traditional group.

Weeks (sessions)	Intensity category	Intensity
Aerobic exercise training progression		
1-2 (6)	Moderate	40-50% HRR
3-6 (12)	Moderate	50-60% HRR
7-10 (12)	Vigorous	60-70% HRR
11-16 (18)	Vigorous	70-80% HRR
Resistance exercise training progression		
1-2 (6)	Moderate (moderate load)	60% 1RM (3 sets, 8-12 repetitions)
3-16 (42)	Vigorous (moderate-to-high load)	70% 1RM (3 sets, 8-12 repetitions)

HRR, Heart rate reserve; 1RM, one-repetition maximum.

session, a 5-min warm-up and cool-down will be performed and may include low-intensity exercise and dynamic or static stretching. Participants will be provided with a Gymstick™ and HR monitor for exercise training. Participants will be asked to perform 20 min of aerobic exercise training independently three times a week, starting at 40-50% HRR and progressing to 70-80% HRR. The aerobic exercise training progression will be consistent with the traditional group shown in **Table 3**. Exercise training HR will be transmitted to a mobile app, and participants will be asked to record the average and maximal HR as well as their RPE and session duration of each aerobic session in a training log.

Resistance exercise sessions will be supervised by qualified exercise professionals and delivered via Zoom in groups. Participants will perform 3 sets of 8-12 repetitions of various resistance exercises using a Gymstick™ with a target RPE of 7 using the OMNI scale by week 3 for each exercise. Resistance exercises may include squats, upright rows, lunges, seated rows, chest press, and calf raises. When the participant rates an exercise lower than 7 on the OMNI scale in consecutive sets or sessions, the resistance (load) of the Gymstick™ will be increased or participants will be asked to increase their repetitions to the upper limit of the prescribed range. Similar to the traditional group, the intensity can be adjusted based on the two-for-two method and observer RPE. Participants will also be asked to record exercise session details in a training log. The total estimated time to complete both the aerobic and resistance exercise session is ∼60-75 min.

Children's Physical Activity Program

Children allocated to the intervention group will participate in a face-to-face physical activity program once a week for 4-months. The SAAFE principles will be utilized to guide the delivery of the program in an engaging and enjoyable manner (131). Weekly sessions will be supervised by an exercise professional and conducted at a community sport center or fitness facility near the participant's residence in small groups of 3-10 participants/family members when possible. The duration of each session will be ∼90 min and consist of an exercise training circuit, foundational movement skills practice, and physically active games. Prior to each session, participants will engage in a 5-10 min warm-up that includes a variety of games, aerobic exercises, and dynamic stretching.

Participants will be provided with HR monitors that will transmit their HR in real-time to an app on an electronic device (e.g., iPad, tablet, or laptop) to monitor exercise intensity during the exercise circuit. The exercise circuit will be conducted in an interval format and encompasses a combination of aerobic and resistance exercises. Exercises may include but are not limited to squats, hopping, broad jumps, push-ups, backward running, and walking lunges. The target session average HR will initially be at moderate intensity (≥40% HRR) and progress to vigorous intensity (≥70% HRR) after 10 weeks, consistent with the adolescent and adult aerobic exercise programs (**Table 3**). The exercise circuit will last ∼30 min.

Following the exercise circuit, participants will practice a variety of foundational movement skills (e.g., kicking, catching, throwing, and hitting) for 5-10 min, which is facilitated by the exercise professional, family members, and caregivers. After the practice period, participants will engage in physically active games for ∼20 min. Each session will conclude with a 5–10 min cool-down that may consist of low-intensity aerobic activities and stretching.

In addition to the weekly face-to-face physical activity sessions, participants will also be provided with a variety of tasks to complete in their own time. These tasks will be directed at promoting a healthy lifestyle or complement the physical activity sessions.

Exercise Training Considerations

The target aerobic exercise training HR range (intensity) will be prescribed using the percentage of HRR method, which more accurately reflects metabolic load compared to prescribing aerobic exercise intensity based on the percentage of peak HR (**Figure 8**). The resting and peak HRs obtained at baseline cardiopulmonary exercise testing will be used for determining the prescribed target HR ranges:

$$\textit{Exercise Training HR}\ (\textit{HRR method}) = \%\ \textit{target intensity} \times \left(\textit{peak HR} - \textit{resting HR}\right) + \textit{resting HR}$$

In participants who are prescribed β-adrenergic blocker agents or other HR limiting drugs, exercise testing and training should occur between 3 and 10 h after the dose was taken (132). If participants are unable to exercise at the prescribed HR range (e.g., chronotropic incompetence) or unable to tolerate aerobic exercise training in the prescribed HR range, aerobic exercise training intensity will be guided by both the observer and participant reported RPE, and the talk test. Furthermore, participants will exercise at least 10-15 beats below the ischemic or discharge threshold in people with stable ischemia or for those who have an implantable cardioverter-defibrillator.

If participants are unable to complete the resistance exercise set with continuous repetitions, an intra-set rest ("cluster" set) may be provided. This method produces comparable results to completing the set using traditional set structures (i.e.,

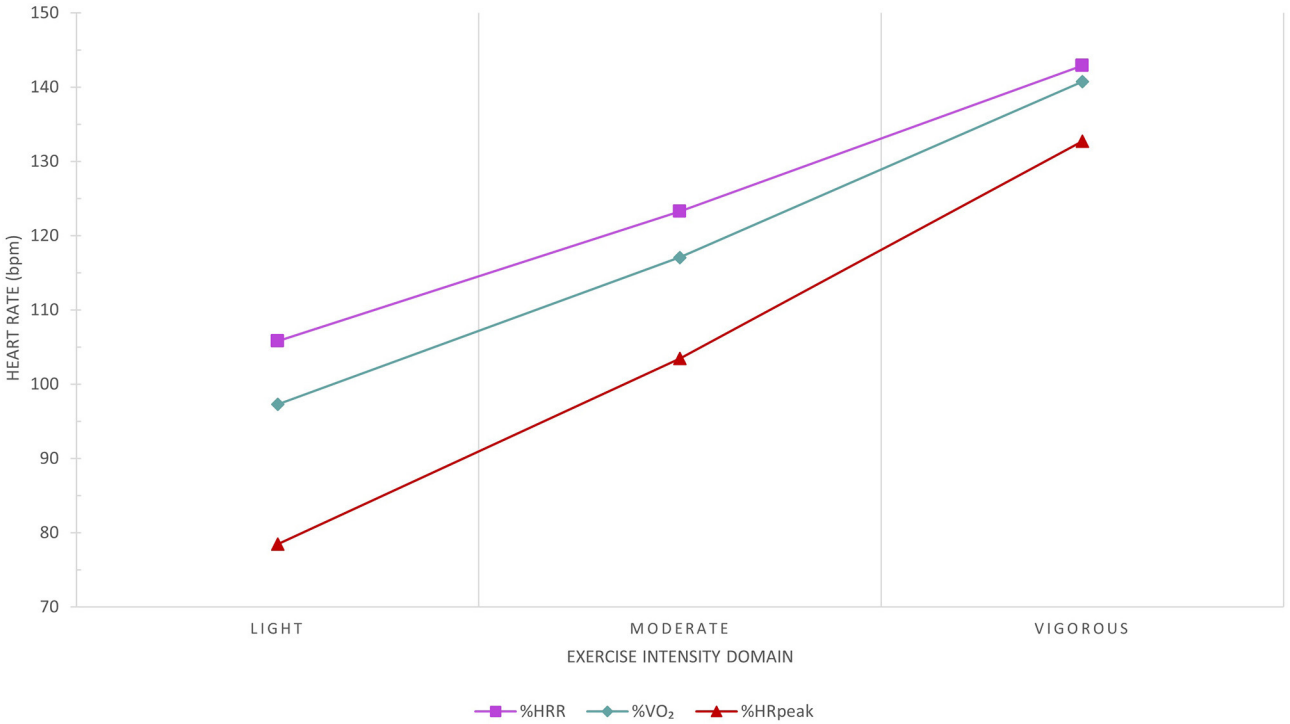

FIGURE 8 | Comparison between the percentage of peak heart rate (HR; [%HRpeak]) and percentage of HR reserve (%HRR) methods to the average reference HR recorded at the corresponding percentage of peak VO_2 (%VO_2) exercise intensity domain. The %HRpeak method significantly underestimates the reference exercise HR. The %HRR method results in clinically insignificant differences to the corresponding reference HR recorded in all exercise intensity domains based on %VO_2 and reflects metabolic load more accurately than the %HRpeak method. Data from 287 congenital heart disease patients at Royal Prince Alfred Hospital.

completing the prescribed repetition range in a set without rest) in healthy and clinical cohorts (133, 134).

In the setting where a participant is unable to complete a prescribed exercise, a suitable alternative that targets the same muscle group will be prescribed.

Usual Care

Participants randomized into the usual care (control) group will continue with routine clinical care as directed by their treating medical team. They will also be instructed to continue with their usual daily activities and will not be restricted or asked to refrain from engaging in physical activity or exercise training. Participants allocated to the usual care group will be offered 4-months of telehealth exercise training (in adolescents and adults) or the physical activity intervention (in children) after their final 12-month testing session.

Maintenance Phase

After 4-months of traditional exercise training, telehealth exercise training, or the physical activity program, participants in the exercise intervention groups will be encouraged to continue to engage in physical activity or exercise training at least two times a week. Adolescent and adult Fontan participants in the exercise intervention groups will be provided complimentary access to a local fitness facility to facilitate ongoing adherence. Children Fontan participants will be encouraged to join community sporting organizations and participate in a range of physical activities. The study team will contact participants every fortnight for the initial 2 months and every month after for the remaining duration of the study to provide remote support. Some people may receive up to 3 "booster" sessions delivered by an exercise professional to promote ongoing physical activity or exercise training participation.

Education

To complement the exercise training and physical activity interventions, participants will also receive education on a variety of topics. This may include topics on understanding their congenital lesion, how to integrate physical activity into their daily routine, and nutrition and healthy eating. Education will be disseminated and delivered by information sheets and pre-recorded online videos.

Safety and Adverse Events

Safety will be evaluated by reviewing the adverse events recorded in each group. All adverse events will be continuously recorded throughout the trial using a case report form. The severity of the reported adverse event (i.e., serious or non-serious) and the likelihood of the event being related to testing or the intervention will be evaluated.

Adherence and Compliance

Adherence and compliance to exercise training will be monitored using various methods, including attendance to sessions, training logs, and HR monitors. In the F-FIT, adherence to the exercise training program will be considered as attending to 80% of the prescribed sessions—with attendance to at least 70% of sessions in the 4 weeks preceding the follow-up assessment visit. Non-adherent participants are defined as participants that attend <20% of the prescribed sessions, and partially adherent participants are considered as those who attend 20-79% of the prescribed sessions.

CONCLUSION

Multiple factors influence aerobic exercise capacity; suboptimal preload appears to be the predominant factor impairing aerobic exercise capacity. Reduced ventricular filling is primarily associated with low lean mass, diastolic dysfunction, and abnormal pulmonary vascular development and function. Preliminary evidence shows exercise training is a safe and effective therapy for improving peak VO_2 in people with a Fontan circulation. The F-FIT aims to provide high-quality evidence on the effects of physical activity and exercise training for increasing aerobic exercise capacity. A telehealth home-based exercise intervention will also be evaluated as a scalable and economical model of exercise training delivery. Furthermore, this multi-center randomized controlled trial will provide insight into the physiological changes associated with exercise training and unravel important pathophysiology.

AUTHOR CONTRIBUTIONS

DT drafted the exercise intolerance review and co-drafted the remaining sections of the manuscript. HG co-drafted the protocol sections of the manuscript. RC supervised the development of the protocol and manuscript. AM, DB, DC, DL, DT, JA, JC, NM, and RC contributed to the conception and design of the study. All authors critically reviewed the manuscript, contributed to study design, and approved the submission of the manuscript.

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Home-Based Long-Term Physical Endurance and Inspiratory Muscle Training for Children and Adults With Fontan Circulation—Initial Results From a Prospective Study

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Background: Patients with congenital heart disease (CHD)—including those after Fontan operation—are encouraged to be physically active.

Aim: To prospectively determine the effects of an individually adapted, home-based cycle ergometer endurance training in combination with inspiratory muscle training (IMT) in pediatric and adult Fontan patients. We, herein, report the results of the initial 10-months follow-up (phase 1).

Methods: 18 patients (median age 16.5 years; range 10-43 years) completed baseline check-ups, and 4 and 10 months follow-up visits, which each included cardiopulmonary exercise testing (CPET), bodyplethysmography (including measurement of respiratory muscle strength), and a quality of life questionnaire (PedsQL^{TM})**.** The training program consisted of a home-based cycle ergometer endurance training on a "Magbike® AM-5i/3i" (DKN Technology®, Clermont-Ferrand, France) and IMT with a handheld "POWERbreathe® Medic plus" device. Patients performed 90 min of endurance training per week in addition to IMT (30 breaths per day, 6-7 times per week). After the first 4 months, patients underwent additional interval training.

Results: After 10 months of training, we observed significant increases in maximum relative workload (W/kg, $p = 0.003$) and in maximum inspiratory (MIP, $p = 0.002$) and expiratory (MEP, $p = 0.008$) pressures. Peak VO_2 values did not increase significantly as compared to baseline ($p = 0.12$) in the entire cohort ($n = 18$), but reached statistical significance in a subgroup analysis of teenage/adult patients ($n = 14$; $p = 0.03$). Patients' subjective quality of life did not show any significant changes after 10 months of training.

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Discussion: In Fontan patients, an individually adapted home-based training is safe and associated with improvements in some CPET variables. However, these improvements did not translate into an improved QoL after 10 months. With an unclear, but most likely negative, impact of the COVID-19 pandemic, improvements in QoL may become evident during further follow-up (phase 2 of the study).

Keywords: Fontan circulation, cardiopulmonary exercise testing (CPET), endurance training, inspiratory muscle training (IMT), quality of life

INTRODUCTION

The development of the Fontan operation and its subsequent modifications represent a mainstay of surgical palliation in children with single-ventricle malformations (1). Due to continuous refinements in surgical techniques, perioperative care, and medical and interventional treatment strategies, which have resulted in improvements in early and late mortality, a growing number of affected children enter into adolescence and adulthood (2–4). Nonetheless, the basic hemodynamic limitations of the Fontan circulation and major long-term comorbidities have remained vastly unchanged (4–6).

Specifically, increased pulmonary vascular resistance and a non-pulsatile pulmonary flow pattern may lead to systemic venous congestion and reduced ventricular preload, thereby decreasing efficacy of the Frank-Starling mechanism. In addition, a decreased heart rate reserve, ventricular fibrosis and/or hypertrophy, and an impaired systolic and/or diastolic function all result in a reduced capacity to increase stroke volume and cardiac output during physical activity (2, 5). Furthermore, Fontan patients exhibit a restrictive lung function pattern, an impaired pulmonary diffusing capacity, and a reduced maximal oxygen uptake (7), which, in turn, are associated with decreases in health-related quality of life (8–11) and exercise tolerance (12–14).

Despite these intrinsic limitations, short term exercise programs and endurance training have been shown to positively effect stroke volume, cardiac output, and lung function, thereby increasing overall physical function, exercise capacity, and quality of life (15–18). Furthermore, inspiratory muscle training (IMT) has been shown to improve cardiac output (19). Thus, patients with congenital heart disease (CHD)—including those after Fontan operation—are encouraged to be physically active and exercise training is recommended on an individual basis (20).

Recently, CHD sports programs were designed to specifically address training and medical needs of CHD patients in several countries. However, a widespread geographic distribution of the Fontan population may limit access to those programs. Therefore, home-based programs have been introduced which demonstrated a similar efficacy as compared to hospital-based programs without an increasing rate of adverse events (17, 21–26). These results led to the recent recommendation to integrate home-based exercise training programs in the follow-up care of patients undergoing Fontan surgery (17, 23). However, efficacy results of individually adapted, home-based training protocols specifically designed for Fontan patients are still sparse. Therefore, we aimed to prospectively determine the effects of an individually adapted, home-based cycle ergometer endurance training (including interval training) in combination with IMT in a cohort of pediatric and adult Fontan patients. Herein, we report the initial results of a 10-months follow-up.

METHODS

Study Design and Population

We conducted a single center prospective study on the long-term impact of a home-based training with individually prescribed and adapted endurance training in combination with inspiratory muscle training (IMT). The endurance training protocol (see below) was developed in co-operation with the Department of Sports Medicine at Charité—Universitätsmedizin Berlin. Patients were enrolled between March 2018 to March 2021. The study is divided into two study periods, with follow-up examinations in phase 1 taking place after 4 and 10 months, while follow-up visits in phase two are planned after 16 and 22 months of training. Herein, we report the results from phase 1.

Participants with Fontan circulation had to be at least 6 years of age. Informed consent of patients or legal guardians was obtained prior to enrollment. The study was reviewed and approved by the Institutional Review Board of Charité—Universitätsmedizin Berlin (EA2/244/17). The patients' medical history and routine cardiac examination were reviewed, and upon inclusion patients underwent a baseline check-up which encompassed cardiopulmonary exercise testing (CPET), bodyplethysmography, including measurement of respiratory muscle strength (CASETM ES Version 6.73, GE Health Care, Germany) (27) and a standardized health-related quality of life questionnaire (PedsQL™–Pediatric Quality of Life Inventory)—including the cardiac module (28). Within the PedsQL™, different questions are allocated to several sub-categories (psychosocial, physical health, heart problems and treatment, treatment anxiety, cognitive problems, and communication). Childrens' body weight was evaluated using the reference values of the KiGGS' data (29). Lung function was evaluated using the GLI reference values (30, 31). Blood pressure values were evaluated according to the recommendations of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (32).

Training Protocol

The training program consisted of a home-based cycle ergometer endurance training on a "Magbike® AM-5i/3i" (DKN Technology®, Clermont-Ferrand, France). Training was adapted individually to each patient's pre-training and

check-up values. Patients performed 90 min of training per week, in 3 or 6 sessions of 30 or 15 min at a time, respectively (**Table 1**). Workload was set in 5 watts steps to 55% of maximum workload obtained during the latest check-up, respectively. After the first follow-up visit (4 months), patients underwent additional interval training (four intervals of 4 min at 80% of the maximum workload separated by 4 min of rest). For safety reasons, patients were urged to perform their training only when a person, who could assist or send for help in case of medical problems, was present. Prior to the initiation of home-based training, all patients underwent a baseline check-up, including CPET evaluation. If no adverse events, including symptomatic hyotonia, syncope, severe desaturation or arrhythmias occurred, patients were eligible for home-based training. An individual safety heart rate limit was set for each patient (blood pressure and saturation monitoring was not available at home in most patients). In addition to endurance training, the study participants executed an inspiratory muscle training with a handheld "POWERbreathe® Medic plus" device (POWERbreathe®, Winsen, Germany) with adjustable expiratory resistance. Inspiratory muscle training was performed at least 6 times a week for 30 consecutive slow and deep breaths. The effort was to be assessed on the 6-20 Borg scale. Participants were to adjust the resistance to achieve a value of 12-15 on the Borg scale.

Monitoring of the training included a training diary, filled out by the participants or their parents, which was checked on a monthly basis. Regular phone calls complemented the assessments of compliance and supported motivation. Based on the interviews, compliance was excellent among all 18 patients who completed the study (completion of at least 85% of the prescribed exercises). Of note, 7/25 initially enrolled patients had to be excluded before final analyses due to a low compliance or voluntary termination of the study.

TABLE 1 | Study protocol.

Baseline		
	CPET + Body + MIP/MEP + QoL	
Training period 1		
16 weeks (4 months)	Inspiratory muscle training (IMT)	30-50% of MIP 1 x 30 breaths per day (6-7 x per week)
	Ergometry	55% of W at VO2max at baseline 3 x 30 min per weeks or 6 x 15 min
	Training diary	Monthly check + weekly calls
Follow-up 1		
16 weeks (4 months)	CPET + Body + MIP/MEP + QoL	
Training period 2		
24 weeks (10 months)	Inspiratory muscle training (IMT)	1 x 30 breaths per day with adapted pressure (6-7 x per week)
	Ergometry	Adapt: 55% of W at VO2max at follow-up 1 2 x 45 min per weeks or 5 x 18 min + Interval training (4 x 4 min at 80% W at VO2max with 3 min of recovery each)
	Training diary	Monthly check + weekly calls
Follow-up 2		
24 weeks (10 months)	CPET + Body + MIP/MEP + QoL	

Body, bodyplethysmography; CPET, cardiopulmonary exercise testing; MEP, Maximum expiratory pressure; MIP, maximum inspiratory pressure.

Statistics

Statistical analysis was carried out using SPSS Version 25 (SPSS Inc., Chicago, IL, USA) In all analyses at least one variable was not in normal distribution, therefore non-parametric tests were used. Differences between groups (the three time points) were analyzed by the non-parametric Friedman test for three or more paired samples. P-values < 0.05 were considered statistically significant. In addition, a-priori power analysis was performed to estimate the required sample size (based on anticipated changes in the PedsQL scores): Assuming a sample size of $n = 20$, significant changes can be seen with a minimal effect size of 0.66 (power 80%, alpha-level 0.05), which would be equivalent to, e.g., an increase of 5% (standard deviation 8%). With only $n = 10$ children enrolled, the required effect size would have to be 0.95 (power 80%, alpha-level 0.05), e.g., equivalent to an increase of 12% (standard deviation 13%).

RESULTS

Demographics

A total of 25 patients were initially enrolled in the study, out of which 18 patients (median age 16.5 years; range 10-43 years) were included in the final analyses. Seven out of the 25 initially enrolled patients were excluded due to a low compliance or voluntary termination of the study. Compliance was assessed by means of a training diary and weekly telephone interviews with patients and parents. These calls were also supposed to work as a motivational strategy. 11/18 (61.1%) were male and 7/18 (38.9%) female. Baseline body weight in adults ranged between 37 and 84 kg (median 65 kg), while in children weight ranged between the 5th and 79th percentile (median 35th percentile). Details on the underlying congenital cardiac malformation are provided in **Table 2**. Of note, three patients (16.7 %) had evidence of an open fenestration at the latest echocardiography before initiation of training and two patients (11.1%) had an epicardiac pacemaker. Cardiac medication remained stable during the study period in all 18 patients. The median oxygen saturation at rest was 97% (range 89-100%). At baseline, the mean resting systolic and diastolic blood pressures in adults were 121 (range 69-143) mmHg and 79 (range 50-86) mmHg. In children, the mean resting systolic blood pressures at baseline was at the 71st (range 4th to 99th)

TABLE 2 | Baseline patients' characteristics.

	Age	Gender	Height (cm)	Weight (kg) baseline/4 months/10 months	Age at Fontan completion	Cardiac malformation	Comment	Medication	Mean pulmonary artery pressure [mmHg]
01	22	F	169	62/55/55	2	TA, PA, intact VS	Fenestration	VKA	14
02	13	F	153	40/43/45	4	PA, VSD, TGA	-	ACEI, VKA	11
03	15	F	170	50/50/51	3	TA, VSD, pulmonary artery ligation	-	VKA	11
04	12	M	158	40/42/45	3	TA, TGA, VSD, s/p Damus-Kaye-Stansel operation	-	VKA	-
05	43	M	167	69/70/70	17	TA, PA, VSD, occlusion left subclavian artery	-	ACEI, HCT, MCRA, VKA, Propafenone, Ivabradine	-
06	12	M	148	49/51/54	3	TA, VSD, sick sinus syndrome	DDD-Pacemaker	ACEI, PDE5 inhibitor, VKA	14
07	20	M	185	68/67/67	5	TA, VSD, coarctation of the aorta, DORV, s/p Damus-Kaye-Stansel operation	-	VKA	13
08	24	M	190	71/70/70	3	TA	-	ASA, HCT	14
09	26	M	187	84/86/88	6	TA	-	VKA	12
10	24	F	156	37/38/38	3	DILV, sick sinus syndrome, AV Block II°	-	ACEI, VKA	11
11	12	M	143	46/47/49	3	HLHS, coarctation of the aorta	Fenestration	ACEI, VKA	-
12	11	M	143	29/31/31	4	DORV, DILV, PS	-	VKA	-
13	11	M	149	38/40/41	3	MA, DORV, VSD	-	ACEI, HCT, VKA	-
14	11	M	150	46/49/51	3	TA, VSD, PS	DDD-Pacemaker	ACEI, VKA	7
15	10	F	135	32/36/39	9	PA, VSD, tricuspid valve dysplasia	Fenestration	ACEI, PDE5 inhibitor, VKA	11
16	18	F	164	57/60/59	3	TA, PS	-	ASA	8
17	27	F	162	58/59/60	24	DORV,VSD,TGA, RVOT stenosis	Fenestration	HCT, MCRA, VKA	12
18	36	F	158	60/59/60	9	DILV, VSD, PS	-	ACEI , ASA	13

DILV, double inlet left ventricle; DORV, double outlet right ventricle; F, female; HLHS, hypoplastic left heart syndrome; M, male; MA, mitral atresia; PA, pulmonary atresia; PS, pulmonary stenosis; RVOT, right ventricular outflow tract; TA, tricuspid atresia; TGA, transposition of great arteries; VS, ventricular septum; VSD, ventricular septal defect; ACEI, ACE inhibitors; ASA, acetylsalicylic acid; HCT, hydrochlorothiazide; MCRA, mineralocorticoid receptor antagonist; VKA, vitamin K antagonist.

percentile. 13/18 patients underwent cardiac catheterization during the 5 years preceding baseline (median 8 months). Invasively obtained mean pulmonary artery pressures (mPAP) ranged between 7 and 14 mmHg (median 12 mmHg), indicating stable Fontan circulation (**Table 2**). The remaining patients showed no indication for invasive diagnostics due to reassuring general condition, echocardiographic results and high oxygen saturations (33).

Cardiopulmonary Function

Cardiopulmonary function was evaluated at baseline, and after 4 and 10 months of training (**Table 3**). After 10 months of follow-up, peak VO_2 values did not increase significantly as compared to baseline (mean 26.50 ± 2.10 ml/min/kg to 28.10 ± 1.95 ml/min/kg; $p = 0.12$) (**Figure 1**). Of note, in the sub-cohort of teenage/adult patients (patients who turned 13 or older during the study period, $n = 14$), the increase in peak VO_2

TABLE 3 | Cardiopulmonary exercise testing (CPET, all patients, $n = 18$).

	Baseline	4 months	10 months	*P*
HF (rest) [bpm]	91.50 ± 3.28	91.44 ± 3.85	85.41 ± 3.33	0.09
HF (max) [bpm]	158.67 ± 7.56	165.22 ± 6.39	161.59 ± 7.63	0.12
Heart rate reserve [bpm]	67.17 ± 6.93	73.78 ± 5.50	76.18 ± 6.16	0.058
Max. power/weight [W/kg]	1.92 ± 0.15	2.14 ± 0.16	2.17 ± 0.19	**0.003**
VO_2max [ml/min/kg]	26.50 ± 2.10	26.99 ± 1.98	28.10 ± 1.95	0.12
AT/reference [%]	48.88 ± 4.08	47.88 ± 3.51	52.00 ± 4.06	0.12
VE/VCO_2 slope	33.02 ± 1.32	33.42 ± 1.10	32.51 ± 1.45	0.07
TCS (rest) [%]	96.18 ± 0.82	95.53 ± 0.97	95.94 ± 0.63	0.98
TCS (max. capacity) [%]	92.67 ± 1.07	92.44 ± 1.15	92.00 ± 1.18	0.29
VC_{insp}/reference [%]	77.75 ± 5.05	81.21 ± 4.78	81.55 ± 4.64	0.87
TLC/reference [%]	85.64 ± 3.64	85.61 ± 3.82	85.28 ± 4.42	0.98
FEV_1/VC_{insp} [%]	92.83 ± 1.95	92.76 ± 1.66	90.91 ± 2.33	0.16
MEP [kPa]	6.87 ± 0.80	7.71 ± 0.84	8.17 ± 1.00	**0.008**
MIP [kPa]	6.41 ± 0.63	8.90 ± 0.89	8.95 ± 0.97	**0.002**

Baseline results and results after 4 and 10 months of training are shown with corresponding P-values (non-parametric Friedman test for three or more paired samples). Significant values are shown in bold. All CPETs were maximal test (RER > 1.0). HF, heart frequency; AT, anaerobic threshold; TCS, transcutan oxygen saturation; FEV1, forced expiratory pressure in 1 s; VCinsp, inspiratory vital capacity; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; TLC, total lung capacity.

reached statistical significance after 10 months of training (23.50 ± 3.86 ml/min/kg to 26.09 ± 2.00 ml/min/kg; $p = 0.03$, **Figure 1**; **Table 4**). Slope values did not decrease significantly during the 10-months training period, in both the overall cohort ($p = 0.07$, **Table 3**) and the sub-cohort of teenage/adult patients ($p = 0.09$, **Table 4**). In addition, in the total cohort maximum relative workload increased within 10 months of training from a mean of 1.92 ± 0.15 W/kg to 2.17 ± 0.19 W/kg ($p = 0.03$) (**Table 3**; **Figure 1**).

Furthermore, in both cohorts no significant changes in resting heart rate or functional heart rate reserve could be demonstrated (**Table 3**). Of note, at baseline, there was no significant difference in the drop of oxygen saturation during exercise when comparing patients with and those without fenestration ($U = 19.5$, $Z = -0.748$, $p = 0.477$). Consistently, these results did not change after 10 months of training ($U = 12.0$, $Z = -1.022$, $p = 0.307$).

Pulmonary Function

9/18 (53%) showed normal pulmonary function, while 6/18 (35%) exhibited a restrictive and 2/18 (12%) an obstructive pattern at baseline. One patient did not tolerate bodyplethysmography at baseline. As expected, vital capacity (VC), total lung capacity (TLC) and FEV1/VC did not show any significant improvements after 10 months of training. However, in the cohort of patients from all age groups maximal inspiratory pressure significantly increased from 6.41 ± 0.63 to 8.95 ± 0.97 kPa ($p = 0.002$; **Table 3**; **Figure 2**) and maximal expiratory pressure from 6.87 ± 0.80 to 8.17 ± to 1.00 kPa ($p = 0.008$, **Table 3**; **Figure 2**). Again, similar results were obtained from the sub-cohort analysis of teenage/adult patients (**Table 4**)

Quality of Life

Patients' subjective quality of life as determined by the PedsQL^{TM} questionnaires did not show any significant changes after 10 months of training (in neither of the sub-categories - psychosocial, physical health, heart problems and treatment, treatment anxiety, cognitive problems and communication, data not shown).

DISCUSSION

We herein show, that an individually adapted home-based training is safe and associated with improvements in some CPET variables. However, these improvements did not translate into an improved QoL after 10 months. Importantly, none of the patients experienced any adverse events during home-based training such as syncope, symptomatic arrhythmia or acute hospitalization.

During the last decades, survival rates in children with CHD have increased substantially. Currently, more than 97% of children with CHD can be expected to reach adulthood (2, 34–36). With an improved long-term survival, aspects of long-term morbidity, cardiopulmonary capacity, pulmonary function, reproductive and psychosocial health and quality of life require closer attention. In patients with Fontan circulation, exercise capacity has been reported to be reduced to about 50-60% (10, 13). However, impaired exercise capacity is known to be associated with adverse outcome in CDH patients, including Fontan patients. Furthermore, CPET is indicated in Fontan patients with pulmonary vascular disease (37) and should be performed on a regular basis in all Fontan patients if possible (38).

Paridon et al. observed peak VO_2 values within the normal range in only 28% of patients. However, a majority of individuals (63%) exhibited an anaerobic threshold within the normal range, suggesting that many Fontan patients tolerate a high level of submaximal and non-maximal activity (3). Thus, endurance training at the lower end of the individually tolerated workload (defined as W/kg at VO_2max = 100%) seems adequate for Fontan patients. However, long-term data

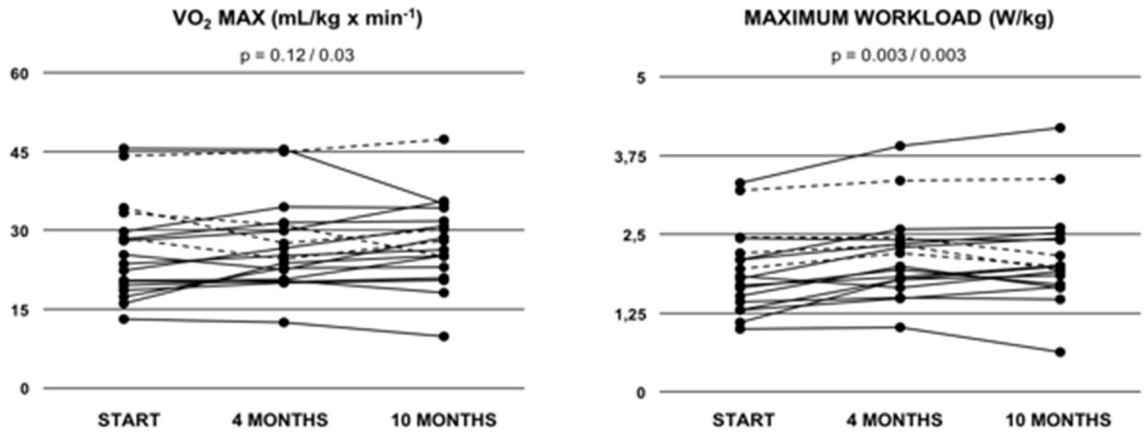

FIGURE 1 | Peak oxygen uptake (VO_2 MAX) and maximum relative workload (W/kg) in Fontan patients during the 10-months training period. Values are given at baseline (start), and after 4 and after 10 months of combined endurance and inspiratory muscle training. Each line represents one patient. Full lines represent teenage/adult patients, while dashed lines indicate patients who remained younger than 13 years throughout the study period. The first *p*-value refers to the total cohort of 18 patients, while the second *p*-value refers to the teenage/adult subgroup analyses only ($n = 14$).

TABLE 4 | Cardiopulmonary exercise testing (CPET, teenage/adult subgroup, $n = 14$).

	Baseline	4 months	10 months	*P*
HF (rest) [bpm]	89.29 ± 4.08	90.36 ± 4.88	83.14 ± 3.71	0.23
HF (max) [bpm]	155.21 ± 8.76	162.21 ± 7.62	157.79 ± 8.51	0.11
Heart rate reserve [bpm]	65.93 ± 7.78	71.86 ± 6.24	74.64 ± 6.71	0.085
Max.power/weight [W/kg]	1.75 ± 0.15	2.00 ± 0.15	2.02 ± 0.17	**0.003**
VO_2max [ml/min/kg]	23.50 ± 3.86	25.43 ± 2.15	26.09 ± 2.00	**0.03**
AT/reference [%]	42.46 ± 2.94	44.94 ± 3.69	48.07 ± 3.38	0.09
VE/VCO_2 slope	32.17 ± 1.71	33.14 ± 1.42	31.31 ± 1.61	0.09
TCS (rest) [%]	95.92 ± 0.98	95.36 ± 1.10	95.92 ± 0.67	0.97
TCS (max. capacity) [%]	92.43 ± 1.31	91.93 ± 1.33	92.31 ± 1.42	0.42
VC_{insp}/reference [%]	71.15 ± 5.12	70.21 ± 4.94	69.00 ± 5.50	0.56
TLC/reference [%]	90.48 ± 2.26	91.13 ± 1.96	89.70 ± 3.00	0.61
FEV_1/VC_{insp} [%]	92.23 ± 4.78	96.14 ± 5.12	103.64 ± 4.11	0.09
MEP [kPa]	6.25 ± 0.80	8.84 ± 1.08	7.87 ± 1.18	**0.045**
MIP [kPa]	6.63 ± 0.73	9.35 ± 1.04	8.38 ± 1.07	**0.014**

Baseline results and results after 4 and 10 months of training are shown with corresponding p-values (non-parametric Friedman test for three or more paired samples). Significant values are shown in bold. All CPETs were maximal test (RER > 1.0). HF, heart frequency; AT, anaerobic threshold; TCS, oxygen saturation; FEV1, forced expiratory pressure in 1 s; VCinsp, inspiratory vital capacity; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; TLC, total lung capacity.

on training studies is still sparse in the Fontan population. A recent review article (39) showed that out of 245 individuals reported in the literature, only 88 (36%) patients trained for more than 3 months and only 30 individuals (12%) trained in studies lasting longer than 8 months. We, herein, report on the 10-months follow-up of 18 patients who underwent an individually adapted, home-based ergometer endurance training (including interval training) in combination with IMT.

Cardiopulmonary Impact

Exercise intolerance in Fontan patients is caused by multiple factors, which include the lack of a subpulmonary ventricle (pump function), chronotropic incompetence, restrictive lung function, reduced muscle mass, and general deconditioning, among others (40, 41). While healthy people improve their cardiac output by increasing both heart rate and stroke volume during exercise, in the Fontan circulation, increases in heart rate are crucial to enhance cardiopulmonary exercise capacity due to a reduced capacity to increase preload (lack of a subpulmonary ventricle) (42). In addition, heart rate reserve is further reduced in several patients by medication and/or iatrogenic damage of the sinus node (43). After 10 months of training, we did not see significant reductions in resting heart rate or increases in functional heart rate reserve (**Tables 3**, **4**). Due to the limited size of our total cohort, a meaningful sub-cohort analysis of patients on specific antiarrhythmic medications and/or sick sinus syndrome was not feasible. However, heart rate reserve

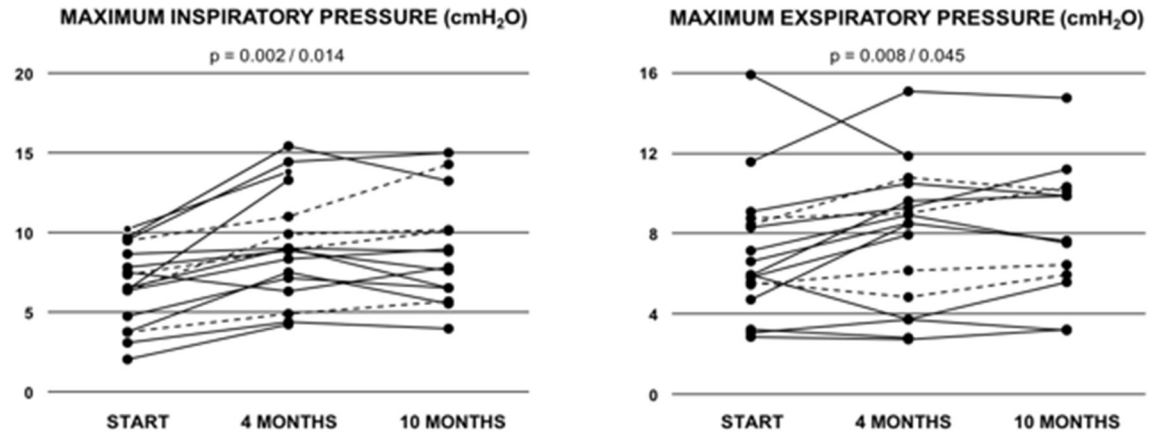

FIGURE 2 | Maximum inspiratory pressure (MIP) and maximum exspiratory pressure (MIP) in Fontan patients during the 10-months training period. Values are given at baseline (start), and after 4 and after 10 months of combined endurance and inspiratory muscle training. Each line represents one patient. Full lines represent teenage/adult patients, while dashed lines indicate patients who remained younger than 13 years throughout the study period. The first *p*-value refers to the total cohort of 18 patients, while the second *p*-value refers to the teenage/adult subgroup analyses only ($n = 14$).

between patients with and those without pacemaker did not differ significantly ($p = 0.9$). This was also true when all patients with impaired chronotopy (antiarrhythmic medication with betablockers, ivabradin or pacemaker patients) were compared to patients without pacemakers or antiarrhythmic medication (data not shown). Thus, it remains unclear if the lack of significant improvements in functional heart rate reserve after training represents an intrinsic limitation in all Fontan patients or if medications and specific heart rhythm anomalies are responsible for these results. Furthermore, it is likely that subtle improvements may only become evident during a longer training period.

Besides heart rate reserve, peak VO_2 and VE/VCO_2 slope are major indicators of cardiopulmonary exercise capacity. Healthy people reach their maximum of peak VO_2 at early adulthood, with values beginning to drop around the age of 30 years. However, in Fontan patients peak VO_2 values already start to decrease disproportionally early during adolescence (10, 44). In our teenage/adult cohort we were able to demonstrate significant improvements in peak VO_2 after 10 months of training, while we did not see significant improvements in the total cohort of 18 patients. In their recent review article incorporating 16 studies on endurance training in Fontan patients, Scheffers et al. report that only 9 out of 16 reviewed studies demonstrated improvements in peak VO_2 (39). Differences in results among studies are likely caused, at least in part, by different follow-up durations as functional parameters, such as peak VO_2 and slope, usually require some time of training before significant improvements become evident.

Of note, previous studies demonstrated significantly lower oxygen saturation values at rest (45) and a pronounced systemic desaturation during exercise in patients with fenestration as compared to those without fenestration (46). In the cohort presented herein, we were unable to confirm these results as our results did not show any differences in saturation values between groups. However, our study only included four patients with fenestration precluding a statistically meaningful subgroup analysis. In addition, the presence of fenestrations was documented by echocardiography preceding the baseline evaluation only. Thus, their hemodynamic relevance remains unclear in our patients. Of note, we did not observe any significant differences (CPET, pulmonary function, QoL) between the patients with and those without fenestration (data not shown).

Pulmonary Function

About one third of the patients in our cohort exhibited a restrictive breathing pattern at baseline, in line with previous reports on lung function test results in Fontan patients (7, 47). The observed restrictive breathing pattern is likely caused by multiple factors, which include diaphragmatic paralysis (48, 49) and a reduced thoracic mobility due to repeated thoracotomies with presence of less flexible scar tissue (49). Previous results on the impact of different physical training programs on lung function testing in Fontan patients revealed conflicting results. While, similar to our results, Fritz et al. failed to show significant improvements in vital capacity, total lung capacity and Tiffeneau-Index (FEV1/VC) after daily inspiratory muscle training over 10 months (50), Hedlund et al. demonstrated an increased vital capacity after endurance training (7).

We observed significant increases in maximum power/weight ratio, as well as in maximum inspiratory (MIP) and expiratory (MEP) pressures after 10 months of combined endurance and inspiratory muscle training. MIP and MEP values at baseline ranged between the 3rd and 25th percentile (P3-P25) and increased to P10-P50 during training (51). Laohachai et al. (19) previously reported that improvements in MIP were associated with positive effects on cardiac output in Fontan patients after 6-week of IMT. Thus, one might speculate that higher inspiratory muscle strength may increase pulmonary blood flow

(by improving the "thoracic pump") and subsequently improve preload, cardiac output and exercise capacity (19). Furthermore, the combination of different training modalities, such as IMT and endurance training may, at least theoretically, booster the positive effects of training in Fontan patients as an improved "thoracic pump" and an overall improved cardiorespiratory capacity both enhance overall physical fitness at multiple circulatory target sites.

Quality of Life

Although we did observe improvements in several parameters of cardiopulmonary exercise capacity, those changes did not translate into patients' subjective quality of life as determined by the PedsQL questionnaires after 10 months of training. Previously, several authors found improvements in quality of life indices by training interventions in Fontan patients (11, 18, 28, 37, 52), while others reported unchanged QoL (23). Although several factors, such as differences in training protocols, duration and compliance, might contribute to these discrepancies in previously reported results, self-reported QoL is generally influenced by a variety of possible confounders (parenteral influence, bias by peer comparison, etc.). In addition, some categories of the quality-of-life questionnaire, such as "treatment anxiety" and "cognitive problems and communication" are unlikely to change by physical training programs.

Furthermore, a home-based training, as performed here, almost completely lacks the social benefit of training together. However, home-based protocols may enable an easy individual adaptation of training plans and facilitate inclusion of more patients as compared to a standard group training at a certain location. While we believe that a longer follow-up may be required to detect improvements in QoL, the study was conducted during a time heavily affected by the COVID-19 pandemic with its detrimental effects on families, social life, school, work, and activities, which likely had a negative impact on general QoL. In this regard, several patients affected by CHD and especially older Fontan patients reduced many of their social activities in order to decrease their risk of infection. Of note, the PedsQL questionnaire had been initially designed for patients up to 18 years. However, in order to allow for comparative analyses we used PedsQL in all patients (children, teenagers and adults). Furthermore, adult patients with Fontan circulation often face specific challenges, which are similar to their situation during childhood (high dependence on parental support etc.).

Limitations

In addition to the previously mentioned confounders, such as the co-occurrence of the COVID-19 pandemic, further limitations apply when interpreting the results presented in this study. First, the number of patients is limited and patients differed in regard to underlying age, gender, cardiac defect, surgical modifications, and medical treatment. Nevertheless, compared to previously reported studies on physical training in Fontan patients, our cohort is of comparably large size and followed-up for a relatively long period of time (10 months during phase 1). In addition, differences in motivation, other health-related problems, and differences in socio-economic backgrounds, supervision by parents, self-awareness of benefit, cognitive abilities and technical execution of training represent further confounders that were unaccounted for in this analysis (27). In addition, due to learning effects, lung function tests are known to improve over time, especially in patients that perform lung function tests for the first time. While we cannot rule out the possibility that learning effects might have contributed to the results, CPET testing and assessment of inspiratory muscle strength is routinely performed during follow-up for all Fontan patients and we usually do not see improvements over time. However, the well-known effects of learning cannot firmly be ruled out. Furthermore, Fontan patients are especially prone to malnutrition and often exhibit a body composition with low muscle mass. Thus, the combined effect of nutritional management together with different physical training programs needs to be evaluated in further studies.

CONCLUSIONS

In conclusion, we show that individually adapted aerobic endurance training in combination with IMT is safe and associated with improvements in certain CPET variables in Fontan patients in a home-based setting. While some CPET measures improved, these improvements did not (yet) translate into an improved QoL. With an unclear, but most likely negative, impact of the COVID-19 pandemic, improvements in QoL may be expected during further follow-up (phase 2 of the study). Additional research efforts on the long-term role of individualized training programs are warranted in order to facilitate improvements (or to prevent premature deterioration) of physical endurance and QoL in Fontan patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Charité Institutional Review Board (EA2/244/17). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SD, PK, HS, and SO planned and conducted the study. SD and H-MS wrote the manuscript. All authors contributed to data collection, analysis, interpretation, and approved the final version of the manuscript.

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Neurodevelopmental and Mental Health Outcomes in Patients With Fontan Circulation: A State-of-the-Art Review

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Children, adolescents and adults living with Fontan circulation face numerous neurological and developmental challenges. As the population with complex CHD increases thanks to outstanding improvement in medical and surgical care, the long-term developmental and mental health sequelae have become a public health priority in pediatric and congenital cardiology. Many patients with a Fontan circulation experience difficulty in areas of cognition related to attention and executive functioning, visual spatial reasoning and psychosocial development. They are also at high risk for mental health morbidities, particularly anxiety disorders and depression. Several hemodynamic risk factors, beginning during the fetal period, may influence outcomes and yield to abnormal brain growth and development. Brain injury such as white matter lesions, stroke or hemorrhage can occur before, during, or after surgery. Other sociodemographic and surgical risk factors such as multiple catheterizations and surgeries and prolonged hospital stay play a detrimental role in patients' neurodevelopmental prognosis. Prevention and intervention to optimize long-term outcomes are critical in the care of this vulnerable population with complex CHD.

Keywords: Fontan procedure, neurodevelopment, mental health, brain injury, congenital heart disease (CHD)

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INTRODUCTION

Remarkable advances in pediatric cardiac surgical and medical care in the last few decades have substantially improved survival rates of patients with the most complex forms of congenital heart disease (CHD). Along with excellent survival and improved short-term outcomes has come recognition of long-term neurodevelopmental and psychosocial morbidities (1–4). Individuals with complex CHD, including those with a Fontan circulation, have an elevated risk for structural brain abnormalities and neuropsychological and mental health disorders, starting early in life and continuing throughout adulthood (5, 6).

The etiologies of neurological vulnerability and injury are multifactorial, additive, and interactive. For complex CHD, such as single ventricle anatomies, genetic factors influencing heart formation may also affect brain development. Indeed, whole exome sequencing of CHD parent-offspring trios revealed substantial overlap between damaging de novo mutations in children with

CHD and those previously known to be associated with neurodevelopmental disorders (7). In addition, disturbed fetal cerebral hemodynamics may reduce cerebral oxygen and substrate delivery to the developing brain, thereby altering typical brain growth and maturation (8). Patient-specific factors such as lower socioeconomic status, (9) preterm and early-term birth (birth between 37 and 38 weeks' gestation) (10, 11), low birth weight (12), and prolonged hospital stay may further increase risk (13–15).

Compared with other forms of CHD, children with single ventricle disease are reported to be the most vulnerable to neurological sequalae (5, 16). *In utero*, these children often have the lowest cerebral oxygen and nutrient delivery, and after birth, they generally undergo multiple infant and early childhood cardiac operations and catheterizations, potentially exposing the brain to repeated stress due to hemodynamic instability, anesthetic exposure, or other medical complications. These risks persist well beyond the infant/toddler period, as children and adolescents with single ventricle face life-long risk for cerebrovascular events and other systemic morbidities that may impact neurological functioning, mental health, and quality of life.

BRAIN ABNORMALITIES FOR PATIENTS WITH SINGLE VENTRICLE CHD

Neuroimaging findings in single ventricle patients across the lifespan range from subtle disturbances in brain maturation and growth to overt injuries evident on clinical imaging. Reductions in brain volumes and other quantitative brain differences emerge as early as the 2nd trimester of pregnancy and persist into adolescence. (17–20) These broad-based developmental disturbances provide a backdrop upon which overt brain injury, such as cerebral white matter injury, acute ischemic stroke, or micro hemorrhage may accumulate over time.

The earliest imaging abnormalities in single ventricle patients emerge in the 2nd trimester of pregnancy. Normal fetal circulation preferentially directs relatively oxygen and nutrient-rich blood to the developing brain while relatively substrate-depleted blood recirculates to the body. In fetuses with single ventricle heart disease, abnormal cardiac anatomy leads to intracardiac mixing, thereby substantially lowering the oxygen and nutrient content of blood directed to the brain. Moreover, in fetuses with hypo plastic or atretic systemic outflow tracts, blood must reach the brain retrograde via the ductus arteriosus. In general, fetuses with CHD show small brain volumes and dysmature gyrification (8, 21–24). In one study, single ventricle heart disease specifically was associated with heightened risk of small total fetal brain volume compared with biventricular forms of CHD (17). Fetal brain size correlates with cerebral oxygen consumption, and regions of brain most vulnerable to low substrate delivery show greatest volumetric reductions (17, 23). These findings lend support to the hypothesis that impaired fetal cerebral oxygen and nutrient delivery plays an important role in these disturbances of brain maturation and growth.

As infants grow into childhood and adolescence, neuroimaging markers of impaired brain growth and development persist. Two large studies of children who underwent the Fontan procedure demonstrate persistent quantitative differences in brain metrics. Watson and colleagues (18) examined 128 children and adolescents who had undergone the Fontan procedure in early childhood. Widespread differences in both regional brain volumes and cortical thickness were present and associated with several medical risks including older age at first operation, more catheterization procedures, and more complications with catheterizations and with surgeries. Separately, the same group assessed an overlapping Fontan cohort for differences in white matter microstructure, again finding widespread differences in white matter microstructure compared to a control group. Of note, these differences in white matter microstructure correlated with Full-Scale IQ and processing speed in the CHD group but not in the control group, suggesting that white matter abnormalities contribute to long-term neurocognitive variability in youth with Fontan circulation (25).

In addition to subtle quantitative differences, clinical brain MRI may detect overt brain injuries. Indeed, one recent study of adolescents and adults with Fontan circulation identified structural brain injury in all 100 participants who underwent brain MRI with the most common injuries being micro hemorrhages (94%) and white matter injury (81%) followed by cerebral infarct (35%), and subcortical gray matter injury (21%) (26).

White matter injury is the most common clinically significant acquired brain injury found in children with single ventricle. About 15–40% of children with single ventricle heart disease have white matter injury visible on MRI prior to surgery, with cumulative injury rates rising as high as 70–80% postoperatively in some studies (20, 26–31). Various factors may contribute to white matter injury, including relative brain dysmaturity (19, 20, 27, 29, 32) and reduced oxygen and nutrient delivery to the developing white matter (27, 33, 34). Perioperative factors including pre- and post-operative hypoxia, longer time to surgery, presence of aortic arch reconstruction, duration of hypothermic cardiac arrest, and postoperative diastolic hypotension have each been shown to correlate with risk of white matter injury. (29, 31, 35, 36) Interestingly, while comparisons are often made between preterm brain injury and white matter injury in CHD, the topology of white matter injury differs between CHD and preterm infants, with CHD infants showing less central injury than preterms (37).

Acute ischemic stroke is the second most common clinically significant brain injury noted in children with single ventricle. Stroke occurs in about 2–20% of children with CHD (29, 38–47). As many children with stroke have no clinical symptoms, higher rates are found in studies where all subjects are screened with MRI compared with studies relying on clinically acquired scans (43, 44, 47). Among patients with CHD, the highest prevalence of stroke is in children with single ventricle; one preoperative study of neonates with HLHS found stroke in 7%, with the rate as high as 13% in a separate study of adolescents who were post-Fontan

(27, 48). About a quarter of strokes in children with CHD are associated with catheterization or other cardiac procedures (40, 46, 49, 50). A multitude of factors likely contribute to thromboembolic risk during the periprocedural period including exposure to non-native materials, high hematocrit, inflammation, sluggish venous flow from high Glenn or Fontan pressures, and prolonged immobilization (42, 51). Abnormal heart structure itself and staged palliation create stroke risk due to direct connections between the venous and arterial circulation. For example, at birth, a patent ductus arteriosus, foramen ovale or atrial septal defect allow passage of thrombi from the venous to arterial circulation; similarly, following the stage 1 Norwood procedure and bidirectional Glenn, venous and arterial blood mix in the single ventricle. After Fontan, residual right-to-left shunting may allow venous thrombotic material to pass directly into the arterial circulation. Cumulatively, these risk factors present an important long-term risk for stroke-related morbidity and mortality (39, 52).

Other types of brain injury may also occur in children with single ventricle. Global hypoxic ischemic brain injury is fortunately rare, but may occur in settings of severe hemodynamic compromise. Clinically significant cerebral hemorrhage is also uncommon, but micro hemorrhages are often seen after cardiopulmonary bypass. One study of a biventricular cohort found that a high burden of micro hemorrhage was associated with poorer neurodevelopmental outcome (53). Further study of the clinical implications of this common finding is warranted. Ultimately, patients with single ventricle heart disease face accumulating risk of developmental brain disturbance or injury, with increasing evidence showing associations between these findings and neurodevelopmental outcome (6, 25, 54).

NEUROPSYCHOLOGICAL AND BEHAVIORAL OUTCOMES THROUGHOUT THE LIFESPAN

Outcomes in Children

Children with single ventricle are reported to have the highest risk of neurodevelopmental disability compared with other forms of CHD. More than two decades ago, a study reported outcomes on 11 survivors of HLHS and found that seven children (64%) presented with profound developmental disabilities (55). Wernovsky et al. measured ability and achievement in a cohort of selected survivors whose Fontan procedure was performed in the 1970s and 1980s (55). Children were a median of 11 years of age at assessment and 6 years after surgery. Median Full-Scale IQ was 95.7 $\pm$ 17.4, significantly lower than that in the normal population; 8% of patients scored in the severe intellectual dysfunction range (<70), which is about three times the expected proportion in the general population. In multivariable analyses adjusting for social class, lower IQ was primarily associated with the use of circulatory arrest and with the anatomic diagnosis of HLHS or "other" complex forms of single ventricle. Independent risk factors for worse achievement included the diagnosis of HLHS and "Other" complex single ventricle, or prior use of total circulatory arrest, as well as with reoperation using cardiopulmonary bypass within 30 days after the Fontan procedure. In another study of Fontan survivors, Goldberg et al. found a Full-Scale IQ score of 101.4 $\pm$ 5.4 within normal ranges for the Fontan group. (56) However, those with HLHS scored significantly lower (93.8 $\pm$ 7.3) than those without HLHS, and additional risk factors for worse neurodevelopmental outcome included lower socioeconomic status, longer duration of circulatory arrest, and occurrence of perioperative seizures. In a more contemporary study in 2012, a nationwide sample of 23 patients with HLHS and other univentricular hearts was reported to have a median cognitive performance within the normal range, with only 26 of patients with HLHS and 23% of those with other types of single ventricle having major neurodevelopmental dysfunction (57).

Some studies have reported that, even if at high risk for neurodevelopmental impairments, today, the overall prognosis for patients with single ventricle CHD may not be significantly different from that of other forms of critical CHD. Indeed, it has been suggested that, despite variations in the severity of some symptoms, children with critical CHD share a relative similar neuropsychological and behavioral phenotype. Indeed, a prospective longitudinal study evaluating neurodevelopmental outcomes in 365 young children with CHD at 4 years of age did not find significant differences in unadjusted scores for full-scale IQ (Fontan 93.3 $\pm$ 17.1 vs. 96.2 $\pm$ 19.8) between survivors of the Fontan procedure and children with CHD who underwent biventricular repair. Scores were also similar for visual perceptive skills, social skills and academic achievement, including math and pre-reading skills. However, preschool children after the Fontan procedure scored significantly lower than those with biventricular repair on processing speed (Fontan 90.8 $\pm$ 15.2 vs. 96.5 $\pm$ 16.9 for biventricular CHD) and displayed more inattention and impulsive behaviors, as rated by their parents (58).

The Single Ventricle Reconstruction Trial, conducted through the Pediatric Heart Network, was designed primarily to compare outcomes of children with HLHS randomized to a right ventricle to pulmonary artery shunt to outcomes of participants randomized to a Blalock-Thomas-Taussig shunt (59). To date no differences have been detected in neurodevelopmental outcomes between the two shunt groups. Children in this cohort have lower scores on developmental assessments at 14 months and at three years of age. (5, 14) Interestingly, patient specific factors and measures of perioperative morbidities, but not treatment strategies, were found to be predictive of lower developmental scores. (5, 13, 14) Long-term follow-up of the cohort enrolled in the Single Ventricle Reconstruction Trial will likely provide further insights on factors associated with impaired neurodevelopmental outcomes for this high-risk patient group.

Outcomes in Adolescents

Interestingly, adolescents with a Fontan circulation appear to be at high risk for general cognitive dysfunction and, particularly, for more prevalent behavioral difficulties. Academic achievement (math and reading scores) is also lower than expected in

adolescents, suggesting long-lasting learning challenges. A single-center cross-sectional study examined neuropsychological outcomes of a sample of 156 adolescents with Fontan circulation at a mean age of 14 years. Full-scale IQ scores (91.6 ± 16.8), mean Mathematics Composite Score (91.9 ± 17.2) and mean Reading Composite Score (92.0 ± 22.9) were significantly lower than the expected population mean of 100 ± 15. More than a third of the Fontan group scored >1 SD below population means for IQ and both academic achievement tests, and between 12 and 19% scored below−2SD below the norms in these tests. Neurocognitive areas of particular vulnerability in the Fontan group are perceptual reasoning, processing speed and executive function. Memory skills can also be problematic for a proportion of these adolescents. In the Boston adolescent Fontan cohort, scores on the General Memory Index of the Children's Memory Scale were 1 and 2SD below the expected population mean in 34 and 18% of patients respectively, which is higher than expected. Similarly, scores on the General Memory Index of the Wechsler Memory Composite were 1 and 2SD lower in 39 and 14% of patients respectively. Visual spatial skills were lower than the referent group when evaluated with the Rey–Osterrieth Complex Figure, copy and recall trials. Patients who underwent the Norwood procedure scored significantly lower than the non-Norwood group for all scores of the Rey Figure (47).

One of the most vulnerable aspects of cognitive development in individuals with critical CHD including those with a Fontan circulation pertains to executive functioning. Executive functions are a set of higher-order neurocognitive skills that include self-regulation, working memory, behavioral and mental flexibility as well as planning and organization skills. Impairments in executive functioning are common in children and adolescents with CHD, and seem more pronounced for adolescents who underwent the Fontan procedure (60–63). In a study of 463 adolescents, of whom 145 had a Fontan circulation, one-third of parents and teachers scored their behavior in the at-risk range for executive dysfunction on the Behavior Rating Inventory of Executive Function (63). In this study, neuropsychological assessment revealed some variations in the profile for executive functioning across the group with Fontan circulation and those with d-transposition of the great arteries and tetralogy of Fallot. All groups with critical CHD presented with deficits in flexibility/and problem solving; however, scores on visuo-spatial executive function tasks were more altered in the Fontan and TOF groups. Executive function issues are at the core of attention deficit hyperactivity disorder (ADHD) and concern more than a third of adolescents with univentricular hearts. Indeed, in a study of 156 adolescents with Fontan circulation, 38% of them had received a lifetime diagnosis of a disruptive behavior disorder (34 ADHD, 10 oppositional defiant disorder, and 1% adjustment disorder with disturbance of conduct). The proportion with ADHD was significantly higher than that of a same-age referent group without CHD and no differences were found between Fontan adolescents with or without a genetic abnormality (64). In another study of 133 adolescents with Fontan circulation born at term (early, 37–38 weeks' gestation or full-term after 39 weeks' gestation), more than one third of parents reported clinically concerning executive function deficits for Fontan adolescents in their daily lives. This was more prominent for metacognition skills, one of the most complex executive skills, requiring anticipation, organization and planning of one's actions (10). In this study, one third of parents also rated adolescents' ADHD symptoms as clinically concerning, whereas only 7% of the adolescents themselves rated their attention and hyperactivity symptoms as concerning. This discrepancy between parent- and self-reports has been commonly reported in previous studies, (65) suggesting that children and adolescents with critical CHD, including Fontan patients, may struggle with identifying or recognizing their own difficulties.

Importantly, the abnormal developmental milestones observed for executive function skills in childhood and adolescence may predispose the individual with CHD to clinical difficulties in self-adjustment, adherence to treatments and overall lower quality of life (66). Given the importance of deficits in executive function and its relevance in predicting long-term social and health outcomes in youth (65, 67), strategies have been designed to palliate these deficits in the population with CHD (68). These interventions, although with modest overall efficacy, provide hope that, at least some of the issues of self-regulation and working memory may be amenable to intervention in adolescents with critical CHD, including those with Fontan circulation. More research is needed to understand the extent of neurobehavioral plasticity in this at-high risk group.

Finally, social cognition is another neurocognitive area of concern for individuals with critical CHD, including those with a Fontan circulation. Adolescents with d-TGA, tetralogy of Fallot and Fontan circulation have worse scores on tests that assess their ability to interpret the emotions of other people, read social cues and recognize their own emotions (65). Bellinger et al. (47) showed that, compared to a referent group, adolescents after the Fontan procedure had lower scores at the Reading the Mind in the Eyes Test, an assessment of a person's ability to identify the emotions of others from their facial expressions. They also had difficulties identifying their feelings as reported in the self-questionnaire of the Toronto Alexithymia Scale and endorsed more autistic tendencies (i.e., autistic traits) in the Autism Spectrum Quotient self-report. A higher number of catheterizations and older age at developmental assessment were associated with worse outcomes at the Reading the Mind in the Eyes test. Autism traits were significantly associated with the presence of a genetic abnormality and higher number of cardiac surgeries.

Overall, risk factors for adverse neurodevelopmental and behavioral outcomes are highly correlated. They can also be additive and/or cumulative, especially for individuals with single ventricle who present with a chronic health condition. Independent risk factors that have emerged across multiple studies include the presence of genetic disorders, lower birth weight and gestational age, lower socioeconomic status and maternal education, longer total circulatory support time, a greater number of operations and catheterizations, longer hospital length of stay, and a greater number of complications.

Outcomes Beyond Adolescence

As the population with Fontan circulation ages, further research is needed to assess the translation of neurodevelopmental and behavioral findings in childhood and adolescence into neurocognitive function in adulthood. Recent studies show that adults with CHD are at risk for persisting neurocognitive deficits, particularly in the domain of executive functions (69), which may alter their professional and personal achievement and quality of life. These deficits seem correlated to alterations of white matter microstructure in subjects with severe CHD, suggesting long-lasting neurological effects of critical CHD for some adults. A binational study using data from Australian and New Zealand Fontan Registry found that young adults with Fontan circulation obtained worse neurocognitive outcomes in several domains compared to those with d-transposition of the great arteries. Moreover, within group comparisons for the Fontan group found that adults with Fontan circulation had more severe impairments than Fontan adolescents in psychomotor function and working memory, a domain of executive functioning. Neurocognitive deficits were associated with reduced gray and white matter brain volumes in the Fontan group (26).

Finally, recognition and management of the neuropsychological and behavioral impairments that affect many but not all patients with Fontan circulation have important implications for patient education, medical adherence, the transition from pediatric to adult healthcare systems, completion of higher education, and adult employment. It also plays a critical role for the long-term mental health outcomes of this population.

MENTAL HEALTH IN PATIENTS WITH A FONTAN CIRCULATION

Living with a chronic health condition, including with Fontan circulation, elevates the risk of psychosocial difficulties in children, adolescents and adults. As a group, many children and adolescents with CHD are at risk of psychosocial adjustment difficulties, particularly according to parental reports (70). DeMaso and colleagues (64) compared the psychiatric and psychosocial status of 156 patients (mean age, 15 years) who had undergone Fontan procedures with that of 111 healthy peers. The patient cohort had a significantly higher rate of lifetime psychiatric diagnosis (65 vs. 22%); anxiety and attention-deficit/hyperactivity disorder were most common. Furthermore, as a group, patients had worse outcomes on measures of global psychosocial functioning, anxiety, depressive symptoms, post-traumatic stress, and disruptive behavior. Risk factors of poorer psychiatric/psychosocial outcomes include male sex, lower birth weight, longer duration of deep hypothermic circulatory arrest, and lower intelligence.

Conversely, in adults, a meta-analysis of international studies using survey assessment of psychological distress revealed no consistent evidence of poorer outcomes among adults with CHD of various subtypes, although methodological heterogeneity was evident (71). The results of 3 North American studies, however, suggest that one third of adults with CHD meet diagnostic criteria for an anxiety disorder when clinical interviews are administered (72–74). Indeed, depression may not be the most prevalent psychiatric disorder in the population with critical CHD. Adults with CHD are particularly at risk of elevated anxiety and post-traumatic stress disorder (74–76). Patients' subjective health status has been more strongly associated with psychosocial outcomes than objective assessment (77), which is an important consideration for physicians faced with the symptomatic adult patient with Fontan circulation. Among adolescents and young adults with Fontan physiology, elevated symptoms of depression have been reported (28 with mild symptoms, 32% with moderate symptoms) and demonstrated to be a negative predictor of quality of life (78). Furthermore, more than half of patients endorsed worry about current health, employment, and living independently (79). MRI of the brain in adolescents with a single ventricle reveals injury in select areas that control anxiety and depression, suggesting a structural basis for the functional deficits seen (80).

Improving the understanding and clinical treatment of neurological and mental health outcomes in adults with CHD is a research priority (81). Congenital cardiologist and related professionals working with people with a Fontan circulation are encouraged to be proactive by developing efficient ways to identify psychosocial adjustment issues, collaborating with psychologists and psychiatrists to prevent mental health morbidities.

CONCLUSIONS

Patients with single ventricle are at high risk for neurologic, developmental, and psychosocial sequelae. A variety of developmental and injurious brain processes may occur, beginning during fetal development. Altered hemodynamics reduce cerebral substrate delivery, leading to abnormal brain growth and development as early as the second trimester of pregnancy. Specific forms of brain injury, such as white matter injury, stroke, or hemorrhage, may occur before, during, or after surgery. Importantly, in neonates with hypoplastic left heart syndrome, who have no medical contraindication, shorten time between birth and surgery may lower the risk of postoperative white matter injury, suggesting a potential neuroprotective effect (82).

Innate patient-related variables, including genetic factors, fetal growth, preterm delivery, and maternal education, may be the most important predictors of future neurodevelopmental outcome. Perioperative factors, such as multiple catheterizations and surgeries, as well as prolonged hospital stay, have been associated with adverse long-term neurodevelopmental outcome. Awareness and recognition of neuropsychological challenges in patients with Fontan circulation can facilitate counseling and increase access to diagnostic assessment and educational resources (4). Periodic surveillance, screening, and evaluation for neurodevelopmental disabilities starting

in early life and beyond are recommended (3, 83, 84). Identification of deficits allows appropriate therapies and patient/community education and creates opportunities to enhance academic, behavioral, psychosocial, and adaptive functioning, thus allowing each individual to achieve his or her optimal potential. Finally, recognizing the remarkable resilience of patients with single ventricle disease throughout their lives serves as inspiration to strive for innovative strategies to better support their long-term quality of life.

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JC and CR wrote the initial draft of the manuscript and revised it and accepted for publication. JN supervised and critically revised the manuscript and accepted for publication. All authors contributed to the article and approved the submitted version.

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A Multimodal Score Accurately Classifies Fontan Failure and Late Mortality in Adult Fontan Patients

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Objectives: Despite the outstanding success of the Fontan operation, it is a palliative procedure and a substantial number of patients experience late failure of the Fontan circulation. Clinical presentation and hemodynamic phenotypes of Fontan failure are considerably variable. While various parameters have been identified as risk factors for late Fontan failure, a feasible score to classify Fontan failure and possibly allow timely risk stratification is lacking. Here, we explored the possibility of developing a score based on hemodynamic, clinical and laboratory parameters to classify Fontan failure and mortality.

Methods: We performed a retrospective study in our cohort of adult Fontan patients from two institutions [$n = 198$, median follow-up after Fontan 20.3 (IQR 15.6–24.3) years], identifying those patients with clinical Fontan failure ($n = 52$, 26.3%). Various hemodynamic, echocardiographic, laboratory and clinical data were recorded and differences between patients with and without Fontan failure were analyzed. We composed a Fontan Failure Score containing 15 parameters associated with Fontan failure and/or mortality and assessed its accuracy to discriminate between patients with and without late Fontan failure as well as late mortality and survival.

Results: Late failure occurred at a median of 18.2 (IQR 9.1–21.1) years after Fontan completion. Mortality associated with Fontan failure was substantial (25/52, 48.1%) with freedom of death/transplantation/take-down of 64% at 5 years and 36% at 10 years after onset of Fontan failure, respectively. Patients with Fontan failure had a significantly higher median Fontan Failure Score compared to non-failing Fontan patients [8 points (IQR 5–10) vs. 2 points (IQR 1-5), $p < 0.001$]. The score accurately classifies Fontan failure as well as mortality as assessed with receiver operating characteristic analysis. Area under the curve of the Fontan Failure Score was 0.963 (95% CI 0.921; 0.985, $p < 0.001$) to discriminate failure and 0.916 (95% CI 0.873; 0.959, $p < 0.001$) to classify mortality.

Conclusion: We have developed an uncomplex yet remarkably accurate score to classify Fontan failure and late mortality in adult Fontan patients. Prospective validation and most likely refinement and calibration of the score in larger and preferably multi-institutional cohorts is required to assess its potential to predict the risk of Fontan failure and late mortality.

Keywords: Fontan operation, univentricular heart disease, adult congenital heart disease, Fontan failure, late mortality

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INTRODUCTION

The Fontan operation represents a milestone in the treatment of children with complex univentricular heart disease (1, 2). The continuous improvements during the past 50 years in surgical techniques, perioperative care, preoperative selection criteria and medical as well as interventional treatment strategies have resulted in substantial decreases in early and late mortality. Thus, a growing number of these patients are entering adolescence and adulthood today (2–4). Despite this outstanding success, it is a palliative procedure and the profoundly unphysiological hemodynamic principles of the Fontan circulation are fundamentally unchanged (2, 5, 6). Unavoidably, the Fontan circulation pathophysiology results in chronic venous congestion and reduced ventricular preload with a chronic low output state. Chronic Fontan circulation failure is associated with progressive clinical heart failure and ultimately premature death or the need of cardiac transplantation (4, 7–9). Importantly, with a continuously growing number of Fontan patients entering into adulthood, a substantial increase in the incidence of Fontan failure can be expected within the near future (10).

Notably, Fontan failure is not a uniform process and the hemodynamic alterations observed in patients with a failing Fontan circulation vary considerably, which has resulted in the conceptualization of distinct hemodynamic phenotypes of Fontan failure (5, 11, 12). Given the heterogeneous and likely multifactorial causes of Fontan failure and the clear lack of evidence concerning optimal therapy of these complex patients, therapeutic success is often limited, especially in patients without surgically or interventionally addressable hemodynamic issues (13–15). Early identification of patients with developing or apparent Fontan failure might allow a more timely and targeted initiation of therapies in order to delay the most likely inevitable hemodynamic demise of the Fontan circulation. Moreover, in light of limited therapeutic options, considerable mortality and increasing transplantation risk, it seems advisable to timely evaluate patients with failing Fontan for cardiac transplantation. However, to determine the optimal time point is a difficult task given the current knowledge gaps. This emphasizes the need of a consensus on precisely defining Fontan failure as well as the necessity of a feasible means to assess varying grades of Fontan failure in terms of risk stratification (16).

A feasible clinical scoring system aiming at classifying Fontan failure severity might prove valuable to address these subjects but is, however, not available at present. Therefore, in our present study we explored the possibility of developing an uncomplex and reproducible yet comprehensive multimodal Fontan Failure Score based on hemodynamic, clinical and laboratory parameters to classify Fontan failure and late mortality.

METHODS

We performed a retrospective cohort study identifying adult Fontan patients from our institutional databases. Patients were included in the study if they were followed in our institutions (German Heart Center Berlin and Charité - Universitätsmedizin Berlin) and ≥18 years of age at their last follow-up visit during the study period from April 1996 to April 2021 (**Supplementary Figure 1**). Latest available demographic, clinical, echocardiographic, cardiopulmonary exercise testing, and hemodynamic data as well as laboratory parameters were recorded from medical charts. The study was approved by the institutional review board and the appropriate Institutional Ethics Committee (Decision Number EA2/126/15); requirement of individual informed consent was waived due to the retrospective nature of the study.

Definition of Fontan Failure

Fontan failure was *a priori* defined as meeting at least one of the following clinical criteria: NYHA functional class IV, NYHA functional class III for ≥12 months without sustained improvement, >2 unscheduled hospital admissions within 12 months for heart failure symptoms, evaluation/listing for cardiac transplantation, and active protein-losing enteropathy and/or plastic bronchitis without remission for ≥6 months. Fontan failure according to our definition was classified for the last available follow-up visit. Onset of failure was then determined by recording the time point at which any criterion of Fontan failure was first met. Active protein-losing enteropathy was defined as a combination of persistent diarrhea and/or recurring edema and/or pleural effusions and/or ascites, decreased serum albumin (<3.5 g/dL) and total serum protein levels (<6.0 g/dL) and confirmation of intestinal protein loss with increased fecal alpha-1 antitrypsin levels (17). Active plastic bronchitis was defined as symptomatic episode requiring hospital admission within the last 6 months in patients with known plastic bronchitis. Initial diagnosis was required to be confirmed by observation of typical fibrinous bronchial casts (18).

Data Acquisition

Data recorded included baseline details of cardiac anatomy and Fontan operation as well as history of arrhythmias (supraventricular and ventricular tachycardia, pacemaker-requiring bradyarrythmia) and most recent demographic data, clinical status and cardiovascular medication obtained at the last available follow-up visit. For our study, history of supraventricular tachycardia (SVT) was defined as occurrence of at least one episode of symptomatic sustained SVT requiring either initiation/adaptation of antiarrhythmic treatment, cardioversion or invasive electrophysiological study documented in patients' medical charts. History of ventricular tachycardia (VT) was defined as either sustained VT recorded during Holter monitoring and/or syncope or implantation of implantable cardioverter/defibrillator after detection of non-sustained VT by Holter monitoring, as documented in medical charts. Cardiovascular medications were grouped and recorded as presented in **Table 1**. A combination of loop diuretics with any other diuretic was counted as two medications. For the exception of sotalol, ß-blockers were not grouped as antiarrhythmic medications. Invasive hemodynamic data were collected from the last cardiac catheterization performed during follow-up. Cardiac catheterizations were exclusively performed under conscious sedation with spontaneous breathing according

TABLE 1 | Characteristics of adult Fontan patients.

	Entire cohort *N* = 198	Adults with failing Fontan *n* = 52	Adults without failing Fontan *n* = 146	*p*
Baseline characteristics				0.350
Anatomy (*n*)				
Tricuspid atresia	74 (37.4%)	20 (38.5%)	54 (37.0%)	
Double inlet left ventricle	36 (18.2%)	10 (19.2%)	26 (17.8%)	
Unbalanced AVSD	18 (9.1%)	6 (11.5%)	12 (8.2%)	
HLHS	6 (3.0%)	0 (0.0%)	6 (4.1%)	
Complex TGA/ccTGA	39 (19.7%)	11 (21.2%)	28 (19.2%)	
PA/IVS	10 (5.1%)	0 (0.0%)	10 (6.8%)	
Other	15 (7.6%)	5 (9.6%)	10 (6.8%)	
Predominant ventricular morphology				0.407
Left ventricle	160 (80.1%)	40 (76.9%)	120 (82.2%)	
Right ventricle	38 (19.9%)	12 (23.1%)	26 (17.8%)	
Heterotaxy (*n*)	17 (8.6%)	4 (7.7%)	13 (8.9%)	0.788
Age at Fontan (years)	4.9 (3.4–11.3)	10.0 (4.2–18.1)	4.5 (3.3–7.4)	**<0.001**
Fontan type (*n*)				**<0.001**
Extracardiac TCPC	97 (49.0%)	12 (23.1%)	85 (58.2%)	
Intracardiac TCPC	74 (37.4%)	22 (42.3%)	52 (35.6%)	
APC	21 (10.6%)	14 (26.9%)	7 (4.8%)	
AVC	6 (3.0%)	4 (7.7%)	2 (1.4%)	
Last follow-up				
Follow-up after Fontan (years)	20.3 (15.6–24.3)	22.7 (15.2–25.7)	19.6 (15.6–23.6)	0.081
Age at last follow-up (years)	25.9 (21.4–32.8)	31.4 (25.4–39.1)	24.1 (20.7–29.8)	**<0.001**
Mortality during follow-up (*n*)	27 (13.6%)	25 (48.1%)	2 (1.4%)	**<0.001**
Ejection fraction (%)	51 (46–58)	48 (37–55)	55 (49–59)	**<0.001**
Atrioventricular valve incompetence (*n*)				**<0.001**
None/trace	74 (37.4%)	11 (21.2%)	63 (43.2%)	
Mild	73 (36.7%)	17 (32.7%)	56 (38.4%)	
Moderate	31 (15.7%)	13 (25.0%)	18 (12.3%)	
Severe	12 (6.1%)	11 (21.2%)	1 (0.7%)	
mPAP (mmHg)	12 (10–14)	15 (11–17)	11 (9–13)	**<0.001**
SVEDP (mmHg)	8 (6–12)	10 (8–14)	8 (6–10)	**<0.001**
TPG (mmHg)	4 (3–5)	4 (3–5)	4 (3–5)	0.741
PVRi (WU*m²)	0.94 (0.66–1.21)	1.02 (0.84–1.44)	0.86 (0.64–1.14)	**0.018**
TCS (%)	94 (91–96)	90 (87–94)	95 (93–97)	**<0.001**
History of arrhythmia (*n*)				
Supraventricular tachycardia	68 (34.3%)	32 (61.5%)	36 (24.7%)	**<0.001**
Ventricular tachycardia	15 (7.6%)	11 (21.2%)	4 (2.7%)	**<0.001**
Pacemaker-requiring bradycardia	52 (26.3%)	25 (48.1%)	27 (18.5%)	**<0.001**
NT-proBNP (pg/mL)	187.9 (76.8–468.9)	872.8 (375.4–1930.0)	114.0 (55.1–213.1)	**<0.001**
RDW (%)	13.9 (13.1–16.3)	17.0 (14.8–18.5)	13.4 (12.8–14.3)	**<0.001**
Cystatin C (mg/L)	1.1 (1.0–1.2)	1.2 (1.1–1.6)	1.1 (0.9–1.2)	**0.008**
Creatinin (mg/dL)	0.85 (0.75–0.97)	0.90 (0.80–1.18)	0.82 (0.75–0.91)	**0.001**
eGFR (ml/min/1.73 m²)	100 (86–119)	86 (68–108)	105 (91–120)	**<0.001**
AST (U/L)	30 (26–30)	30 (26–38)	31 (26–36)	0.999
ALT (U/L)	32 (21–41)	22 (15–39)	33 (25–41)	**0.009**
Total bilirubin (mg/dL)	1.10 (0.82–1.70)	1.30 (0.79–2.16)	1.10 (0.82–1.50)	0.340
gGT (U/L)	76 (49–127)	96 (62–180)	68 (46–109)	**0.014**
CPET VO_2peak (mL/kg/min)	21.7 (16.7–27.1)	14.1 (11.5–17.2)	23.6 (20.0–28–1)	**<0.001**
CPET VO_2peak (% of reference)	58 (45–70)	38 (32–46)	64 (54–73)	**<0.001**

(Continued)

TABLE 1 | Continued

Cardiovascular medication				
Loop diuretics	61 (30.8%)	45 (86.5%)	15 (10.3%)	
Other diuretics	77 (38.9%)	43 (82.7%)	34 (23.3%)	
ß-blockers	80 (40.4%)	38 (73.1%)	42 (28.8%)	
ACE inhibitor/AT1 blocker	81 (40.9%)	20 (38.5%)	61 (41.8%)	
Pulmonary vasodilator	36 (18.2%)	19 (36.5%)	17 (11.6%)	
Sacubitril/valsartan	4 (2.0%)	3 (5.8%)	1 (0.7%)	
Antiarrhythmics	52 (26.3%)	29 (55.8%)	23 (15.8%)	
Inotropes	10 (5.1%)	10 (19.2%)	0 (0.0%)	
Any medication	152 (76.8%)	52 (100%)	100 (68.5%)	**<0.001**
>1 medications	107 (54.0%)	51 (98.1%)	56 (38.4%)	**<0.001**
>2 medications	72 (36.4%)	47 (90.4%)	25 (17.1%)	**<0.001**

Data are presented as median (interquartile range) or frequencies (percentages). P-values < 0.05 are considered statistically significant and highlighted in bold.
Missing data: failing Fontan group AST n = 16 (30.8%); ALT n = 5 (9.6%); bilirubin n = 15 (28.8%); NT-proBNP n = 8 (15.4%); eGFR, gGT n = 2 (3.8%); RDW n = 3 (5.8%); cardiopulmonary exercise testing VO2peak n = 9 (17.3%); catheterization data n = 1 (1.9%) and non-failing Fontan group AST n = 45 (30.8%); ALT n = 42 (28.8%); bilirubin n = 63 (43.1%); NT-proBNP, eGFR n = 40 (27.4%); gGT, RDW n = 44 (30.1%); VO2peak n = 30 (20.6%); catheterization data n = 38 (26.0%); echocardiographic data n = 6 (4.1%).
ACE, angiotensin converting enzyme; ALT, alanine aminotransferase; APC, atriopulmonary connection; AST, aspartate aminotransferase; AT1, angiotensin II type 1 receptor; AVC, atrioventricular connection; AVSD, atrioventricular septal defect; ccTGA, congenitally corrected TGA; CPET, cardiopulmonary exercise testing; eGFR, estimated glomerular filtration rate; gGT, γ-glutamyltransferase; HLHS, hypoplastic left heart syndrome; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PVRi, pulmonary vascular resistance index; RDW, red cell distribution width; SVEDP, systemic ventricular end-diastolic pressure; TCPC, total cavopulmonary connection; TCS, transcutaneous oxygen saturation; TGA, transposition of the great arteries; TPG, transpulmonary pressure gradient; VO_2peak, peak oxygen uptake.

to our routine institutional protocols. In our institution, we generally do not perform routine cardiac catheterizations during follow-up at fixed ages or intervals; however, we have a policy of liberally performing clinically indicated catheterizations. Systemic ventricular end-diastolic pressures (SVEDP), mean Fontan/pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure were recorded; mean transpulmonary pressure gradient was calculated as mPAP—mean pulmonary capillary wedge pressure. Pulmonary vascular resistance (PVR) was determined by Fick's principle as previously described using oximetry (19). PVR is reported in Wood units (WU) and was indexed to body-surface area (pulmonary vascular resistance index PVRi, $WU*m^2$) (20). Echocardiographic data from last available follow-up examinations were extracted. To assess the systolic function of the single ventricle, ejection fraction (EF) was quantified using the modified Simpson's method (21). The degree of atrioventricular valve regurgitation was classified as absent/trace, mild, moderate or severe as documented by visual or quantitative assessment (22). Peak oxygen consumption (VO_2peak), defined as highest mean oxygen uptake throughout exercise over a 30 s period, was recorded from the most recent cardiopulmonary exercise testing (CPET) and is reported as absolute as well as percentage of age- and sex-specific reference values, respectively. Laboratory parameters collected included N-terminal pro-brain natriuretic peptide (NT-proBNP), red cell distribution width (RDW), total bilirubin, γ-glutamyltransferase (gGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine and cystatin C. Estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulae based on serum creatinine or, if additionally available, creatinine and cystatin C (23, 24). In patients with reoperation mortality, only data preceding the time point of reoperation was recorded.

Failing Fontan Score

From the parameters collected, those with significant differences between patients with and without Fontan failure were considered to be included in the final score composition. The final score contained 15 items: ejection fraction, grade of atrioventricular valve incompetence, SVEDP, mPAP, PVRi, history of SVT, history of VT, presence of pacemaker, eGFR, RDW, NT-proBNP, gGT, transcutaneous oxygen saturation at rest (TCS), VO_2peak and number of cardiovascular medications (excluding antithrombotic therapy). For the Fontan Failure Score, metric and ordinal variables were dichotomized. Cut-off values for dichotomization were pragmatically defined taking into account laboratory reference values, clinical considerations, previous definitions, distribution of values, discrimination between both groups by likelihood ratio and a minimal reduction of area under the curve (AUC) in receiver operating characteristic (ROC) curves by dichotomization. A score point was assigned for each value above the defined threshold and points summed up to the final Fontan Failure Score ranging from 0 to 15 points.

Statistics

Statistical analyses were performed using SPSS (version 23, IBM Corp., Armonk, NY, USA) and R (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria), graphs were prepared using Prism 9.2 (GraphPad Software Inc., La Jolla, CA, USA). Data distribution was tested using D'Agostino-Pearson test. Variables are expressed as figures (percentages) and median (interquartile range, IQR). Continuous variables were compared

using non-parametric Mann-Whitney test since the majority of variables displayed non-normal distribution. Fisher's exact test or Chi-Square-Test were used for categorical and ordinal data. Survival and freedom from transplantation or Fontan takedown as combined endpoint was assessed using Kaplan-Meier survival analysis. Receiver operating characteristic (ROC) curves were employed to assess accuracy of discriminating primary (Fontan failure) or secondary (mortality) outcomes. Potential risk factors for primary outcome were evaluated with univariable and multivariable logistic regression analysis. Those parameters with significant results ($p < 0.05$) in univariable analysis were considered for the multivariable model. Predictors were handled without transformation. To reduce the problem of overfitting and generation of invalid models caused by limited cohort sizes and number of events in combination with large numbers of analyzed predictors, the number of predictors entered into the multivariable model was limited to seven. Non-modifiable parameters (i.e., age at Fontan operation as well as the dichotomous categorical variables status post SVT, VT and pacemaker-implantation) and potentially modifiable parameters were analyzed separately. During model development, all combinations of 6–7 candidate predictors were entered and compared using the Akaike information criterion; patients with missing variables were excluded from analysis. In addition, a backward selection based on Akaike information criterion was performed. In all analyses, *p*-values < 0.05 were considered statistically significant.

RESULTS

Patient Cohort and Clinical Course of Fontan Failure

Patients' characteristics are summarized in **Table 1**. From a total of 573 Fontan patients followed in our institutions during the study period, 198 were adult at their last follow-up [median age 25.9 (IQR 21.4–32.8) years] and included in the study. Of them, 148 (74.7%) were originally operated in our institutions. From all adult Fontan patients, 52 (26.3%) were classified as patients with Fontan failure by our *a priori* defined criteria. Twenty-nine (55.8%) patients had heart failure corresponding to NYHA functional class III persisting for >12 months without clinical improvement, 18 (34.6%) had >2 unscheduled hospital admissions for worsening of heart failure symptoms within 12 months, 14 (26.9%) had active PLE and 8 (15.4%) patients had heart failure corresponding to NYHA functional class IV; 15 (28.8%) patients fulfilled more than one criterion of Fontan failure.

Of note, patients with Fontan failure were older at the time of Fontan procedure and at last follow-up (**Table 1**) while the median follow-up duration after Fontan procedure did not differ significantly compared to patients without failure. The most frequent underlying cardiac morphologies were tricuspid atresia and double inlet left ventricle and the majority had a left ventricular morphology of the systemic ventricle. Median follow-up in failing Fontan patients was 22.7 (IQR 15.2–25.7) years. Late clinical Fontan failure occurred at a median of 18.2 (IQR 9.1–21.1) years after Fontan completion. Freedom from Fontan failure in the entire cohort of adult patients was 91.7% at 10, 80.6% at 20, and 61.0% at 25 years after Fontan operation, respectively.

Mortality of patients with Fontan failure was substantial, 25 (48.1%) patients died during follow-up. Kaplan-Meier estimates for freedom of death/transplantation/take-down were 64% at 5 years and 36% at 10 years after onset of Fontan failure, respectively (**Figure 1**). Causes of death were reoperation mortality (10/25, 40.0%), terminal circulatory failure/end-stage heart failure (5/25, 25.0%), sepsis/endocarditis with multiorgan failure (4/25, 16.0%), sudden cardiac death (3/25, 12.0%) and persistent heart failure despite mechanical circulatory support (3/25, 12.0%). In those who died, evaluation for cardiac transplantation was performed in 12/25 (48.0%) patients, of whom 4/12 (33.3%) were not accepted for transplantation by the institutional transplantation board due to precarious clinical condition and 1/12 (8.3%) patient declined cardiac transplantation. Four patients died on the waiting list and 2 patients during evaluation for transplantation. Overall, 5 patients with failing Fontan were transplanted with 2 early postoperative deaths due to graft failure requiring mechanical support and multiorgan failure, respectively.

Variables Associated With Fontan Failure

Analyzed parameters are presented in **Table 1** (graphed depiction in **Supplementary Figure 2**). Baseline characteristics in respect to underlying cardiac malformation, ventricular morphology and presence of heterotaxy did not differ significantly between patients with and without Fontan failure. However, extracardiac Fontan modification was more common in patients without failure compared to those with clinical Fontan failure. A large number of variables differed significantly between those patients with Fontan failure and those without failure in comparative analyses (**Table 1**) as well as univariable analyses (**Table 2**). Failing Fontan patients had higher Fontan/pulmonary artery and ventricular filling pressures, higher PVRi, reduced ejection fraction, higher degree of AVVI, lower oxygen saturation, reduced cardiopulmonary capacity, higher NT-proBNP values, impaired renal function and increased gGT. In addition, they were more likely to have a history of SVT or VT and pacemaker implantation and were administered a larger number of cardiovascular medications. As an interesting finding, RDW was also significantly higher in patients with Fontan failure. In the multivariable analyses, two models were developed analyzing potentially variable and non-modifiable predictors, respectively (**Table 2**). VO_2peak, NT-pro-BNP, RDW and number of cardiovascular medications (multivariable model 1) as well as age at Fontan procedure, APC/AVC types of Fontan modification, presence of pacemaker and history of VT (multivariable model 2) were independent predictors of Fontan failure.

Composition and Accuracy of Fontan Failure Score

Our final Fontan Failure Score includes a set of 15 clinical, echocardiographic, invasive hemodynamic and laboratory parameters: EF, grade of AVVI, SVEDP, mPAP, PVRi, eGFR,

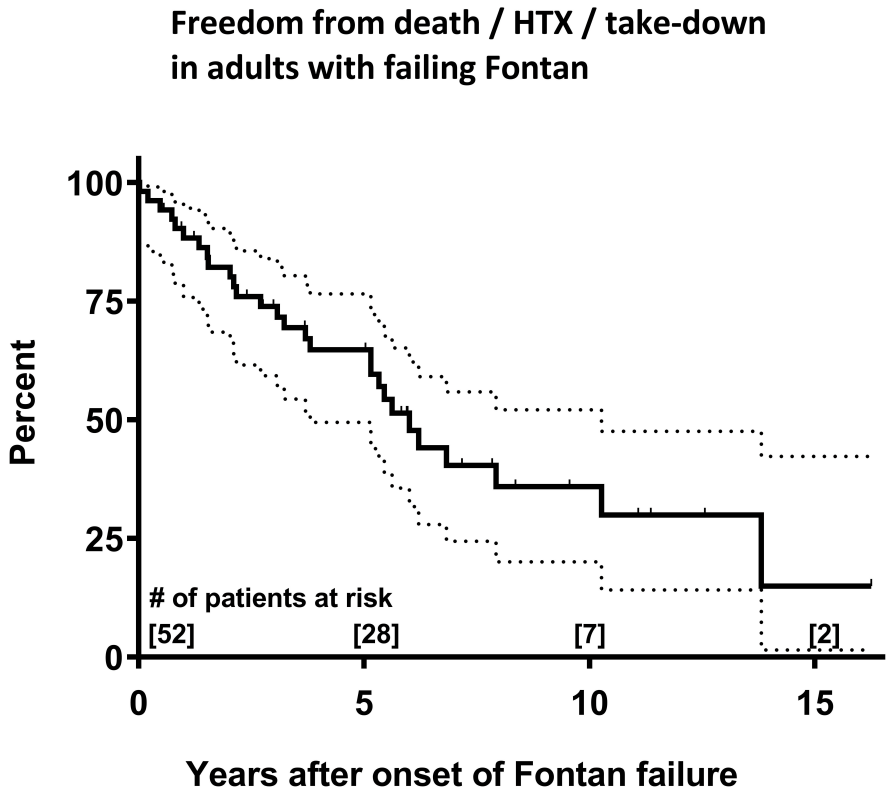

FIGURE 1 | Kaplan-Meier survival estimates for the combined endpoint of survival and freedom from cardiac transplantation and Fontan take-down in failing Fontan patients after onset of failure. Dotted lines represent 95% confidence interval. HTX, cardiac transplantation.

NT-proBNP, gGT, RDW, percentage of reference VO_2peak, TCS, history of SVT, history of VT, presence of pacemaker and number of cardiovascular medications. Non-dichotomous variables were dichotomized as follows: EF $\leq$ 45%, AVVI > mild, SVEDP $\geq$ 12 mmHg, mPAP $\geq$15 mmHg, PVRi $\geq$2.5 WU*m², eGFR < 90 ml/min/1.73 m², RDW > 14.5%, NT-pro-BNP > 500 pg/mL, gGT > 100U/L, TCS at rest < 93%, VO_2peak < 50% of reference and >2 cardiovascular medications. For each score item value beyond the defined threshold, one score point was assigned and points summed up to the final Fontan Failure Score ranging from 0 to 15 points.

The distribution of the Fontan Failure Score values stratified for patients with and without Fontan failure is depicted in **Figure 2**. Patients with Fontan failure had a significantly higher median Fontan Failure Score compared to non-failing Fontan patients [8 points (IQR 5–10) vs. 2 point (IQR 1–5), $p < 0.001$]. The score showed a remarkable accuracy in discriminating Fontan failure patients as assessed by ROC analysis. Area under the curve (AUC) of the Fontan failure score was 0.963 (95% CI 0.921; 0.985, $p < 0.001$) to discriminate failure (**Figure 3**). With a cut-off of $\geq$4 points in the Fontan Failure Score, sensitivity was 100.0% and specificity 81.4% with a positive predictive value (PPV) of 65.0% and a negative predictive value (NPV) of 100.0% to classify Fontan failure (**Table 3**). In univariable analysis, the Fontan Failure Score was a significant predictor of Fontan failure ($p < 0.001$) with an odds ratio of 2.647 (95% CI 1.981; 3.536) per score point. Also mortality was accurately classified by the Fontan Failure Score with an AUC of 0.916 (95% CI 0.873; 0.959, $p < 0.001$). For the discrimination of mortality, sensitivity was 100.0%, specificity 69.0%, PPV 33.8%, NPV 100.0% for a threshold of $\geq$4 points of the Fontan Failure Score (**Table 3**). Median Fontan Failure Score in patients that died during follow-up was significantly higher compared to survivors [9 points (IQR 6–11) vs. 2 points (IQR 1–4), $p < 0.001$].

DISCUSSION

In our study, we have developed an uncomplex yet remarkably accurate score to classify Fontan failure in a comparably large cohort of adult Fontan patients. Our multimodal Fontan Failure Score is composed of several clinical, hemodynamic, echocardiographic and laboratory variables usually collected during routine follow-up examinations of Fontan patients which makes it a feasible means to systematically assess Fontan patients for signs of failure and may provide an estimate of severity of Fontan failure.

Acknowledging the truly unique success achieved by the Fontan palliation in allowing the survival of patients with formerly virtually lethal cardiac malformations into adulthood,

TABLE 2 | Univariable and multivariable analysis for Fontan failure.

Univariable analysis				
Variable	**Odds ratio**	**95% CI**	***p***	***n***
Age at Fontan (years)	1.075	1.033; 1.119	**<0.001**	198
Age at last follow-up (years)	1.078	1.038; 1.118	**<0.001**	198
Ventricular morphology LV (*n*)	0.722	0.334; 1.563	0.401	198
Heterotaxy (*n*)	0.853	0.265; 2.742	0.789	198
Fontan modification APC/AVC (*n*)	8.059	3.330; 19.505	**<0.001**	198
TCS (%)	0.781	0.711; 0.858	**<0.001**	190
Ejection fraction (%)	0.920	0.886; 0.955	**<0.001**	194
AVVI >moderate (*n*)	5.368	2.589; 11.131	**<0.001**	190
mPAP (mmHg)	1.360	1.203; 1.537	**<0.001**	155
SVEDP (mmHg)	1.215	1.099; 1.342	**<0.001**	151
TPG (mmHg)	1.097	0.848; 1.420	0.481	153
PVRi (WU*m²)	2.215	1.273; 3.854	**0.005**	143
RDW (%)	2.138	1.694; 2.697	**<0.001**	180
eGFR (mL/min/1.73 m²)	0.964	0.948; 0.981	**<0.001**	156
AST/GOT (U/L)	1.005	0.989; 1.021	0.403	155
ALT/GPT (U/L)	0.992	0.978; 1.005	0.226	166
gGT (U/L)	1.004	1.000; 1.007	**0.035**	169
Total bilirubin (mg/dL)	1.296	0.948; 1.774	0.104	147
NT-proBNP (pg/mL)	1.001	1.001; 1.002	**<0.001**	166
CPET VO_2peak (% of reference)	0.854	0.814; 0.897	**<0.001**	174
Pacemaker (*n*)	4.081	2.055; 8.103	**<0.001**	198
s/p SVT (*n*)	4.889	2.493; 9.589	**<0.001**	198
s/p VT (*n*)	9.524	2.880; 31.495	**<0.001**	198
Cardiovascular medications (*n*)	4.373	2.893; 6.608	**<0.001**	198
Multivariable analysis (model 1, potentially variable predictors)				***n* = 124**
RDW (%)	3.566	1.111; 11.440	**0.033**	
NT-proBNP (pg/mL)	1.005	1.000; 1.011	**0.047**	
CPET VO_2peak (% of reference)	0.825	0.684; 0.994	**0.043**	
Ejection fraction (%)	1.032	0.860; 1.239	0.743	
Cardiovascular medications (*n*)	6.188	1.135; 33.731	**0.035**	
Multivariable analysis (model 2, non-modifiable predictors)				***n* = 198**
Age at Fontan (years)	1.058	1.012; 1.105	**0.012**	
Fontan modification APC/AVC (*n*)	4.193	1.502; 11.701	**0.006**	
Pacemaker (*n*)	2.497	1.116; 5.588	**0.026**	
s/p SVT (*n*)	2.204	0.965; 5.035	0.061	
s/p VT (*n*)	7.811	2.030; 30.051	**0.003**	

Parameters with units in parentheses and number of cardiovascular medications were entered as continuous variables; the remaining parameters were entered as categorical variables. Degree of atrioventricular valve regurgitation as well as type of Fontan modification were dichotomized for analysis as >mild vs. none/mild and APC/AVC vs. extracardiac and intracardiac TCPC, respectively. VO_2peak from cardiopulmonary exercise testing was analyzed as percentage of patient's age and sex-specific reference values.

P-values < 0.05 are considered statistically significant and highlighted in bold.

ALT, alanine aminotransferase; APC, atriopulmonary connection; AST, aspartate aminotransferase; AVC, atrioventricular connection; CI, confidence interval; CPET, cardiopulmonary exercise testing; eGFR, estimated glomerular filtration rate; gGT, γ-glutamyltransferase; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PVRi, pulmonary vascular resistance index; RDW, red cell distribution width; SVEDP, systemic ventricular end-diastolic pressure; SVT, supraventricular tachycardia; TCS, transcutaneous oxygen saturation; TCPC, total cavopulmonary connection; TPG, transpulmonary pressure gradient; VO_2peak, peak oxygen uptake; VT, ventricular tachycardia.

the experiences from the past decades have led to the sobering recognition that the Fontan procedure is nevertheless of a palliative character only (25). The hemodynamic characteristics of the Fontan circulation are profoundly unphysiological and the increasing availability of long-term follow-up data in a growing number of patients in recent decades has demonstrated its significant intrinsic limitations (4, 8, 25, 26). In the absence of a subpulmonary ventricle in Fontan circulation, systemic ventricular preload and consequently cardiac output are critically dependent on passive pulmonary blood flow, which in turn is essentially dependent on a low pulmonary vascular resistance as well as preserved systolic and diastolic ventricular function. Unavoidably, the Fontan circulation pathophysiology results in chronic venous congestion and reduced ventricular preload with

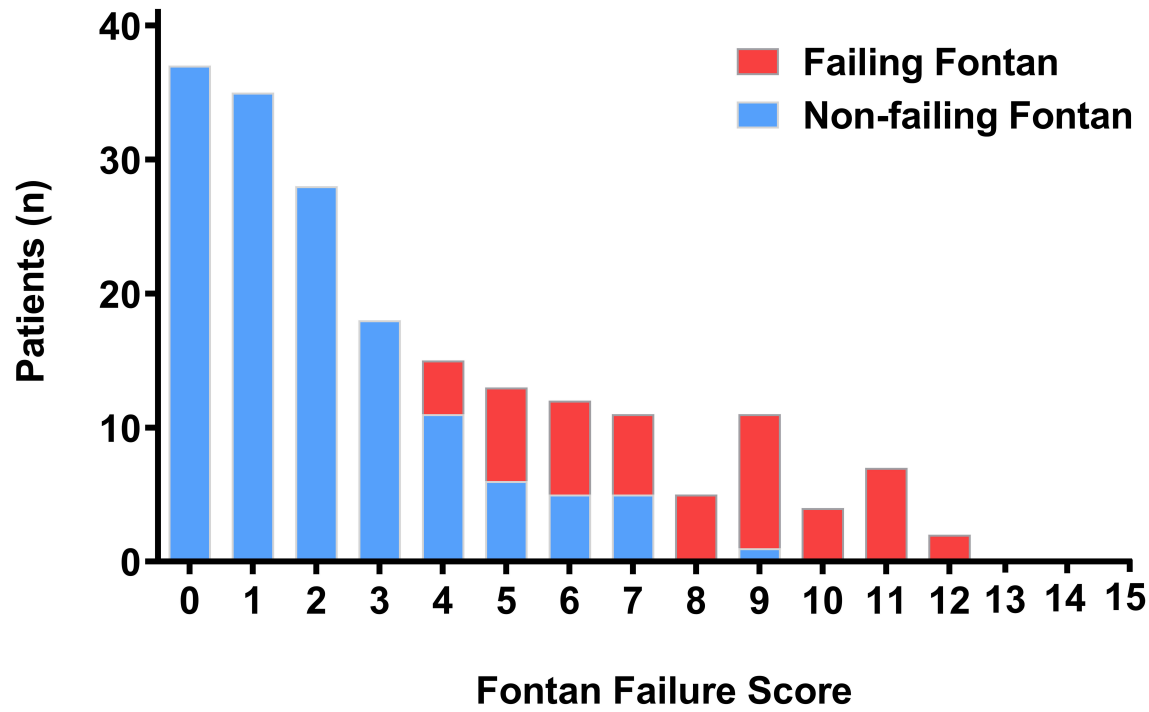

FIGURE 2 | Distribution of the Fontan Failure Score in our cohort of adult patients. Columns represent number of patients stratified for those with (red) and without (blue) Fontan failure. The abscissa indicates summed points of the Fontan Failure Score.

a chronic low output state (5, 27). As Fontan patients age, there is a continuous hemodynamic attrition of the Fontan circulation resulting in progressive heart failure and secondary organ dysfunctions with associated co-morbidities such as arrhythmias, exercise intolerance, cyanosis, protein-losing enteropathy, plastic bronchitis, Fontan associated liver disease, chronic kidney disease, frailty and coagulation disorders (7, 17, 27–31). The hemodynamic deterioration may have variable characteristics and courses but is considered to be ultimately inevitable, resulting in irreversible Fontan failure and premature death or the requirement of cardiac transplantation. As pointed out by recent population-based projections, the number of Fontan patients and consequently the number of these patients aging into adulthood will grow considerably (10). Accordingly, a substantial increase in the incidence of late Fontan failure and the number of adult Fontan patients experiencing severe and eventually life-expectancy limiting complications has to be expected within the near future.

Fontan Failure Definition

Despite the general agreement that the Fontan circulation is predestinated to eventual failure, a common definition of Fontan failure was not available until recently, when consensus definitions of Fontan associated morbidities including "Fontan circulatory failure" have been presented (18). As much as these important efforts to systematize and harmonize scientific and clinical reporting have to be sincerely acknowledged, Fontan failure was, however, defined rather descriptively and imprecise, rendering the definition to be of limited practicability to exactly classify patients in care and in clinical research. The facts that signs and symptoms of Fontan failure are variable, often develop subtly over longer periods of time and circulatory decompensation may not necessarily be irreversible likely contribute to the difficulties in establishing an unambiguous definition. Moreover, it has been recognized that the assessment of heart failure in patients with congenital heart disease is challenging due to the patient's adaptability to their chronically reduced output state and often clinically unapparent deterioration (26, 32). In the present study, we have employed stringent, pragmatic clinical criteria to define Fontan failure in our cohort. These are arbitrary, however, we intended to encompass the variable spectrum of Fontan failure manifestation; not only including persistent heart failure, refractory protein-losing enteropathy and plastic bronchitis

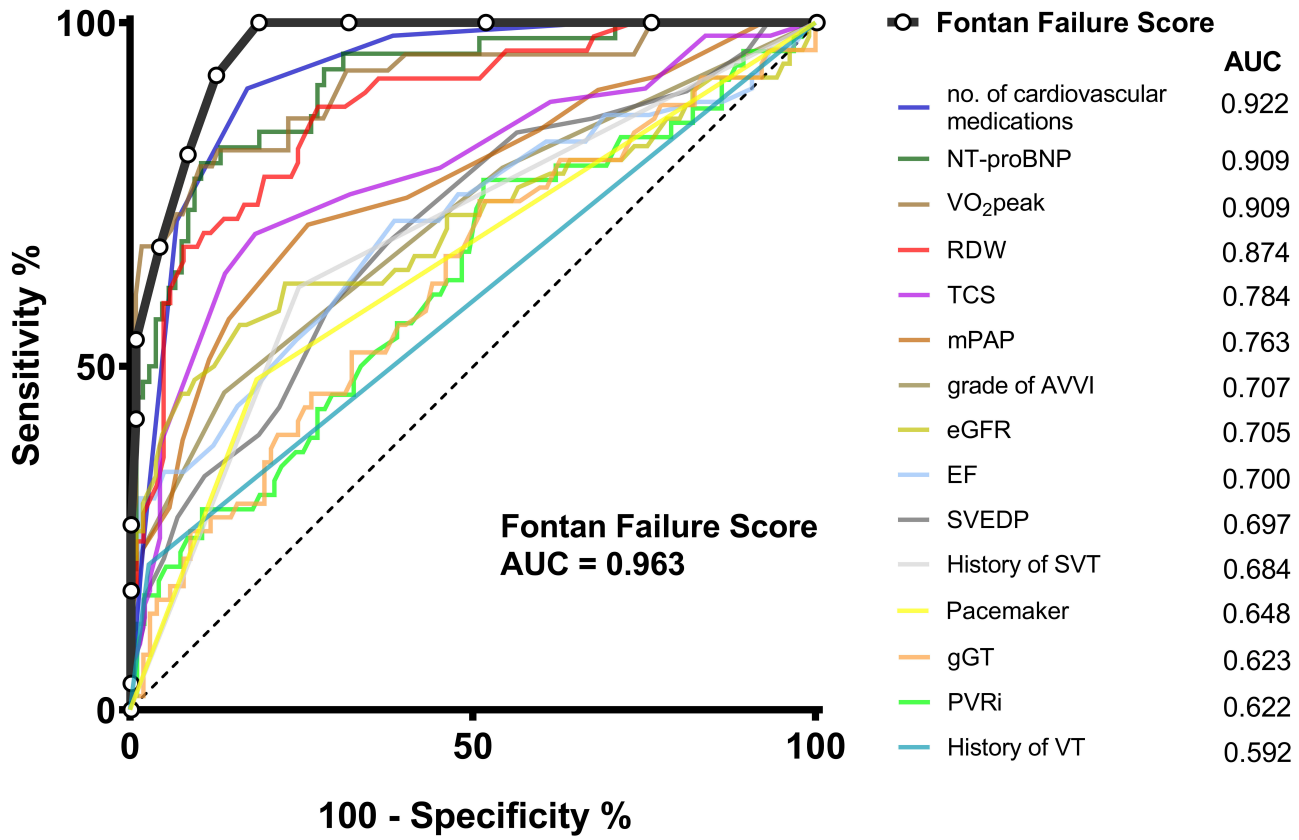

FIGURE 3 | Receiver operating characteristic curves of the Fontan Failure Score and its components to discriminate Fontan failure in our cohort of adult Fontan patients. Area under the curve for each parameter is indicated in the legend. AUC, area under the curve; AVVI, atrioventricular valve incompetence; EF, ejection fraction; eGFR, estimated glomerular filtration rate; gGT, γ-glutamyl transferase; mPAP, mean pulmonary artery/Fontan pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PVRi, pulmonary vascular resistance index; RDW, red cell distribution width; ROC, Receiver operating characteristic; SVEDP, single ventricular end-diastolic pressure; SVT, supraventricular tachycardia; TCS, transcutaneous oxygen saturation at rest; VO2peak, peak oxygen uptake in cardiopulmonary exercise testing; VT, ventricular tachycardia.

but also conditions with frequent circulatory decompensations requiring hospital admittance and therapeutic interventions such as recurrent dysrhythmias. Nonetheless, classification by our Fontan failure definition, is also certainly not unambiguous and might be prone to inconsistencies based on variabilities in patient assessment and institutional practices. Of note, there is accumulating evidence that Fontan failure is not a uniform process since the hemodynamic alterations observed in patients with failing Fontan may vary considerably (5, 6, 11, 12). This has resulted in the conceptualization of distinct hemodynamic phenotypes of Fontan failure (11). However, up to now, the proposed classifications of Fontan failure phenotypes are largely grounded on theoretical and observational considerations and await substantiation by systematic analysis of hemodynamic data in adequately sized patient cohorts. Future studies will have to invest further effort in the important task to more precisely characterize and define Fontan failure.

Assessment of Fontan Failure

A large variety of parameters has been shown to be significantly associated with adverse late outcome after Fontan operation including anatomic features, peri- and postoperative variables, single ventricular function, atrioventricular valve regurgitation, arrhythmias, cardiopulmonary capacity and signs of secondary organ dysfunction among others (8, 9, 33–39). While these might be useful for a vague estimate of a given patients risk for adverse events, they are unfeasible for the assessment of the severity of hemodynamic impairments. Moreover, findings were not always consistent across studies, resulting in uncertainties concerning the appraisal of individual risk factors' impact on prognosis.

A clinical scoring system aiming at classifying Fontan failure and grading Fontan failure severity might prove valuable to address several urgent issues. It may allow a more reliable longitudinal evaluation of individual Fontan patients' clinical status and facilitate detecting deterioration of the Fontan

TABLE 3 | Fontan Failure Score accuracy according to thresholds.

Threshold Fontan failure score	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)	+LR	–LR
Primary outcome: Fontan failure						
4	100.0 (93.2; 100.0)	81.4 (74.1; 87.4)	65.0	100.0	5.2	0.0
5	92.3 (81.5; 97.7)	87.6 (81.1; 92.5)	73.8	97.0	7.9	0.1
6	80.8 (67.5; 90.4)	91.7 (86.0; 95.7)	78.8	92.5	10.5	0.2
7	67.3 (52.9; 79.7)	95.7 (91.2; 98.5)	85.0	88.6	15.9	0.4
8	53.9 (39.5; 67.8)	99.3 (96.2; 99.9)	96.6	85.8	78.6	0.5
9	42.3 (28.7; 56.8)	99.3 (96.2; 99.9)	95.8	83.3	64.6	0.6
10	26.9 (15.6; 41.0)	100.0 (97.5; 100)	100.0	78.9	-	0.8
11	17.3 (8.2; 30.3)	100.0 (97.5; 100)	100.0	77.2	-	0.8
12	3.9 (0.5; 13.2)	100.0 (97.5; 100)	100.0	74.5	-	1.0
Secondary outcome: mortality						
4	100.0 (87.2; 100.0)	69.0 (61.5; 75.8)	33.8	100.0	3.2	0.0
5	92.6 (75.7; 99.1)	76.6 (69.5; 82.7)	38.5	98.5	4.0	0.1
6	77.8 (57.7; 91.4)	81.9 (75.3; 87.3)	40.4	95.9	4.3	0.3
7	74.1 (53.7; 88.9)	88.3 (82.5; 92.7)	50.0	95.6	6.3	0.3
8	63.0 (42.4; 80.6)	93.0 (88.1; 96.3)	58.6	94.1	9.0	0.4
9	51.9 (32.0; 71.3)	94.2 (89.5; 97.2)	58.3	92.5	8.9	0.5
10	33.3 (16.5; 54.0)	97.7 (94.1; 99.4)	69.2	90.3	14.3	0.7
11	25.9 (11.1; 46.3)	98.8 (95.8; 99.9)	77.8	89.4	22.2	0.7
12	7.4 (0.9; 24.3)	100.0 (97.9; 100.0)	100	87.2	-	0.9

+LR, positive likelihood ratio; –LR, negative likelihood ratio; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

circulation. Thereby it could help in determining the appropriate time points for therapeutic interventions and ultimately cardiac transplantation. In addition, by providing a more objective assessment of Fontan failure, it would allow more accurate interindividual comparisons in patients with heterogeneous phenotypes and severities of Fontan failure which would represent an important tool for future studies investigating outcome and interventions in patients with failing Fontan. Previously, a score to assess the risk of late mortality after Fontan operation has been proposed (40). The meta-analysis integrates data from various prior studies and includes a large number of Fontan patients. Such score might prove feasible in identifying Fontan patients with increased late mortality risk, however, the score is unable to identify Fontan failure or grade Fontan failure severity which would clearly be of broader clinical value since it would offer the possibility of timely interventions in order to prevent late mortality rather than assessing an overall mortality risk for an unknown future time frame. Moreover, the practicability of this score seems limited as it included several non-modifiable parameters such as preoperative hemodynamics, anatomic features and type of Fontan modification and several distinct risk factors have been combined to single score items (40). Therefore, we conducted the present study seeking to develop a practicable, uncomplex scoring system that yet accurately identifies patients with Fontan failure.

Differences Between Failing and Non-failing Fontan Patients

In our cohort of adult Fontan patients we have assessed a variety of variables. While for most of the hemodynamic parameters studied, we observed quite anticipated results in failing Fontan patients in respect to overall reduced systolic ventricular function, increased ventricular filling pressures and Fontan pressures as well as slightly increased PVR (**Table 1**; **Supplementary Figure 2**), several of our additional findings are particularly notable.

For NT-proBNP or BNP as biomarkers for heart failure, previous studies have yielded somewhat inconsistent results in Fontan patients. One study reports a correlation with functional class of Fontan patients while others did not find a clear association with Fontan failure; overall, the number of studies on this subjects are quite limited (41–43). Moreover it has been reported that atriopulmonary Fontan modifications (APC) have higher BNP levels compared to extracardiac Fontan modifications (41, 42). In our cohort, we found a significant difference of NT-proBNP levels between failing and non-failing Fontan patients and therefore included it in our Fontan Failure Score. Analyzing different Fontan modifications, we also found significantly higher NT-proBNP levels in APC compared to the extracardiac modification in non-failing Fontan patients [483.8 (IQR 270.0; 787.5) vs. 78.4 (IQR 44.9; 172.2) pg/mL, $p < 0.001$, **Supplementary Figure 3**], however there was no significant difference between modifications in failing Fontan patients ($p = 0.790$, **Supplementary Figure 3**). We would conclude that although individual values and particular cut-offs might not accurately identify suboptimal Fontan hemodynamics, NT-proBNP nevertheless represents a useful parameter that could well indicate circulatory deterioration in Fontan patients during longitudinal follow-up.

In regard to RDW, it has previously been recognized to be associated with heart failure and predictive for resulting mortality

in adults with normal biventricular anatomy, irrespective of the presence of anemia (44, 45). There is, to the best of our knowledge, only one previous report that studied this parameter in Fontan patients (46). The authors observed a correlation of increased RDW with impairment of Fontan hemodynamics in terms of increased central venous pressure and decreased mixed venous oxygen saturation and cardiac index. However, the study cohort was rather small-sized and included only children. Our study is the first to show that RDW is also a promising variable to indicate hemodynamic impairment in a large cohort of adult Fontan patients. RDW was significantly increased in adults with Fontan failure (**Table 1**) and it displayed a good discrimination between failing and non-failing Fontan patients (**Figure 3**). Since RDW is an inexpensive and readily available laboratory parameter, our data suggests that it should be included in the routine follow-up blood tests of Fontan patients.

Previously it has been reported that simple clinical variables such as oxygen saturation (TCS) are predictive for adverse outcome in adult Fontan patients (39). We also recently showed that cyanosis is an independent risk factor for mortality during long-term follow-up across age groups in Fontan patients (47). In our cohort, TCS is slightly but significantly lower in failing Fontan patients (**Table 1**) and satisfyingly classifies Fontan failure (**Figure 3**). Although reasons for cyanosis in Fontan patients are multifactorial, TCS is an appealingly simple parameter for the longitudinal assessment, indicative of attrition of the Fontan circulation. The same holds true for the number of cardiovascular medications. In previous studies, diuretic therapy has been related to late mortality after Fontan, likely representing a surrogate parameter for circulatory failure (36, 48). Not surprisingly, in our cohort the number of prescribed cardiovascular medications was significantly higher in failing Fontan patients, however, it unexpectedly accurately discriminated failing Fontan patients with an AUC of 0.922 (**Figure 3**). These simple variables collected during detailed standardized follow-up examinations by themselves may already have a good capacity to indicate deterioration and anticipate Fontan failure.

Fontan Failure Score

Our final multimodal Fontan Failure Score is composed of a total of 15 parameters. These include well-established risk factors of adverse late outcome but also less recognized indicators, as discussed above. Choice of variables was also guided by the rationale to analyze parameters indicative of hemodynamic deterioration and secondary organ dysfunction commonly collected during comprehensive follow-up according to current recommendations (16). Also weighing up feasibility of the score by limiting components to a reasonable number of parameters that are routinely collected during follow-up against a maximum of discrimination accuracy as well as limiting the number of non-variable parameters which might reduce the score's ability to indicate clinical improvement during longitudinal assessments were taken into consideration during score composition.

Our score, however, was only evaluated in our development cohort and yet requires external validation to reliably assess its diagnostic precision and validity with a priori set cut-offs. It will also likely need refinement and calibration. Moreover, our Fontan Failure Score offers the possibility of grading Fontan failure severity, however to assess the appropriateness of grading and determining meaningful discriminating cut-offs, longitudinal studies will be required. Various additional diagnostic modalities and parameters that may potentially improve accuracy of the Fontan Failure Score were not investigated in our study. In agreement with previous studies, laboratory parameters indicative of hepatic injury such as transaminases and bilirubin were in general only marginally elevated in the Failing Fontan patients although Fontan-associated liver disease (FALD) is a frequent co-morbidity during long-term follow-up (31, 49, 50). Only gGT showed a significant increase in our patients with Fontan failure and was included in the Fontan Failure Score. Nonetheless, also gGT is reported to only inconsistently correlate with severity of chronic hepatic injury in FALD (49, 50). Other non-invasive modalities assessing the extent of FALD that can easily be implemented in routine follow-up examinations such as hepatic ultrasound and transient elastography might be superior indicators of FALD progression and thereby deterioration of Fontan hemodynamics. Concerning CPET, reduced cardiopulmonary capacity indicating limited cardiac output as a result of compromised Fontan hemodynamics is a known predictor of adverse late events and mortality (37, 51). Nevertheless, additional parameters assessed in CPET beyond VO_2peak such as limited heart rate reserve have been shown to correlate with adverse outcome and might classify Fontan failure more accurately (48, 52). Moreover, additional laboratory parameters such as serum uric acid, previously observed to be related to reduced exercise capacity and unfavorable outcome in adult Fontan patients, might prove valuable to increase our score's precision to classify Fontan failure (53).

In addition, several components of our score may be affected by confounders. For example, number of cardiovascular medication is likely influenced by practice variability among institutions, which has been reported to be considerable; a fact that is largely based on the profound lack of evidence concerning heart failure treatment in failing Fontan patients (54, 55). Also increased PVR, as an important pathophysiologic component of Fontan failure, will be affected by pulmonary vasodilator treatment. In fact, more than half of our failing Fontan patients received pulmonary vasodilators. In respect to renal function assessment, it has been suggested that creatinine-based determinations of eGFR overestimate actual glomerular filtration rate and cystatin C-based eGFR might be more reliable (30, 56, 57). In our study, cystatin C was available in only 16 (33.3%) of the failing Fontan patients and in 56/198 (28.3%) of the entire cohort of adult Fontan patients. Nonetheless, comparing both methods of eGFR determination in our cohort showed higher eGFR values in the creatinine-based calculation with a fixed bias (mean 17.9 $\pm$ 12.7 ml/min/1.73 m^2, corresponding to 18.6 $\pm$ 14.2%, $p < 0.001$) as assessed by Bland-Altman plot. Thus, the method of eGFR calculation likely affects the assessment of renal function and thereby potentially the Fontan Failure Score.

Yet, despite these restrictions and potential confounders, our Fontan Failure Score shows a remarkable diagnostic accuracy, precisely discriminating patients with and without Fontan failure

in our cohort with an AUC of 0.963 in ROC analysis. In addition, also mortality was accurately classified by the Fontan Failure Score. These promising results suggest that our proposed Fontan Failure Score may represent a useful and precise clinical tool to identify patients with developing Fontan circulation failure that may facilitate diagnostic and therapeutic decision making in the long-time care of Fontan patients. It therefore represents an important step towards a more accurate identification and systematic assessment of late Fontan failure.

Limitations

Beyond limitations already discussed, additional limitations of this study are inherent to its restriction to patients from two institutions as well as its retrospective observational design for which consistency in data acquisition and follow-up examinations are not given. Not all parameters were available for the entire cohort, which potentially introduces some selection bias and, importantly, limits statistical analyses and multivariable modeling. Thresholds of dichotomized parameters were set reasonably according to distribution and discrimination; however, they are nonetheless arbitrary. Interpretability of peak VO_2, as effort-dependent variable, is limited since we did not record parameters indicating exercise effort. Fontan failure criteria were retrospectively determined from medical records but clinical symptoms were not assessed which might result in some misclassification bias. We only analyzed patient's last follow-up visit and retrieved information from medical records to define the time point of fulfilling our criteria for Fontan failure. However, our analyses do not take longitudinal clinical changes of patients in respect to periods of improvement or decompensation between these time points and its relation to the proposed Fontan Failure Score into account. Therefore, future prospective longitudinal studies are indispensable to validate our score, evaluate its accuracy to predict Fontan failure and assess the impact of initiated therapies. Echocardiographic determination of single ventricular function has important limitations. More reliable modalities such as cardiac MRI were only inconsistently performed and therefore not analyzed. We have only assessed adult Fontan patients and our Fontan Failure Score might yield differing results in the pediatric age group, since Fontan failure in children is likely to be governed by distinct mechanisms (58, 59).

CONCLUSIONS

We have developed an uncomplex but remarkably accurate score to classify Fontan failure and late mortality in adult Fontan patients. The Fontan Failure Score is comprised of several clinical, hemodynamic, echocardiographic and laboratory parameters usually collected during routine follow-up examinations. This renders the score a feasible means to assess Fontan patients for signs of failure. Prospective longitudinal validation and most likely refinement and calibration of the score in larger and preferably multi-institutional cohorts are required to explore its potential to grade Fontan failure severity and to actually predict the risk of Fontan failure and late mortality.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study involving human participants was reviewed and approved by Ethics Committee of the Charité - Universitätsmedizin Berlin. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PK conceptualized the study, performed data acquisition and analysis, and drafted the manuscript. SO and FB were involved in conceptualization and data analysis as well as review and editing. AS, MS, FD, JN, and FB helped in data acquisition and reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.767503/full#supplementary-material

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REVIEW
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Late Fontan Circulatory Failure. What Drives Systemic Venous Congestion and Low Cardiac Output in Adult Fontan Patients?

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The Fontan circulation provides definite palliation for children born with a single anatomical or functional ventricle by diverting systemic venous blood directly to the pulmonary arteries, effectively rendering systemic venous return into portal vessels to the lung. Although this restores pulmonary blood flow and avoids the mixture of oxygenated and deoxygenated blood, it also results in elevated systemic venous pressures and low cardiac output. These are the two hallmarks of any Fontan circulation and the cause of Fontan circulatory failure later in life. We highlight the determinants of systemic venous return, its changed relationship with the pulmonary circulation, how it affects preload, and the changed role of the heart (myocardium, valves, and heart rate). By critically evaluating the components of the Fontan circulation, we hope to give some clues in how to optimize the Fontan circulation and avenues for future research.

Keywords: univentricular heart, Fontan circulation, cavopulmonary connection, Fontan circulatory failure, heart failure

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INTRODUCTION

Francois Fontan and Eugene Baudet's pioneering work on the surgical treatment of patients with tricuspid atresia eventually led to the development of the Fontan operation (1). The surgeons' main aim was to restore pulmonary blood flow and to eliminate the mixture of venous and oxygenated blood. Whilst this remains crucial to the concept of the Fontan circulation, Drs Fontan and Baudet's hypothesis that this required some form of an atrial (or ventricular) "pump" was later superseded when de Leval nicely illustrated that the right atrium as a valveless chamber does not contribute to blood flow at the higher venous pressures observed in Fontan patients. The right atrium also has no reservoir function, rather causing energy loss than contributing to hemodynamic efficiency (2). The use of computational fluid dynamics avant-la-lettre to demonstrate the advantage of the total cavopulmonary connection over the atriopulmonary connection is testimony to the innovation that has made advancements in the field of congenital heart disease possible.

While the Fontan operation became the final palliation for thousands of patients with a single anatomical or functional ventricle worldwide, pediatric and adult congenital cardiologists are increasingly confronted with the limitations posed by the circulation created many years ago (3–5). There is no doubt that the surgical intervention has dramatically improved the longevity and quality of our patients' lives, but long-term morbidity and mortality remain high (4). Exercise intolerance, Fontan-associated liver disease, protein loosing enteropathy, plastic

bronchitis, arrhythmia, thrombo-embolic complications, and neuro-cognitive limitations are just a few of the complications related to Fontan circulatory failure that clinicians are increasingly seeing in clinical practice.

The extent of the definition of "Fontan circulatory failure" recently proposed in ESC Heart Failure also underscores our lack of knowledge with regards to Fontan physiology and likely also translates into a lack of effective treatment options for Fontan circulatory failure (6). As Fontan, Baudet, Marcelletti, and de Leval did in the past, there is an urgent need for innovative solutions improving palliation of single ventricle physiology and tackling the complications unintentionally caused by the construction of a Fontan circulation. Although we have published a more theoretical approach to conceptualize the Fontan circulation (5), the aim of this introductory article is to present our current understanding of Fontan physiology and the different sources and components of Fontan attrition over time into adult life. There is no doubt that every Fontan circuit constructed bears in itself the components of its own failure. But since innovation follows understanding based on simple observation, the case of the failing Fontan is not necessarily hopeless.

CREATING THE FONTAN CIRCULATION

De Leval's observations paved the way for the modern version of a Fontan circuit: the total cavopulmonary connection (2). In the neonatal period and early infancy, interventions guarantee adequate systemic flow (coarctectomy, Damus-Kaye-Stansel, or Norwood arch repair in case of obstruction) while simultaneously balancing pulmonary blood flow (banding or shunt). This is followed by diversion of systemic venous return from the superior caval vein to the pulmonary artery at the age of 3–9 months (bidirectional Glenn or partial cavopulmonary shunt), followed by Fontan completion at the age of 2–4 years (connection of the inferior caval vein to the pulmonary artery) (7).

From the beginning, it was clear that not all Fontan circulations would be created equal. For example, a patient starting off with slightly higher pulmonary vascular resistance, pulmonary artery hypoplasia, distortion of the pulmonary arteries, AV valve regurgitation, or ventricular dysfunction will likely have worse Fontan physiology after palliation. Maybe more significantly, this also stresses the importance of a carefully and considerate construction of the Fontan circulation and especially its most limiting building block: pulmonary circulation. Allowing sufficient growth of the pulmonary arteries prior to referring for a Glenn may be crucial if one considers the implications of small changes in pulmonary vascular resistance on cardiac output and systemic venous pressure in a Fontan patient as outlined below (8–10).

What is in essence an extra-cardiac operation nevertheless has dramatic consequences for the cardiovascular system. The Fontan circuit consists of the surgical venous connection and the graft, the pulmonary arteries, the pulmonary capillaries, and pulmonary veins and renders the systemic venous return into portal vessels to the lung (5). Since systemic venous return is connected directly to the pulmonary arteries without a subpulmonary ventricle, the Fontan circuit imposes an additional flow restriction, causing upstream congestion and decreased downstream flow (11). The main function of the Fontan circuit is to generate sufficient hydraulic power to overcome the resistance of the pulmonary circulation at rest and during exercise.

PHYSIOLOGY OF THE FONTAN CIRCULATION

Venous Return: In the Driver's Seat

Fontan at Rest

It remains remarkable that venous pressure in the Fontan portal system is sufficient to generate pulmonary blood flow. In ideal circumstances, a mean pulmonary arterial pressure of (at least) 15 mmHg is required to keep the pulmonary vasculature patent (i.e., higher than alveolar pressure and distal pulmonary venous pressure) (12). In a Fontan patient, this is accomplished by a combination of mainly passive and weakly active forces [peripheral muscle contraction (13), respiratory inspiration (14, 15), and downward displacement of the atrioventricular valve expanding atrial volumes (12)]. We must also consider that the absence of a subpulmonary ventricle in the Fontan circulation has additional consequences such as a lack of dilatation and recruitment of pulmonary blood vessels, lack of kinetic energy, asymmetric pulmonary perfusion, and loss of pulsatility. Loss of pulsatility may further increase the energy necessary to propel blood through the pulmonary vasculature. Since normally one third of the energy generated by the right ventricle is absorbed by the pulmonary blood vessels in systole and restituted in diastole to maintain patency of the distal vessels, it follows that pulmonary impedance increases when hydraulic power converts into a pure pressure gradient as is the case in the Fontan circulation.

Second, since the superior caval vein (±30% of venous return), inferior caval vein (±45% of venous return), and hepatic veins (±25% of venous return) now function as portal vessels to the lungs, factors determining systemic venous return will determine filling of the systemic ventricle and eventually cardiac output. Macé et al. described that such a circulation results in a downward shift of the venous return curve (16). As this would result in decreased venous return, not matching (required) cardiac output, blood volume increases as a physiologic adaptation to the Fontan state. This increases cardiac output at the expense of an increase in systemic venous pressures and increased overall blood volume. Simultaneously (and advantageously), the higher systemic venous pressure will result in recruitment of pulmonary blood vessels, hence lowering pulmonary vascular resistance.

Third, there is a shift of the mean circulatory filling pressure, which is usually located at the level of peripheral small veins and venules to the pulmonary vasculature. With the atrial pressure as back pressure, the venous resistance is now similar to pulmonary vascular resistance. This shift illustrates the importance of the pulmonary circulation and how it functions as a dam causing congestion upstream and low flow downstream, the two hallmarks of Fontan physiology (16). From this it comes to

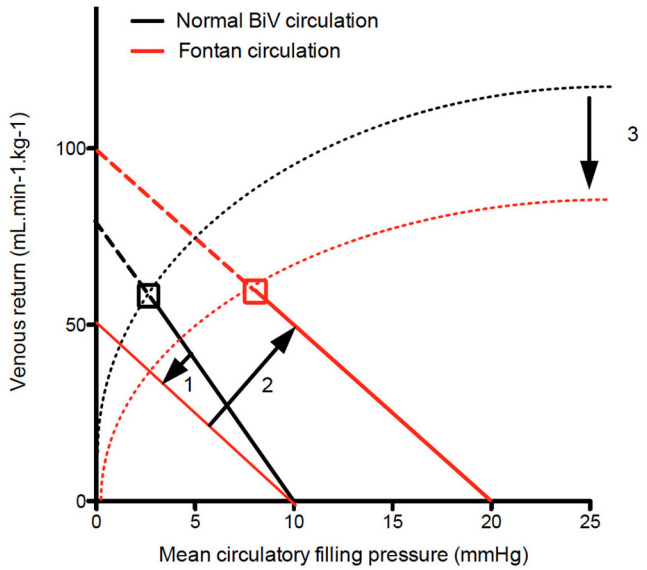

FIGURE 1 | Venous return curve. In Fontan patients the venous return curve shows on downward rotation due the pulmonary vasculature (and hence PVR) being incorporated in venous return (1). Volume load brings back venous return at the level of biventricular circulation at the expense of an increase in mean circulatory filling pressure (2). Finally since left atrial pressure is the backpressure for venous return, increased left atrial pressure will result in decrease cardiac output. The dashed lines indicate the Frank Starling curve, indicating lower contractility (3).

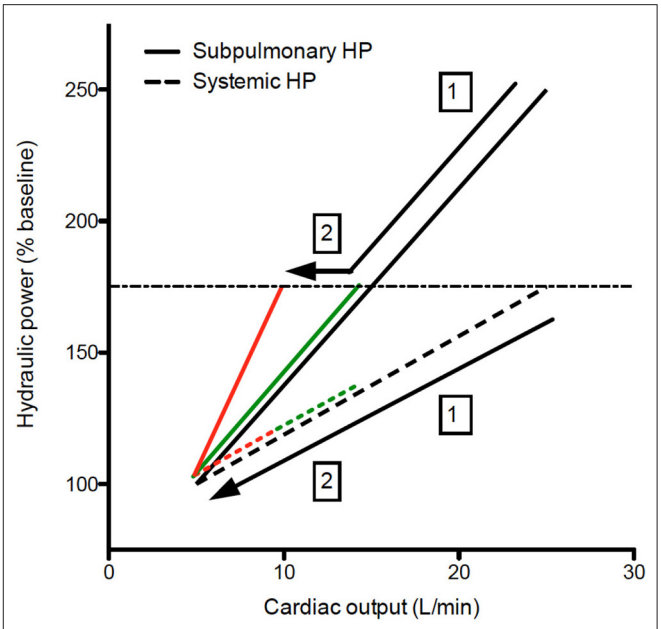

FIGURE 2 | Hydraulic power relative to cardiac output during exercise. Both on healthy controls and Fontan patients, the increase in hydraulic power as expressed relative baseline to augment cardiac output is larger on the subpulmonary ventricle, even in NYHA Fontan patients (green lines), the increase in hydraulic power (and hence cardiac output) is limited (1). NYHA ≥ 2 Fontan patients (red lines), a steeper increase in hydraulic load will further limit the increase in cardiac output during exercise (2). The dashed horizontal line represent hemodynamic reserve of the Fontan patients, which is limited due to the absence of a subpulmonary ventricle. Black line, controls; Green lines, NYHA 1 Fontan; Red lines, NYHA ≥ 2 Fontan.

reason that factors affecting mean filling pressure (blood volume and venous muscle tone), atrial pressure (atrial compliance, contractility, and valve competence and resistance but also ventricular filling pressures) and venous resistance (autonomic tone, muscle pump, intra-abdominal pressure, flow inefficiency, pulmonary artery dysplasia, and pulmonary vascular resistance) will affect venous return (**Figure 1**).

Fontan During Exercise

Exercise capacity is determined by the ability of the cardiorespiratory system to deliver oxygenated blood to the working muscles, thereby providing substrate for energy generation. Normally the main factor determining oxygen delivery is the cardiac output (CO) generated by the hydraulic power of each ventricle (17). In a normal circulation right atrial pressure (and systemic venous pressure) changes little during exercise (18), making systemic venous return largely independent of "afterload" because of the intervening right ventricle. In a Fontan circulation, there is no subpulmonary pump, so systemic venous return (provided by the peripheral muscle pump, venous compliance, and venomotor tone) is responsible for providing the work necessary to augment flow. Prior research has consistently demonstrated that very little work is required to generate CO against the vascular load of the pulmonary circulation under resting conditions (see also paragraph above) (19, 20). This is also the condition sine qua non for a working Fontan circulation. However, during exercise, pulmonary artery pressure normally increases in a near-linear manner such that there is a dramatic increase in the work required by the subpulmonary pump in order for CO to augment normally (21–23). Moreover, intensive exercise training results in disproportionate subpulmonary cardiac remodeling, highlighting the disproportionate effect of exercise on the subpulmonary pump (24). Insufficient systemic venous return augmentation during exercise in Fontan patients due to limitations in the ability to increase systemic venous pressures against pulmonary vascular load is the primary source of exercise limitation in a Fontan circulation. Indeed, Egbe et al. clearly indicated that steeper pressure-flow plots (independent of the cause) are associated with worse exercise tolerance (25). But their study in poor Fontan patients and our earlier study in "good" Fontan patients also highlights the significant limitations in CO augmentation (i.e., CO at peak exercise) during exercise when compared to a normal biventricular system (25, 26) (**Figure 2**).

It is well-known that ventricular and stroke volumes oscillate with respiration. In a normal biventricular physiology this results in peak right and left ventricular volumes (and stroke volume) at peak inspiration and expiration, respectively, a differential effect which is maintained throughout exercise (27). In a Fontan circulation, Inferior caval vein flow shows marked respiratory variability with inspiratory facilitation and expiratory inhibition,

which becomes less evident during exercise (28). So aside from maintaining a low systemic venous pressure (at rest and during exercise), providing sufficient hydraulic power to increase CO (during exercise), the right heart and pulmonary circulation are important to buffer venous return and keep left ventricular stroke volume constant (at rest but especially during exercise). Indeed, we have shown that the respiratory pump in Fontan patients causes a respiratory-induced variation in stroke volume (which appears to exacerbated during exercise) which is only partly attenuated by the pulmonary circulation (15).

The paragraphs above delineate the importance of systemic venous return for a well-functioning Fontan circulation. They also suggest considering the place of the pulmonary circulation which renders superior and inferior caval vein as well as hepatic veins into portal vessels toward the pulmonary circulation with its advantages (pulmonary blood flow) and disadvantages (increased systemic venous pressure, decreased cardiac output, and increased stroke volume variation at rest but especially during exercise). In doing so, preload to the ventricle which is usually abundant, becomes limited and systemic venous return through the pulmonary circulation becomes the main determinant in the regulation of pulmonary blood flow and hence exercise capacity.

Understanding the importance of the Fontan portal circuit for a well-functioning Fontan circulation may also give us some clues in how to optimize the Fontan circulation.

Power loss in the TCPC has been a point of intensive research since pressure gradients across surgical connections, uneven distribution of pulmonary flow to the lungs, and collision of flow is disadvantageous for the Fontan circulation (29, 30). Offsetting of the caval anastomoses was recognized early on, and adaptations for the Fontan connection reducing power loss have been suggested. Oftentimes, the size of the Fontan conduit (either small from the beginning, or reduced in size whilst aging) may result in suboptimal hemodynamics which will be exacerbated during exercise as assessed by 4D MRI flow (31–33). Likely optimizing the Fontan conduit early in life (allowing sufficient pulmonary artery growth and additional shunt if needed) and later in life (stenting of the conduit to adult size or stenting of a hypoplastic left pulmonary artery if present) are required to maintain optimal Fontan hemodynamics as long as possible (5). Splanchnic vasoconstriction and decreased venous compliance are present in a well-functioning Fontan circulation, but failure of these compensatory mechanisms has been observed (34, 35). Regular exercise (36), compression stocking in case of varicose veins, and paracentesis in case of tense ascites may be of use in selected patients. Pulmonary vasodilators have been studied in patients with a Fontan circulation but the overall net clinical benefit in the two largest randomized controlled trials (FUEL trial and TEMPO trial) with an improvement in peak oxygen consumption of 3–5% has been limited so far (37, 38). Most centers (including ours) would advocate diuresis in case of Fontan circulatory failure with elevated systemic venous pressures, but the effects of decreasing overall blood volume in a preload dependent circulation requires more study (especially on its early and long term effect on cardiac output) (3). Furthermore, the extent to how much systemic venous pressure can increase during exercise requires further study, since this may pose a natural limitation to exercise capacity in Fontan patients (18, 26) and explain exacerbated reductions in peak CO in failing Fontan patients (**Figure 3**).

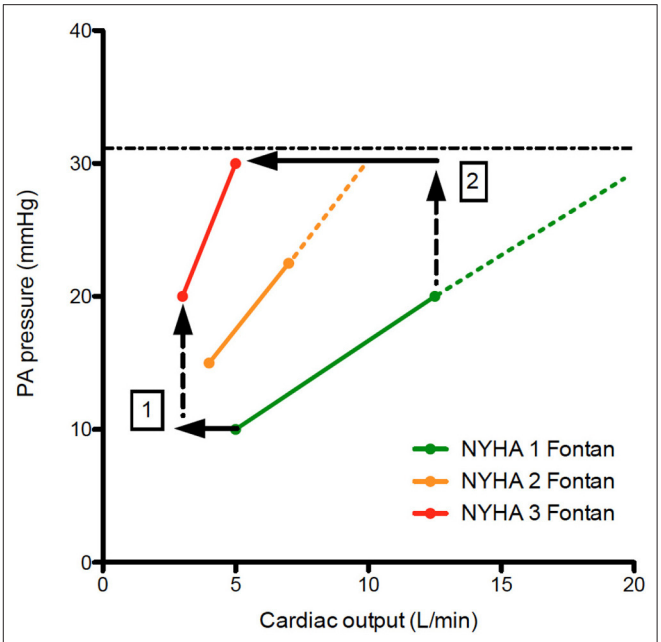

FIGURE 3 | Pressure flow plots indicating the increase in PA pressure vs. cardiac output during exercise. When comparing NYHA 1 Fontan patients with NYHA 2&3 Fontan patients, note there is a decrease in cardiac output despite increase in resting PA pressure (1). During exercise, the increase in PA pressure is steeper for NYHA 2&3 patients. A hypothetical maximum of PA pressure (systematic venous pressure) results is an exacerbated decrease in cardiac output resulting in significant functional limitation of the Fontan patient (2). The dashed lines represent hemodynamic reserve of the Fontan patient.

The Heart: The Co-pilot as Bystander

A Preload Deprived Heart

Most cardiac lesions and most cardiac patients are characterized by cardiac dysfunction due to pressure and/or volume overload of the systemic or subpulmonary ventricle. But there is remarkably little evidence evaluating the effect of chronic volume deprivation on the ventricle (5). The paragraphs above illustrate why the systemic ventricle in a Fontan circulation lacks preload at rest and during exercise. Since there is no subpulmonary ventricle, even low-level changes in pulmonary vascular resistance (PVR) cause significant changes in cardiac output. Indeed, Egbe et al. showed that Fontan patients who have low cardiac index, measured during cardiac catheterization or echocardiography, coupled with higher PVR had the highest risk for Fontan circulatory failure (39, 40).

The Myocardium

The staged Fontan palliation is associated with significant changes in volume load to the ventricle which evolves from being volume overloaded (prior to the Glenn) to preload deprived (after Glenn and Fontan completion) (41). This and other factors

(surgical insult) may result in ventricular dilation, eccentric hypertrophy [increased mass:volume ratio due to a decrease in ventricular volume with increased wall thickness (42)] and could cause systolic and/or diastolic dysfunction (43). Indeed, systolic and diastolic dysfunction has been observed prior and after the Fontan operation (44) and relate to the degree of volume load prior to Fontan completion (45) and even to outcome (46). Other studies did show a normal contractile response to dobutamine, suggesting that in most Fontan patients ventricular function is not the main factor limiting CO at rest or during exercise (47). However, it is also true that due to expanding indications for Fontan repair, borderline ventricles have been incorporated into Fontan circuits in more recent years. This, in combination with aging of the ventricle in older Fontan patients, will render ventricular dysfunction (systolic and diastolic) a more important issue in the years to come (26). Aging may even be accelerated in Fontan patients similarly to what has been observed in sedentary people where the left ventricle becomes stiffer (due to lack of exercise induced ventricular stretching) and evolves toward heart failure with preserved ejection fraction phenotype (48, 49). Increased afterload (which could contribute to systolic and diastolic deterioration) has been reported, but may be secondary to decreased output in order to maintain blood pressure (50). Moreover, studies evaluating Ace inhibitors in patients with a Fontan circulation have been negative so far (51, 52). Indications for Ace inhibitors in 2-ventricle circulations, such as the presence neurohormonal activation, greater than mild ventricular dysfunction or atrioventricular valvular regurgitation, or increased afterload, have not been replicated in the Fontan cohort and warrant a considered approach in prescribing these drugs for Fontan patients (ref Wilson). When evaluating data from the article by Egbe et al. on pressure-flow plots during exercise, Fontan patients with a steeper pressure-flow curve also have a steeper increase in pulmonary wedge pressure during exercise (25, 26). This is all the more surprising in a preload limited circulation where one would expect a decrease in wedge pressure during exercise (if these were normal ventricles) (26, 53). Moreover, in the absence of a subpulmonary ventricle, even low-level changes in left atrial pressures will cause significant changes in cardiac output as is evident in differences in peak CO between Fontan subgroups (**Figure 4**).

When creating a Fontan circulation, the pediatric cardiologist and congenital cardiac surgeon have made tremendous advances, especially when balancing adequate pulmonary artery growth whilst preventing excessive volume load to the ventricle (5, 8, 10). The importance of physical activity (which introduces pulsatility to the pulmonary vasculature and improves filling of the ventricle with stiffness-reducing stretching) as well as preventing the accumulation of risk factors for a heart failure with preserved ejection fraction phenotype (obesity, hypertension, diabetes) cannot be understated during the life trajectory of any Fontan patients. Improved assessment and understanding of diastolic function in patients with a Fontan circulation is an unmet clinical need that hampers innovation and should be addressed. Continuous (milrinone) or intermittent (levosimendan) infusion of inotropes can improve organ perfusion and reduce venous congestion. In a large series of Fontan patients undergoing transplantation, 74% of patients received inotropic support. The potential benefit of a combination of diuretics with inotropes (resulting in systemic and pulmonary vasodilation in combination with inotropy) to maintain a euvolemic state requires further study.

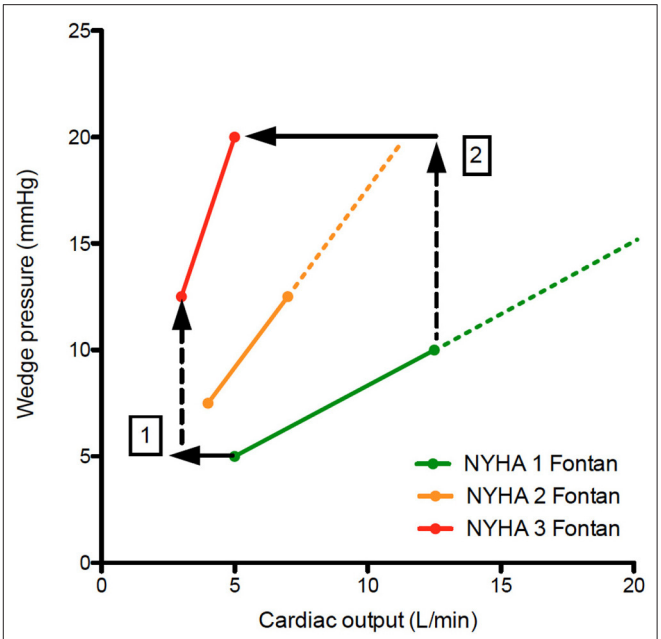

FIGURE 4 | Pressure flow plots indicating the increase in wedge pressure vs. cardiac output during exercise. When comparing NYHA 1 Fontan patients with NYHA 2&3 Fontan patients, note there is a decrease in cardiac output despite increase in wedge pressure (1), which becomes more pronounced during exercise (2). This is counterintuitive in a preload dependent circulation. Diastolic dysfunction (which may be a consequence of preload deprivation) will exacerbate systemic venous hypertension and cardiac output limitation during exercise.

Heart Rate

In Fontan patients the sinus node may be dysfunctional, either congenitally or damaged during multiple surgeries. Although chronotropic limitation has been extensively described in Fontan patients, prior studies have demonstrated that atrial pacing at rest does not augment CO, that at comparable exercise levels Fontan patients already have a faster heart rate, and that pacing beyond maximal heart rates does not improve exercise capacity (54–56). Whereas, CO augmentation in healthy controls is achieved by an increase in heart rate and stroke volume, in Fontan patients increase in CO is primarily achieved by increases of transpulmonary flow (or venous return). Indeed, increase in heart rate relative to metabolic demand is robust or even enhanced in Fontan patients. However, when stroke volume starts falling and CO plateaus, heart rate ceases to increase. All this suggests chronotropic constraint to prevent collapse should heart rate further increase (with falling stroke volumes) (57). The Bainbridge reflex could explain causality, but a direct feedback

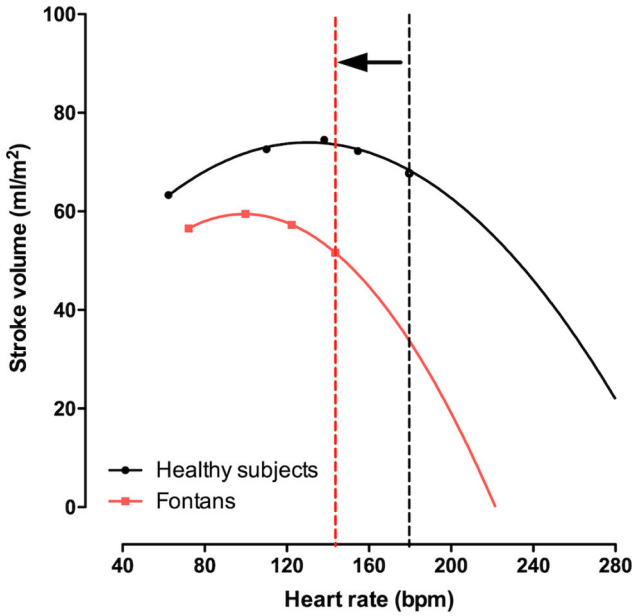

FIGURE 5 | Stroke volume index vs. heart rate during exercise. In Fontan patient heart rate and exercise capacity is limited. In a significant proportion of Fontan patients, heart rate relative to workload is preserved (or even increased). Nevertheless, heart rate reserve is still reduced, which may be a physiologic mechanism preventing a full in stroke volume (and cardiac output). This highlighted in the figure, where the infliction point (vertical dashed line) beyond which a further increase in heart rate would result in falling cardiac output.

mechanism as CO cannot be maintained is another possibility (**Figure 5**).

A more aggressive rhythm control management strategy (including atrial pacing for junctional rhythms, DC cardioversion, ablation, and medical therapy) is warranted in Fontan patients. Not only would they not tolerate faster heart rates (58), preservation of atrial suction and contraction and optimizing diastolic filling time is important in preload dependent circulations (59).

The Atrioventricular Valve(s)

The atrioventricular valve(s) are often structurally abnormal in patients with a Fontan circulation, but functional atrioventricular valve regurgitation due to ventricular and/or annular dilatation, prior volume, and/or pressure overload has been described as well (60). Atrioventricular valve regurgitation is common, with about one fifth of patients presenting with moderate or severe atrioventricular valve regurgitation. Although its consequences have been well-described with a 2- to 3-fold increased risk of Fontan circulatory failure (61), its management after Fontan completion remains cumbersome (62). The highest risks for significant atrioventricular valve regurgitation are observed in patients with mitral atresia and a common atrioventricular valve and less frequently in patients with two valves or patients with tricuspid atresia (61). Experience from the Mayo clinic indicates that early intervention (before Fontan completion) has better outcome and that valve interventions after completion are associated with an increased risk of mortality or need for transplantation (63). Pathophysiology is straightforward, with increases in atrial pressure resulting in increased systemic venous pressures, lower cardiac output, and decreased reserve during exercise.

Neurohormonal State

Although we as clinicians feel that the interventions and altered Fontan circulatory hemodynamics trump all else, there is convincing evidence of neurohormonal activation in virtually all patients with a Fontan circulation (including asymptomatic patients) (64). Similar observations have resulted in the development of- and evidence related to the use of ace inhibitors, angiotensin receptor blockers, mineralocorticoid receptor blockers, and betablockers in acquired heart failure, eventually improving outcome of those patients; however, studies to replicate these findings in the Fontan population have been negative until now.

Deterioration of the Fontan circulation also often coincides with an increased risk for thrombosis and thromboembolic events, which are frequent in Fontan patients, occurring in up to 33% of patients, and are often serious (mode of death in 25% of patients) (65–67). Several reports have indicated coagulation factor abnormalities, both prothrombotic (plasminogen deficiency, antithrombin 3 deficiency, and protein S and C defiency) as well as procoagulant (increase in factor VIII), which have been related to increased venous pressure (potentially affecting protein synthesis in the liver) (66). The contribution of inflammation, which has been observed in patients with a Fontan circulation, to thrombosis risk has not yet been investigated (68).

With limited patient numbers and insufficient power to perform adequate randomized controlled trials in Fontan patients, it may seem hopeless to even invest in similar research in Fontan patients. However, one could argue that a Fontan patient represents a prime example of a patient in a thrombo-inflammatory state with increased neurohormonal activation destined to develop diastolic dysfunction. A better understanding of the underlying pathomechanisms with identification of therapeutic targets may not only serve the Fontan patient, but the underserved HFpEF patient as well.

Limitations

Further elaboration on the influence of arterio-venous and veno-venous collateral flow, the development of Fontan-associated liver disease, and abnormal lymphatics on Fontan hemodynamics is beyond the scope of this review, but should be considered in any patient with Fontan circulatory failure.

CONCLUSIONS

The Fontan circulation provides a unique solution for patients with a single functional or anatomical ventricle, expanding life expectancy and quality of life. However, every Fontan circulation carries within itself the seeds of its own decay (69). Increased systemic venous pressures (and the subsequent development of Fontan-associated liver disease and abnormal lymphatics)

and low cardiac output at rest, but especially during exercise (causing exercise intolerance), are the key components of every Fontan circulation and deteriorate slowly over time. The Fontan portal system redefines the place of the pulmonary circulation as the main factor influencing systemic venous return and hence cardiac output. This also infers that even small changes in atrial pressure could have large effects on cardiac output. Following this, the deleterious effects of diastolic dysfunction (accelerated aging, chronic deprivation), systolic dysfunction, atrioventricular valve regurgitation, and/or atrial dysfunction will be enhanced in the Fontan circulation. There is a responsibility for patients and caregivers alike during the life trajectory of a Fontan patient. The pediatric cardiologist and congenital cardiac surgeon should always aim for the perfect Fontan circulation, the patient should maintain an active, healthy lifestyle, avoiding weight gain, and the adult congenital cardiologist should not accept suboptimal hemodynamics (i.e., AV valve regurgitation, undersized Fontan conduits, or pulmonary artery hypoplasia). There is a need for innovation, such as retraining of the pulmonary vasculature and ventricle using right-sided assist devices prior to transplant, further research on implantable right-sided assist devices, aims to reduce the risk of AV valve surgery, and novel pathways to improve the thrombo-inflammatory state in Fontan patients.

AUTHOR CONTRIBUTIONS

AV: writing manuscript. GC and TS: critical review manuscript. MG: writing and critical review manuscript. All authors contributed to the article and approved the submitted version.

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Fontan Circulation Associated Organ Abnormalities Beyond the Heart, Lungs, Liver, and Gut: A Systematic Review

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Introduction: Patients with a Fontan circulation are at risk for sequelae of Fontan physiology during follow-up. Fontan physiology affects all organ systems and an overview of end-organ damage is needed.

Methods: We performed a systematic review of abnormalities in multiple organ systems for patients with a longstanding Fontan circulation. We searched online databases for articles describing abnormalities in multiple organ systems. Cardio-pulmonary abnormalities, protein losing enteropathy, and Fontan associated liver disease have already extensively been described and were excluded from this systematic review.

Results: Our search returned 5,704 unique articles. After screening, we found 111 articles relating to multiple organ systems. We found abnormalities in, among others, the nervous system, pituitary, kidneys, and musculoskeletal system. Pituitary edema—relating to the unique pituitary vasculature- may affect the thyroid axis. Renal dysfunction is common. Creatinine based renal function estimates may be inappropriate due to myopenia. Both lean muscle mass and bone mineral density are decreased. These abnormalities in multiple organ systems may be related to Fontan physiology, cyanosis, iatrogenic factors, or lifestyle.

Conclusions: Health care providers should be vigilant for hypothyroidism, visual or hearing deficits, and sleep disordered breathing in Fontan patients. We recommend including cystatin C for assessment of renal function. This review may aid health care providers and guide future research.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021232461, PROSPERO, identifier: CRD42021232461.

Keywords: univentricular congenital heart defects, neurology, renal disease, endocrinology, long term outcomes, metabolism, musculoskeletal system, Fontan circulation

INTRODUCTION

Patients suffering from univentricular congenital heart defects (CHD), in which only one ventricle is sufficiently developed, are commonly palliated with the Fontan procedure. This series of operations diminishes mixing of deoxygenated and oxygenated blood and reduces volume overload of the single ventricle (1). However, the resulting Fontan circulation, in which the systemic and pulmonary circulation are connected in series, is highly abnormal (2). Although the early and intermediate-term survival of Fontan patients has improved significantly over the last 40 years, end-organ sequelae are common and may affect other organs than the cardiovascular system (3).

As survival has improved, the adult Fontan patient population is rapidly growing. A recent study estimated the prevalence of Fontan patients (in Europe, Oceania, and the USA) will increase from 66 per million in 2020 to 79 per million in 2030, an increase of nearly 20% (4). Furthermore, the proportion of adult patients will grow from 55 to 64% in the same time span (4). Long-term follow up has revealed several complications, where the abnormal Fontan circulation affects different organ systems and may lead to multi-organ failure. Well-known life-threatening Fontan-related complications are plastic bronchitis (PB) and protein losing enteropathy (PLE) (3). Other (end-organ) consequences of the long standing Fontan circulation are not well-characterized, nor fully understood (5).

For adequate management of these patients in the context of their growing life expectancy, it is crucial to gain insight in all possible complications of this highly abnormal circulation. As Fontan associated liver disease, PLE, PB, and thrombo-embolic complications have already been extensively described elsewhere (6–8), the present study aims to add to the current literature by providing a review of abnormalities described in organ systems beyond the heart, lungs, liver, and gut for patients with a longstanding Fontan circulation.

METHODS

Search Strategy

This systematic review has been registered to PROSPERO prior to search (ID: CRD42021232461). The electronic search was performed using Embase, Medline and the Cochrane Central Register of Controlled Trials. In order to find articles, the search term included terms related to the Fontan procedure and to different types of organ systems. The complete search strategy is supplied in the **Supplementary Material**. The search was conducted on January 18th 2022. All articles from inception to the search date were considered. All articles describing abnormalities in organ systems in patients with a longstanding Fontan circulation were considered, including case reports, case series, retrospective studies, and prospective studies.

Exclusion Criteria

Articles were excluded from the study when one or more of the following exclusion criteria were met:

- Articles were not written in English;
- Articles did not at least include a subgroup analysis of patients with a completed Fontan circulation (in the setting of papers reporting on different types of CHD);
- Articles regarding the effects of a Fontan circulation on the lungs, cardiovascular system, liver, thrombo-embolism or PLE;
- Articles detailing only short-term outcomes, i.e., <1 year following Fontan completion;
- Articles not deemed relevant to the research question by the authors' unanimous consensus. These articles are listed in the **Supplementary Material**;
- Commentaries, reviews, meta-analyses, systematic review, and conference abstracts.

Data Collection Process

All articles were manually screened for eligibility by one of two authors (ER or VAV). First, titles and abstracts were screened. In case of any doubt, a consensus meeting with 2 or more authors was held. Secondly, the full texts of articles not excluded based on title and abstract were screened by the same observers. If there was doubt whether a study was relevant to the research question in- or exclusion was decided upon in a consensus meeting with JPGvdV and WAH. The articles excluded for this reason are listed in the **Supplementary Material**.

The included articles were classified based on which organ system(s) were studied in the respective article. Articles may be included in more than 1 category. The full articles were read and information regarding the function of organ systems of Fontan patients was extracted by hand. Due to the scope of this research and the wide variety of outcome measures, we took a narrative approach to describing study findings. All findings that provided insight in potential dysfunction of the organ system was deemed relevant. No formal quality assessment for articles was performed because of the wide variety of study designs included in our search strategy.

Throughout this review, data is presented as "mean ± standard deviation" or as "median [interquartile range]," unless otherwise specified.

RESULTS

Search Results

Our search returned 5,704 unique publications. The selection process is shown in the flowchart (**Figure 1**). After completing the assessment for eligibility, 111 studies were included in this systematic review. The publications were sorted into the following groups: neurology ($n = 32$); kidneys ($n = 19$); the muscular system ($n = 18$); endocrinology ($n = 13$); metabolism ($n = 10$); neoplastic disease ($n = 9$); bone ($n = 9$); the immune system ($n = 5$); the auditory system ($n = 4$); reproductive system ($n = 4$); sleep-disordered breathing ($n = 3$); dermatology ($n = 3$); ophthalmology ($n = 2$); dental abnormalities ($n = 2$); gastro-intestinal ($n = 1$).

All included studies are summarized in **Supplementary Table 1**. The main findings per organ system are summarized in **Figure 2**.

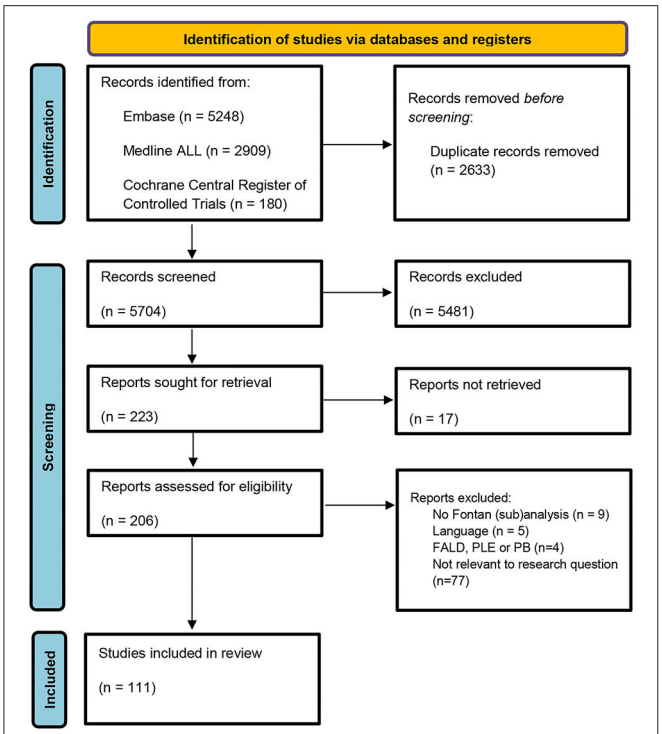

FIGURE 1 | Search strategy flowchart. FALD, Fontan associated liver disease; PLE, protein losing enteropathy; PB, Plastic bronchitis.

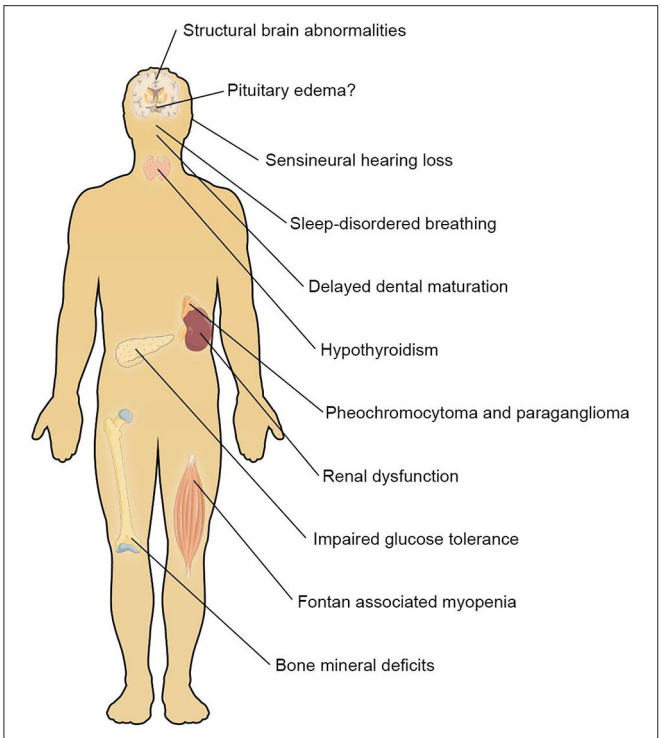

FIGURE 2 | Main findings per organ system.

Neurology

Central Nervous System Abnormalities

Structural abnormalities on central nervous system (CNS) imaging have been assessed in 14 studies using multiple imaging modalities (**Table 1**). CNS abnormalities noted included (multi)focal abnormalities, developmental malformations, and ischemic changes in watershed areas (9–16). Most of these studies included only adolescent Fontan patients. Verall et al. found adult patients had more impaired neurocognitive scores compared to adolescent patients, however, no relation was found between age and severity of abnormalities on neuro-imaging (16). Diffuse CNS abnormalities in univentricular CHD patients are present even before birth, possibly relating to exposure to hypoxia *in utero* (10, 11). Following each cardiac surgery, ischaemic abnormalities appear to increase in number and size (10). Of note, one study found that in a cohort of 144 adolescents 13% had evidence of stroke on MRI after Fontan completion (10). Remarkably, 40% of these patients did not have a clinical history of stroke, suggesting that the occurrence of stroke can be clinically silent (10). Total and regional brain volumes are generally decreased in Fontan patients compared to controls (17, 19–22). All studies assessing brain volumes included only adolescent patients and no studies assessed brain volumes in adult patients. Decreased brain volumes may relate to prolonged cyanosis in infancy, decreased cardiac output, nutritional deficiencies, and peri-operative injuries (11, 19). Whether these findings relate to neurocognitive outcome is not clearly established. Contrary to other brain structures, the pituitary has an increased volume in Fontan patients (18). This is further explored in the *Endocrinology* section of this review. Fontan patients underperform compared to their peers on several functional measures, including visual processing speed, psychomotor function, emotional cognition, and gross motor function (10, 23, 24). Imaging abnormalities related to functional outcomes in some (9, 13, 14), but not all studies (10, 16).

Cerebral Hemodynamics

Cerebral hemodynamics have been assessed by 3 studies (25–27). Saiki et al. investigated the response to inferior caval vein occlusion during cardiac catheterization (to isolate the upper body circulation as a proxy for cerebral circulation) in Fontan patients aged 6.7 ± 2.6 years (25). They found Fontan patients have an increased cerebral-to-systemic cardiac output ratio compared to patients with structurally normal hearts. This might reflect a compensatory mechanism to preserve cerebral blood flow in a context of reduced cardiac output. Cerebral local tissue oxygenation, assessed by near infrared spectroscopy, decreases during exercise for pediatric Fontan patients (26). This response is not seen for healthy controls. Cerebral deoxygenation during exercise may play a role in the impaired exercise performance of Fontan patients. Wong et al. found adult Fontan patients have an impaired response in cerebral blood flow to cognitive stimuli compared to controls (27).

TABLE 1 | Neurologic imaging abnormalities.

References	Patient population	N	Controls	Imaging techniques	Main findings	Relation with functional outcomes	Comments
Structural abnormalities							
Sarajuuri et al. (9)	U-CHD patients median age 5.7 years (range 5.0–7.5)	27	N/a	1.5T MRI. CT when contra-indications	Ischaemic changes in watershed areas in 7/20 (35%) patients	Full-scale IQ lower in group with abnormalities (97 vs. 69, $p = 0.045$)	
Bellinger et al. (10)	Fontan patients aged 15 ± 3 years	144	111 healthy controls	1.5T MRI or 3T MRI incl T2 weighted acquisition	Any abnormalities in 66% of patients. Mostly focal or multifocal abnormalities	Focal abnormalities related to several behavioral disorders, but not general intelligence	*
Watson et al. (11)	Fontan patients aged 15 ± 3 years	128	48 healthy controls	1.5T MRI or 3T MRI incl. cortical thickness	Any abnormalities in 65% of patients	Not assessed	Study assessed both structural abnormalities and regional volumes*
Pike et al. (12)	Fontan patients aged 16 ± 1	20	36 healthy controls	T2-relaxometry MRI	Widespread higher T2-relaxation values	Not assessed	**
Watson et al. (13)	Fontan patients aged 15 ± 3	102	47 healthy controls	Diffusion tensor imaging	Evidence of widespread altered white matter microstructure	Fractional anisotropy for several tracts correlated with both full scale IQ and processing speed	*
Singh et al. (14)	Fontan patients aged 16 ± 1	18	31 healthy controls	3T MRI	Decreased gray matter density in several regions	Prefrontal, occipital, and temporal gray matter density relates to mood and cognitive ability	**
Singh et al. (15)	Fontan patients aged 16 ± 1	27	35 healthy controls	Diffusion tensor imaging	Multiple brain sites in U-CHD showed increased MD values	Not assessed	**
Verrall et al. (16)	Fontan patients aged 23 ± 8	100	41 healthy controls; 50 TGA patients	3T MRI incl T2 weighted acquisition	Structural brain injury in 100% of subjects	Only white matter injury was associated with worse paired associate learning. Severity of infarct, subcortical gray matter injury and microhemorrhage unassociated	

(Continued)

TABLE 1 | Continued

References	Patient population	N	Controls	Imaging techniques	Main findings	Relation with functional outcomes	Comments
(Regional) volumes							
Watanabe et al. (17)	HLHS patients subset of cohort aged 16 ± 6 y	4	19 healthy controls	1.5T MRI	Decreased frontal gray matter volume in HLHS patients	Not assessed	***
Watson et al. (11)	Fontan patients aged 15 ± 3 years	128	48 healthy controls	1.5T MRI or 3T MRI incl. cortical thickness	Reduced volumes in 29% of regions. Cortical thickness reduced in 50% of regions	Not assessed	Study assessed both structural abnormalities and regional volumes
Muneuchi et al. (18)	Fontan patients aged 9 [8–12]	40	40 healthy controls	1.5T MRI	Increased pituitary volumes	Not assessed	***
Cabrera-Mino et al. (19)	Fontan patients aged 16 [15–17]	25	38 healthy controls	3T MRI	Reduced mammilary body volume	Corrected mamillary bodies volumes correlated with MoCA and delayed memory recall scores in SVHD and controls	**
Noorani et al. (20)	Fontan patients aged 16 ± 1	23	37 healthy controls	3T MRI incl T2 weighted acquisition	Significantly reduced caudate volume	Caudate volumes correlated with PHQ-9, BAI, GMI, and MoCA scores	**
Hiraiwa et al. (21)	Fontan patients aged 9 ± 2	18	9 TGA patients	1.5T MRI	Smaller TBV compared to TGA patients	Full-scale IQ correlated with total brain volume (9 TGA patients included)	Only last follow-up considered, as not all patients had undergone Fontan palliation at first visit***
Pike et al. (22)	Fontan patients aged 16 ± 1	25	38 healthy controls	3T MRI	Reduced right, but not left, hippocampal volume	WRAML2 scores correlated with hippocampal volumes	**

*U-CHD, univentricular congenital heart disease; HLHS, hypoplastic left heart syndrome; TGA, transposition of the great arteries; MRI, magnetic resonance imaging; CT, computed tomography; TBV, total brain volume; MoCA, Montreal cognitive assessment; PHQ, patient health questionnaire; BAI, Beck anxiety inventory; GMI, Global mindset inventory; WRAML2, Wide range assessment of memory and learning 2. *, **, and *** denote studies with overlapping study populations.*

The Autonomic Nervous System

Adult Fontan patients have increased circulating levels of norepinephrine (28, 29), increased sympathetic tone of muscle nerves (30), and reduced heart rate variability (31, 32). Each of these factors is considered a marker of increased autonomic sympathetic tone. The age of patients in these studies ranged from the early twenties to late thirties. One study evaluated the autonomic nervous system in pediatric Fontan patients (33). Similar to the findings in adults, the authors found increased circulating levels of norepinephrine and reduced heart rate variability (among other factors relating to sympathetic tone). Increased sympathetic tone can be a compensatory mechanism in heart failure (30). Heart rate variability may be explained by other factors than increased sympathetic tone in Fontan patients. Indeed, heart rate recovery following maximal cardiopulmonary exercise testing—a process also governed by the autonomic nervous system- was normal in Fontan patients (31). Ohuchi et al. found sympathetic activity was not related to hemodynamics, clinical history, or time since Fontan completion (33). Sympathetic activity seems increased for Fontan patients from childhood, although the clinical consequences—including the effects on heart rate and clinical prognosis-remain uncertain.

Central Nervous System Infections

Our search returned 4 case reports of Fontan patients (aged 11–28 years) with cerebral abscesses (34–37). Fontan patients are considered to be at increased risk for hematogenous spread of pathogens to the central nervous system due to shunting (37). In a nationwide cohort study in Denmark the risk of CNS infections (not limited to cerebral abscesses) was 0.93 per 1,000 person years for univentricular CHD patients (38). This represents a 3-fold (1.13–8.17) increased risk compared to the general population.

Headaches

In a cross-sectional study of 54 Fontan patients, aged 26 ± 9 years, 50% of patients complained of frequent headaches (39). We found one case report of a Fontan patient with frequent headaches caused by pseudotumor cerebri (40). Pseudotumor cerebri is a condition caused by elevated intracranial pressure, which may relate to Fontan physiology. More research is needed to estimate the prevalence of pseudotumor cerebri in Fontan patients, but pseudotumor cerebri may be considered as a cause for refractory headaches in Fontan patients.

Renal System

Renal dysfunction (RD) has been demonstrated in Fontan patients in 8 studies (41–50). The overall prevalence of RD (defined as estimated glomerular filtration rate (eGFR) <90 mL/min/1.73m^2, as assessed by creatinine-based methods) in Fontan patients is estimated to be 10–20% (41–43, 49). Moderate to severe RD ($eGFR_{creatinine}$ <60 mL/min/1.73m^2) was found in 1–4% of Fontan patients (41–43, 49). Renal dysfunction was generally less common in cohorts of younger patients (41, 44, 48), compared to those with older patients (42, 43, 50).

The use of creatinine-based GFR estimation methods have been debated, since muscle mass is often reduced in Fontan patients. Alternative methods may be more reliable (42–44, 51). Cystatin C is a marker of renal function that is not dependent on muscle mass (44). Differences between $eGFR_{creatinine}$ and $eGFR_{cysC}$ can be large in the Fontan population (42–44, 51). There is no consensus yet on the appropriate use of $eGFR_{cysC}$ or $eGFR_{creatinine}$ in Fontan patients. No studies compared cystatin C GFR estimations to invasive measurements. Further studies are necessary to determine the best method to non-invasively evaluate renal function.

Pathophysiology

The pathophysiology of renal dysfunction in Fontan patients is incompletely understood. Cyanosis, erythrocytosis, limited perfusion, and renal congestion have been suggested as factors leading to renal dysfunction (48, 49, 52–55). The histopathological features of the kidneys of Fontan patients with renal dysfunction range from mild changes to focal segmental glomerulosclerosis (55–57). Adaptive focal segmental glomerulosclerosis is a renal disease commonly seen in patients with cyanotic CHD. In contrast, we also found one case report where the structures of tubules and glomerulus were preserved despite severe renal dysfunction (55). In this case renal dysfunction may be reversible (55). Focal segmental glomerulosclerosis may occur in older patients (ages of case reports ranged from 24 to 41 years old) (56, 57) compared to renal dysfunction with preserved renal structure (one case report in a 14 year old patient) (55).

Longitudinal Assessment

Four studies assessed renal function longitudinally (41, 47, 51, 58). Overall, most studies find renal function decreases over time for Fontan patients (47, 51, 58). In one cohort study creatinine increased during a 5-year follow-up (58). In a cross-sectional study the rate of decline in invasively measured GFR was 9.92 ml/min/1.72m^2 per decade following the Fontan procedure (51). Motoki et al. found a significantly higher $eGFR_{creatinine}$ in adolescent Fontan patients vs. the adult Fontan patients (113 ± 25 vs. 147 ± 19 ml/min/1.72m^2, $p < 0.01$) (47). Only the study by Khuong et al. found no overall decrease in renal function over a 7 ± 5 year follow-up (41). Nevertheless, a subgroup analysis showed that patients with normal renal function at baseline had decreasing renal function over the follow-up duration (41).

Prognostic Value of Renal Function

Several studies assessed the prognostic value of renal function for clinical outcomes, such as hospitalization and death for Fontan patients. Cystatin C predicted a composite endpoint of non-elective cardiovascular hospitalization and mortality, adjusted for age and NYHA class [HR for RD 3.25 (95% CI 1.26–8.40)] (43). Creatinine based GFR predicted mortality in some (41, 50), but not all studies (43, 46). One study found $eGFR_{creatinine}$ predicted unscheduled hospitalization (46). Ohuchi et al. (46) found creatinine predicted unscheduled hospitalization for adults, but not children. Overall, renal function seems to relate to clinically important long term outcomes.

Other Findings

Proteinuria is a marker of kidney damage. Five studies assessed proteinuria in Fontan patients and found a prevalence of 10–65%

(42, 44, 51, 52, 54). One study found the prevalence is 3 times higher compared to the general population (52). The presence of proteinuria does not seem to be related to GFR, implying these phenomena may have different underlying processes (44). Renal vascular resistance is higher for Fontan patients, and correlates with renal function, exercise capacity, and mortality during a median 32 months follow-up (59). In a study of structural abnormalities of the kidneys several findings were reported: increased parenchymal echogenicity in 6%, cortical thinning in 4%, discrete scarring in 4%, pelvicalyceal system dilatation in 1%, and enlargement of the kidneys in 3% of patients (51).

Muscular System

Our search returned eighteen articles discussing the muscular system in Fontan patients. Lean muscle mass is decreased for Fontan patients compared to healthy controls (60–63). Fontan associated myopenia, defined as a lean muscle mass Z-score of −2 or lower, is present in 39% of Fontan patients (63). Bio-impedance measurements and MRI-derived muscle mass estimations—which are more easily obtained estimations of muscle mass- are also abnormal for Fontan patients (64–66). No studies directly compared these methods of lean muscle mass estimation to current gold standards. Nevertheless, these methods may provide more easily obtainable measurements in clinical practice.

Factors Related to Muscle Mass

Lean muscle mass Z-scores were not related to age for Fontan patients (62). However, isometric knee extension muscle strength is impaired for adolescent Fontan patients, but not during childhood, which suggests that muscular impairment increases with age (67). Markers of neurohormonal activation, sex hormones, and inflammatory mediators did not relate to lean muscle mass, implying the role of these factors is limited in the pathogenesis in myopenia (63). Vitamin D deficiency is common in Fontan patients (62, 63). Studies into the effect of vitamin D status on muscle mass found conflicting results (62, 63). Furthermore, Fontan patients have less active lifestyles than healthy peers, which may play a role in muscle mass development (68). Overall, determinants of lean muscle mass deficits in Fontan patients are not clearly established. Few hypotheses regarding the pathophysiology of Fontan associated myopenia have been proposed.

Muscle Mass Related Functional Outcomes

Fontan patients have impaired exercise capacity, as well as decreased functional parameters of muscle strength (69–71). The role of lean muscle mass on exercise capacity in Fontan patients is uncertain (63, 65). The pathophysiology of exercise impairment in Fontan patients is likely multi-factorial. It has been hypothesized that the calf muscle pump plays an important role in augmenting single ventricular preload in the context of a Fontan circulation. Calf muscle size is reduced for Fontan patients compared to healthy references (68). Leg lean mass relates to exercise capacity as well as cardiac index during exercise (72). Importantly, Cordina et al. found that peak oxygen uptake, muscle strength and total muscle mass could be increased by resistance training (73). Resistance training could be a valuable treatment modality for cardiovascular, and general, health in Fontan patients.

Muscle Oxygenation

Six articles investigated the oxygenation of muscles in Fontan patients (26, 61, 74–76). Several studies evaluated muscle oxygenation with near-infrared spectroscopy (26, 74, 76). Muscle oxygenation is decreased at baseline, relating to reduced arterial oxygen saturation, but displays a normal response to exercise (26). Several markers of muscle oxygenation during exercise—but not resting conditions- relate to overall exercise capacity (74). Muscle oxygenation defects may increase with age (76). Parameters of muscle oxygenation during exercise may be preserved in children (6–12 years), but impaired for adolescents (13–18 years) (76). Vandekerckhove et al. did find impaired muscle oxygenation during exercise in patients aged 11.8 ± 2.8 years (26).

Studies evaluating muscle energy metabolism by phosphate spectroscopy found phosphocreatine recovery rate, a measure of aerobic capacity, was reduced in Fontan patients aged 30 ± 2 years compared to controls (61). Fore-arm blood flow, which is considered a proxy for general muscular blood supply, relates to reduced skeletal muscle diameter and strength in Fontan patients (75). Decreased muscular oxygenation may be an important determinant of exercise capacity in Fontan patients.

Endocrinology

The pituitary is an important organ in many endocrine axes. The volume of the pituitary, in contrast to most brain structures, is larger in Fontan patients than control subjects (18). Pituitary volumes in Fontan patients increased with age, but at a rate similar to healthy controls (18). Increased pituitary volumes may relate to the circulation of the pituitary, which has a portal system, similar to the liver. The large pituitary volumes may reflect pituitary edema, which may have consequences for hormone production. Several endocrine axes are discussed below. No studies assessed the growth hormone axis in Fontan patients.

Thyroid Axis

Three studies investigated the thyroid axis (39, 50, 77). Kuwata et al. in a retrospective study of 35 pediatric Fontan patients who underwent cardiac catheterization, found 12 patients (33%) had subclinical hypothyroidism (77). In retrospective cohort studies 13–55% of Fontan patients were diagnosed with hypothyroidism at follow-up (39, 50). TSH levels related to ventricular function and central venous pressure, implying Fontan physiology (including pituitary congestion) may play a central role in hypothyroidism (77). Amiodarone therapy has been proposed as a cause for hypothyroidism in Fontan patients. However, no patients in the previously mentioned study by Kuwata et al. used amiodarone (77). It should be noted no studies prospectively studied the thyroid axis at long-term follow-up for Fontan patients. How thyroid function develops with a long-standing Fontan circulation is currently not known.

Parathyroid Axis

Sharma et al. found, in a retrospective study of 68 pediatric Fontan patients, that parathyroid hormone levels were highly increased in Fontan patients compared to healthy controls [59 (43–59, 61–82) pg/mL vs. 23 (17–30) pg/mL, $p < 0.001$] (44). Other studies in children found comparable parathyroid hormone levels for Fontan patients (78, 79). No studies assessed parathyroid function in adults. Parathyroid hormone levels do not relate to exercise capacity (78).

Serum parathyroid levels are mainly regulated by serum calcium status, but also influenced by—among others- phosphate status, renal function, and vitamin D sufficiency. Two studies found a high prevalence (70 and 81%, respectively), of vitamin D deficiency in Fontan patients (78, 79). Vitamin D supplementation can increase vitamin D levels and decrease parathyroid levels (49 ± 32 vs. 68 ± 41 ng/L, $p < 0.001$) (79). Due to discrepancies between several studies, the exact etiology and clinical importance of hyperparathyroidism in Fontan patients remains unclear. Nevertheless, it seems important to monitor vitamin D levels on a regular basis for these patients.

Renin-Angiotensin-Aldosterone System

Fontan patients have increased serum renin, angiotensin II, and aldosterone levels compared to healthy controls in both children (80) and adults (81). Plasma sodium levels (Na) are heavily affected by the renin-angiotensin-aldosterone system and diuretic use. One study found 30% of Fontan patients have hyponatremia (82). Plasma Na increased with age for patients without medication use (82). Plasma Na is an independent predictor for unscheduled rehospitalization (82). Another study found a correlation between plasma renin activity and renal vascular resistance (59). Abnormalities in the renin-angiotensin-aldosterone axis are well-described. However, the clinical value of these measurements seems limited and are heavily confounded by medication use.

Sex Hormones

Menon et al. in a cross-sectional study of 299 adolescent Fontan patients, assessed Tanner stages (using a self-assessment pictorial Tanner stage questionnaire), and found that more than half of the Fontan patients (58%) had a delay in one of the Tanner stage parameters (83). There was a median delay of 1.5–2 years between Fontan patients and the normal population in achieving the Tanner stages in both sexes. The only independent factor associated with the delay in puberty was a history of more than two cardiac surgeries. Besides multiple surgeries with cardiopulmonary bypass, delayed puberty is thought to be caused by decreased cardiac output, cyanosis, and endocrine abnormalities (83).

Apetite-Related Hormones

Shiina et al. in a prospective study of 46 adult Fontan patients, showed that in the Fontan patient group plasma ghrelin levels, a hormone primarily related to increased appetite, were lower than those in controls ($P < 0.05$) (66). Ghrelin is an orexigenic hormone. It has many functions, including regulation of glucose and fat metabolism and stimulation of GH release. Furthermore, it has a favorable effect on cardiovascular function (decreases vascular resistance and increases cardiac output). It is seen as a potential therapeutic target in congestive heart failure (66). In Fontan patients, the decreased ghrelin levels may contribute to cardiovascular dysfunction, growth stunting and metabolic abnormalities. However, the exact role of ghrelin in these processes remains poorly understood.

Metabolism

Glucose Metabolism

Studies into the glucose metabolism have elucidated several abnormalities: adult Fontan patients have lower fasting glucose (29, 84). However, HbA1c -a marker of long term glycemic status- and C-peptide—a marker of endogenous insulin production- are both increased (29). The results from an oral glucose tolerance test are more unfavorable for Fontan patients compared to healthy controls (29, 85). A large study of 275 patients found thirty-four percent of patients had impaired glucose tolerance and five percent had diabetes mellitus (85). Furthermore, oral glucose tolerance decreased over a follow-up of 6.5 ± 2.7 years for a subset of 175 patients aged 20 ± 7 years (85). Remarkably, HbA1c decreased during this time frame (85). Fasting glucose is increased in pediatric patients, although glucose tolerance may be preserved at this age (in contrast to in adults) (84, 85).

The abnormal glucose metabolism may be related to hepatic dysfunction in Fontan patients, as the liver plays an important role in glucose homeostasis (85). The (paradoxically) decreased HbA1c may relate to an increase erythrocyte turnover due to residual hypoxia in Fontan patients (85). Furthermore, myopenia may contribute to plasma glucose levels, as skeletal muscle is a major consumer of plasma glucose. Adiponectin, a regulator of glucose metabolism and insulin sensitivity -among other functions-, was higher for Fontan patients compared to controls. The exact pathophysiology of abnormal glucose metabolism in Fontan patients is incompletely understood. Abnormal glucose metabolism was a predictor of overall mortality and unplanned hospitalization in adult patients (46, 85). Furthermore, it related to increased renal vascular resistance (59).

Lipid Metabolism

Most (84, 86), but not all (29, 46), studies found Fontan patients have lower total cholesterol compared to healthy peers (84, 86). High density lipoprotein (HDL), non-HDL and low density lipoprotein (LDL) cholesterol subtypes were each decreased (29, 84, 86). Total cholesterol did not differ between pediatric and adult Fontan patients (46). Total cholesterol levels did not predict unplanned hospitalization or mortality (46). The prognostic value of individual cholesterol subtypes was not considered in this study (46). Michel et al. performed a comprehensive metabolic analysis of phospholipid and acetylcarnitine metabolism and found metabolites of each class of lipid (phosphatidylcholine, lysophosphatidylcholine, sphingomyelin, and acylcarnitines) were decreased in Fontan patients (87). In a different metabolomics study including patients with heart failure, similar differences in acylcarnitines between patients and controls were found, and several

acylcarnitines and amino acids differed between patients with and without heart failure (88). Saraf et al. found adiponectin, a hormone of lipid catabolism, was increased in Fontan patients compared to controls (81). During stress, cardiomyocytes may preferentially utilize more glucose, rather than lipid. As such biomarkers of energy metabolism may relate to a heart failure phenotype, which may be used as biomarkers for prognosis.

Amino Acid Metabolism

The amino acid metabolism has been studied in Fontan patients with a dominant left ventricle (89). Serum concentration of several amino acids, among which glutamic acid and hydroxyproline, are increased, whereas other amino acids are decreased (among others taurine, asparagine, and threonine). The methionine sulfoxide to methionine ratio is decreased in Fontan patients compared to healthy controls and negatively correlates with exercise capacity (89). A shift in amino acid metabolism may relate to altered myocardial energy metabolism, increased protein turnover, or oxidative stress and endothelial dysfunction (89).

Neoplastic Disease

Our search returned 6 articles related to neoplastic disease. Diller et al. studied the causes of death for different CHD diagnoses. They found neoplastic disease accounted for 3% of Fontan patients deaths (90). This was lower than the percentage for all CHD patients (6.3%), but noteworthy, higher absolute mortality rates in Fontan patients complicate direct comparisons (standardized mortality ratio was 23.4 for Fontan patients and 2.3 for all CHD patients, both compared to healthy references) (90). Heart failure was the most common cause of death for Fontan patients, accounting for 52% of deaths (90).

Furthermore, our search returned 6 case reports and case series detailing in total 13 Fontan patients—aged 11 to 38.5 years—with pheochromocytoma (PHEO) or paraganglioma (PGL) (91–96). Both are catecholamines-producing neuroendocrine tumors. Song et al. found a cumulative incidence of PHEO and PGL of 2.5% in Fontan patients >10 years old on active follow-up (91). The risk of PHEO or PGL in patients with cyanotic CHD is increased compared to people without CHD (OR 6.0, 95% confidence interval 2.6–13.7, $p < 0.0001$) (97). Of note, eight out of eighteen of the cyanotic CHD patients in this study had a Fontan palliation (97).

Two cases of neuroendocrine tumors (NET) were described in a case series by Vural et al. (98). A grade 2 NET of the jejunum was found in a 20 year old woman and a pancreatic NET was found in a 12 year old boy (98).

Chronic hypoxia could play an important role in the development of neoplasms (91–96). Hypoxia inducible factors (HIFs) have been proposed to induce tumor growth in PHEO and PGL (92). Furthermore, underlying genetic defects may predispose to both univentricular CHD and neoplasma (91, 94). Clinicians should be aware of the higher risk of PHEO and PGL in Fontan patients and be vigilant for clinical symptoms of excess catecholamine production.

Bone Abnormalities

Our search on bone abnormalities in Fontan patients yielded 9 articles (39, 68, 78, 99–104). Five studies assessed bone mineral density (BMD) Z-scores measured by either Dual Energy X-ray Absorptiometry (DEXA) or peripheral Quantitative Computed Tomography (pQCT). Each found BMD is mildly decreased in Fontan patients compared to age-related references (68, 99, 100, 102, 104). These studies are summarized in **Table 2**. BMD Z-scores are within normal range for the majority of patients. D'Ambrosio et al. found a prevalence of 29% for a BMD in the osteopenic range (i.e., $Z \leq 1$) and 4% ($n = 1$) in the osteoporotic range ($Z \leq 2.5$) (99). Diab et al. found a Z-score of -2 in 20% ($n = 13$) of their study population (100). The prevalence was lowest in the youngest age group (5–9 years, 5%) and highest in oldest age group (16–18 years, 35%). This is worrisome, as most studied Fontan patients are relatively young, and may develop osteoporosis in adulthood. When indexing BMD values to references (such as Z-scores) the delayed development of children with a Fontan circulation should be taken into account. Since Z-scores are age dependent, a delay in puberty can lead to a deceptively low BMD. Bone age can be determined by hand radiograph, and bone-age-related Z-scores, rather than calendar age-related Z-scores, may provide a more precise way of indexing BMD for Fontan patients (100).

Pathophysiology

Several hypotheses for the pathophysiology of BMD deficits in Fontan patients have been proposed. Hypoxia and reduced cardiac output are common features of Fontan physiology. Hypoxia may increase osteoclast activity and bone resorption (39, 99). Reduced circulation of bone marrow, in the context of reduced cardiac output, may impair bone formation (103). Disturbances in the calcium-vitamin D-parathyroid hormone axis have been reported in Fontan patients (68, 99, 100, 102). The use of some medications, such as glucocorticoids, may have an impact on bone health (68, 100). Physical activity is a necessary stimulus for optimal bone development (68). Fontan patients may have less active lifestyles compared to healthy peers (68). Sarafoglou et al. found weight bearing bones were less affected than non-weight bearing bones, which may relate to physical exercise (102).

Serum Biomarkers of Bone Health

Serum biomarkers related to bone development have been studied in Fontan patients. Bone Specific Alkaline Phosphatase (BALP) serum levels, a biomarker produced by osteoblasts, are reduced in Fontan patients compared to controls (103). Osteopontin, a component of the bone matrix, is decreased in the serum of Fontan patients compared to controls (102). No studies directly related BALP or osteopontin to BMD or clinical outcomes. The clinical implications of these biomarkers in Fontan patients are currently unclear, but they might represent a biomarker of bone metabolism that is easily obtained in clinical practice (103).

TABLE 2 | Bone mineral density Z-scores.

Study	*N*	Age (years)	Measurement	BMD Z-scores		*P*-value
				Location	Value	
Witzel et al. (104)	6	18.6 ± 3.1	pQCT	Radius trabecular	0.0 ± 1.0	0.98
Sarafoglou et al. (102)	10	12.1 ± 1.8	DEXA	L1–L4	−0.5 ± 1.1	Not reported
				Total body	−0.6 ± 1.1	Not reported
			pQCT	Radius trabecular	−30 (95% CI: −59, −1)*	**0.041**
				Radius cortical	−15 (95% CI: −64, 35)*	0.533
				Radius total	−42 (95% CI: −87, 4)*	0.070
Diab et al. (100)	64	5–18	DEXA	L2–L4	−1.0 ± 1.3	Not reported
				Total body	−0.2 ± 1.2	Not reported
D'Ambrosio et al. (99)	28	26 ± 7	DEXA	Hip	−0.6 ± 1.1	**0.01**
				Spine	−0.7 ± 1.1	**<0.01**
Avitabile et al. (68)	43	12.8 [5.1–33.5]	pQCT	Tibia trabecular	−0.9 ± 1.0	**<0.001**
				Tibia cortical	−0.2 ± 1.0	0.27

*pQCT, Peripheral quantitative computed tomography; DEXA, dual energy X-ray absorptiometry; CI, confidence interval; *Raw data provided instead of Z-scores. P values < 0.05 were considered statistically significant and are shown in bold.*

Clinical Outcomes

The risk of fractures related to osteoporosis has not extensively been studied in Fontan patients. One study described the occurrence of fractures and found no patients with a history of frequent fractures (100). Acquired scoliosis is more common in Fontan patients compared to the general population (12 vs. 2–3%) (101). Furthermore, the prevalence of scoliosis increased with age (estimated prevalence 0–10% for patients with 0–5 years of follow-up since Fontan completion vs. 30–45% for patients with >10 years of follow-up) (101). Scoliosis is most commonly considered a complication of (often multiple) thoracotomies related to Fontan surgery, but decreased BMD may also play some part in the etiology of scoliosis in Fontan patients (39).

The Immune System

We found 3 studies which described the prevalence of lymphopenia in Fontan patients (without PLE), and one study describing cytokine expression in Fontan patients (81, 105–107). Rates of lymphopenia (defined as a lymphocyte count below 1,000 cell/ml) ranged from 12 to 32% (105–107). Morsheimer et al. found the proportion of patients with lymphopenia to be significantly higher in patients who had a Fontan palliation over 10 years ago, whereas Alsaied et al. found no difference in age between patients with and without lymphopenia (105, 107). Lymphopenia in Fontan patients may be related to Fontan associated liver disease (105, 106), (subclinical) enteric lymph loss –a similar pathology to PLE-(107), and overall lymphatic congestion due to increased central venous pressure (78). No studies assessed the effects of lymphopenia on risk of infective diseases for Fontan patients.

Cytokine expression has been analyzed by Saraf et al. (81). Different types of pro-inflammatory cytokines were significantly elevated in Fontan patients compared to healthy controls. These included Tumor Necrosis Factor-α, Interleukin-6, Growth/differentiation Factor-15, and β2-macroglobulin. This could indicate that even clinically stable Fontan patients may have chronic subclinical inflammation, similar to patients with congestive heart failure (81).

The Auditory System

We found 4 studies detailing disorders in the auditory system in Fontan patients. Gopineti et al. estimated the prevalence of sensorineural hearing loss (SNHL) in children who had undergone congenital heart surgery (108). The prevalence in Fontan patients was 14.7% (11 out of 75), compared to 0.35% in the general adolescent population. Other studies found a prevalence of hearing disability in 0–13% of pediatric Fontan patients (9, 23, 24). Overall, we found 14 cases out of 151 study subjects (9%) in these studies (9, 23, 24, 108). The age of patients in these studies ranged from 5 to 12 years. No studies assessed hearing disability in adult patients. Hearing disabilities may be caused by inner ear ischemia, hypo perfusion, hypoxia and high doses of furosemide (108). Audiology screening at regular intervals in childhood for all patients with a Fontan circulation seems reasonable.

Reproductive System

Our search returned 4 articles in total, of which 3 articles regarding abnormalities in the female sex organs (109–111) and one regarding sexual function in males (112).

Two studies assessed the placenta in pregnant patients with a Fontan circulation (109, 110). In total 31 pregnancies were described, of which 12 pregnancies resulted in live births (109, 110). Only 7 pregnancies were delivered at term (109, 110). Both studies found placental weight varied significantly across pregnancy. An important proportion of placentas had low weight for gestational age (109, 110). Histological examination revealed all placentas had some form of histological hypoxic lesions. Philips et al. found prominent sub-chorionic fibrin deposition in all placentas (110). In the study by Yokouch-Konishi et al. (109)

seven of eight placentas had a chronic subchorionic hematoma. Other histopathologic changes included lesions associated with maternal vascular malperfusion, villous stromal fibrosis, and placental hypervascularity. The authors speculate that Fontan physiology may be associated with these placental abnormalities. Chronic hypoxemia, high systemic venous pressures and low cardiac output may play a part in the development of poor placental health, and subsequently pregnancy outcomes, in Fontan patients (110).

Canobbio et al. found most (69%) female Fontan patients have normal menstrual patterns (111). Some (31%) Fontan patients older than 18 years reported abnormal flow patterns during menstruation. These complaints included oligo-menorrhea, amenorrhea, and menorrhagia. No comparison to healthy peers was made in this study. The authors propose prolonged cyanosis may relate to menstrual disorders. It should be noted subjects in this study underwent Fontan completion at an old age (mean 18.3 years), compared to current clinical practice (111). Extrapolating these findings to contemporary Fontan patients may therefore be inappropriate.

Rubenis et al. in a survey of 54 male Fontan patients aged 28 ± 3 years, studied sexual function in Fontan patients (112). The prevalence of erectile dysfunction did not differ between patients and controls. Overall satisfaction was lower in Fontan patients (8.3 ± 1.9 vs. 9.5 ± 0.8 out of 10, $p < 0.001$), relating to reduced sexual desire. Other domains of sexual satisfaction did not differ vs. controls. It should be noted only 40% of eligible patients participated in this survey. Due to the sensitive nature of the survey, selection bias and self-reporting may have confounded the results of the study. Chronic venous congestion and decreased perfusion are considered risk factors for erectile dysfunction (112). Health care providers could address concerns regarding sexual health for Fontan patients.

Sleep-Disordered Breathing

Our search yielded three articles related to sleep disordered breathing in Fontan patients (113–115). Sleep-disordered breathing, which includes obstructive sleep apnea (OSA), is often seen in patients with acquired heart failure, but its role in congenital heart disease is less extensively studied (113). One retrospective study found twenty-two out of fifty-five (40%) Fontan patients underwent polysomnography (PSG) at any time (113). Out of these patients 77% was diagnosed with sleep-disordered breathing (31% of the total study cohort). Forty one percentage suffered from nocturnal hypoxemia (absolute desaturation of ≥5% from baseline saturation) and 36% suffered from OSA. Sleep-disordered breathing incidence or severity did not relate to patients' age. OSA can cause hemodynamic changes due to obstruction of the upper airway, hypoxic pulmonary vasoconstriction, and increased pulmonary vascular resistance. This could be a substantial problem in Fontan patients, where blood flow to the lungs is entirely passive (113). Health care providers should be alert for symptoms of sleep-disordered breathing-such as daytime somnolence, fatigue, and cognitive decline- in Fontan patients, which may easily be confused for general symptoms associated with a Fontan circulation.

Continuous positive airway pressure (CPAP) ventilation, the gold standard for OSA treatment, may have detrimental effects on the Fontan circulation by increasing intrathoracic and pulmonary arterial pressure (114). Echocardiography or cardiac catheterization can be used to titrate CPAP parameters and optimize airway pressures with regard for circulatory function (114, 115).

Dermatology

Our search returned 3 articles, of which 2 regarding lower limb varices and one regarding impaired wound healing. Varicose veins and venous insufficiency of the lower extremities are common features in the general population. Bhatt et al. found no differences in the prevalence of clinical signs of chronic venous insufficiency -such as reticular veins, edema, varicose veins, or ulceration- between Fontan patients and healthy controls (116). However, the prevalence of venous reflux assessed by duplex ultrasonography in Fontan patients was higher compared to healthy controls (51 and 10%, respectively) (116). The prevalence of venous reflux did not relate to patients' age. In a study by Pike et al. 11/54 Fontan patients (20%) were diagnosed with varicose veins of the lower extremities (39). The prevalence of varicose veins, or venous insufficiency, of the lower legs does not seem to be increased in Fontan patients. The calf muscle pump may play an important role in the Fontan circulation by augmenting venous return.

Kovacevic et al. described a case report of a 2-year-old boy with impaired wound healing after—otherwise uncomplicated- neurosurgery for head trauma (117). The impaired wound healing could be related to Fontan physiology as the central venous pressure is coupled with the intracranial pressure. Increased intracranial pressure may thus impair scalp perfusion (117).

Ophthalmology

Only 2 articles were found detailing the long-term consequences of the Fontan circulation on the eyes or vision. Hagemo et al. found 4 out of 15 HLHS patients who underwent extensive examination at long term follow-up presented with strabismus (23). Another study found vision impairment in 1 of 34 (3%) Fontan patients (24). These were secondary end-points for smaller studies and are not extensively discussed in their respective studies. As such, the prevalence and impact of eye conditions and vision impairment in Fontan patients remains unclear. Early detection of visual deficiencies may provide Fontan patients with adequate support and limit developmental delay from visual impairments. Screening of vision at regular intervals during childhood seems reasonable.

Dental Disorders

We found two studies concerning dental health in Fontan patients. One study compared 268 healthy controls (age 9.4 ± 3.4 years) to 165 children with CHD (8.0 ± 3.2 years) and 103 children with acquired heart disease (11.4 ± 2.7)

years (118). The amount of debris of calculus found on teeth surfaces did not differ between these groups. However, Fontan had lower dental ages (1.1 ± 0.8 years below chronological age). Children with acquired heart disease did not differ significantly from the healthy controls (118). No mechanism for the delayed dental maturation was proposed by authors (118).

As previously discussed, Fontan patients are at increased risk of hematogenous spread of infection due to shunting. We found one case report on a Fontan patient with a brain abscess due to *Strepcoccus gordonii*, a pathogen commonly found in dental plaque (37). This highlights the need for good dental hygiene (37). Good dental health may prevent serious sequelae from bacteraemia in Fontan patients.

Gastro-Intestinal System

Fontan associated liver disease and PLE are common sequelae of a Fontan circulation, which have been discussed in previous reviews (6, 119). These topics were considered out of the scope of this current review.

One study assessed the hemodynamic response to food ingestion of 15 Fontan patients, aged 27.6 [21.8–34.6] years, compared to 15 healthy controls (120). At baseline Fontan patients have significantly greater baseline regional vascular impedance in the kidneys and legs, but no differences in the superior mesenteric or celiac artery. After food ingestion there are no significant differences in global hemodynamic response and change in systemic vascular impedance, but some regional changes. Most notably, lower limb vascular impedance in healthy controls increases temporarily. However, in Fontan patients lower limb vascular impedance decreases following food intake. The researchers hypothesized the changed responsiveness of the lower leg vascular impedance could be a result of the gut-released vasodilating hormones in response to food ingestion. Fontan patients may not sufficiently be able to counteract this vasodilation by increasing the sympathetic tone in the lower legs (120).

DISCUSSION

The Fontan circulation impairs systemic circulation, venous return, and lymphatic drainage in all organ systems. The goal of this systematic review was to provide an overview of abnormalities in organ systems beyond the heart, lungs, liver, and gut in patients with a longstanding Fontan circulation. We found abnormalities in many of these organ systems (see **Supplementary Table 1**). Main findings –those that have been described in various studies- are discussed below, as well as findings which are of concern, but are currently more scarcely studied.

Main Findings

Structural Brain Abnormalities

Structural brain abnormalities are common in Fontan patients (9–11, 13, 14, 16). The volume of several brain structures was decreased (17, 19–22). Whether this relates to functional outcomes remains unclear (17, 19–22). Central nervous system abnormalities are present *in utero* and exacerbate during patients' lifetime, most likely relating to peri-operative injuries and thrombo-embolic events (10, 11). Peri-operative neuroprotection strategies, such as anti-inflammatory drugs or ischaemic preconditioning, may limit peri-operative injury (121, 122). Neurodevelopmental screening programs during childhood need to be performed on regular basis and therapies should be employed if needed and available (123).

Bacteremia and CNS Infections

Fontan patients are at 3-fold increased risk of CNS infections compared to healthy peers (38). This may relate to hematogenous spread of pathogens due to shunting. Current guidelines recommend endocarditis prophylaxis in patients with e.g., recent intra-cardiac surgery, cyanosis, prosthetic valves, or prior endocarditis (124, 125). Good dental hygiene may prevent bacteremia (37).

Musculoskeletal System

We found abnormalities in the musculoskeletal system in Fontan patients. Both muscle and bone mass are decreased in Fontan patients (61–63, 68, 99, 100, 102, 104). Fontan patients may have bone mineral density defects from a young age. Reduced bone mineral density may relate to cyanosis, reduced cardiac output or reduced physical activity. Fontan patients can safely participate in physical exercise, which may improve muscle mass and improve bone development, among other health benefits (126).

Renal Dysfunction

Renal dysfunction is a common problem in the Fontan population. Renal function deteriorates over time, but may be present even in cohorts of pediatric patients, as early as a median 10 years after Fontan completion (44). Renal structure may be preserved despite severe renal dysfunction, in which case renal dysfunction may be reversible (55). The European Society of Cardiology (ESC) guidelines for adults with CHD advise annual renal function assessment, but do not provide advice on the method of renal function assessment (124). Creatinine-based GFR estimations can be confounded by Fontan-associated myopenia (42, 43). Cystatin C can be used to estimate GFR independent of muscle mass (127, 128). However, the accuracy of cystatin C remains to be determined in Fontan patients, as thyroid dysfunction and glucocorticoid activity may affect cystatin C levels (129). We advise screening of renal function with both cystatin C and creatinine. Future research should focus on the optimal method of renal function assessment.

End-Organ Findings of Potential Concern

The following findings were less frequently reported in literature but nonetheless of potential concern. The volume of the pituitary was larger in Fontan patients than in control subjects (18). This is in contrast to most brain structures, which are smaller in Fontan patients. The pituitary has a portal circulation (similar to the liver) (18). The pituitary as such may be especially vulnerable to increased central venous pressure, which may

lead to pituitary edema and hormonal disturbances. Few studies have systematically assessed pituitary hormone axes in Fontan patients. Small studies found hypothyroidism is a common problem, with an estimated prevalence between 13 and 55% (39, 50, 77). Other hormone axes have scarcely been studied. Studies regarding the growth hormone axis would be of particular interest, given growth stunting and delayed puberty—processes influenced by growth hormone axis activity—occurs in Fontan patients and the growth hormone axis is usually the first affected axis in panhypopituitarism (130).

With regard to malignancies in Fontan patients, we found 13 case reports of neuroendocrine tumors, especially pheochromocytoma and paraganglioma (91–96). Chronic hypoxia or underlying genetic defects—which may also underlie the congenital heart defect—could play an important role in the development of such neoplasms (91–96). Health care providers should be aware of the risk of NET in Fontan patients and be vigilant for clinical symptoms of excess catecholamine production.

Hearing loss -although reported only in smaller retrospective studies- was remarkably prevalent in Fontan patients (9, 23, 24, 108). Hearing loss may result from hypo-perfusion, peri-operative injury, or bolus furosemide administration. Screening may aid in early detection of hearing deficiencies.

We found a prevalence of sleep disordered breathing of 36% in Fontan patients (113–115). This is on the high end of estimates for the general population (131). Interestingly, in (biventricular) congestive heart failure, the pathophysiology of heart failure and sleep disordered breathing is closely related (132). Sleep disordered breathing may increase pulmonary vascular resistance and impair hemodynamics of the Fontan circulation (113). Conversely, congestive heart failure may cause noctural soft-tissue swelling of the upper airway (similar to the pathophysiology of orthopnea) (132). CPAP is often the first choice of treatment for sleep-disordered breathing. Establishing CPAP thresholds for Fontan patients may be more difficult due to the hemodynamics of the Fontan circulation, as high airway pressure may increase pulmonary vascular resistance (114, 115). Sleep-disordered breathing is a diagnosis that needs to be considered when a Fontan patient presents with symptoms of sleep-disordered breathing, e.g., excessive daytime sleepiness, snoring, and morning headaches. Safe thresholds for CPAP can be established by monitoring using echocardiography or cardiac catheterization (114, 115).

Due to the systematic nature of our review, we also found various minor abnormalities in multiple organ systems. These abnormalities, such as dental abnormalities, abnormalities of the autonomic nervous system, etc. may be of limited clinical consequence, or data on these problems is currently of insufficient quality of evidence to affect clinical routine.

Pathophysiology of Organ Abnormalities

Cyanosis in Early Infancy

Cyanosis occurs in early infancy and may persist following Fontan palliation (due to residual right-to-left shunting). Cyanosis stimulates erythrocyte production (which in excess may impair capillary perfusion), induces metabolic stress, and activates hypoxia-mediated biological pathways, which may lead to organ dysfunction (122, 133). Importantly, cyanosis has been implicated in the pathogenesis of neuro-endocrine neoplasms in Fontan patients (91–96). Other Fontan sequelae in which cyanosis has been implicated include structural brain abnormalities (10, 11), renal dysfunction (53, 55), and delayed puberty (83).

Fontan Physiology

Fontan physiology is characterized by decreased cardiac output and increased central venous pressure. Decreased cardiac output may lead to decreased perfusion of organs. This has been implicated as a cause of among others renal dysfunction (41, 48), decreased BMD (103), and decreased brain volumes (11, 19).

Increased central venous pressure may lead to venous congestion and hamper lymphatic drainage. Impaired lymphatic drainage is considered an important factor in the pathogenesis of plastic bronchitis and PLE (7). Impaired lymphatic drainage may occur in any organ system and may play a role in the lymphopenia seen in Fontan patients (78). Venous congestion may play a role in, among others, the development of pituitary congestion and renal dysfunction (18, 54).

Thrombo-Embolic Events

Following Fontan completion, patients remain at increased risk for thrombo-embolism (8). Stroke is considered an important cause of CNS abnormalities, and may relate to other abnormalities described in this review. Micro-emboli may impair end-organ function of among others kidney and spleen (134, 135). The risk of thrombo-embolic events should be minimized during follow-up. Anti-coagulation therapy is commonly recommended, although current guidelines acknowledge the evidence for benefit is limited, and indicate anti-coagulation only for patients with a history of thrombo-embolism or arrhythmia (124, 125).

Iatrogenic Factors

Several iatrogenic factors may relate to the abnormalities described in this systematic review. Fontan patients typically undergo multiple cardiothoracic procedures in childhood. Peri-operative conditioning, which may include cardiopulmonary bypass, exposes the body to significant oxidative stress (136, 137). This peri-operative injury has been implicated in the pathogenesis of structural brain abnormalities (10), renal dysfunction (48), and delayed puberty (83).

Medication use is common in Fontan patients compared to healthy peers (138). Side effects of medication may account for some abnormalities described in this review. For example, bolus administration of furosemide may account for the high prevalence of hearing disabilities (108).

Lifestyle

Fontan patients may lead different lifestyles compared to healthy peers (139). They may participate less frequently in physical activities (139). This may contribute to the myopenia

and decreased bone mineral density seen in Fontan patients (100). Vitamin D deficiency is common in Fontan patients, which may be influenced by dietary and exercise habits (78, 79). Vitamin D deficiency may contribute to myopenia and decreased BMD in Fontan patients (78, 100). Parathyroid function—which may be abnormal in Fontan patients—is also closely related to vitamin D status. Vitamin D status can safely and effectively be improved for Fontan patients with dietary supplementation (79). However, the effect of dietary supplementation on bone mineral density has not been evaluated.

Limitations

Despite our study's strengths, some limitations should be considered. No formal quality assessment for articles was performed. Because of our broad and descriptive research question, we anticipated a large variety of study designs. Formal quality assessment tools are usually limited to a specific study design. We took a narrative approach to describing the results of the search, rather than performing meta-analyses, as the differing study designs complicates direct comparisons.

A broad systematic search strategy was necessary to provide a complete overview for our research question. Defining objective exclusion criteria, while providing a clinically relevant overview, proved difficult. Some articles were excluded because they did not relate to the research question. These articles were excluded by author consensus and are provided in the online supplement. Despite these limitations, we provide an extensive overview of abnormalities in multiple organ systems.

CONCLUSIONS

We performed a systematic review of abnormalities in multiple organ systems for patients with a longstanding Fontan circulation. We found abnormalities in multiple organ systems including the brain, kidney, and musculoskeletal system. An overview is provided in **Supplementary Table 1**. Organ abnormalities may be related to Fontan physiology, cyanosis, iatrogenic factors—such as peri-operative injury or medication use-, or lifestyle-related factors. Based on our results we recommend—in addition to current guidelines-: 1) assessment of renal function should be based on cystatin C in addition to creatinine; 2) health care providers should be vigilant for hypothyroidism, visual or hearing deficits, and sleep disordered breathing in Fontan patients; 3) physical exercise may be employed to improve Fontan cardiovascular function, Fontan-associated myopenia, and bone mineral deficits, among other health benefits. Our findings may aid health care providers and provides suggestions for future research.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

ER and VV: methodology, investigation, and writing—original draft. JV: conceptualization, writing—original draft, writing—review and editing, visualization, and supervision. GT: investigation and writing—original draft. CC and FU: writing—review and editing. WH: writing—review and editing and supervision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.826096/full#supplementary-material

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Increased Risk for Thromboembolism After Fontan Surgery: Considerations for Thromboprophylaxis

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The Fontan circulation introduces an increased risk of thromboembolism which is associated with substantial mortality and morbidity. Adverse outcomes of thromboembolic complications post-Fontan surgery vary in both nature and severity, ranging from local tissue infarction and pulmonary embolism to Fontan failure and ischemic stroke. Furthermore, recent studies have identified that subclinical stroke is common yet underdiagnosed in Fontan patients. Fontan patients are commonly treated with antiplatelet agents and/or anticoagulants as primary thromboprophylaxis. Optimal thromboprophylaxis management in the Fontan population is still unclear, and clinical consensus remains elusive despite the growing literature on the subject. This perspective will describe the nature of thromboembolism post-Fontan surgery and provide evidence for the use of both current and emerging thromboprophylaxis options for children and adults living with Fontan circulation.

Keywords: Fontan, anticoagualtion, direct-acting oral anticoagulant (DOAC), warfarin, aspririn, stroke, thromboemboilc disease

INTRODUCTION

The Fontan procedure has enabled increasing numbers of pediatric patients with an array of single-ventricle physiologies to survive into adulthood. However, the Fontan circulation introduces an increased risk of thromboembolism (TE), which is in turn associated with substantial mortality and morbidity (1–3). Adverse outcomes of thromboembolic complications post-Fontan surgery vary in both nature and severity, ranging from local tissue infarction and pulmonary embolism, to Fontan failure and ischemic stroke (2, 4). Fontan patients are therefore commonly treated with antiplatelet agents or various anticoagulants, as prophylaxis to attenuate this increased thrombotic risk. However, the optimal management in the Fontan population remains unclear, and clinical consensus regarding thromboprophylaxis remains elusive (5).

This perspective aims to provide a brief outline of the nature of TE post-Fontan surgery, as well as insight into the growing body of literature evaluating the outcomes of conventional, as well as emerging thromboprophylactic regimes in the pediatric and adult Fontan populations.

TE POST-FONTAN SURGERY

Post-Fontan TE in the short- and long-term following surgery remains a significant complication of the procedure, and an enduring cause of morbidity and mortality (6, 7). Thromboembolic complications arising from the Fontan circuit commonly present in the arterial circulation as intracardiac thrombosis, ischemic stroke or arterial embolism, and in the venous circulation as central venous thrombosis or pulmonary embolism (2–4, 8, 9).

The Fontan circulation itself presents a highly thrombogenic environment and an accompanying complex pathophysiology, impacting all three elements of Virchow's triad: endothelial cell dysfunction, abnormal blood flow and a hypercoagulable state (10) (**Figure 1**).

Endothelial injury results directly from surgical disruption of the endothelium and the introduction of thrombogenic prosthetic material in the Fontan circuit (11, 12). As a consequence of endothelial cell activation, release of anti-thrombotic factors is impaired, and secretion of pro-thrombotic mediators is enhanced, priming the Fontan vasculature for thrombus formation (13–15).

Abnormal blood flow in the Fontan circulation is caused by turbulence, stasis and a reduced pulmonary artery flow rate dictated by the low returning venous pressure (16), all of which contribute to local initiation of coagulation and an increased thrombotic risk (17).

Hypercoagulability caused by coagulation factor abnormalities has been outlined in a number of studies both prior to and following the Fontan procedure (11, 18–20). In particular, decreased levels of circulating anticoagulants Protein C, Protein S and antithrombin have been reported (17, 19–21), though a lack of adequate pediatric reference ranges has limited meaningful interpretation of these reports (2, 10). An increased level of coagulation factor VIII and decreased levels of factors II, V, VII and X in Fontan patients have also been described when compared to age-matched controls (22). Coagulation abnormalities being compounded by the development of liver dysfunction and/or protein-losing enteropathy post-Fontan surgery (and its associated serum protein imbalances) presents an additional mechanism for the dysregulation of hemostasis (23–25). There is a paucity of pediatric cohort studies using age-appropriate reference intervals to investigate thromboembolic phenomena in the Fontan circulation, limiting insight into coagulopathy for the youngest post-Fontan patients.

Cardiac surgery increases the likelihood of post-operative thromboembolic complications in both children and adults (4, 26–28). The reported increased risk of thrombosis following Fontan surgery is likely multi-factorial, owing to the insertion of central venous lines, the use of cardiopulmonary bypass and the variable surgical manipulation of tissue (29–31). Recent studies have also suggested that the altered hemodynamics resulting from stenosis and thrombosis may be related to the graft material selected and the Fontan procedure performed (12), with Deshaies et al. specifying a possible lower thromboembolic risk in the case of extracardiac conduit Fontan surgery (32). However, a number studies have found no correlation between Fontan circuit type and thrombosis (7, 25), and further research is needed to investigate these conflicting findings.

Despite TE being recognized as a common complication post-Fontan surgery, there is considerable variation in the reported incidence. For example, the incidence of venous thrombosis varies from 4 to 19% and the incidence of stroke ranges from 3 to 19% (33–37). Additionally, the incidence of intracardiac thrombosis has been reported to be between 17 and 33% (38–40), with the thrombi most commonly observed in the systemic venous atrium (48%) and pulmonary venous chamber (44%)(25).

A prospective, multi-center, randomized controlled trial conducted by Monagle et al. assessed thromboprophylaxis post-Fontan surgery (41) and demonstrated a clinically detected incidence of thrombosis of 7% and an overall incidence of thrombosis within the first two years post-Fontan surgery of 22%. Interestingly, all TEs observed in this study were venous and there was no record of arterial thrombosis. A *post hoc* analysis of Monagle et al.'s trial by McCrindle et al. demonstrated a time-related freedom from thrombosis of 69% at 2.5 years post-randomization (31). The highest time-related risk of thrombosis was observed during the immediate post-operative period up until six months post-surgery which was followed by a lower but increasing risk of thrombosis in the next two years. These results are supported by multiple studies which have also observed an immediate high risk of thrombosis in the first year post-Fontan (37, 39, 42–44) with thrombosis risk leveling off at 3.5 years before being followed by a second peak at 10 years post-Fontan (34, 45). Regarding long term incidence of TE, an Australian national registry including 1006 survivors of the Fontan operation demonstrated freedom from thromboembolic events was 82% at 25 years post-Fontan (95% CI, 74–87%) (46).

Interestingly there is emerging evidence that subclinical thrombosis is highly prevalent following Fontan surgery. A recent cross-sectional study that utilized magnetic resonance imaging (MRI), demonstrated that stroke was highly prevalent with an incidence of 39% at $>$ 5 years post Fontan (3). Of these, only 6% of patients were diagnosed clinically. Similarly, Monagle et al. determined that the overall thrombosis rate was 22%, with a clinically detected thrombosis rate of 7%, suggesting that silent thrombosis is highly prevalent in this population (41). Whether silent thrombosis is clinically important remains unknown, however, given the widespread nature, certainly warrants further investigation.

Discrepancies in reports of thromboembolic complications can likely be attributed to variability in outcomes measured (e.g., intracardiac thrombus, pulmonary embolism, clinical or silent thrombosis), diagnostic imaging technique used, patient age, thromboprophylactic regimen, and inconsistencies in follow-up duration (1, 5, 7, 9, 47–49). Additional prospective studies are therefore necessary to reconcile these differences.

THROMBOPROPHYLAXIS IN THE FONTAN POPULATION

The current clinical guidelines and consensus denote that thromboprophylaxis post-Fontan surgery is appropriate to

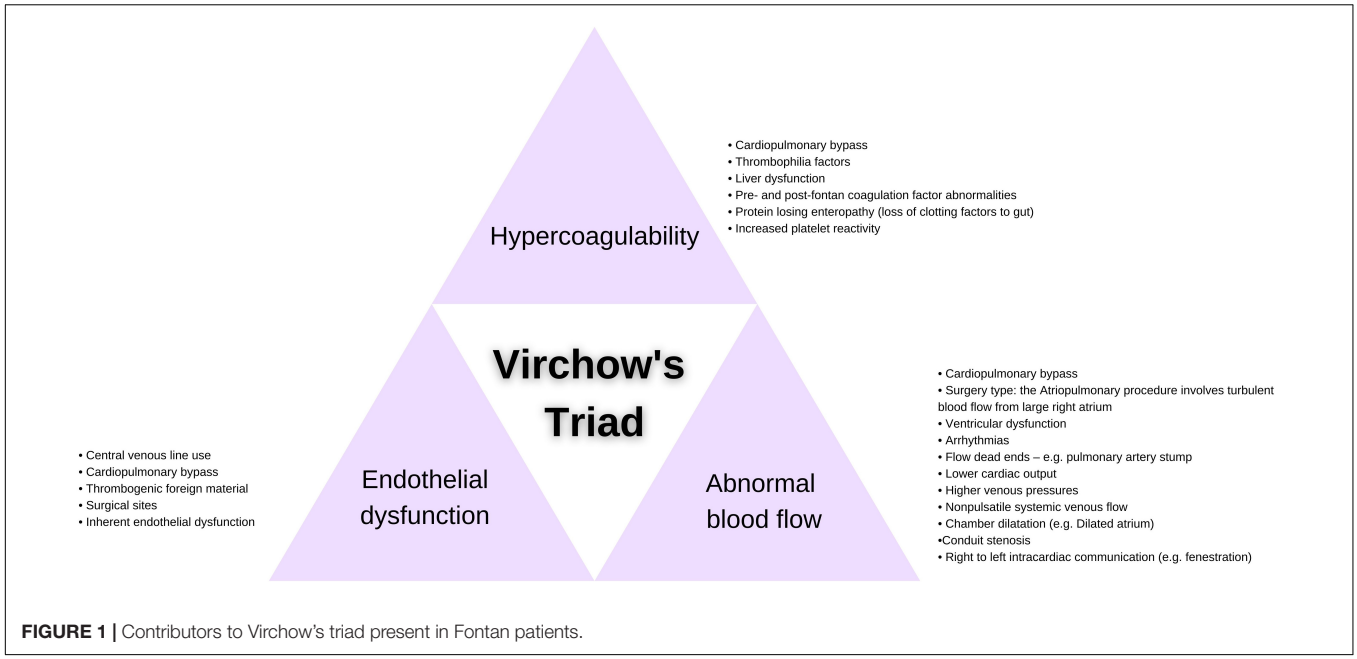

FIGURE 1 | Contributors to Virchow's triad present in Fontan patients.

reduce the risk of thrombosis in the Fontan circulation. Guidelines from the American Heart Association (AHA), American College of Cardiology (ACC) and the American College of Chest Physicians (ACCP) all nevertheless highlight that additional studies are needed to provide sufficient evidence for defining an optimal post-Fontan antithrombotic regime (50–53). The latest AHA recommendations state:

1. "Given the increased risk of the Fontan population for thromboembolic events, some form of thromboprophylaxis is warranted.
2. It is reasonable for all patients with a Fontan-class circulation to receive aspirin as thromboprophylaxis, whereas anticoagulation with warfarin should be reserved for patients with presumed risk factors, previous thrombotic events, or for older Fontan populations.
3. Both antiplatelet and anticoagulant agents retain a significant residual risk of post-Fontan surgery thrombosis.
4. The comparative safety and efficacy of DOACs for thromboprophylaxis in the Fontan patient remains to be determined."

For children post Fontan surgery, the ACCP recommends aspirin or therapeutic UFH followed by vitamin K antagonists such as warfarin. The ACCP guidelines state that aspirin use for pediatric antiplatelet therapy should be administered in doses of 1–5 mg/kg per day, and pediatric patients receiving VKAs should be monitored to achieve a target INR of 2.5 (range 2.0–3.0) (51). The optimal duration of thromboprophylaxis remains to be determined however many patients continue therapy for life.

The emerging use of direct oral anticoagulant (DOAC) therapies post-Fontan surgery may present a promising alternate course of thromboprophylaxis in both children and adults. Studies of emerging anticoagulants must be carefully designed to ensure comparable safety and efficacy of these antithrombotic agents, particularly in complex cardiac populations (50, 54).

Currently, there are insufficient outcome data to recommend DOACs in a patient with a Fontan circulation (50, 55). Important considerations regarding the prescription of a suitable thromboprophylactic agent are outlined in **Table 1**.

Aspirin and Warfarin

Fontan patients are generally prescribed lifelong thromboprophylactic treatment with aspirin or warfarin to mitigate the risk of thrombosis post-surgery. However, the superiority of aspirin or warfarin as a thromboprophylactic agent following Fontan palliation remains to be determined. Selection of a suitable thromboprophylactic regime must therefore consider mechanistic differences, drug interactions and monitoring requirement, as well as patient-related factors such as diet, concomitant medications and pre-existing conditions or history.

Warfarin is an oral anticoagulant that disrupts the vitamin K cycle, inhibiting the synthesis and activation of vitamin K-dependent clotting factors II, VII, IX, and X, as well as the anticoagulant proteins C, S, and Z. As a vitamin k antagonist (VKA), warfarin reduces the overall activation and efficacy of the coagulation cascade, permitting an antithrombotic state in the Fontan circulation. Warfarin use has a number of limitations, including a narrow therapeutic range, significant drug and food interactions and necessitating regular monitoring to ensure safe, controlled and effective anticoagulation (56).

Aspirin, or acetylsalicylic acid (ASA), is an oral antiplatelet drug that prevents the generation of thromboxane A2, irreversibly inhibiting platelet activation and aggregation to

TABLE 1 | Comparison of considerations when prescribing warfarin, aspirin, and direct oral anticoagulants.

	Warfarin	Aspirin	Direct oral anticoagulants
Mechanism of action	• Reduces synthesis of active Vitamin K dependent clotting factors	• Inhibits platelet aggregation	• Direct inhibition of factor Xa or thrombin
Considerations	• Affected by patient-related factors (e.g., medications, diet) • Increased risk of bleeding • Can be reversed by giving vitamin K (important if emergency surgery required) • Quality of Life may be decreased • Potential reduction in bone density	• Increased risk of bleeding • Not reversible • Aspirin resistance	• Increased risk of bleeding • Depend on renal and hepatic function for adequate clearance • Do not all have approved reversal agents • Insufficient outcome data to substantiate safety and efficacy in Fontan
Monitoring requirements	• Regular venous monitoring with INR (narrow therapeutic range)	• Not monitored	• Regular monitoring not required
Convenience	• Oral tablet • Regular monitoring required	• Oral tablet	• Oral tablet • Rapid offset, requires strict adherence for anticoagulative effect

Modified from Attard et al. (10).

impair downstream platelet plug and thrombus formation (57). Although, monitoring of aspirin is not routinely performed in most clinical settings, the possible development of aspirin resistance and a consequential increased risk of thrombosis in a subset of the Fontan population must be considered. Preliminary estimates from small sample cohort studies of postoperative aspirin resistance in the Fontan population have ranged from 50 to 73% (58–60). However, future studies are needed to comprehensively assess the incidence of aspirin resistance in the Fontan patients, as well as its significance as a risk factor for thromboembolism.

With differing modes of action and considerations presented by each drug, several studies have aimed to compare outcomes of aspirin and warfarin after Fontan surgery. The study by Monagle et al. remains the only randomized trial to directly compare outcomes of warfarin and aspirin as thromboprophylaxis post-Fontan surgery (41). The initial results from a cohort of 111 Fontan patients, show that there was no significant difference in thrombotic outcomes between those receiving aspirin and warfarin over the two years post-Fontan surgery (41). However, a secondary analysis of this RCT revealed a 3.5-fold increased risk of thrombosis associated with poorly controlled warfarin therapy ($\leq$30% of INR values within target range when compared to patients who consistently achieved target INR levels or received aspirin (31). This finding is consistent with a retrospective study from Faircloth et al. where high time within therapeutic INR for warfarin was associated with significantly lower rates of thrombotic and bleeding events in the Fontan population (61), indicating the importance of maintaining INR within a target range for effective warfarin thromboprophylaxis in the Fontan population.

A recent multicenter study by Attard et al. (3) utilized MRI, bone densitometry (dual-energy x-ray absorptiometry, DXA), bleeding and Quality of Life (QoL) tools to assess outcomes of aspirin and warfarin use after more than five years after Fontan surgery. This cross-sectional study provides some of the most comprehensive evidence of the long-term outcomes of thromboprophylaxis post Fontan surgery. The key findings of the study were the widespread prevalence of asymptomatic stroke (39%) and cerebral micro-hemorrhage (96%) in the Fontan population, irrespective of thromboprophylaxis type. In addition, high bleeding rates were reported in both groups, with bleeding being more frequent in the warfarin group. Bone mineral density (BMD) was reduced across the cohort compared with the general population; however, BMD was poorer in those receiving warfarin. In the warfarinized patient a reduction in BMD is most likely caused via warfarin's inhibition of the vitamin K-dependent protein osteocalcin, impairing its key role in bone mineralization. Given the young age of the study cohort, inadequate bone mass accumulation is of particular concern as it is associated with increased fracture risk and osteoporosis in later life (62). Given the widespread levels of reduced BMD that were observed, BMD screening in the Fontan population, particularly those receiving long-term warfarin therapy may be warranted. Furthermore, selection of aspirin as primary thromboprophylaxis in the absence of contraindications may therefore improve bone health outcomes and in turn decrease a possible increased risk of fracture and osteoporosis in the Fontan population.

QoL has also become an increasingly significant metric used when assessing the wider impact of different clinical interventions in pediatric anticoagulant populations (63). Interestingly, in the Attard study, quality of life was similar between the warfarin and aspirin groups (3). Perhaps not surprisingly, in the warfarin group, home INR monitoring was associated with improved QoL scores compared to those receiving community monitoring. Previous studies have also demonstrated an improved QoL score when patients on warfarin commenced Home INR monitoring (64). Furthermore, a reduction in financial burden were demonstrated to both the family and the broader healthcare system when home INR monitoring was employed (65).

These findings, alongside the persistent debate regarding the relative efficacy of aspirin and warfarin, highlight that more favorable thromboprophylactic therapies are likely needed to resolve the significant residual risk of thrombosis and cerebrovascular injury in the aging Fontan population.

Emerging Antithrombotic Therapies

Given the limitations of VKAs as thromboprophylaxis, there has been extensive research into novel therapies in the broader population indicated for anticoagulation, though studies specific to safety and efficacy in patients with a Fontan-class circulation remain in their infancy (50, 66). Among the new classes of oral anticoagulants that have been developed are direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (apixaban, endoxaban, rivaroxaban). These novel antithrombotic agents are collectively referred to as direct oral anticoagulants, or DOACs.

Rivaroxaban, like apixaban and endoxaban, is a highly selective direct inhibitor of factor Xa (67). By acting primarily to inhibit FXa, rivaroxaban hinders the flux through the intrinsic and extrinsic pathways of the coagulation cascade, ultimately impairing downstream thrombin generation and thrombus formation (68). Dabigatran instead inhibits both fibrin-bound and unbound (free) thrombin directly, restricting its powerful thrombogenic function as the final effector in the coagulation cascade (69).

DOACs offer attractive benefits when compared to VKA anticoagulants such as warfarin, namely their rapid onset of action, minimal drug and food interactions and predictable pharmacokinetics, avoiding the need for regular patient monitoring (70). However, adequate renal function is crucial to avoid an increased risk of hemorrhage during DOAC use in the adult congenital heart disease (ACHD) population (71).

While evidence-based analysis of DOACs for primary thromboprophylaxis in the Fontan population is rare across the published literature, there is a growing body of research (66). In a single-center study, Georgekutty et al. reported the first retrospective data on the safety and efficacy of DOACs as either primary or secondary thromboprophylaxis in 21 adult patients with a Fontan-type circulation (72). Over a cumulative 316 patient-months, one thrombotic event occurred in a patient with a failing Fontan physiology and Protein-losing enteropathy, and no major bleeding events were observed (median follow-up 13 months).

A larger multicenter prospective study by Yang et al. assessed DOAC use in 530 ACHD patients, with 14% (n = 74) having a Fontan-class circulation (73). All major bleeds and 50% of thromboembolic events occurred in Fontan patients (n = 3, 4.1%), emphasizing the susceptibility of the Fontan population to hemostatic complications. Further analysis of this Fontan cohort nevertheless determined comparable rates of thromboembolism and major bleeding to VKAs as short-term thromboprophylaxis (74). A recent retrospective multicenter study by Kawamatsu et al. consisting of 139 adult Fontan patients similarly proposed that DOACs may present benefits over VKAs in safety and efficacy, reducing the risk of thrombosis and hemorrhage (75).

Although the safety and efficacy of DOACs compared to VKAs has primarily been evaluated in adults, a recent trial investigated the safety and efficacy of rivaroxaban compared to aspirin in children post-Fontan procedure (81). The UNIVERSE study compared thromboprophylaxis with rivaroxaban or aspirin in 112 children post-Fontan surgery and revealed that patients who received rivaroxaban had a similar safety profile to those who received aspirin. A lower thrombotic event rate was also observed in the rivaroxaban group (2% vs. 9%) however this difference was statistically insignificant (76).

However, recent literature has also suggested that DOACs may incur significant risks when used for thromboprophylaxis in circulations that are intercalated with artificial surfaces, as is the case for the Fontan population. Three independent trials assessing dabigatran or rivaroxaban against standard of care in cardiac surgery patients were terminated prematurely due to safety concerns, as there was an excess of thromboembolic and hemorrhagic events experienced by patients in the DOAC treatment groups (77–79).

These adverse trial events occurred in patients whose circulations were exposed to significant amounts of synthetic material—namely mechanical heart valves (77), Left Ventricular Assist Devices (78) and transcatheter aortic-valve replacements (79). Given the similar reliance on thrombogenic artificial surfaces in the two dominant current Fontan procedures, the lateral tunnel and extracardiac conduit (12, 32), these studies indicate the need for careful consideration of possible complications when assessing the use of DOACs in the Fontan circulation.

There are currently three ongoing studies examining the safety and efficacy of DOACs as thromboprophylaxis for adult congenital heart disease (ACHD). A prospective multi-center observational study is aiming to assess routine apixaban use in ACHD, including Fontan-class circulations, and atrial arrythmias (NCT03854149) (80). There is also one ongoing interventional randomized control trial evaluating the safety and efficacy of DOACs in the pediatric Fontan population. The SAXOPHONE study (Safety of ApiXaban On Pediatric Heart disease On the preventioN of Embolism), entails a comparison of antithrombotic viability and QoL between apixaban and existing standard of care anticoagulants—VKAs and low molecular weight heparin in acquired and congenital heart disease pediatric patients (NCT02981472) (54). The SAXOPHONE study will stratify patients based on diagnosis into three groups: single ventricle, acquired and all other congenital heart disease. The single ventricle group will include Fontan patients and therefore this group can be analyzed to determine the efficacy of apixaban in the pediatric Fontan population. The outcomes of these trials will be extremely important to the field.

CONCLUSION

Recent literature has determined that cerebrovascular injury is a frequent occurrence after Fontan surgery, regardless of thromboprophylaxis type. In addition to TE incidence, several important secondary clinical outcomes have been identified that should be considered when determining an individual's thromboprophylaxis regime.

Hence, the following recommendations should be considered for managing post-Fontan TE risk:

1. Where no further clinical complexities exist, it is reasonable to offer aspirin to Fontan patients as thromboprophylaxis. However, before one could be definitive about optimal thromboprophylaxis, consideration must bex given to important clinical features such as cardiac and lung function.
2. Routine BMD screening should be considered all Fontan patients, particularly those on long-term warfarin therapy. As with all populations that are particularly vulnerable to osteopenia/osteoporosis, vitamin D sufficiency and adequate dietary calcium intake are important factors to ensure bone mass accrual and maintenance. Furthermore, patients should be encouraged to engage in weight bearing exercise, in line with their physical capabilities.
3. When warfarin is indicated, a comprehensive anticoagulation service that facilitates home INR monitoring can be of great benefit to the patient in terms of both QoL and financially.
4. The routine use of DOACs as primary thromboprophylaxis after Fontan surgery is not currently recommended given the current limited evidence of efficacy in this cohort.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SV and CS: literature search. CA, SV, CS, VI, and PM: drafting of the manuscript. CA, VI, and PM: editing of the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Impairments in Pulmonary Function in Fontan Patients: Their Causes and Consequences

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Patients with a Fontan circulation lack a sub-pulmonary ventricle with pulmonary blood flow passively redirected to the lungs. In the Fontan circulation, ventilation has a significant influence on pulmonary blood flow and cardiac output both at rest and with exercise. Children and adults with a Fontan circulation have abnormalities in lung function. In particular, restrictive ventilatory patterns, as measured by spirometry, and impaired gas transfer, as measured by the diffusing capacity of carbon monoxide, have been frequently observed. These abnormalities in lung function are associated with reduced exercise capacity and quality of life. Moderate to severe impairment in lung volumes is independently associated with reduced survival in adults with congenital heart disease. Skeletal and inspiratory muscle weakness has also been reported in patients with a Fontan circulation, with the prospect of improving respiratory muscle function through exercise training programs. In this review, we will present data on cardiopulmonary interactions in the Fontan circulation, the prevalence and severity of impaired lung function, and respiratory muscle function in this population. We will discuss potential causes for and consequence of respiratory impairments, and their impact on exercise capacity and longer-term Fontan outcome. We aim to shed light on possible strategies to reduce morbidity by improving respiratory function in this growing population of patients.

Keywords: Fontan, pulmonary function, respiratory muscle, restrictive lung disease, diffusing capacity of carbon monoxide

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INTRODUCTION

Children born with univentricular anatomy undergo procedures in early life resulting in the Fontan circulation. This is routinely performed as staged procedures, resulting in systemic venous return from the superior and inferior vena cava (SVC and IVC) draining passively into the pulmonary arteries, bypassing a sub-pulmonary pump. The completion of the Fontan circuit reduces desaturation and unloads the functionally single ventricle. Heart rate, ventricular function, respiration, and skeletal and respiratory muscle strength all affect the performance of the Fontan circulation.

Since its initial description, the Fontan procedure has undergone several modifications to improve the circulation's efficiency and reduce overall morbidity and mortality. However, morbidity in this population is still high. The Fontan circulation results in high systemic venous pressure, chronic venous congestion, and reduced pulmonary blood flow, cardiac output, and ventricular function. In addition, multiple other adverse factors may be present including

chronotropic incompetence, non-uniform distribution of pulmonary blood flow, chest wall and spinal deformities, pleural adhesions, diaphragmatic palsy, and respiratory and skeletal muscle weakness. With advances in surgical techniques and medical therapy, there are an increasing number of Fontan patients surviving to older adulthood. However, complications related to the Fontan circulation are common, including ventricular systolic and diastolic dysfunction, arrhythmia, venous thrombosis, protein-losing enteropathy, plastic bronchitis, ascites, and hepatic fibrosis and carcinoma (1, 2). Approximately 50% of patients require another intervention by 15 years after Fontan completion (3, 4), and freedom from Fontan failure (defined as occurrence of death, protein-losing enteropathy, plastic bronchitis, poor functional class, or heart transplant) at 50 years of age is only 30% (5).

Abnormal lung function and respiratory muscle weakness have been documented in Fontan patients. Moderate to severe impairment in lung volumes are independently associated with reduced survival in adults with congenital heart disease (6). Fontan patients have reduced total lung capacity and vital capacity, with a restrictive ventilatory pattern (7, 8). These impairments of lung function are associated with reduced exercise capacity (9, 10). For these reasons, treatments directed at improving lung function both before and after Fontan completion are of great interest. Further advances in medical care are actively being sought to reduce late morbidity and mortality after Fontan completion. As yet, very few medical therapies have been shown to be effective. Cardiopulmonary rehabilitation has been shown to improve surrogate outcome measures in patients with a Fontan circulation such as aerobic capacity.

CARDIOPULMONARY INTERACTIONS IN THE NORMAL CIRCULATION

Respiration induces changes in intrathoracic pressures and thereby lung volumes, which in turn affects preload, afterload, and stroke volume. Lauson et al. described the influence of respiration on changes in circulatory pressure in normal subjects, those with chronic lung disease, and those with rheumatic heart disease (11). They found only small variations in pressures during tidal breathing consistent with minimal changes in heart rate or stroke volume. However, during deep inspiration, they found an increase in systemic venous return and right ventricular (RV) stroke volume, and a decrease in left ventricular (LV) stroke volume. In the normal circulation, the majority of LV filling occurs during the first portion of ventricular diastole with atrial systole providing a small contribution at end diastole. Using electrocardiographic and respiratory gated echocardiography, Riggs and Snider demonstrated that the reduction in LV stroke volume during inspiration is secondary to a reduction in early LV filling and not during atrial systole (12, 13). Heart rate also increases with inspiration (12). Several mechanisms for these effects of inspiration have been proposed: (1) an increase in pulmonary venous capacitance, (2) reduced diastolic filling time secondary to the accelerated heart rate, (3) an increase in systemic afterload secondary to increase in intrathoracic pressure, and (4) alterations in the interventricular septal shape secondary to RV filling resulting in increased LV diastolic pressure (12, 14).

Systemic venous return from the SVC and IVC are dependent on the existence of a pressure gradient between the extra-thoracic venous system and the right atrium (15). The venous system is a low-resistance, low-pressure, and high-compliance circulation. During inspiration, a decrease in intra-pleural pressure occurs from contraction of the external intercostal and diaphragmatic muscles, causing an increase in right atrial transmural pressure (pressure exerted across the wall) (11). This results in the right atrial chamber distending and a reduction in right atrial pressure, increasing systemic venous return. With contraction of the diaphragmatic muscles during inspiration, intra-abdominal pressure increases, and transmural pressure of the abdominal vessels decreases. This effectively causes constriction of the abdominal vessels, increasing IVC return to the right atrium. Once right atrial pressure increases, systemic venous return decreases (16). Through an adrenergic response, veno-constriction occurs, increasing vascular pressure and maintaining venous return. In addition to this, the renin–angiotensin–aldosterone system is activated, increasing reabsorption of water and sodium back into the circulation, vasoconstricting arterioles, and releasing anti-diuretic hormone.

Riggs and Snider also noted an increase in RV filling during inspiration, in both early and late diastole (12). Compared with LV filling, they found a greater portion of RV filling occurring during atrial systole. This may be augmented by the diaphragm descending and transiently compressing compliant hepatic sinusoids and portal venules (17). In summary, in the normal circulation, inspiration is associated with increased RV and reduced LV stroke volume.

CARDIOPULMONARY INTERACTIONS IN THE FONTAN CIRCULATION

In the Fontan circulation, systemic venous return is independent of a ventricular pump and relies on a balance between systemic and pulmonary vascular resistance (PVR). The initial belief was that a contractile chamber (right atrium) acting as a pump to drive pulmonary forward flow was important in the Fontan circulation (18). Subsequent animal studies, however, demonstrated that right atrial contraction had a limited role in actively pumping blood forward against higher resistance in the pulmonary arteries (19, 20). de Leval et al. examining Fontan hemodynamics *in vitro*, demonstrated that a contractile chamber did not improve forward flow and did in fact limit pulmonary forward flow detrimental to the circulation by increasing upstream resistance (21).

The importance of spontaneous respiration in the Fontan circulation was highlighted by Fontan and Baudet in 1971, stating that "respiratory assistance should be stopped early because positive pressure prevents central venous return" (18). Subsequent studies have shown respiration to be an important factor, with inspiration augmenting antegrade blood flow into the pulmonary arteries, through inducing negative intrathoracic pressure (22, 23). Spontaneous breathing has been shown to

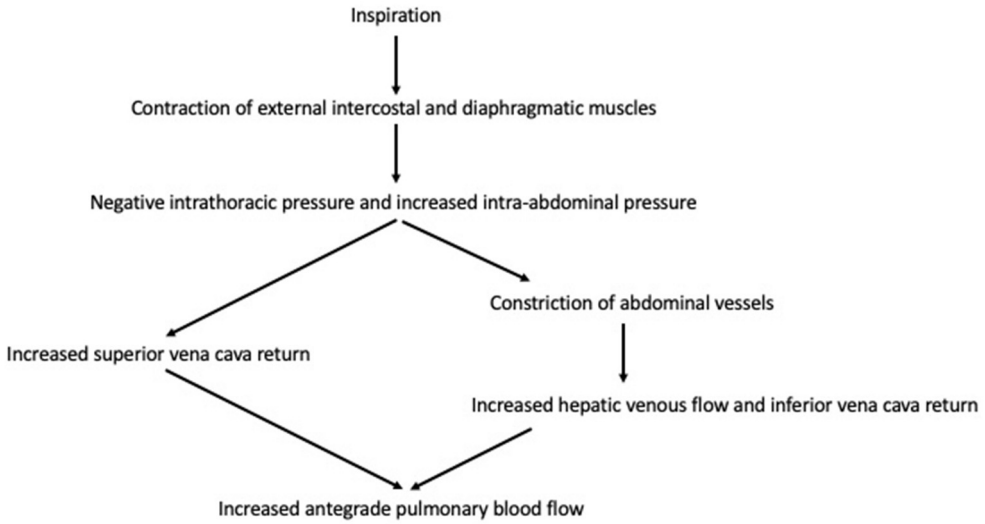

FIGURE 1 | Cardiopulmonary interactions in Fontan circulation.

be the main determinant of cardiac output in Fontan patients (23, 24). Penny and Redington demonstrated that inspiration augments antegrade pulmonary blood flow in an atriopulmonary Fontan circulation, with pulmonary forward flow nearly 64% higher during inspiration than expiration (22). Antegrade pulmonary blood flow and peak velocity increased during atrial systole, and was further augmented with inspiration (22).

Redington et al. also demonstrated augmentation of pulmonary blood flow during inspiration, and attenuation or cessation of this antegrade flow at beginning of expiration in the Fontan circulation (23). They found that during normal tidal breathing, the cardiac cycle had no significant effect on pulmonary blood flow. Through performing breathing maneuvers, they could demonstrate an increase in antegrade pulmonary flow during prolonged forced inspiration against a closed glottis (Mueller maneuver), and cessation to flow with forced expiration (Valsalva), apart from some low-velocity pulsatile flow during ventricular systole.

Consistent with previous studies demonstrating an increase in venous return to the RV, Hsia et al. confirmed higher forward flow in the hepatic veins and IVC during inspiration in both normal and Fontan subjects (24). In normal subjects, there was biphasic forward flow within the hepatic veins and IVC, with a small amount of reversal during atrial systole. This normal pattern was absent in Fontan subjects where the atrium was excluded from the circulation. Thirty percent of flow through the Fontan conduit was dependent on respiration, compared with 15% in normal subjects. Approximately 55% of hepatic flow was respiratory dependent. They postulated that this was secondary to hepatic venous congestion and reduced compressibility. They also found that gravity had a more significant hemodynamic effect on Fontan than normal subjects, with reduced net forward flow and increased flow reversal when erect (24). Shafer et al. also demonstrated the effects of expiration in Fontan subjects during exercise, with a reduction in stroke volume during exercise with an expiratory load (25).

In summary, these studies demonstrate the alterations from normal in cardiopulmonary interactions in the Fontan circulation (**Figure 1**). The effects of respiration are more pronounced, with inspiration augmenting pulmonary antegrade flow. These changes are induced by changes in intrathoracic and intra-abdominal pressures, thereby influencing SVC and IVC return.

ROLE OF MRI IN ASSESSMENT OF RESPIRATORY EFFECTS OF PULMONARY BLOOD FLOW AT REST AND WITH EXERCISE

Using phase-contrast techniques, cardiac magnetic resonance imaging (CMR) provides a unique opportunity to study cardiopulmonary interactions of the Fontan circulation. Respiratory variability in flows through the Fontan circulation has been shown with CMR, with increased flow rates during inspiration (26–29). For example, Hjortdal et al. examined the effects of breathing on flow during exercise (26). Inspiratory time initially increased during exercise. At rest, mean aortic flow was marginally lower during inspiration than expiration and was more dependent on the cardiac cycle than respiration. Stroke volume was also lower during inspiration, and this was unchanged with exercise. In contrast, IVC flow was higher during inspiration at rest, with a smaller differential during exercise. They found no respiratory dependence on SVC flow, but noted limitations in their real-time flow MRI technique.

Using real-time free breathing methods, Wei et al. measured respiration and flow in Fontan subjects during rest and exercise (27). They also demonstrated increased IVC flow with inspiration, which persisted with exercise, and additionally showed increased SVC flow during inspiration. However, there was no significant change in total systemic venous flow between breath holding and free breathing, which could be accounted

for by the exaggeration of reduced or even reversed flow during expiration. They also demonstrated a significant increase in aortic, SVC, and IVC flows with exercise. These findings are in keeping with Hjortdal et al. apart from the increase in SVC flow with exercise. This difference may be explained by differences in real-time flow techniques and a younger cohort in Wei's et al. study population (12.4 ± 4.6 years compared with 20.0 ± 6.3 years) (26, 27).

Significant increases in systemic venous and aortic flow pulsatility with respiration have been shown, with variability between vessels (26, 30). Gabbert et al. developed a detailed matrix to assess venous flow hemodynamics in the Fontan circulation, to quantify respiratory and cardiac dependence of flow (30). They found that although respiration had a significant effect on systemic venous flow pulsatility, the predominant determinant of IVC flow was the heart and not the lungs. These findings were supported by Fogel et al. who showed that ∼70% of systemic venous flow at rest was cardiac dependent, with the highest flow occurring at end-systole and early-diastole (28). Like others, Fogel et al. also showed increased flow during inspiration at the mid-conduit level.

In a small cohort, where we were examining the hemodynamic responses to inspiratory muscle training (IMT), we used CMR to assess aortic and pulmonary flow at rest and during exercise (31). We found that both stroke volume and ejection fraction increased with exercise. We also demonstrated increased pulmonary flow during inspiration at rest. Although IMT improved inspiratory muscle strength and ventilatory efficiency on exercise testing, aortic and pulmonary forward flow did not change.

CMR has further evaluated changes in pulmonary blood flow during exercise in the Fontan circulation. Changes in pulmonary forward flow are both cardiac and respiratory dependent. Systemic venous return, particularly IVC return, and pulmonary antegrade flow increases during inspiration at rest.

DETERMINANTS OF CARDIAC OUTPUT IN THE FONTAN CIRCULATION

In the normal circulation, cardiac output is a function of stroke volume (itself influenced by contractility, preload, and afterload) and heart rate. Several factors can potentially limit cardiac output in the Fontan circulation. Primarily, the lack of a sub-pulmonary ventricle results in preload insufficiency (32, 33) with consequent adverse ventricular remodeling (34, 35) and impaired diastolic ventricular filling (36, 37). As a result of this preload insufficiency, increasing heart rate may have a blunted ability to increase cardiac output in the Fontan circulation (38). Other factors likely to impact cardiac output in the Fontan circulation include systolic dysfunction (34, 39), increased systemic afterload (40), and abnormal ventriculo-arterial coupling (41).

Numerous studies have shown the importance of PVR in the Fontan circulation and is now thought to be the major determinant of cardiac output (42, 43). As the systemic and pulmonary circuits in the Fontan circulation are connected without a pump in between, stroke volume is dependent on pulmonary venous return (preload), which in turn is dependent on PVR. Gewillig and Goldberg demonstrated changes in cardiac output with alterations in ventricular systolic function and PVR (44). Mild increases in PVR cause significant reduction in cardiac output. Factors that can influence PVR include patency of the Fontan circuit, branch pulmonary arteries, pulmonary capillary bed and pulmonary veins, and respiratory function.

Pulmonary vasculature development is abnormal in patients with complex congenital heart. Antenatal hemodynamic factors can alter pulmonary artery size and arborization, and pulmonary venous and lymphatic anatomy. The connection between the cardiac and pulmonary circulations is evident embryologically with lung endoderm protruding into the mesoderm as the heart tube elongates and folds (45). By 20 weeks of gestation, pre-acinar pulmonary arteries have already formed, and any mal-development of cardiac structure has already occurred. Therefore, hemodynamic changes within the circulation, such as a restrictive atrial septum in hypoplastic left heart syndrome, can adversely affect pulmonary artery development. Lack of pulsatile pulmonary flow in the Fontan circulation has been shown to be associated with endothelial dysfunction and abnormal vascular development (46, 47). This has also been shown on histological specimens, with Levy et al. documenting in a study of lung biopsies from 18 Fontan patients, variable intimal proliferation and muscularization of terminal bronchiole and alveolar duct arteries (48). Whether abnormalities of pulmonary vascular development can impact alveolar development remains to be determined.

Augmentation of cardiac output is usually achieved by increases in heart rate, preload and/or myocardial contractility, and reduced afterload. With exercise, for example, biventricular stroke volume increases in the setting of adequate preload reserve (43). In the Fontan circulation, ventricular function does not predict exercise performance, suggesting that it is not the main limitation of exercise capacity (49). The sub-pulmonary ventricle has now been shown to also play a significant role during exercise in the normal circulation (50, 51). La Gerche and Gewillig elegantly discussed the effects of increased RV afterload, and reducing LV preload and consequently cardiac output; they further proposed that without a sub-pulmonary pumping chamber in the Fontan circulation, PVR becomes the limiting factor of cardiac output limitation (51).

ACUTE CHANGES IN PULMONARY VASCULAR RESISTANCE AND POSITIVE PRESSURE VENTILATION IN THE FONTAN CIRCULATION

Pulmonary blood flow and PVR are the major determinants of cardiac output in the Fontan circuit and are significantly affected by respiration. In a normal circulation, PVR is the main determinant of pulmonary afterload and is affected by lung volumes (52). Reduction in intrathoracic pressure with inspiration aids antegrade pulmonary blood flow and consequently cardiac output.

Positive pressure ventilation (PPV) is frequently used in the management of respiratory failure in postoperative cardiac

patients. However, it has been shown to reduce cardiac output likely secondary to increases in PVR and reduced systemic venous return. The hemodynamics of a Fontan circulation are dependent on low PVR and sufficient venous return, and hence the adverse effect of PPV is augmented in the Fontan circulation (53). PPV can be used to increase pressures during inspiration (IPPV) and expiration (PEEP), resulting in increased intrathoracic pressures. Applying pressure during expiration prevents intrathoracic pressures from returning to normal, thereby limiting systemic venous return and cardiac output (54–56). Cournand and Motley showed that reduction in cardiac output was inversely proportional to the pressure delivered (57). This reduction in cardiac output is exaggerated in the Fontan circuit, also reducing antegrade flow from the SVC into the branch pulmonary arteries. These findings highlight the importance of early extubation and/or minimizing positive pressure post-operatively after Fontan completion (23, 58). Jardin et al. proposed that in otherwise healthy patients with respiratory distress syndrome, leftward displacement of the interventricular septum limits LV filling and cardiac output (56). Ventricular–ventricular interaction is also present in Fontan patients with Fogel et al. demonstrating marked differences in the wall motion of systemic right ventricles depending on the presence of a left ventricle, through a magnetic resonance tagging technique (59). They concluded that this ventricular–ventricular interaction plays a significant role in the mechanisms of the systemic ventricle in the Fontan circulation. However, the role of respiratory-dependent septal shift in "biventricular" Fontan patients (i.e., those with two ventricles present) is unknown.

Since the nineteenth century, negative pressure ventilation (NPV) has been used in paralyzed patients with respiratory insufficiency. It has been shown to improve both pulmonary blood flow and cardiac output, particularly in the Fontan circulation, and is associated with improved systemic venous return (15, 60–63). NPV applies sub-atmospheric pressures to the thorax during inspiration, causing the thorax to expand, thereby reducing alveolar pressures, lowering PVR, and augmenting systemic venous return (64).

Shekerdemian et al. converted patients in intensive care after Fontan completion from PPV to NPV and demonstrated acute improvement in pulmonary antegrade flow (15). This was associated with improved mixed venous saturations and increasing cardiac output, without changes in heart rate, by over 50% during both the acute and late post-operative periods (15), highlighting the importance of the respiratory system in the post-operative Fontan circulation. Charla et al. also examined the role of 10 min of NPV and biphasic ventilation (BPV) in the ambulatory Fontan population (65). Using CMR, they also found baseline low pulmonary blood flow compared with controls. With both NPV and BPV, there was a significant improvement in both pulmonary blood flow and cardiac output compared with controls. This is most likely secondary to changes in intrathoracic pressures, as previously demonstrated with normal inspiration (22). They saw a greater improvement with BPV, which was postulated as being due to BPV supporting both the inspiratory phase and maintaining intra-abdominal pressures during expiration, thereby minimizing retrograde flow (65). This was supported by their demonstration of increased IVC and hepatic venous flows. In addition, subjects tolerated short-term external ventilation well and their willingness to continue external ventilation correlated with the improvement in pulmonary blood flow (65). These studies examining NPV in Fontan patients have assessed acute hemodynamic response only. Long-term safety, tolerability, and efficacy of NPV remain an interesting area for future research.

RESTRICTIVE LUNG DISEASE

Reduced Lung Volumes

Lung volume, alveolar surface area, and number increases from 29 weeks' gestation to at least 12 weeks postnatally, with a close association to body weight (66). During the first 3 years of life, increases in lung volume are predominantly due to increases in alveolar number rather than size. Subsequently, alveoli increase in both number and size, continuing through childhood and into adolescence, although at a reduced rate, with 95% of alveolar surface area in adults being formed after birth (67). Lung development is altered, with abnormal lung parenchyma and pulmonary vasculature, in subjects with congenital heart disease, even in the absence of medical procedures and surgical intervention (68).

Prior to Fontan completion, neonatal palliation of pulmonary blood flow may result in abnormalities of pulmonary vascular development. After Fontan completion, pulmonary blood flow is non-pulsatile with altered wall shear stress and reduced pulmonary endothelial function (46). The degree to which alveolar development is impacted by abnormal pulmonary vascular development in patients with a Fontan circulation remains to be determined. Lung development may also be adversely impacted by other factors commonly seen in patients with congenital heart disease: desaturation, mechanical ventilation, lymphatic dysfunction, multiple sternotomies and thoracotomies, scoliosis or pectus deformity, and postoperative complications such as pleural adhesions and diaphragmatic palsy. Diaphragmatic palsy, for example, can reduce ventilatory function by ∼25%, particularly in the setting of generalized respiratory muscle weakness (69).

Animal studies have demonstrated abnormal lung parenchyma after Fontan completion (70). Kanakis et al. (70) demonstrated normal lung parenchyma in 8 pigs at baseline, with rapid development of a mononuclear infiltration, in keeping with bronchiolitis, within 2 h of Fontan completion. Pulmonary capillary recruitment has also been demonstrated in isolated dog lungs, with rises in pulmonary arterial pressure and pulsatile flow (71). This finding suggests that long-term non-pulsatile flow, in the setting of Fontan circulation, causes adverse parenchyma lung remodeling and increases in PVR. Numerous studies have shown reduced total lung capacity and vital capacity in Fontan patients, suggestive of small lungs (7, 8, 72–77). The prevalence of restrictive lung disease is high at 58–60%, with all studies finding reduced forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and a normal or high FEV_1/FVC ratio (9, 10, 77). Ohuchi et al. found reduced total lung capacity (TLC), vital capacity, and functional residual capacity in Fontan subjects

compared with controls (8). Although their Fontan cohort had normal residual volumes, RV/TLC ratio was increased indicative of air trapping. These authors speculated that repeated surgical interventions lead to reduced mechanical mobility of the lungs, causing air trapping (8). Matthews et al. also found an increased RV/TLC ratio but an increased residual volume when measured by plethysmography (Z-score 2.46 ± 1.87) compared with the standard helium dilution single breath test used in other studies (72). They speculated that the difference between methods was due to the single breath test only measuring gas communicating with large airways.

In a large cohort of Fontan subjects aged 6–18 years from the Pediatric Heart Network Fontan Cross-Sectional study, Opotowsky et al. found a high percentage (45.8%) of subjects with low FVC (76). This low FVC was not associated with any demographic or clinical variable. Guenette et al. found significantly reduced FEV_1 and FVC in their Fontan cohort compared with controls, with 65% having a restrictive pattern (78). Moderate restriction was identified in 44% of subjects studied by Turquetto et al., which was associated with presence of postural deviations (e.g. kyphosis and scoliosis) and previous thoracotomies (9). Restrictive lung disease has also been associated with number of interventions, low body mass index, scoliosis, and diaphragmatic paralysis (10).

Ohuchi et al. found that vital capacity was associated with the number of other previous surgical procedures performed (average of 1–2.4 procedures) and demonstrated that during follow-up (0.7–17.5 years), vital capacity decreased significantly (73). The significance of the restrictive lung disease is highlighted by Callegari et al. finding a correlation between FEV_1 % predicted and self-reported quality of life scores, related to physical functioining (10).

Ventilatory Limitation to Exercise in Patients With a Fontan Circulation

In Fontan subjects, reduced FVC is associated with low peak oxygen consumption (VO_2) and reduced exercise capacity, and is a predictor of survival in adults with congenital heart disease (6, 79). In adults with congenital heart disease, presence of restrictive lung disease is a strong predictor of exercise capacity (79). It is now recognized that a significant proportion of patients with a Fontan circulation have ventilatory rather than circulatory limitations to exercise capacity (10, 76, 78).

Guenette et al. reported higher activity-related dyspnea in their Fontan cohort compared with controls (78). In keeping with previous studies, Guenette et al. also found significantly reduced FEV_1, FVC, maximal voluntary ventilation, and diffusing capacity of carbon monoxide (DLCO), with a restrictive ventilatory pattern (78). They examined the cardiopulmonary response to exercise in Fontan subjects, noting significantly reduced peak minute ventilation (VE) compared with controls, secondary to reduced peak tidal volume. Fontan subjects adopted a more rapid breathing pattern at any given exercise intensity. To further characterize ventilatory limitation to exercise, these authors performed inspiratory flow-volume loops during exercise. This demonstrated a higher end inspiratory lung volume, indicative of reduced inspiratory reserve volume. There was no evidence of dynamic lung hyperinflation. Ventilatory equivalence of carbon dioxide (VE/VCO_2) slope, a marker of ventilatory efficiency, during exercise was significantly elevated. Their findings suggest that the restrictive pattern of lung function in Fontan subjects contributes to an abnormal ventilatory response to exercise. Previous studies have also shown elevated ventilatory equivalence of oxygen (VE/VO_2) at both rest and exercise in functionally single ventricle patients (80) Like other studies (9, 10), Turquetto et al. also found a strong correlation between peak VO_2 and lung function parameters (FEV_1, FVC, total lung capacity, and diffusing capacity of carbon monoxide) (9).

Impairments in pulmonary function can impact exercise capacity, with Opotowsky et al. demonstrating that a low FVC was predictive of low peak VO_2, and a stronger determinant than ventricular morphology or dysfunction (76). They also showed that Fontan subjects with an elevated VE/VCO_2 slope were more likely to have a low breathing reserve (BR), suggestive of ventilatory limitation of exercise. In comparing those with ventilatory limitation of exercise (defined as BR $<$ 20%) and those with presumed cardiac limitation (BR $>$ 20%), low FVC, high VE/VCO_2 slope, and high body mass index independently predicted ventilatory limitation.

REDUCED DLCO

DLCO is a measure of lung gas transfer from alveolar gas to hemoglobin within the pulmonary capillaries. It is affected by diffusion across the alveolar-capillary membrane, hemoglobin levels, and capillary blood volume. Therefore, reduced DLCO may be secondary to reduced capillary blood volume available for gas transfer, reduced alveolar volume, and/or abnormal alveolar membrane conductance. DLCO is strongly associated with aerobic capacity, measured by peak VO_2 (81).

Fontan patients have reduced DLCO, ranging from Z-scores of −2.85 to −3.1 (7–9, 72, 74). Matthews et al. proposed that the reduction in DLCO may be due to two mechanisms: (1) the non-pulsatile nature of the pulmonary blood flow inducing changes within the pulmonary bed and causing thickening of the alveolar capillary membrane; (2) recurrent microembolism (72). Larsson et al. also proposed that the non-pulsatile nature of pulmonary blood flow impairs gas exchange within the lungs (7). This is in keeping with Levy et al. who demonstrated thick-walled distal pulmonary arteries, with wall thickness correlating to outcomes (48). Idorn et al. examined the etiology of reduced DLCO in more detail through assessing different components of DLCO (74). In their cohort, they found reduced pulmonary capillary blood volume but normal diffusing capacity across the alveolar membrane. Their data suggested preserved alveolar membrane function and reduced pulmonary perfusion. These authors also found an increase in DLCO and increased capillary blood volume in the supine compared with sitting position. They speculated that this may be secondary to improved perfusion of the upper lobes, secondary to blood flow being more gravity

dependent in the absence of a sub-pulmonary pump. In a small cohort of 19 Fontan patients, del Torso et al. also found abnormalities in lung perfusion in 8 of their 19 patients, with majority being localized perfusion defects (82). Matsushita et al. went on to demonstrate normal ventilation in Fontan patients (83) and like others showed gravity-dependent blood redistribution (84, 85).

Further studies potentially utilizing double diffusion (DLCO and the diffusing capacity of nitric oxide, DLNO) are required to determine the exact etiology of low DLCO in the Fontan population.

RESPIRATORY MUSCLE WEAKNESS IN PATIENTS WITH CONGENITAL HEART DISEASE

Greutmann et al. have documented generalized muscle weakness involving the skeletal and respiratory muscles in patients with congenital heart disease (86). They studied 41 subjects with congenital heart disease, including 11 subjects with single ventricle physiology. Maximal inspiratory pressure (MIP) was significantly reduced in the congenital heart disease group, measuring 75 ± 26 cmH_2O (77±27%) compared with 102 ± 32 cmH_2O in the control group. Inspiratory muscle weakness was greater than expiratory muscle weakness. MIP and maximal expiratory pressure (MEP) correlated significantly with peak VO_2. In addition, subjects with globally reduced respiratory muscle strength (both MIP and MEP) had lower maximal voluntary minute ventilation, which at peak exercise was also associated with peak VO_2. Similarly, Turquetto et al. examined respiratory muscle strength in 27 Fontan patients (9) by using two non-invasive modalities, MIP and sniff nasal inspiratory pressure (SNIP). They also found reduced muscle strength, measuring MIPs of 76 ± 23 cmH_2O (63 ± 16% predicted) in males and 81 ± 33 cmH_2O (71 ± 32% predicted) in females. SNIP was measured at 99 ± 24 cmH_2O (72 ± 31%) in males and 84 ± 13 cmH_2O (82 ± 12%) in females. Furthermore, they found an association between SNIP and peak VO_2. This respiratory muscle weakness may contribute to reduced lung volumes, as seen in Fontan patients.

IMPROVING FONTAN OUTCOMES BY IMPROVING PULMONARY FUNCTION

With the identification of pulmonary abnormalities in Fontan patients, research studies are now determining ways to improve lung function, with the hope to improve exercise capacity, quality of life, and morbidity. With the identification of reduced skeletal and respiratory muscle strength, and better understanding of altered cardiopulmonary interactions in the Fontan circulation, mechanisms to improve lung function have been proposed.

Respiratory Muscle Training

Like skeletal muscles, respiratory muscles can be trained with regular pressure loading. Respiratory muscle weakness affects exercise capacity by predisposing them to fatigue and an increased perception of dyspnea (87). During maximal exercise, 14–16% of cardiac output supplies the respiratory muscles (88). It has been speculated that strengthening respiratory muscles can augment skeletal blood flow by reducing blood diverted to the respiratory muscles.

IMT has been studied in a number of conditions including chronic heart failure (89–91). It has been shown to improve exercise capacity through strengthening of the inspiratory muscles and attenuating the exaggerated peripheral vasoconstriction in exercising limbs (92).

We were the first to show that 6 weeks of IMT improved inspiratory muscle strength (measured by MIP), ventilatory efficiency of exercise (measured by VE/VCO_2), and resting cardiac output in young Fontan patients (31). This was performed with patients training for 30 min a day at 30% of individual MIP, with an increase in threshold at 3 weeks. MIP improved from 69 ± 22 cmH_2O to 103 ± 32 cmH_2O, which is more comparable with MIP found in healthy controls (9). In a subsequent pilot study, Wu et al. assessed the effects of 12 weeks of IMT for 30 min a day at 40% of their initial measured MIP. Although they found no improvement in MIP, there was an improvement in peak work rate, and a trend toward improved peak VO_2 and ventilatory efficiency (93). Fritz et al. looked at a longer 6-month period of IMT, with subjects training for 10–30 repetitions a day and a load that was increased at the patient's discretion. They found improvement in resting oxygen saturations, indicative of improvement in ventilation/perfusion matching, but no improvement in lung function or exercise capacity (94). They proposed that the differences in study findings are secondary to different IMT regimes.

More recently, Turquetto et al. performed a randomized controlled trial looking at combined IMT and aerobic training (95). Fontan subjects were randomized to either personalized aerobic training or IMT, and a non-exercise group was used as a control. Their IMT regime consisted of 3 sets of 30 repetitions at 60% of individual MIP for 4 months, with adjustment in load throughout the duration. Aerobic training consisted of 60-min supervised, individually prescribed exercise training (treadmill, light resistance, and stretching) 3 times a week for 4 months. They found an improvement in peak VO_2 with both these training regimes, but a higher improvement in the aerobic training group.

Ait Ali et al. explored this concept further through the assessment of controlled breathing (respiratory training) in Fontan patients, training both the inspiratory and expiratory muscles (96). They used a method that forms the basis of a yoga practice, involving conscious diaphragmatic contraction and relaxation. This involved weekly 2-h sessions for 3 months of respiratory training. Diaphragmatic respiration increased intrathoracic negative pressure, optimizing systemic venous return. They demonstrated improvement in peak VO_2 and endurance time.

These studies are suggestive that with the correct training regime, including adjustments of the load according to the patient's individual MIP, both IMT and respiratory

training have the potential to improve exercise capacity. However, larger studies need to be undertaken to determine the potential benefits, particularly in the setting of other physical activity programs. IMT is a simple and safe intervention that can be used to improve respiratory muscle strength.

Resistance and Endurance Training

Due to the effects of gravity, when exercising, peripheral skeletal muscles need to pump against gravity to maintain diastolic filling. In the Fontan circulation, pulmonary blood flow is dependent on IVC return. Lower limb venous compliance correlated with calf surface area and muscle mass (97). Cordina et al. therefore hypothesized that enhancement of lower limb muscle mass could improve cardiac output (98). They achieved this through a 20-week gym-training program where they found that isolated muscle resistance training improved exercise capacity.

Hedlund et al. examined the effects of endurance training on Fontan patients, through individualized endurance training programs, including supervised weekly training sessions for 45 min over the duration of 12 weeks (75). These programs consisted of a variety of sports running, dancing, cycling, and swimming. They reported increases in vital capacity after 3 months of training, which was not observed in their control group. In a separate study, they also found improved quality of life, as reported by the Fontan patients and their parents, highlighting the importance of some form of exercise in this population (99). The benefits on lung function of aerobic and/or resistive exercise programs in patients with a Fontan circulation remain to be tested.

CONCLUSION

Patients with a Fontan circulation have abnormal cardiopulmonary interaction, in the setting of their systemic and pulmonary circulations being in series. Due to this, the physiological changes with inspiration are more pronounced in subjects with a Fontan circulation, and respiration has a more crucial role in regulating cardiac output. The critical dependence of ventilation in determining cardiac output in the Fontan circulation is highlighted by the acute use of NPV or BPV immediately post-Fontan completion to improve antegrade pulmonary blood flow and cardiac output. Fontan patients have been shown to have reduced lung volumes with restrictive lung disease, and abnormal lung gas transfer. The exact etiology of these changes still needs to be studied in more detail. In addition, Fontan patients have reduced skeletal and respiratory muscle strength, further limiting exercise capacity. We and others have shown potential benefits to respiratory muscle training. The benefits of aerobic and skeletal muscle training with or without respiratory muscle training remain to be determined.

AUTHOR CONTRIBUTIONS

KL and JA wrote and revised the article. Both authors contributed to the article and approved the submitted version.

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Persistent Liver Dysfunction in Pediatric Patients After Total Cavopulmonary Connection Surgery

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Background: Studies have reported early liver dysfunction (LD) after cardiac surgery is associated with short and long-term mortality. In this study, we aimed to investigate risk factors for persistent LD after total cavopulmonary connection (TCPC) surgery.

Methods: This is a retrospective case-control study. We defined persistent LD as LDs occurring between postoperative day 1 (POD1) and POD7 and sustaining at least on POD7, while transient LD as LDs occurring between POD1 and POD7 and recovering at least on POD7. Multivariable logistic regression analysis was applied and central venous pressure (CVP) was considered continuously or in quantiles.

Results: Postoperative LD occurred in 111 (27.1%) patients. Transient and persistent LD occurred in 65 (15.9%) and 46 (11.2%) patients, respectively. Aortic cross-clamping (ACC) (odds ratio [OR] 2.55, 95% CI 1.26–5.14) and postoperative CVP (OR 1.34, 95% CI 1.18–1.51) were risk factors for persistent LD, also identified for postoperative any LD and transient LD. Adding postoperative CVP to the model only including ACC significantly improved persistent LD prediction (△AUC 0.15, $p = 0.002$). Compared with CVP $\leq$ 14 mmHg, adjusted ORs and 95% CI of persistent LD for CVP of 14–16 and $>$16 mmHg were 3.11 (1.24, 7.81) and 10.55 (3.72, 29.93), respectively. Patients with persistent LD might have a longer length of mechanical ventilation (mean difference, 13.5 h) and postoperative hospital stay (mean difference, 7 days), and higher postoperative costs (mean difference, 6.7 thousand dollars) compared to those with transient LD.

Conclusions: Intra-operative application of ACC and postoperative elevated CVP were independent risk factors for persistent LD in pediatric patients following TCPC surgery. Compared to patients with transient LD, patients with persistent LD might have a longer length of mechanical ventilation and postoperative hospital stay, and higher postoperative costs. We should pay more attention to patients with high postoperative CVP to prevent their persistent LD occurrence.

Keywords: anesthesia, congenital heart disease, pediatric cardiac surgery, total cavopulmonary connection surgery, liver dysfunction, central venous pressure, risk assessment

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INTRODUCTION

The liver is usually a "forgotten" organ in the perioperative management of patients undergoing congenital the heart surgery when compared to the kidney. Complex cardiac lesions such as single ventricles have certain anatomic and hemodynamic features that predispose these patients to hepatic dysfunction (1). Hepatic function abnormalities can even be seen before and early after total cavopulmonary connection (TCPC) surgery (2), due to the unique circulatory characteristics including elevated central venous pressure (CVP) and impaired cardiac output (3).

As ScienceDaily's science news reported in 2017, all patients will suffer from some liver diseases of different degrees in severity, which is just a matter of time, and the severity degrees of these liver diseases become poorer over time since Fontan or TCPC procedure (4). The risk of developing liver cirrhosis, one of the most severe liver diseases, is as high as 43% in 30-year follow-up after Fontan operation (5). Therefore, Fontan-associated liver disease has become an important issue both early and late after Fontan surgery, and positive actions including paying attention to postoperative liver dysfunction and timely identifying its risk factors should be taken to reduce progressive deterioration of liver function after TCPC surgery.

Previous studies reported that the incidence of the liver dysfunction (LD) after open-heart surgery was as high as 25.6% in neonate patients (6), even up to 53.3% in adult patients (7). LD after adult cardiac surgery was associated with prolonged length of mechanical ventilation, hospital stay, and even in-hospital and long-term mortality (8). Some risk factors for hepatic dysfunction after adult cardiovascular surgery have also been identified, such as low cardiac ejection fraction, aortic cross-clamping (ACC) time, cardiopulmonary bypass (CPB) time, etc. (9, 10). Furthermore, a recent study of a large sample size (n = 11, 198) reported that postoperative initial CVP of $>$11 mmHg was associated with a higher risk for postoperative liver dysfunction and in-hospital mortality in adult patients after cardiac surgery (11). But the relationship between high CVP and LD after TCPC surgery remains unclear and there is also no report about the risk factors for LD in patients after TCPC surgery. To address these current knowledge gaps, this study was designed to identify risk factors for LD and the relationship between postoperative CVP and LD in 409 children undergoing TCPC surgery.

MATERIALS AND METHODS

Study Population

All data were from the Fuwai TCPC cohort (12). Pediatric patients under 12 years old who underwent TCPC surgery were consecutively included. Patients were excluded if they died or had extracorporeal membrane oxygenation or had missing values of postoperative alanine aminotransferase (ALT) or aspartate aminotransferase (AST). This is a retrospective observational study. Informed consent was waived because this study was a retrospective study.

Definition of the Liver Dysfunction

We operationally defined LD as postoperative ALT or AST $\geq$ 2 times above the normal upper limit according to the definition of LD in a previous study published in the Journal of the American College Cardiology in 2019 (6). The diagnosis of LD between postoperative day 1 (POD1) and POD7 was based on the maximal ALT or AST levels that were collected between POD1 and POD7. We defined transient LD as patients who developed LD between POD1 and POD7 and did not have LD between POD7 and POD14 or POD7 and discharge. Patients, who developed LD between POD1 and POD7 and still had LD between POD7 and POD14 or POD7 and discharge, were defined as having persistent LD.

Variable Definition and Collection

Preoperative peripheral oxygen saturation was recorded when inhaling air at the time of admission to the hospital. The echo data (ventricle ejection fraction and ventricle end-diastolic diameter) were measured in the main ventricle. We defined senior surgeons as surgeons who performed an average of TCPC procedures over 10 cases per year. The mean arterial blood pressure and the corresponding CVP were the mean of the first six measurements (one measurement per 30 min) after admission to the intensive care unit (ICU).

Fluid balance (ml/kg) was calculated: fluid balance = [(amount of crystalloids + colloids + red cell + plasma + platelets + priming volume) - (blood loss + urine output + ultrafiltrate + residual blood in CPB machine)]/weight. Z-scores indexed to body surface area were applied when calculating the main ventricular end-diastolic diameter z-score. The estimated glomerular filtration rate was computed according to the previous study (13). Vasoactive-inotropic score (VIS) was referred to in the previous formula (14).

Other perioperative variables were also collected, which included gender, age at operation, weight, history of prior cardiovascular surgery, and anatomical diagnosis, Nakata index from cardiovascular CT or catheterization, pulmonary artery pressure from catheter data (pulmonary vascular resistance not reported in all catheter reports, but pulmonary artery pressure did) or from internal jugular venous pressure if patients with prior Glenn surgery, echo data, preoperative blood biomarkers (blood routine test, liver and renal function test, and isoenzyme of creatine kinase-MB), usage of dexamethasone, platelet transfusion, CPB time, and POD0 maximal lactate.

Indications for fenestration included unexpected conditions that occurred during the operation, heterotaxy syndrome, postoperative CVP $>$ 15 mmHg, CPB $>$ 150 min, concomitant atrioventricular valve surgery, pulmonary vascular resistance $>$ 4U/m^2 or average pulmonary artery pressure $>$ 15 mmHg, McGoon ratio $<$ 1.8 or pulmonary artery index $<$ 250 mm^2/m^2, asymmetric development of pulmonary arteries, moderate or above cardiac dysfunction, and non-sinus rhythm.

In-Hospital Clinical Outcomes

The in-hospital outcomes included duration of ICU stay and postoperative hospital stay, length of mechanical ventilation, renal replacement treatment, and postoperative hospitalization costs (conversion: 1 US dollar ≈ 6.5 RMB). Renal replacement treatment included peritoneal dialysis and CRRT.

Statistical Analysis

The statistical analysis was approved by Institutional Review Board. The R package "missForest" with a random forest algorithm was used to impute the missing data. Differences in the distribution of data before and after imputation were evaluated. Student's *t*-test or Mann-Whitney *U* tests were used to analyze quantitative data, and X^2 or Fisher exact tests were used to analyze categorical data, as appropriate, these statistic methods were used to test the significance of the difference between transient and no LD or persistent and no LD or persistent and transient LD.

Postoperative CVP was included in analysis continuously or in quantiles of 0.75 and 0.9. Collinear relationships between potential risk factors were performed before multivariate analysis. Univariate logistic regression and multivariate logistic regression analyses using the backward elimination stepwise method were applied to identify risk factors for any LD, transient LD, and persistent LD. Multivariate logistic regression analysis was started with variables with $p \leq 0.2$ in univariate logistic regression analysis. The adjusted odds ratio (OR) and 95% CI were obtained through multivariate logistic regression analysis with the entrance of all univariables ($p \leq 0.2$ in univariate logistic regression analysis).

The calibration curve and Hosmer–Lemeshow goodness-of-fit test were used to assess the fitness or calibration of models, and the receiver operating characteristic curve and the areas under receiver operating curves (AUCs) were used to evaluate the discrimination ability of the logistic models. We used the DeLong's method to compare the AUCs of two model predictions (15). Two subgroups (age ≤ 4 years old and prior Glenn surgery) were operationally selected to examine whether the logistic models can be applied to a subgroup populations of different characteristics, *via* calculating Hosmer–Lemeshow goodness-of-fit test and AUCs. $p \leq 0.05$ was considered statistically significant. All analyses were performed in R software (version 3.6.4).

RESULTS

Characteristics of the Study Population

From July 2010 to June 2019, a total of 419 children patients (≤12 years old) underwent TCPC surgery. In total, five children who died during hospitalization were excluded because of missing serum creatinine, and also complicated and uncontrolled confounders in these patients, one of the five deaths had a normal ALT or AST between POD1 and POD7 but had LD on POD10. Three children with ECMO after TCPC were excluded due to dilution of ALT and AST within the circuit. Two patients were excluded because of missing ALT and AST. After the exclusion criteria, 409 cases were included in the final analysis. The flow chart is shown in **Figure 1**. The rate of missing data in this study population ranged from 0.2 to 3.9%. Complete data were seen in 372 (90.5%) cases. Among the identified risk factors included in the final logistic models, no one had missing data (**Supplementary Table 1**). The differences in distributions among data before and after imputation were not significant.

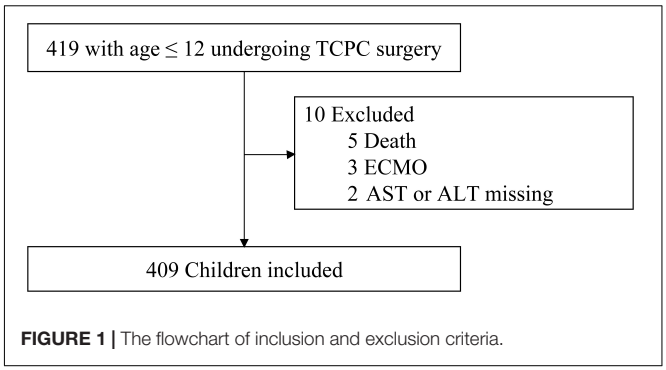

FIGURE 1 | The flowchart of inclusion and exclusion criteria.

The median and interquartile range of the age and weight were 5.3 (4, 7.4) years old and 18 (15, 21) kg, respectively. The top three diagnoses in these patients were an unbalanced atrioventricular septal defect, tricuspid atresia, and unbalanced double outlet right ventricle. Twenty-six patients (6.4%) had a diagnosis with heterotaxy syndrome and 17.9% of patients with unbalanced atrioventricular septal defects were with isomerism. Most of the patients (97.1%; n = 397) underwent extracardiac TCPC and the other 12 patients underwent internal tunnel TCPC. The percentages of right and left ventricle morphology were 41.8 and 39.1%, respectively. All patients underwent CPB and 29.1% (n = 119) patients were performed with ACC. A percentage of 68% patients had prior Glenn surgery (N = 278) and 4.6% patients had prior B–T shunt (N = 19). The baseline characteristics and perioperative data are displayed in **Table 1**. No patients had preoperative ALT or AST ≥ 2 times above normal the upper limit.

Risk Factors for the Liver Dysfunction

After multivariate analysis with backward elimination stepwise regression method and starting with variables of $p \leq 0.2$ in univariate logistic regression analysis, primary diagnosis (tricuspid atresia as ref.; unbalanced atrioventricular septal defect OR 2.74[1.01, 7.5]; pulmonary atresia OR 4.57[1.4, 14.92]; unbalanced double outlet right ventricle OR 1.59[0.52, 4.91]; double inlet ventricle OR 0.34[0.03, 3.36]; pulmonary atresia OR 4.57[1.4, 14.92]; other types OR 1.51[0.44, 5.18]; LR-test p = 0.024), intra-operative maximal VIS (OR 1.05[1.01, 1.1]), CPB time (OR 1.01[1.002, 1.02]), ACC (OR 3.01[1.53, 5.93]), and postoperative CVP (OR 1.16[1.04, 1.29]) were independent predictors for transient LD, which derived from multivariate logistic regression analysis with the comparison between transient LD group and no-LD group, while application of ACC (OR 2.55[1.26, 5.14]) and postoperative CVP (OR 1.34[1.18, 1.51]) were identified as independent risk factors for persistent LD (**Table 2**), which derived from multivariate logistic regression analysis with the comparison between persistent LD group and no-LD group. Intra-operative maximal VIS (OR

TABLE 1 | Patient characteristics and perioperative information according to the liver function development.

Variables	No-LD (*n* = 298)	Transient LD (*n* = 65)	Persistent LD (*n* = 46)	Overall (*n* = 409)
Gender (male)	191 (64.1%)	34 (52.3%)	32 (69.6%)	257 (62.8%)
Age (years)	5.3 (4.0, 7.1)	5.0 (3.7, 7.0)	5.6 (4.0, 9.0)	5.3 (4.0, 7.4)
Weight (kg)	18.0 (15.0, 21.0)	17.5 (15.0, 21.0)	17.5 (15.5, 23.8)	18.0 (15.0, 21.0)
Preoperative SpO2 (≤80%)	101 (33.9%)	23 (35.4%)	15 (32.6%)	139 (34.0%)
Priori Glenn surgery n (%)	198 (66.4%)	50 (76.9%)	30 (65.2%)	278 (68.0%)
Priori B-T shunt surgery n (%)	11 (3.7%)	6 (9.2%)	2 (4.3%)	19 (4.6%)
Heterotaxy syndrome diagnosis n (%)	16 (5.4%)	5 (7.7%)	5 (10.9%)	26 (6.4%)
Ventricle morphology n (%)				
Intermediated	51 (17.1%)	18 (27.7%)	9 (19.6%)	78 (19.1%)
Left	121 (40.6%)	19 (29.2%)	20 (43.5%)	160 (39.1%)
Right	126 (42.3%)	28 (43.1%)	17 (37.0%)	171 (41.8%)
Anatomical diagnosis n (%)				
Unbalanced AVSD	74 (24.8%)	27 (41.5%)	11 (23.9%)	112 (27.4%)
Tricuspid atresia	73 (24.5%)	6 (9.2%)	10 (21.7%)	89 (21.8%)
Unbalanced DORV	59 (19.8%)	11 (16.9%)	9 (19.6%)	79 (19.3%)
Double inlet ventricle	25 (8.4%)	1 (1.5%)	7 (15.2%)	33 (8.1%)
Pulmonary atresia	24 (8.1%)	12 (18.5%)	4 (8.7%)	40 (9.8%)
Others	43 (14.4%)	8 (12.3%)	5 (10.9%)	56 (13.7%)
Nakata index	196 (140, 256)	172 (132, 223)	159 (116, 195)	188 (135, 245)
Pulmonary artery pressure (mmHg)	11.4 ± 3.4	11.4 ± 3.3	11.7 ± 3.3	11.5 ± 3.4
Main ventricle EF (<55%)	39 (13.1%)	6 (9.2%)	2 (4.3%)	47 (11.5%)
Main ventricle EDDz	−0.4 (−4.8, 2.8)	−1.7 (−4.3, 2.2)	−1.4 (−5.6, 2.0)	−1.1 (−4.8, 2.7)
Preoperative biomarkers				
Hemoglobin (g/L)	17.6 ± 2.7	17.7 ± 2.5	17.6 ± 2.4	17.6 ± 2.6
Albumin (g/L)	44.2 ± 3.3	44.0 ± 3.9	44.2 ± 3.9	44.2 ± 3.5
Platelet count ($\times 10^9$/L)	253 ± 85	275 ± 91	267 ± 83	258 ± 86
ALT (U/L)	15 (11, 20)	14 (11, 18)	16 (13, 19)	15 (11, 20)
AST (U/L)	28.2 ± 7.6	29.7 ± 7.3	28.2 ± 7.5	28.4 ± 7.5
Total bilirubin (mg/dl)	0.77 (0.58, 1.05)	0.78 (0.53, 1.35)	0.75 (0.61, 1.04)	0.77 (0.58, 1.08)
eGFR (mL/min/1.73 m^2)	103 (92.0, 115)	98.6 (89.7, 115)	101 (93.1, 117)	101 (91.5, 117)
CK-MB (IU/L)	24 (20, 33)	26 (20, 32)	26 (22, 31)	25 (20, 33)
Anesthesia and operation				
Senior surgeons n (%)	192 (64.4%)	43 (66.2%)	29 (63.0%)	264 (64.5%)
VISm	10.9 ± 6.5	16.1 ± 8.8*	13.6 ± 8.8*	12.0 ± 7.5
Use of dexamethasone n (%)	260 (87.2%)	51 (78.5%)	43 (93.5%)†	354 (86.6%)
Platete transfusion *n* (%)	176 (59.1%)	51 (78.5%)*	27 (58.7%)†	254 (62.1%)
CPB time (min)	108 ± 43.4	146 ± 57.2*	131 ± 67.5*	117 ± 51.1
Aortic cross-clamp n (%)	65 (21.8%)	37 (56.9%)*	17 (37.0%)*†	119 (29.1%)
Fenestration n (%)	119 (39.9%)	30 (46.2%)	22 (47.8%)	171 (41.8%)
Fluid balance (mL/kg)	8.0 (−8.7, 24.0)	8.9 (−11.4, 21.0)	19.8 (−2.8, 35.4)*	8.9 (−8.5, 25.1)
POD0 maximal lactate (mmol/L)	2.08 ± 1.28	2.84 ± 1.72*	2.87 ± 2.21*	2.29 ± 1.52
POD0 CVP (mmHg)	12.1 ± 3.1	13.1 ± 3.0*	13.4 ± 3.3*	12.4 ± 3.1
POD0 MAP (mmHg)	60.4 ± 9.4	59.7 ± 11.5	59.3 ± 9.8	60.2 ± 9.8

*LD, liver dysfunction; SpO2, peripheral oxygen saturation; ASVD, atrioventricular septal defect; DORV, double outlet right ventricle; EF, ejection fraction; EDDz, end-diastolic diameter z-score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; CK-MB, isoenzyme of creatine kinase-MB; VISm, intraoperative maximum vasoactive inotropic score; CPB, cardiopulmonary bypass; POD0, postoperative day zero; CVP, central venous pressure; MAP, mean arterial blood pressure. Quantitative variables: means ± SD or median (interquartile range); categorical variables: frequency (percentage). *$p \leq 0.05$ compared with no-LD group; †$p \leq 0.05$ compared with transient LD group.*

1.05[1.02, 1.08]), CPB time (OR 1.01[1.007, 1.01]), ACC (OR 2.52[1.44, 4.43]), and postoperative CVP (OR 1.24[1.13, 1.35]) were independent risk factors for postoperative any type of LD.

Postoperative CVP was divided into three segments using 0.75 and 0.9 quantiles of CVP as the two cutoffs, namely, 14 and 16 mmHg. The same 5 risk factors were identified for transient LD and the same 2 risk factors for persistent LD. After adjustment of gender, priori Glenn surgery, ventricle morphology, anatomical diagnosis, AST, total bilirubin, intra-operative maximal VIS, use of dexamethasome, transfusion

TABLE 2 | Univariate and multivariate logistic analysis for persistent liver dysfunction.

Variables	Univariate analysis		Multivariate analysis*	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Weight (kg)	1.04 (1, 1.08)	0.065		
Heterotaxy syndrome (yes vs. no)	2.15 (0.75, 6.18)	0.181		
Nakata index	0.997 (0.994, 1.01)	0.143		
Main ventricle EF (<55%)	0.3 (0.07, 1.3)	0.058		
Pre-OP ALT (U/L)	1.03 (1, 1.06)	0.072		
Intra-OP maximal VIS	1.05 (1.01, 1.09)	0.018		
Intra-OP dexamethasone (yes vs. no)	2.09 (0.62, 7.09)	0.194		
Intra-OP fluid balance (ml/kg)	1.01 (1, 1.03)	0.038		
CPB time (min)	1.0083 (1.0028, 1.014)	0.004		
Aortic cross-clamp (yes vs. no)	2.1 (1.09, 4.06)	0.031	2.55 (1.26, 5.14)	0.01
POD0 maximal lactate (mmol/L)	1.32 (1.1, 1.6)	0.002		
POD0 CVP (mmHg)	1.31 (1.16, 1.48)	0.001	1.34 (1.18, 1.51)	<0.001

*OR, odds ratios; CI, confidence interval; OP, operative; ALT, alanine aminotransferase; VIS, intraoperative maximum vasoactive inotropic score; CPB, cardiopulmonary bypass; POD0, postoperative day zero; CVP, central venous pressure. *Multivariate analysis with backward elimination stepwise regression method and starting with variables of $p \leq 0.2$ in univariate logistic regression analysis.*

of platelet, CPB time, ACC, and POD0 maximal lactate ($P \leq 0.2$ in univariate logistic regression analysis), the adjusted ORs and 95% CIs of transient LD for CVPs of 14–16 and >16 mmHg were respectively 1.23 (1.001, 2.9) and 2.78 (1.16, 9.23) using CVPs at ≤ 14 mmHg as reference. After adjustment of weight, diagnosis of heterotaxy syndrome, Nakata index, main ventricle ejection fraction, ALT, intra-operative maximal VIS, use of dexamethasone, intra-operative fluid balance, CPB time, ACC, POD0 maximal lactate ($P \leq 0.2$ in univariate logistic regression analysis), the adjusted ORs and 95% CIs of persistent LD for CVPs of 14–16 and >16 mmHg were, respectively, 3.11 (1.24, 7.81) and 10.55 (3.72, 29.93) using CVPs at ≤14 mmHg as reference. After adjustment of weight, prior B–T shunt surgery, diagnosis of heterotaxy syndrome, ventricle morphology, anatomical diagnosis, Nakata index, main ventricle ejection fraction, platelet counts, total bilirubin, intra-operative maximal VIS, transfusion of platelet, CPB time, ACC and POD0 maximal lactate, the adjusted ORs and 95% CIs of any LD for CVPs of 14–16 and >16 mmHg were, respectively, 2.05 (1.06, 3.98) and 7.43 (3.07, 17.99) using CVPs at ≤14 mmHg as reference. The adjusted ORs are presented in **Table 3**.

Performance of the Persistent Liver Dysfunction Models

The model only including preoperative variables identified no factors for persistent LD. When adding the intra-operative variables, the model identified ACC as the risk factor for persistent LD and its AUC was 0.58 (95% CI, 0.51–0.65). When further addition of postoperative CVP to the model only including ACC, the discrimination power was notably improved (△AUC, 0.15; DeLong $p = 0.002$). The AUC was 0.73 (95% CI, 0.65–0.81) in the model including these two factors. The calibration and ROC curves are displayed in **Figures 2A,B**. The AUCs for persistent LD in the subgroup with age ≤4 years old and prior Glenn subgroup were 0.74 (0.55, 0.93) and 0.74 (0.64, 0.84), respectively (**Figure 2C**). The corresponding Hosmer–Lemeshow test $p > 0.05$.

TABLE 3 | Univariate and multivariate logistic analysis of the association between postoperative CVP and postoperative any type of LD, transient LD and persistent LD.

Events	CVP (mmHg) in quantiles/Continuously	Number and rate of events n (%)	Crude OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*
Any type of LD (*n* = 111)	≤14	69 (21.3%)	Reference	-	Reference	-
	14–16	22 (39.3%)	2.31 (1.27, 4.19)	0.006	2.05 (1.06, 3.98)	0.033
	>16	20 (69.0%)	5.83 (2.63, 12.91)	<0.001	7.43 (3.07, 17.99)	<0.001
	Continuously	-	1.22 (1.12, 1.33)	<0.001	1.21 (1.11, 1.33)	<0.001
Transient LD (*n* = 65)	≤14	45 (13.9%)	Reference	-	Reference	-
	14–16	12 (21.4%)	1.90 (1.001, 3.93)	0.048	1.23 (1.001, 2.90)	0.038
	>16	8 (27.6%)	2.94 (1.04, 8.33)	0.043	2.78 (1.16, 9.23)	0.009
	Continuously	-	1.17 (1.06, 1.30)	0.002	1.15 (1.02, 1.31)	0.029
Persistent LD (*n* = 46)	≤14	24 (7.41%)	Reference	-	Reference	-
	14–16	10 (17.9%)	3.1 (1.37, 7.04)	0.007	3.11 (1.24, 7.81)	0.016
	>16	12 (41.4%)	11.5 (4.59, 28.83)	<0.001	10.55 (3.72, 29.93)	<0.001
	Continuously	-	1.31 (1.16, 1.48)	<0.001	1.26 (1.10, 1.45)	<0.001

*OR, odds ratios; CI, confidence interval; CVP, central venous pressure; LD, liver dysfunction. *With adjustment for variables of $p \leq 0.2$ in univariate logistic regression analysis.*

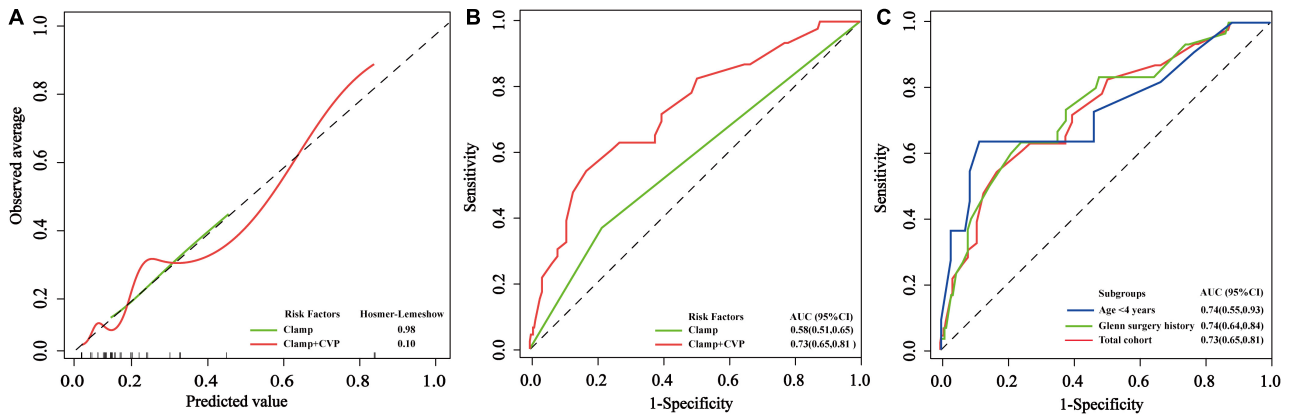

FIGURE 2 | The performance of the logistic regression models for persistent LD. **(A)** Calibration curves and corresponding *p*-values from Hosmer–Lemeshow goodness-of-fit test in the total cohort. **(B)** The receiver operating characteristic curves and their areas under receiver operating curves in the total cohort. **(C)** The receiver operating characteristic curves were used for evaluating the performance of the persistent LD logistic regression model in the two subgroups with age ≤4 years old and prior Glenn's surgery.

Postoperative In-Hospital Clinical Outcomes

One hundred and eleven patients (27.1%, 111/409) developed LD between POD1 and POD7 of TCPC surgery and 58.6% (65/111) of LDs were transient LD (15.9% of the total cohort). Among the 409 patients, 46 patients (11.2%) had persistent LD. The median and interquartile range of postoperative hospital stay of the total cohort was 19 (13, 34) days. The median and interquartile range of postoperative hospital stay in patients with transient and persistent LD were 21 (15, 33) and 28 (17, 40) days, respectively, with a significant increase in longer hospital stay of an average of 7 days in persistent LD group.

Among 278 patients with prior Glenn procedures, 86 patients (30.9%, 86/278) had ACC, which accounted for 21% of the total cohort. Compared to patients with no ACC, patients with ACC had a higher rate of transient LD (31.1 vs. 9.7%) and persistent LD (14.3 vs. 10%).

We divided CVPs into three segments using two cutoffs (14, 16 mmHg), namely, 0.75, 0.9 quantiles of CVPs. Persistent LD rates in patients with CVPs at ≤14, 14–16, >16 mmHg were 7.4, 17.9, 41.4%, respectively, while transient LD rates among those three segments of the CVP group were 13.9, 21.4, 27.6%, respectively (**Table 3**).

A percentage of 41.8% of patients (n = 171) had creation of fenestration. There were no differences between the fenestration group and non-fenestration group for postoperative CVP, postoperative LD, length of mechanical ventilation, and use of renal replacement treatment (all $P > 0.05$). Compared with patients in non-fenestration group, the creation of fenestration might be associated with shorter postoperative hospital stay (median length 21 vs. 18 days, $p = 0.029$).

Compared with patients in the no LD group, the development of transient and persistent LD after TCPC surgery might be associated with a longer length of mechanical ventilation and postoperative hospital stay, a higher rate of renal replacement treatment, and higher postoperative hospitalization costs. Compared with transient LD, the development of persistent LD might be associated with a longer length of mechanical ventilation (30.5 vs. 17.0 h), postoperative hospital stay (28 vs. 21 days), and higher postoperative costs (28.3 vs. 21.6 thousand US dollars). In-hospital outcomes among no-LD, transient, and persistent LD are presented in **Table 4**.

DISCUSSION

This study demonstrated that the development of LD was common (27.1%, 111/409) and about half of them (46/111) worsen to persistent LD (11.2% of the total cohort, 46/409). Development of persistent LD was linked to poor in-hospital outcomes, especially to the length of mechanical ventilation, postoperative hospital stay, and postoperative hospitalization costs. Intra-operative application of ACC and postoperative CVP were identified as independent risk factors for any LD, transient LD, and persistent LD. Our findings are helpful to develop an

TABLE 4 | Postoperative short-term outcomes of the study patients.

Variables	No-LD (n = 298)	Transient LD (n = 65)	Persistent LD (n = 46)
ICU stay (days)	2 (1, 4)	4 (2, 8)	6 (2, 11)
Length of mechanical ventilation (hours)	10.0 (6.0, 19.0)	17.0 (9.0, 52.0)*	30.5 (19.0, 70.8)*†
Postoperative hospital stay (days)	17 (12, 32)	21 (15, 33)*	28 (17, 40)*†
Renal replacement treatment n (%)	12 (4.0%)	15 (23.1%)*	13 (28.3%)*
Postoperative costs (thousands US dollars)	16.8 ± 9.7	21.6 ± 11.1*	28.3 ± 14.2*†

*LD, liver dysfunction; Quantitative variables: median (interquartile range); Categorical variables: frequency (percentage). *p-value ≤ 0.05 compared with no-LD group; †p-value ≤ 0.05 compared with transient LD group. 1 US dollars ≈ 6.5 RMB.*

early risk stratification for persistent LD in these vulnerable patients following TCPC surgery and improve their outcomes.

The incidence of postoperative LD varies under different criteria of LD and ranges from 19 to 53.3% (6, 7, 16–19). This study defined the LD on the basis of AST or ALT, which might underestimate the incidence of LD because we did not consider bilirubin in the definition of LD. Some studies defined LD as ALT or AST higher than the normal upper limit (7). The study in the Journal of the American College Cardiology defined LD as ALT or AST 2 times higher than the normal range, which was the criteria used in this study, and in which the incidence of LD was slightly lower than that in our study (25.6% vs. 27.1%) (6), this might be explained by more palliative surgery (all TCPC surgery) in our study, which was associated with a higher risk of hepatic injury when compared with other cardiac surgery (16). The incidence of LD was lower than that in a previous study (27.1 vs. 53.3%), in which LD was defined as ALT or AST higher than the normal upper limit (7). Furthermore, the definition of LD after cardiac surgery still needs further investigation, and statistically driven cutoffs of LD and a combination of liver ultrasonography, clinical scoring system, and other specific biomarkers might be a future direction in this area.

Previous studies have shown persistent organ injuries had more and more severe clinical outcomes, even long-term mortality when compared with transient organ injuries (17, 18). In our study, patients with persistent LD had longer lengths of mechanical ventilation and postoperative hospital stay, and higher postoperative costs when compared to those with transient LD, which suggested that persistent LD might have a more substantial influence on the clinical outcomes and we should pay more attention to the persistent LD.

Congestion is one of the fundamental factors for the development of liver injury and a relatively high CVP is essential to patients after TCPC surgery, which seems to be a paradox. A previous studies suggested CVP $<$ 14 mmHg as management criteria in a Fontan circulation (19). In our study, postoperative CVP was an independent risk factor for both transient and persistent LD, and a postoperative CVP at 14–16 mmHg was associated with 3.1-fold higher risks of persistent LD compared with a CVP $\leq$ 14 mmHg, and risks of persistent LD for CVP at $>$16 mmHg increased to 10.6-fold. A previous study also indicated that better short-term outcomes were achieved in the sildenafil group with a relatively low mean pulmonary artery pressure after the Fontan operation (20). However, the optimal CVP cutoffs considering both high-CVP-related complications and Fontan circulation requirements, still need further study.

Aortic cross-clamping is often used in cardiac surgery and provides a good vision of the surgical field. In this study, patients with concomitant atrioventricular surgeries, pulmonary arterioplasty, and other circumstances such as torturous vessel, complex surgeries, severe adhesion, and so on, underwent the TCPC using ACC. Previous studies have identified ACC time is a risk factor for hepatic dysfunction in patients undergoing acute type A aortic dissection surgery (21), which was consistent with our results. In this study, the application of aortic cross-clamping was an independent risk factor for both transient and persistent LD, which might be attributed to increased inflammation response and impaired cardiac function in patients undergoing aortic cross-clamping. However, the concrete mechanism requires further investigation.

In this study, we obtained 12 univariables with $p \leq 0.2$ for persistent LD *via* univariate logistic regression analysis. We performed multicollinearity analysis, and we also used multivariate logistic regression analysis with backward elimination stepwise regression method to avoid severe multicollinearity among these covariates. Eventually, the correlation coefficients of ACC and CPB time were 0.56 with $p < 0.001$, and the correlation coefficients of ACC and POD0 maximal lactate were 0.36 with $p < 0.001$. Other pair-wise correlation coefficients of these 12 univariables for persistent LD were $<$0.2 with $p > 0.5$. Intra-operative ACC and postoperative CVP were independent risk factors for persistent LD in the model adjusting eight variables after excluding CPB and POD0 maximal lactate. Furthermore, with all these 12 univariables entering logistic regression, only postoperative CVP was an independent risk factor, but when using multivariate logistic regression analysis with backward elimination stepwise regression method and starting with all these 12 univariables, intra-operative ACC and postoperative CVP were identified as two risk factors for persistent LD. Therefore, we used multiple regression methods (entering and stepwise regression methods) and subtypes of LDs (any type of LD, transient LD, and persistent LD) to increase the robustness of our results. However, the relationship among CPB time, POD0 maximal lactate, and persistent LD still needs to be studied.

Among 409 patients, 131 patients (32%) had no prior Glenn surgery before TCPC surgery and most of them were the cases in their early years (before 2014) and underwent single-stage TCPC without prior Glenn. The older operation age when coming to the hospital and the relatively poorer economic status in our country may drive patients or doctors to choose the single-staged TCPC (22). In our study, prior Glenn surgery was not a protective or risk factor for LD, and patients with prior Glenn history had severe adhesion after the first cardiac surgery and surgeons needed some time to release the adhesion under CPB in these patients. Despite these differences in the populations in our study, the models for persistent LD can be applied to the subgroups of age $\leq$4 years old and prior Glenn surgery and their AUCs were more than 0.7.

Limitations

Our study had several limitations. First, the results from this study might be subject to updates of clinical practice, therefore no causal conclusion can be made from this retrospective study, the real relationship between perioperative LD and poor outcomes like liver fibrosis etc., still needs further study. Second, not all potential parameters were included, such as the velocity of hepatic artery flow, transient elastography, and cardiac magnetic resonance-derived metrics, because these variables were not routinely assessed when hospitalization. Third, our study was limited by failing to demonstrate that the recovery of liver function after POD14 or discharge because not all patients tested their liver function after POD14 or discharge, especially in patients with transient LD. Last, this study indicated that

postoperative CVP was a robust risk factor for LD, but the exact cutoff of optimal postoperative CVP still needs further study.

CONCLUSION

In Chinese pediatric patients after TCPC surgery, LD after TCPC surgery was a common complication. The incidence of persistent LD was as high as 11.2%. Intra-operative application of ACC and postoperative CVP were identified as independent risk factors for any LD, transient LD, and persistent LD. Postoperative LD was linked to poor short-term clinical outcomes, and patients with persistent LD had a longer lengths of mechanical ventilation and postoperative hospital stay, and higher postoperative costs when compared to those with transient LD. We should pay more attention to patients with higher postoperative CVP (especially > 14 mmHg) to reduce their persistent LD occurrence.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Chinese Academy of Medical Sciences Fuwai Hospital. Written informed consent for participation was not provided by the participants' legal guardians/next of kin because: this study was a retrospective study.

AUTHOR CONTRIBUTIONS

YJ, FY, XL, and SY conceived and designed the study. QPL, ZS, HW, YL, XW, and QL arranged, analyzed, and interpreted the data. QPL, ZS, YJ, SY, and FY drafted the manuscript or revised it critically. All authors contributed extensively to the work presented in this manuscript and read and approved the version to be submitted.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.820791/full#supplementary-material

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Pulmonary Arteriovenous Fistulae After Fontan Operation: Incidence, Clinical Characteristics, and Impact on All-Cause Mortality

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Background: The Fontan operation is a surgical procedure used in children with univentricular hearts. Pulmonary arteriovenous fistulae (PAVF) is a major complication after a Fontan operation. However, the incidence and related clinical pathophysiology of PAVF remain unclear.

Purpose: This study aimed to clarify the incidence of PAVF, its clinical characteristics, and its influence on all-cause mortality.

Methods and Results: We serially assessed the presence of PAVF using pulmonary artery angiography and/or contrast echocardiography during catheterization in 391 consecutive patients who underwent the Fontan procedure and compared the results with the Fontan pathophysiology and all-cause mortality. PAVF developed in 36 patients (9.2%), including 30 diffuse- and six discrete-PAVF types. The PAVF-free rates at 1, 5, 10, 15, 20, and ≥25 years after Fontan operation were 97, 96, 93, 88, 87, and 83%, respectively. The mean arterial blood oxygen saturation (SaO_2) in patients with diffuse PAVF at each corresponding postoperative stage were 90, 91, 91, 91, 89, and 88%, respectively, indicating lower SaO_2 levels than those in patients without PAVF (all $p < 0.01$). However, there was no difference in the SaO_2 levels between patients with discrete PAVF and those without PAVF. During a median follow-up period of 2.9 years after the last catheterization, 31 patients, including 12 patients with PAVF, died. Patients with PAVF, especially those with diffuse PAVF, had a higher mortality rate ($p = 0.01$) than those without PAVF (hazard ratio: 3.6, 95% confidence interval: 1.6–7.8, $p = 0.0026$).

Conclusion: Patients who underwent Fontan surgery had an increased incidence of PAVF as they aged. Discrete PAVF did not influence SaO_2 or mortality, whereas the presence of diffuse PAVF caused hypoxia and was associated with all-cause mortality.

Keywords: Fontan operation, pulmonary arteriovenous fistulae, arterial oxygen saturation, heart failure, mortality

INTRODUCTION

The Fontan procedure is a palliative surgery that aims to improve survival in infants born with a functionally univentricular circulation. Although most patients who undergo the Fontan operation can survive into adulthood, the postoperative morbidity and mortality rates remain high, probably because of the longstanding unique hemodynamics (1). Of the well-known post-Fontan complications, such as heart failure, arrhythmias, and protein-losing enteropathy, pulmonary arteriovenous fistulae (PAVF) is a major and serious complication (2, 3). The close association of maldistribution or lack of hepatic venous flow to the pulmonary arteries bilaterally has been repeatedly demonstrated; therefore, the "hepatic factor" hypothesis has been proposed as a cause of PAVF (2, 3). However, the mechanism of PAVF formation or how it causes damage remains unknown. Furthermore, PAVF-related clinical characteristics, such as its incidence and/or impact on prognosis, have not been well-described because of difficulties in detecting PAVF, especially incipient PAVF, as there is no visible influence on Fontan hemodynamics, including arterial oxygen saturation (4). Thus, only a few studies have addressed the long-term impact of PAVF on Fontan survivors. Therefore, a serial comprehensive assessment of the pathophysiology of the Fontan circulation gave us a unique opportunity to clarify its impact (5). Accordingly, the aims of the present study were: (1) to clarify the incidence of PAVF; and (2) to assess the association between PAVF and the Fontan pathophysiology, including all-cause mortality.

MATERIALS AND METHODS

Participants

Overall, 485 patients underwent the Fontan operation between October 1979 and February 2018 at our institution. Of these, postoperative hemodynamic assessments using cardiac catheterizations were performed in 414 patients who had survived for at least 6 months after the operation. Our follow-up policy included a postoperative serial comprehensive assessment of the Fontan pathophysiology, including cardiac catheterizations, to improve the long-term outcome at 1 year postoperatively. Furthermore, the patients were followed-up every 5 years postoperatively (5). In December 1994, we started to assess the presence of PAVF using bubble contrast echocardiography as described below. We excluded 23 patients who had undergone Fontan and who had never been assessed for PAVF before December 1994. Thus, a total of 391 patients who had undergone Fontan were finally included in this study.

Hemodynamics, Ventricular Function, and Brain Natriuretic Peptide

Cardiac catheterization using biplane cineventriculography was performed in all patients, except for 10 patients who were suspected of being allergic to contrast media. In the included patients, the hemodynamic variables measured included the central venous pressure (CVP, mmHg), cardiac index (CI, L/min/m^2), pulmonary and systemic artery resistances (U•m^2), morphological right and left ventricular volumes (using the Simpson's rule), and ejection fraction (EF, %) (4). The end-diastolic ventricular volume was divided by the body surface area to obtain the end-diastolic volume index (EDVI, mL/m^2). Atrioventricular valve regurgitation was estimated using color flow mapping and was graded as follows: none to mild, moderate, or severe during hospitalization. The plasma levels of brain natriuretic peptide (BNP) (pg/mL) were also measured.

Assessment of Pulmonary Arteriovenous Fistulae

Diagnosis of Pulmonary Arteriovenous Fistulae and Veno-Venous Collaterals

At the end of catheterization, PAVF was diagnosed using bubble contrast echocardiography with the injection of approximately 3–5 mL of agitated saline solution, selectively into the right and left pulmonary arteries, and the contrast images were visualized using an equivalent of a standard apical four-chamber view (Vivid q scanner, GE Medical Systems Israel Ltd., Haifa, Israel). The magnitude (contrast in the functional systemic atrium and ventricle) was graded as non-mild, moderate, and severe (5, 6). Severe and moderate were considered diagnostic of PAVF. The presence of veno-venous collaterals (VVC) from any of the superior vena cava (SVC), inferior vena cava (IVC), and/or the innominate vein, to the pulmonary veins and functional left atrium, was also assessed by applying the same contrast echocardiography with an injection of agitated saline solution into these three great veins. The same grading of PAVF was applied to the VVC.

Unbalanced Pulmonary Artery Flow Distribution From the Hepatic Vein and Inferior Vena Cava

We evaluated the degree of unbalanced pulmonary artery flow distribution (PAFD) from the hepatic vein and IVC in 381 patients by performing angiography. Because of difficulties in grading the unbalanced PAFD, we judged it as positive when the right or the left pulmonary artery was not fully visible with a lack of ipsilateral peripheral artery images in our clinical conference as shown in **Figures 1A–C**.

Type of Pulmonary Arteriovenous Fistulae Based on the Morphology

We categorized our patients into three groups based on the morphology of the PAVF (i.e., diffuse-, discrete-, and non-PAVF), according to a previous study (4).

Type of Pulmonary Arteriovenous Fistulae Based on the Time-Course

We focused on patients who were diagnosed with PAVF at the latest Fontan evaluation (catheterization) and categorized these patients into four subgroups based on the time course after the Fontan operation: those with D-Type PAVF, which had disappeared within 1–5 years after the Fontan operation, were excluded from the final statistical analyses. The A-type PAVF, which had newly developed and continued after the operation. The P-Type PAVF was present before and continued

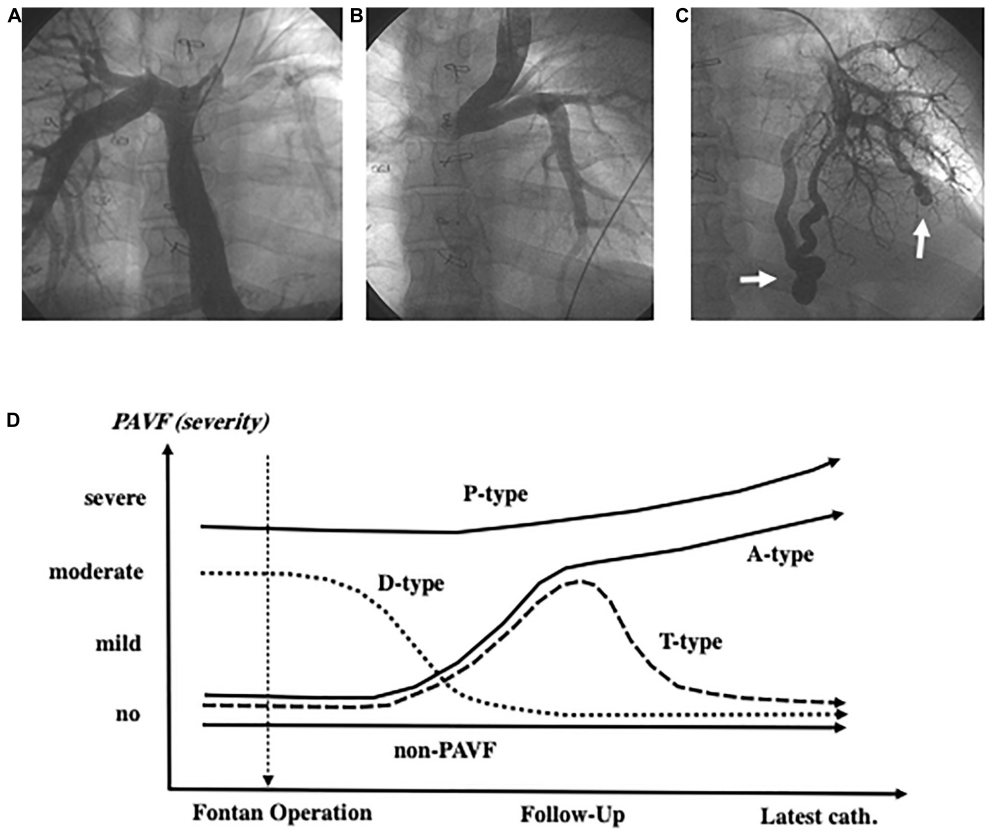

FIGURE 1 | Angiography of the inferior vena cava shows an image of the very thin left pulmonary artery **(A)**. The left pulmonary artery is not visible because of diminished left pulmonary blood flow due to collision of blood flow between the left superior vena cava and the inferior vena cava **(B)**. Arrows indicate discrete-pulmonary arteriovenous fistulae **(C)**. PAVF classification based on the time course after the Fontan operation **(D)** and the definition of each type (A, T, D, P) is described in the "Materials and Methods" section. PAVF, pulmonary arteriovenous fistulae.

after the operation. The T-type PAVF had newly developed and disappeared due to successful specific intervention (**Figure 1D**).

Pulmonary Function and Cardiopulmonary Exercise Tests

Patients who had undergone Fontan also underwent a symptom-limited treadmill exercise using a ramp protocol and the peak oxygen uptake (VO_2) along with the percutaneous oxygen saturation (SpO_2) (PULSOX-Me300, Konica Minolta, Tokyo, Japan) throughout exercise testing. The exercise has induced a decline in SpO_2 from rest to peak exercise was calculated (7) and the respiratory exchange ratio (= VCO_2/VO_2) at peak exercise of $\geq$1 was considered to be the peak effort of exercise performed in this study. We also measured vital capacity (VC; L), the percentage forced expiratory volume in 1 s (Spirosift SP-600, Fukuda Denshi, Tokyo), and VC was calculated as the percentage of the body height predicted normal value in our institute.

Statistical Analysis

Because of skewed data distribution in the plasma BNP level, the logarithmic value was used for some subsequent statistical analysis. Data are expressed as means ± standard deviations (SD) or calculated as medians with interquartile ranges where appropriate. Differences in demographics, hemodynamics, pulmonary function, and cardiopulmonary exercise variables were analyzed using one-way ANOVA with Turkey's *post hoc* test among the three groups. A univariate linear regression analysis was used to evaluate relationships between the continuous variables, and a multivariate linear regression analysis was used to detect the main correlates. Comparisons of prevalence of heterotaxy, medication usage, and type of surgical procedures were analyzed using chi-square or Fisher's exact test. A status free from the onset of PAVF after the Fontan operation and death after the assessment of PAVF at the latest catheterization was estimated using the Kaplan–Meier method, and the differences in these event-free statuses between the groups were assessed using the log-rank tests. Cox's proportional hazards model was used to predict the associations between clinical variables and the onset of PAVF or all-cause mortality. Variables that proved to be significant predictors of the outcome in the univariate analysis ($p < 0.05$) were included in the multivariate model to determine the independent predictors. All analyses were performed using the statistical software JMP 12 (SAS Institute, Cary, NC, United States). A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

Prevalence, Incidence, and Type of Pulmonary Arteriovenous Fistulae

Concerning PAVF, the number of patients that we could evaluate at 1, 5, 10, 15, 20, and ≥25 years after Fontan operation were 391, 325, 259, 182, 107, and 53, respectively. After excluding four patients who had been diagnosed with D-Type PAVF, we identified a total of 36 patients with PAVF (9.2%), including 29 patients (80%) with diffuse PAVF, six patients (17%) with discrete PAVF, and one patient (3%) with diffuse and discrete PAVF. The latter was categorized as having diffuse PAVF because the dominant lesion was a diffuse PAVF. A comparison of clinical characteristics of patients with diffuse, discrete, and non-PAVF is presented in **Table 1**. Regarding the classification based on the serial time-course of PAVF, Type-A PAVF was the most frequent type ($n = 25$, 70%), followed by Type-P in eight (22%), and type-T in three (8%) patients. The prevalence and the types of PAVF (diffuse or discrete, A, D, T, or P) throughout the follow-up period are presented in **Figures 2A,B**. Type-D is presented in **Figure 2A**. When we assumed that the follow-up time was 0 in Type-P patients, the free rates from any PAVF, excluding Type-D, at 1, 5, 10, 15, 20, and ≥25 years after Fontan operation, were 98, 97, 94, 89, 87, and 83%, respectively (**Figure 3A**). The free rates from the diffuse or discrete PAVF are also presented in **Figures 3B,C**.

Among the patients who had undergone evaluation for the presence of PAVF, those who had undergone a complete evaluation of VVC (i.e., injections of agitated saline solution into the SVC, IVC, and innominate vein) were 100, 121, 153, 126, 78, and 48 at 1, 5, 10, 15, 20, and ≥25 years after the Fontan operation, respectively. The presence of VVC was confirmed in 74 (74%), 97 (80%), 97 (63%), 82 (65%), 50 (64%), and 26 (54%) patients, respectively; when patients with PAVF were separately analyzed, VVC at all postoperative stages was observed in 2 (100%), 6 (86%), 12 (100%), 11 (85%), 8 (100%), and 7 (100%) patients, respectively.

The SaO_2 levels at each postoperative stage were significantly lower in patients with than in those without VVC (93 ± 4% vs. 95 ± 2%, 93 ± 3% vs. 95 ± 1%, 94 ± 3% vs. 95 ± 3%, 93 ± 3% vs. 95 ± 2%, 93 ± 6% vs. 96 ± 2%, and 92 ± 5% vs. 95 ± 2% at 1, 5, 10, 15, 20, and ≥25 years after the Fontan operation, respectively; $p < 0.05$).

Unbalanced Pulmonary Artery Flow Distribution and Pulmonary Arteriovenous Fistulae

In our routine clinical conference, unbalanced PAFD from the hepatic vein and/or the IVC was identified in 16 (57%) out of 28 patients with diffuse PAVF, and in two (33%) out of six patients with discrete PAVF. In contrast, 26 (7.5%) out of 347 patients without PAVF were judged as having an unbalanced PAFD, which was much lower than the rate of unbalanced PAFD in patients without PAVF ($p < 0.0001$). None of the four D-type patients had unbalanced PAFD. Interestingly, seven of the 21 patients (33%) with Type-A PAVF, excluding two patients with liver cirrhosis and two patients who had undergone surgical redirection of the Fontan route, had shown significantly improved "balanced" PAFD when compared to the initial unbalanced PAFD at 1 year after the Fontan operation. A typical case is presented in **Figures 4A,B**.

TABLE 1 | Subject characteristics.

PAVF	Diffuse	Discrete	No	*p*
Cases (*n*)	30	6	355	
Age (year) at latest cath.	14 ± 10	22 ± 6	16 ± 10	0.1805
Male (%)	67	67	58	0.565
Age at 1st Fontan (year)	5 ± 6	8 ± 5	4 ± 5	0.0433
NYHA class	1.8 ± 0.8#	1.7 ± 0.5	1.3 ± 0.6	<0.0001
Heterotaxy (%)	47	67	26	0.0084
Right Isomerism	10	33	21	0.3613
Left Isomerism	37	33	5	<0.0001
SVtype (LV:%)	40	17	40	0.4734
Diagnosis (%)				
UVH	27	17	23	
TA	27	17	19	
DORV	27	50	18	
HLHS	3	0	5	
Others	16	16	35	
Current Type of Repair (%)				0.0087
APC	3	0	1	
IAR	57	67	19	
ECR	40	33	80	
Procedures prior Fontan (%)				
APS	50	50	57	0.7492
PAB	30	17	31	0.7348
Glenn	47	33	65	0.051
Fenestration	17	0	12	0.3551
Medications (%)				
Diuretics	60	33	41	0.1299
Anti-coaglant	77	83	75	0.8806
ACEI/ARB	23	67	36	0.1019
Beta blocker	17	33	26	0.4732
Anti-arrhythmia	17	17	9	0.3598

ACEI, angiotensin converting enzyme inhibitor; APC, atriopulmonary connection; APS, aortopulmonary shunt; ARB, angiotensin receptor blocker, connection; APS, aortopulmonary shunt; ARB, angiotensin receptor blocker; DORV, double outlet right ventricle; ECR, extracardiac rerouting; HLHS, hypolastic left heart syndrome; IAR, intraatrial rerouting; LV, left ventricle; NYHA, New York Heart Association; PAB, pulmonary artery banding; SV, systemic ventricle; TA, tricuspid valve atresia; UVH, univentricular heart. Values are mean ± SD. #Indicate p < 0.05 vs. group of Discrete and No, respectively.

Comparison of Clinical Characteristics Based on the Pulmonary Arteriovenous Fistulae Morphology

Patient Characteristics

A summary of the comparisons is provided in **Table 1**. Compared to patients without PAVF, diffuse-PAVF showed greater NYHA class and a high prevalence of heterotaxy syndrome, especially in

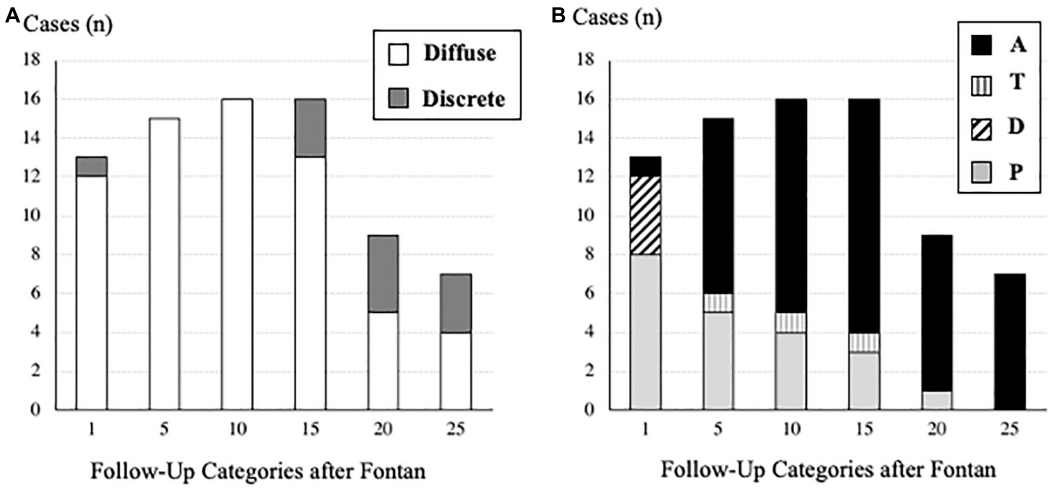

FIGURE 2 | (A) Number of cases of pulmonary arteriovenous fistulae based on the morphology (diffuse or discrete) in each follow-up category after the Fontan operation. **(B)** Number of cases of pulmonary arteriovenous fistulae based on the time-course (A, T, D, P) in each follow-up category after the Fontan operation. Definition of each type (A, T, D, P) is described in the "Materials and Methods" section.

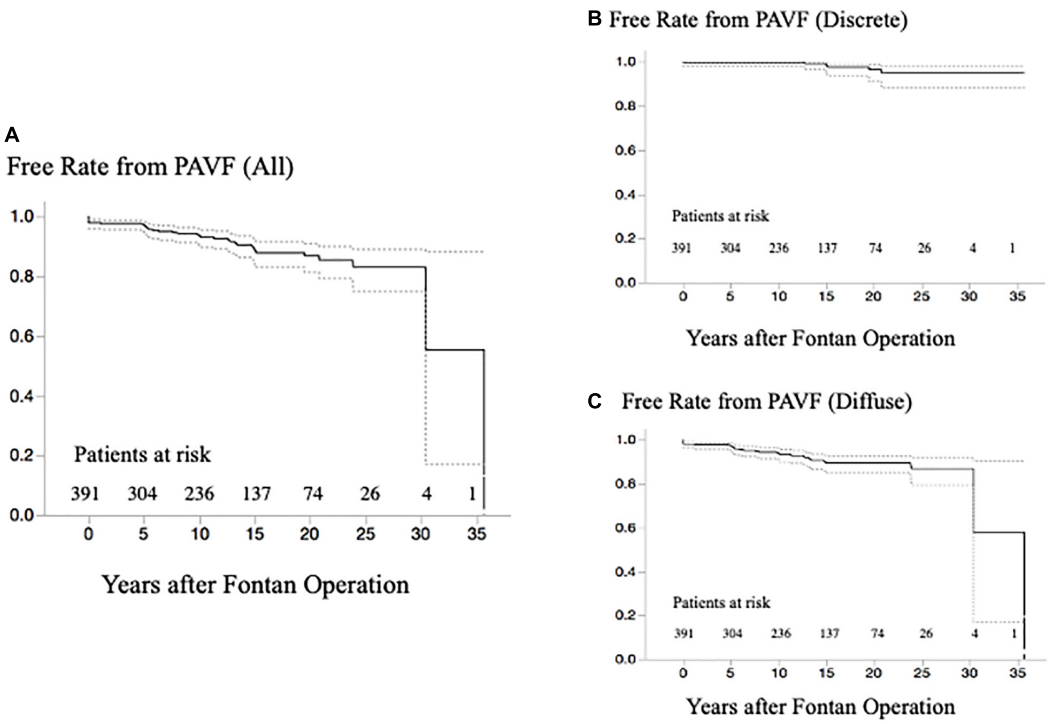

FIGURE 3 | (A) Free rate from any PAVF after the last evaluation of PAVF at catheterization. **(B)** Free rate from any discrete-PAVF after the last evaluation of PAVF at catheterization. **(C)** Free rate from any diffuse-PAVF after the last evaluation of PAVF at catheterization. PAVF, pulmonary arteriovenous fistulae.

those with left isomerism ($p < 0.0001$). The same statistical trend was observed in patients with discrete-PAVF.

Hemodynamics and Cardiopulmonary Function

The comparisons of hemodynamic and cardiopulmonary variables among the three PAVF groups are summarized in **Table 2**. Compared to patients without PAVF, those with diffuse PAVF showed increased CVP, CI, and EDVI with lower SaO_2, resembling a phenotype of high cardiac output heart failure. In contrast, the patients with discrete PAVF showed lower CI and high Rs, resembling a phenotype of low cardiac output heart failure, whereas there were no differences in the cardiac function, CVP, or SaO_2 between the discrete- and non-PAVF groups. In addition, the SaO_2 level for patients with diffuse,

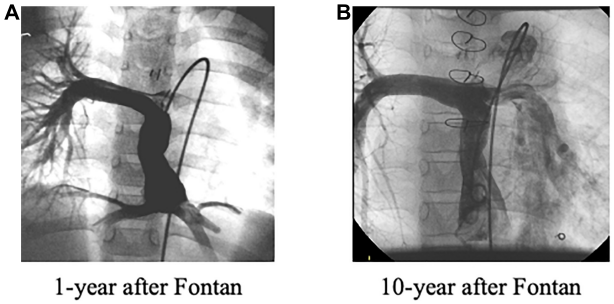

FIGURE 4 | (A) Unbalanced pulmonary artery flow distribution at 1 year after the Fontan operation. **(B)** Improved unbalanced, i.e., "balanced," pulmonary artery flow distribution was observed at 10 years after the Fontan operation due to significantly increased left pulmonary flow.

discrete, and non-PAVF after Fontan operation were 90 ± 8%, 93 ± 2%, and 94 ± 3% ($p < 0.0001$) at 1 year postoperatively; 91 ± 7%, 93 ± 1%, and 94 ± 3% ($p < 0.0001$) at 5 years postoperatively; 91 ± 7%, 94 ± 1%, and 95 ± 2% ($p < 0.0001$) at 10 years postoperatively; 91 ± 5%, 92 ± 2%, and 95 ± 2% ($p < 0.0001$) at 15 years postoperatively; 89 ± 11%, 94 ± 2%, and 95 ± 3% ($p = 0.0011$) at 20 years postoperatively; and 88 ± 9%, 93 ± 1%, and 94 ± 3% ($p = 0.0007$) at ≥25 years postoperatively, respectively. This also indicates significantly lower SaO_2 levels only in patients with diffuse PAVF.

Regarding the cardiopulmonary variables, patients with diffuse-PAVF had the lowest peak VO_2 and the highest VE/VCO_2 with significantly low SpO_2 during the exercise tests, including a greater SpO_2 decline, compared to patients without PAVF ($p < 0.001$–0.0001).

Specific Therapy for Pulmonary Arteriovenous Fistulae and All-Cause Mortality

Specific Therapy

Of the 36 patients with PAVF, no specific PAVF therapy, apart from oxygen inhalation, was used in 19 patients with diffuse PAVF and one patient with discrete PAVF. Catheter coil embolization was successfully used in all the remaining five patients with discrete PAVF. For the remaining 11 patients with diffuse PAVF, the therapies used included surgical redirection of the Fontan route in five patients, catheter balloon dilatation for stenosis between the Fontan route and the pulmonary artery with PAVF in three patients, multiple catheter coil embolization in two patients, and surgical redirection with additional catheter coil embolization in one patient with diffuse and discrete PAVF. Of these 16 patients who received specific therapies, 14 underwent the scheduled catheterization with an interval of 5 years. Of these, the overall SaO_2 level did not change significantly (92 ± 3–90 ± 7%, $p = 0.100$), although SaO_2 increased in seven patients (50%). SaO_2 increased in all three patients with T-type PAVF, whereas it decreased in two P-type patients. In the three T-type patients, the diffuse-PAVF disappeared 5 years after the specific therapies, which included balloon dilatation for stenosis between the Fontan route and the right pulmonary artery in two patients, and surgical redirection of the Fontan route in one patient.

All-Cause Mortality

During a median follow-up period of 2.9 years after the last PAVF evaluation (15.9 years after the first Fontan operation), 31 patients died (due to heart failure in 11, sudden death in 6, cancer in 4, protein-losing enteropathy in 3, liver failure and stroke in 2 each, and due to other causes in 3 patients) (**Figure 5A**). Of the 36 patients with PAVF, no death occurred in patients with discrete-PAVF, and 12 patients with diffuse PAVF died (due to heart failure in 8, stroke in 2, and sudden death and liver failure in 1 patient each). Survivals based on PAVF morphology, after the latest evaluation, are presented in **Figure 5B**. Patients with diffuse-PAVF had a 3.6-fold higher risk of all-cause mortality than those without diffuse PAVF (hazard ratio [HR]: 3.60, 95% confidence interval: 1.59–7.81, $p = 0.0026$). Univariate Cox's hazard model with hemodynamic variables revealed that high CVP, low SaO_2, increased EDVI, low EF, and high plasma BNP levels were

TABLE 2 | Hemodynamics and exercise physiology in PAVF patients at the time of detection.

PAVF	Diffuse	Discrete	No	*p*
Cases (*n*)	30	6	355	
Time course of PAVF				
A/P/T	20/7/3	5/1/0	–	
Hemodynamics				
CVP (mmHg)	12 ± 3#	10 ± 3	10 ± 3	0.0003
CI (L/min/m2)	3.3 ± 1.3†#	2.2 ± 0.4#	3.0 ± 0.6	0.0004
Rp (U•m2)	1.5 ± 0.8	1.5 ± 0.5	1.3 ± 0.6	0.2566
Rs (U•m2)	24 ± 12†	35 ± 9#	24 ± 7	0.0006
SaO2 (%)	89 ± 9†#	93 ± 2	94 ± 3	<0.0001
Hemoglobin (g/dl)	15 ± 2	16 ± 3	14 ± 2	0.0883
Cardiac function				
EDVI (ml/m^2)	94 ± 36#	89 ± 34	75 ± 25	0.0007
EF (%)	56 ± 12	53 ± 8	55 ± 9	0.806
AVVR ≥ mod (%)	11	0	9	0.5395
Log BNP (pg/mL)	2.9 ± 1.1	3.2 ± 0.6	2.8 ± 0.9	0.3646
Exercise Physiology (*n*)	(14)	(6)	(280)	
Peak VO2 (% of N)	50 ± 15#	52 ± 13	59 ± 14	0.0081
SpO2 (%)				
Rest	92 ± 4#	91 ± 1#	94 ± 3	0.0007
Peak	84 ± 7#	84 ± 3#	90 ± 5	<0.0001
Decrease	−7 ± 5#	−7 ± 3	−4 ± 3	0.0002
VE/VCO2 at peak (% of N)	134 ± 23†#	110 ± 22	115 ± 19	0.0001
Pulmonary function (*n*)	(14)	(6)	(250)	
Vital Capacity (% of N)	73 ± 14	68 ± 12	80 ± 16	0.0547
FEV1.0 (%)	87 ± 10	85 ± 8	87 ± 7	0.8501

AVVR, atrioventricular valve regurgitation; BNP, brain natriuretic peptide; CI, cardiac index; CVP, central venous pressure; EF, ejection fraction of the systemic ventricle; EDVI, end-diastolic volume index of the systemic ventricle; FEV1.0, forced expired volume in one second; Rp, resistance of the pulmonary artery; Rs, resistance of the systemic artery; SaO2, arterial oxygen saturation; SpO2, percutaneous artery oxygen saturation; VE/VCO2, ventilatory equivalent for carbon dioxide output; VO2, oxygen uptake. Values are the mean ± SD. #,†Indicate p < 0.05 vs. groups of No and Discrete, respectively.

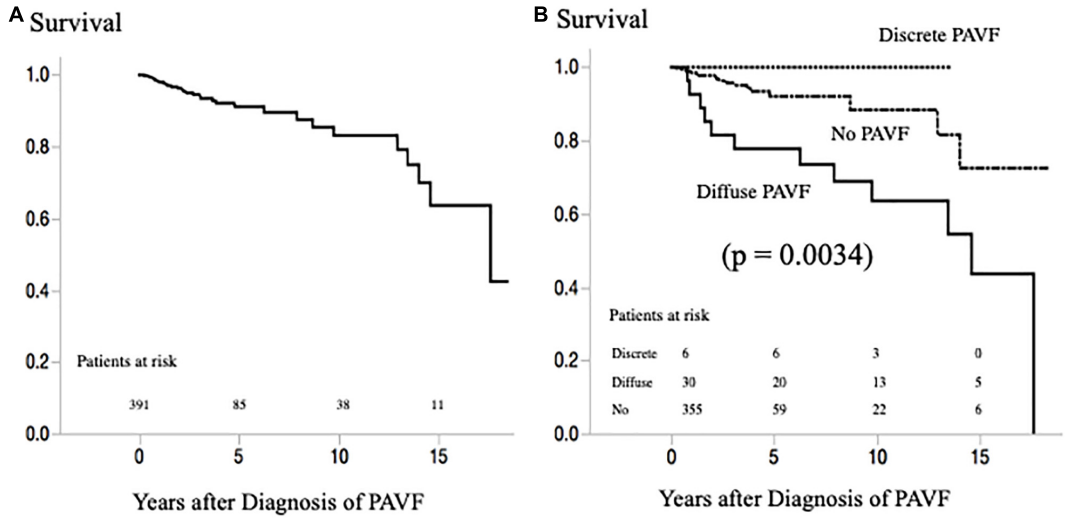

FIGURE 5 | (A) Survival rate after latest evaluation of PAVF in all patients with a Fontan circulation. **(B)** Survival rate after latest evaluation of PAVF according to the morphology of PAVF. PAVF, pulmonary arteriovenous fistulae.

associated with a high risk of all-cause mortality ($p < 0.05$–0.0001). Of these hemodynamic variables and the presence of diffuse PAVF, the diffuse-PAVF, along with EF ($p = 0.0145$) and log BNP ($p < 0.0001$), were the independent predictors of all-cause mortality (HR: 3.57, 95% confidence interval: 1.14–9.80, $p = 0.0181$).

DISCUSSION

To our knowledge, this study is the first to report a comprehensive clinical profile of patients who had undergone Fontan with PAVF. Interestingly, we found the following: (1) we reconfirmed a close association between PAVF development and unbalanced PAFD; (2) the incidence of PAVF gradually increased as patients aged, although some cases of diffuse-PAVF disappeared after Fontan operation with balanced PAFD; (3) a high prevalence of VVC was found and VVC often coexisted with PAVF; (4) a specific therapy for PAVF was applied in half of the affected patients and long-term (5-year) efficacy (increase in SaO_2) was observed in half of them; and (5) patients with diffuse-PAVF had a worse Fontan pathophysiology than those with discrete-PAVF or non-PAVF in terms of hemodynamics and all-cause mortality.

Pulmonary Arteriovenous Fistulae and Hepatic Venous Flow

The "hepatic factor" hypothesis has been proposed to explain the mechanism of PAVF development after the Fontan operation; however, this factor has not been identified (2, 3, 8). In this study, we reconfirmed this phenomenon in our large cohort through visual evaluation, and liver cirrhosis was associated with bilateral diffuse-PAVF in two of our patients. Diffuse-PAVF may be one of the clinical phenotypes of Fontan-associated liver disease because of the high incidence of liver cirrhosis long after Fontan operation (9). Interestingly, diffused-PAVF disappeared with specific therapy immediately after diagnosis in three patients (T-type). PAVF may be inevitable after bidirectional cavopulmonary anastomosis (10), and early Fontan completion after this anastomosis may eliminate the possibility of developing PAVF (11). Especially, a much higher prevalence of D-type PAVF may be expected immediately after the Fontan operation when compared to the observed low prevalence of type-D ($n = 4$) at 1 year postoperatively.

We also confirmed a high prevalence of PAVF in patients with left isomerism who had undergone a Fontan operation (12). The high prevalence may be attributed mainly to the difficulties in equalizing hepatic flow distribution to the bilateral pulmonary arteries in cases where there is a small amount of hepatic flow compared to the greater systemic venous flow from the supra vena cava, which could easily produce streaming of the hepatic flow (11). In this regard, a similar Fontan route configuration with bidirectional cavopulmonary anastomosis may occur as these patients age and could lead to PAVF due to the consequent unbalanced stream of hepatic venous flow as demonstrated in our type-A patients.

Unbalanced Pulmonary Artery Flow Distribution and Staging of Pulmonary Arteriovenous Fistulae

We should consider that the grade of unbalanced PAFD may depend on the stage of PAVF. In the early stages of PAVF where the pathophysiology may be reversible, the affected pulmonary artery receives low hepatic venous flow, thus, showing marked unbalanced PAFD. After this initial stage, ipsilateral pulmonary artery resistance gradually decreases as PAVF progresses and the ipsilateral pulmonary artery blood flow gradually increases. Finally, in the advanced stage of PAVF with even lower pulmonary artery resistance, where the pathophysiology may be

irreversible, the affected pulmonary artery receives even more hepatic venous flow, showing an improved, i.e., "balanced" PAFD. We experienced seven such patients as described in **Figure 4**. This advanced PAVF further progresses to hypoxia even though the affected pulmonary artery can receive adequate "hepatic factor" because of the irreversible PAVF. This is why the degree of unbalanced PAFD does not always correlate with the presence of PAVF. In addition to these patients with "balanced" PAFD, our P-type patients also support this concept. The time interval from cavopulmonary bidirectional anastomosis, including Kawashima ($n = 3$) and Glenn ($n = 3$) procedures, to the Fontan operation, was 5.3 ± 3.7 years (range: 1.3–11 years), and this may have been long enough to establish advanced PAVF. As a result, surgical redirection was not effective although this intervention usually works shortly after the PAVF onset (13). Thus, it may be very important to recognize stage-dependent PAFD in patients with PAVF in terms of the diagnosis, as well as the appropriate therapy. In this regard, our three T-type patients did benefit from our follow-up policy.

Conversely, we encountered patients without PAVF with unbalanced PAFD, although the prevalence was low. We need to follow these patients carefully because they may tend to develop PAVF in the future, although we cannot deny another possible cause of PAVF other than "hepatic factor" (14).

Impact of Pulmonary Arteriovenous Fistulae on Fontan Pathophysiology

Despite having no differences in PAFD or clinical background, there were distinct differences in the impact on Fontan pathophysiology between the diffuse- and discrete PAVF. Patients with diffuse-PAVF showed elevated CVP, high CI, and low SaO_2 with greater EDVI, and had a high risk of all-cause mortality; all of which resembled the hemodynamic phenotype of Fontan failure with high cardiac output (5). In addition, liver cirrhosis may also be associated with a poor prognosis in patients with PAVF (15). However, no death occurred among our patients with discrete PAVF, including the patient with discrete and diffuse PAVF, despite their low cardiac output. The possibility of successfully performing a catheter intervention, as well as minimal influence on cardiovascular function may be associated with a better long-term outcome. Further studies may be required to clarify which factor(s), including genotypic factors, determine the morphological phenotype of PAVF (4).

High Prevalence of Veno-Venous Collaterals

We confirmed the high prevalence of VVC (60–80%), especially in patients with PAVF (85–100%), with mild hypoxia, which indicates the difficulty of identifying incipient diffuse-PAVF with conventional diagnostic approaches, such as measuring arterial oxygen saturation or computed tomography (CT). Considering the importance of therapeutic timing of PAVF, the scheduled comprehensive assessment may be beneficial in some patients with PAVF similar to T-type patients, as demonstrated in this study.

Study Limitations

This study had some limitations. First, unbalanced PAFD was evaluated visually in our clinical conference. A more objective approach, such as flow analysis using magnetic resonance imaging (MRI), may have been ideal, although PAFD depends on the PAVF stage. Second, in addition to underestimation of the overall prevalence of D-type PAVF, we could not exclude the possibility that our four D-type patients may have had T-type PAVF. Third, we did not check for the presence of a portosystemic shunt, which is another cause of PAVF, in all our patients. Fourth, because the incidence of PAVF may largely depend on the type of surgery applied, our results may not be generalized and should be interpreted with caution. Finally, we had no specific selection criteria that were used to identify candidates that required specific intervention. In our clinical conference, the therapeutic options were selected based on patients' clinical conditions, the feasibility of catheter and/or surgical techniques, and the types of PAVF (morphology and time-course). Therefore, the efficacy of our specific management of PAVF may also not be generalized; therefore, large-scale prospective multicenter studies may be necessary for the future to standardize the management strategy of this unique Fontan-associated complication.

CONCLUSION

We reconfirmed a close association between PAVF and unbalanced PAFD. The incidence of PAVF gradually increased as patients aged, although some diffuse-PAVF disappeared after the Fontan operation with balanced PAFD. The long-term efficacy of PAVF-specific therapy was observed in some patients. Our study is the first to report that patients with diffuse-PAVF had a worse Fontan pathophysiology than those with discrete-PAVF or non-PAVF in terms of hemodynamics and all-cause mortality.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the National Cardiovascular Center (M23-002-5). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HO designed the study, interpreted the data, and critically reviewed the manuscript. AM, KF, TI, HS, IS, and KK undertook

data collection and critically reviewed the manuscript. MN contributed to data analyses, data interpretation, and critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Lymphatic Disorders in Patients With Single Ventricle Heart Disease

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Lymphatic abnormalities in patients with single ventricle physiology can lead to early Fontan failure and severe Fontan complications, such as protein-losing enteropathy (PLE), plastic bronchitis (PB), chylothorax, and edema. Recent developments in lymphatic imaging and interventions have shed new light on the lymphatic dysfunction in this patient population and the role of the lymphatic circulation in PLE, PB, and chylothorax. In this study, we reviewed some of the latest developments in this field and discuss new treatment options for these patients.

Keywords: lymphatics, protein-losing enteropathy (PLE), plastic bronchitis, chylothorax, DCMRL, lymphangiography, ascites

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INTRODUCTION

The lymphatic system plays a key role and has three main functions, namely, immune regulation, long-chain fatty acid absorption, and tissue fluid circulation. Several decades ago, the lymphatic system was studied extensively. However, due to a lack of a simple lymphatic imaging technique and lymphatic interventional techniques, the system was forgotten. This led to the term the forgotten circulation. However, in the past decade, advances in lymphatic imaging and interventional techniques have now brought this circulatory system back into the limelight. In patients with congenital heart disease (CHD) especially single ventricle heart disease, the lymphatic system plays a key role in several often-devastating diseases and is a major cause of Fontan failure.

LYMPHATIC ANATOMY AND PHYSIOLOGY

In general, lymphatic channels collect fluid from the peripheral organs and the peripheral tissue and transport centrally toward the main channel for lymphatic drainage called the thoracic duct. At the proximal end of the thoracic duct at the level of T11-L1, there is a sack called the cisterna chyli. This sack collects fluid from the lower extremities, the liver, and the mesentery. Under normal conditions, approximately 8 L of fluid a day are absorbed into the lymphatic ducts and approximately 2–3 L a day flow through the thoracic duct (1). The liver and the intestine each contribute approximately 40% of thoracic duct flow. The thoracic duct also receives lymphatic flow from the lungs and the heart. The thoracic duct then courses superiorly just anterior to the vertebral bodies and connects to the junction of the internal jugular vein and subclavian vein usually on the left side. Multiple studies using various lymphatic imaging modalities have demonstrated numerous thoracic duct anatomic variances (2, 3). A bicuspid valve sits at the mouth of the thoracic duct outlet and prevents reflux and blood back into the thoracic duct (4).

In the periphery terminal, lymphangions are made of a porous layer of lymphatic endothelial cells connected by microtubules to the extracellular matrix. When the tissue swells due to edema, the gap between lymphatic endothelial cells widens due to the connections to the extracellular matrix, allowing more fluid to enter the collecting lymphatic ducts. Once inside, the lymphatic ducts' fluid is propelled forward by several forces. First, lymphatic ducts undergo rhythmic contractions due to a muscle layer in the duct wall (1, 5). Second, negative pressure exerted by the thorax during inspiration pulls fluid into the thoracic duct. Finally, it is also possible that muscle contractions contribute also to moving fluid forward, assuring that unidirectional flow are multiple valves throughout the system (5).

The Starling equation describes the rate of tissue and lymphatic fluid formation in relation to the difference between the oncotic and hydrostatic pressures (6). In addition, many extrinsic factors can also affect lymph flow and tissue fluid content. Medications, such as inotropes, have been shown to cause rhythmic lymphatic contractions in a dose-dependent manner (7). In patients with CHD, central venous pressure is particularly important as it increases lymphatic production, especially by the liver, and impedes lymphatic drainage at the lymphovenous junctions (8).

In addition, the patients with abnormal physiology with CHD likely have an underlying congenital or genetic susceptibility to developing lymphatic flow disorders. This is likely the reason why some patients with elevated CVP do not have lymphatic problems, while others with relatively low CVP can have severe lymphatic issues. Evidence for this has been published by Biko et al. who demonstrated nutmeg lung in fetuses with T2 imaging that is known to correlate with pulmonary lymphangiectasia (9). In most cases, the underlying genetics for these diseases is not known but in patients with certain syndromes, such as Noonan syndrome and trisomy 21, the genetic defects are known.

LYMPHATIC IMAGING

One of the most important advances in clinical lymphatics has been the development of minimally invasive lymphatic imaging techniques. Older imaging techniques, such as lymphoscintigraphy, are still used in some institutes as diagnostic tools and do have some benefits in patients with lymphatic flow disorders. However, to a large extent, magnetic resonance (MR) lymphangiography has now become the imaging modality of choice for most patients.

Non-contrast MR lymphangiography is one such technique that uses heavily weighted T2 sequences to image slow-moving non-bloody fluids (10). This technique is fast and non-invasive and has a good spatial resolution. However, it lacks dynamic information and is consequently insufficient for completely characterizing the lymphatic circulatory system. Recently, Biko et al. reported on the correlation between T2 findings in the thorax of patients who underwent superior cavopulmonary connection and Fontan outcomes (11). The paper demonstrated a strong correlation between poor Fontan outcomes and high-grade thoracic lymphatic abnormalities (**Figure 1**). This imaging should be used as a screening tool for all thoracic lymphatic abnormalities in all single ventricle patients prior to Fontan completion.

To fully characterize the circulatory system, anatomical, physiological, and flow information is needed. Dynamic contrast MR lymphangiography is now the standard method for imaging the central lymphatic system. In this technique, needles are placed inside lymph nodes or lymphatic ducts and the position is confirmed with a conventional iodinated contrast agent or by ultrasound. The needles are fixed and patients are transferred to an MRI scanner where they undergo dynamic and static contrast-enhanced MR imaging. This technique has a good spatial resolution as well as good temporal resolution allowing us to visualize the lymphatic flow and organ lymphatic perfusion. As a result, this imaging modality has transformed our understanding of lymphatic flow disorders and has allowed us to diagnose the etiology of several lymphatic diseases, such as protein-losing enteropathy (PLE) and plastic bronchitis (PB). Dori et al. published on the use of intranodal dynamic contrast lymphangiography (IN-DCMRL) in an animal model and then in a patient with PB (12, 13). Around the same time, Krishnamurthy et al. published on the use of this technique in patients with chylothorax (14). IN-DCMRL is the imaging modality of choice for viewing the lumbar lymphatic networks, cisterna chyli, and thoracic duct. However, abnormalities in flow originating from the two main contributors to thoracic duct flow, which are the liver and mesentery, are normally not visualized with this technique. Biko et al. recently published on the development of intrahepatic DCMRL (IH-DCMRL) (15). In a recent manuscript, Smith et al. showed the correlation between the different hepatic lymphatic flow patterns and systemic lymphatic diseases (16). In addition, Lemley et al. demonstrated that all patients with PLE have duodenal involvement with IH-DCMRL (17). In contrast, most patients without PLE do not have duodenal involvement with hepatic injection. Consequently, it is possible that intrahepatic imaging could be used as a screening tool for patients with PLE. The second major contributor to central lymphatic flow is the mesentery. Historically, this part of the lymphatic system has been difficult to access and has not been imaged in humans. However, this has now changed, and Dori et al. just published on the development of intramesenteric DCMRL (IM-DCMRL) (18). The utility of this imaging modality in patients with CHD is currently under investigation.

Ultrasound contrast lymphangiography is another technique that was recently published (19). This technique is good for assessing thoracic duct outlet patency which needs to be confirmed in all patients undergoing a thoracic duct decompression (TDD) procedure.

LYMPHATIC INTERVENTIONS

All patients with a suspected lymphatic abnormality should undergo cardiac catheterization to rule out a reversible cause of lymphatic failure, such as superior vena cava (SVC) stenosis, and to assess hemodynamics. In addition, medical management, including high-dose Aldactone, sildenafil, steroids, and other medications, should be optimized. Due to stroke risk, prior

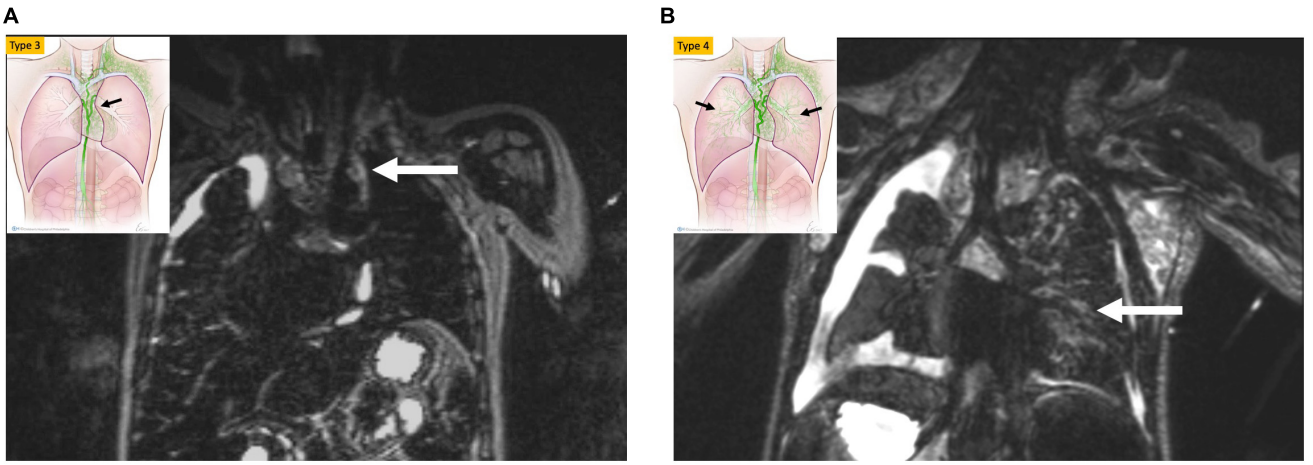

FIGURE 1 | MIP coronal projection of T2 weighted lymphatic mapping showing patient with bright signal extending to the mediastinum (arrow) (type 3) in **(A)** and into the lung parenchyma (arrow) type 4 in **(B)**.

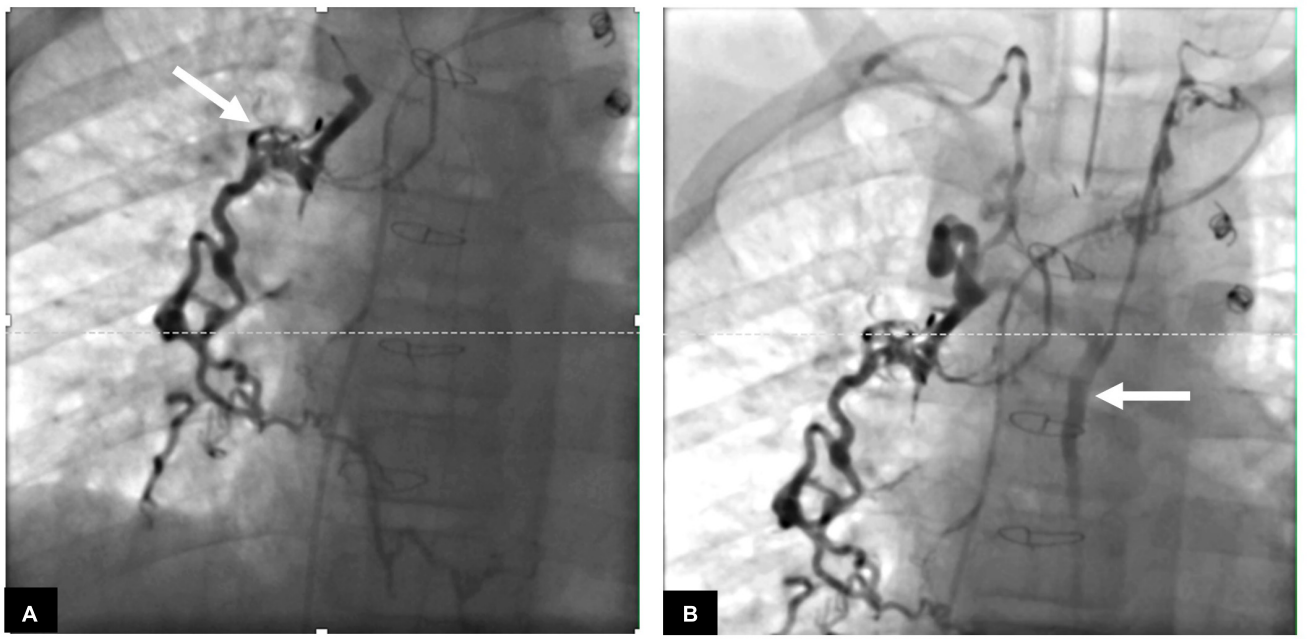

FIGURE 2 | (A) AP fluoroscopy image of selective lymphatic embolization of a left sided dilated duct (arrow) with cyanoacrylate glue. **(B)** Contrast injection in the thoracic duct post-procedure demonstrating intact thoracic duct (arrow) with connections to both the left and right venous angles.

to lymphatic intervention, cardiac catheterization should be performed to determine all sources of the right to left shunting, including fenestration patency and veno-venous collaterals in patients with single ventricle anatomy and atrial septal defect (ASD) and ventricular septal defect (VSD) in other patients. In some cases, coil embolization of collateral vessels might be warranted as well as temporary balloon occlusion of shunts. However, because anticoagulation cannot be used during lymphatic procedures, careful consideration needs to be given to the decision to temporarily close a fenestration with a balloon and wire. The lymphatic patient population is particularly hypercoagulable, and systemic thrombus formation could also result in a thromboembolic stroke.

Lymphatic interventions in general can be divided into two groups, namely, those that are meant to occlude unwanted lymphatic ducts, such as thoracic duct embolization (TDE), and those that are meant to decompress the entire lymphatic system, such as lymphovenous anastomosis (LVA) (8). Minimally invasive procedures that occlude flow include ethiodized oil embolization, TDE, selective lymphatic duct embolization

(SLDE), as well as several other procedures that are meant to selectively target lymphatic networks that are causing symptoms. In patients with CHD, selective embolizations that maintain thoracic duct patency are always preferable (**Figure 2**). Minimally invasive procedures to decompress the lymphatic system are now also available for all possible cardiovascular

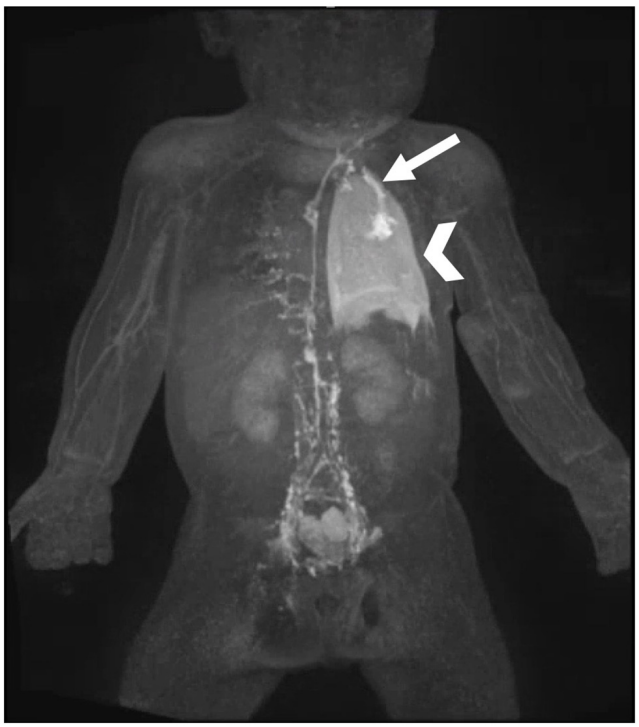

FIGURE 3 | MIP coronal projection of IN-DCMRL demonstrating leak of contrast into the left pleural space (arrowhead) from dilated channel connected to the pericardium and originating from the distal TD (arrow).

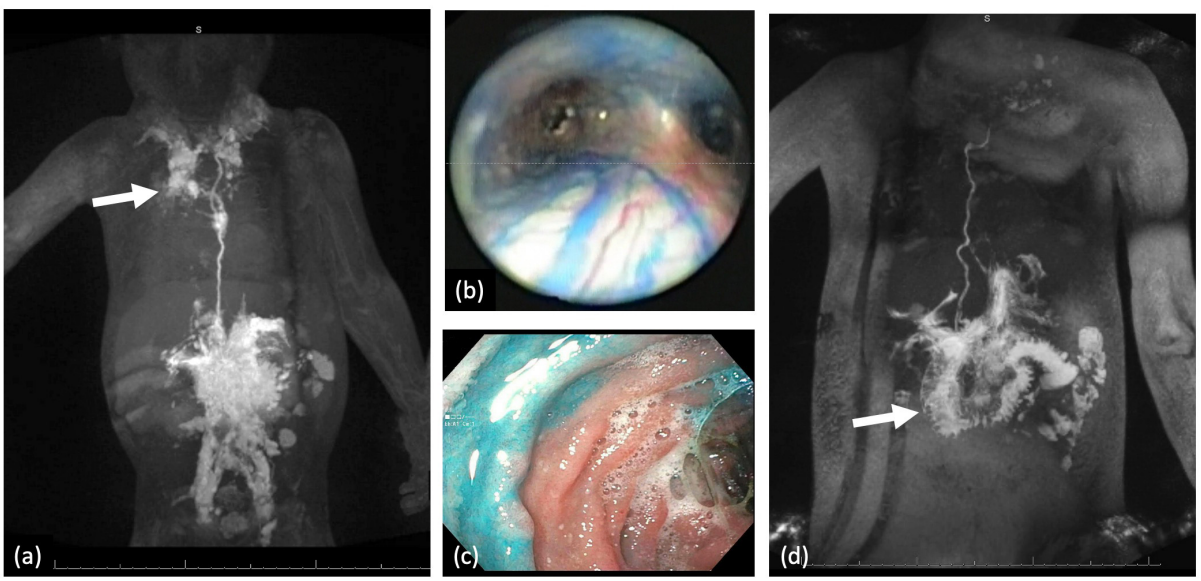

FIGURE 4 | (a) MIP coronal projection of IN-DCMRL demonstrating mediastinal and bilateral PLPS more on the right (arrow). **(b)** In a patient with PB blue dye injection into the TD demonstrated dilated peribronchial lymphatic networks. **(c)** Blue dye injection into the liver demonstrating leak into the duodenal lumen. **(d)** MIP coronal projection of IH-DCMRL demonstrating leak into the duodenal lumen characteristic of PLE (arrow).

anatomies (20). Surgical procedures that occlude flow include surgical thoracic duct ligation (TDL) and pleurodesis. Most often, minimally invasive procedures have replaced the surgical occlusive procedures and are the interventional modality of choice, if available. Surgical procedures to decompress the thoracic duct include the Hraska procedure or innominate vein turndown (21–24). While the right to left shunting is of concern in both the minimally invasive and surgical decompression procedures, this often is not an issue and patients tolerate the procedures well. In some cases, banding of the internal jugular vein is needed (25).

LYMPHATIC FLOW DISORDERS

Lymphatic flow disorders can lead to tissue edema, effusions, or organ dysfunction. Trauma, such as due to surgical procedure, can lead to an effusion. In patients with CHD, traumatic effusions are often associated with open-heart surgery. Historically traumatic leaks were thought to be due to injury to the thoracic duct. This is almost never the case, except during vascular ring repair, because the thoracic duct is posterior to the surgical field. Most often, traumatic effusions are due to injury to lymphatic ducts that are connected to the pericardium (**Figure 3**) (26). However, the most common causes of effusions, both in the chest and abdomen, are lymphatic production and conduction abnormalities which together with lymphatic channel dysfunction leads to abnormal organ perfusion and resultant leaks (26).

FLOW DISORDERS IN THE THORAX

Three types of thoracic lymphatic flow abnormalities are often encountered in patients with CHD. These include pleural effusions, pericardial effusions, and PB (13, 26, 27). The etiology of all three abnormalities is almost always abnormal perfusion of the mediastinal, peribronchial networks, and pulmonary interstitial lymphatic networks which we have termed pulmonary lymphatic perfusion syndrome (PLPS) (**Figures 4a,b**). The degree of thoracic lymphatic abnormalities can be screened with a T2-weighted MRI which should be performed in all patients prior to Fontan completion.

PLEURAL AND PERICARDIAL EFFUSIONS

Pleural or pericardial effusions tend to occur mostly after Fontan completion but can be seen in neonates as well. In contrast, PB is most often encountered in single ventricle patients after Fontan palliation and is rare prior to this stage although it can also occur in patients with superior pulmonary connection depending on the severity of the lymphatic conduction abnormality. Chylothorax and chylopericardium are effusions that receive lymph draining from the mesentery and are diagnosed based on fluid triglyceride levels greater than 110 mg/dl if the patient is on a full-fat diet, high lymphocyte percentage (80–100%), and presence of chylomicrons. Our management protocol for these patients involves 2–4 weeks

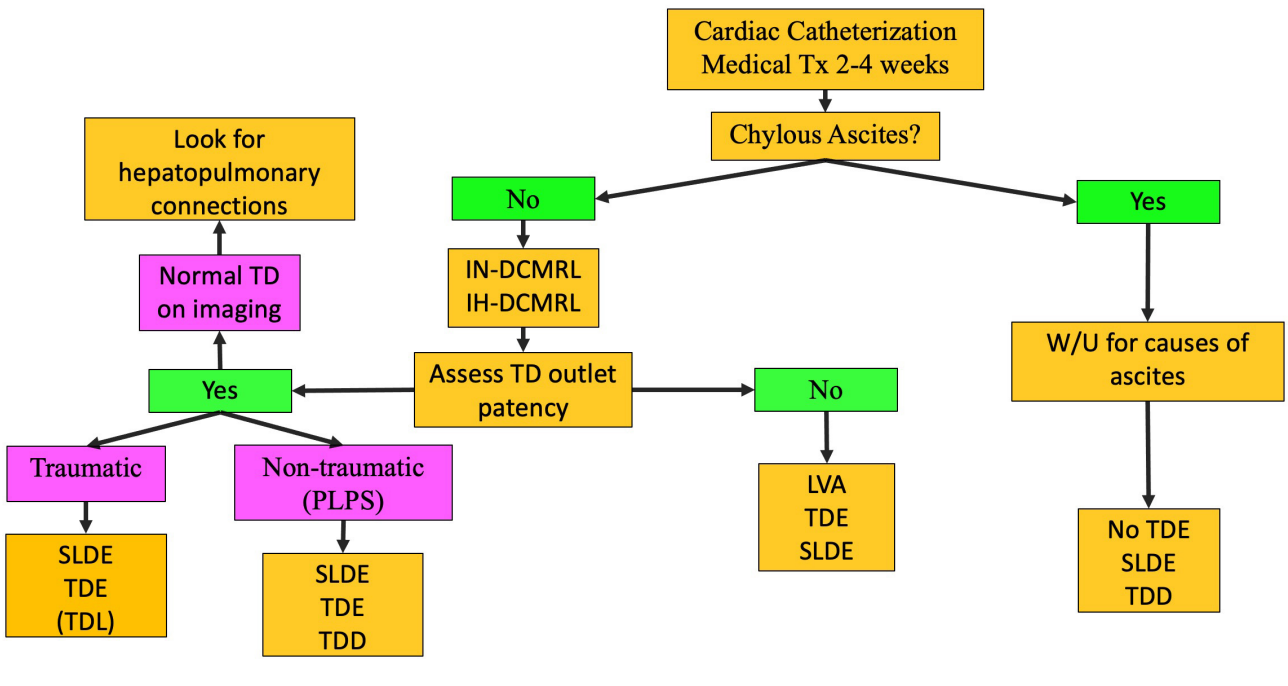

FIGURE 5 | Chylothorax treatment pathway (TD-thoracic duct, DCMRL-dynamic contrast lymphangiography, IN-intranodal, IH-intrahepatic, SLDE-selective lymphatic duct embolization, TDL-thoracic duct ligation, TDE-thoracic duct embolization, TDD-thoracic duct decompression, LVA-lymphovenous anastomosis, PLPS-pulmonary lymphatic perfusion syndrome).

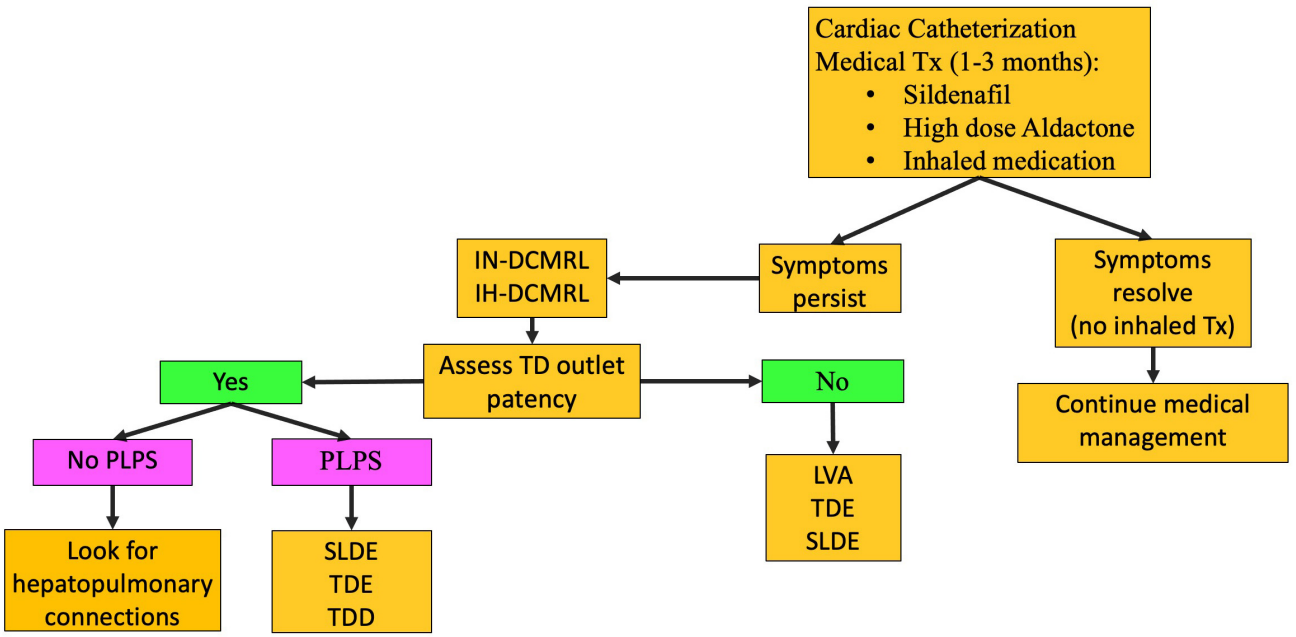

FIGURE 6 | PB treatment pathway (TD-thoracic duct, DCMRL-dynamic contrast lymphangiography, IN-intranodal, IH-intrahepatic, SLDE-selective lymphatic duct embolization, TDL-thoracic duct ligation, TDE-thoracic duct embolization, TDD-thoracic duct decompression, LVA-lymphovenous anastomosis, PLPS-pulmonary lymphatic perfusion syndrome).

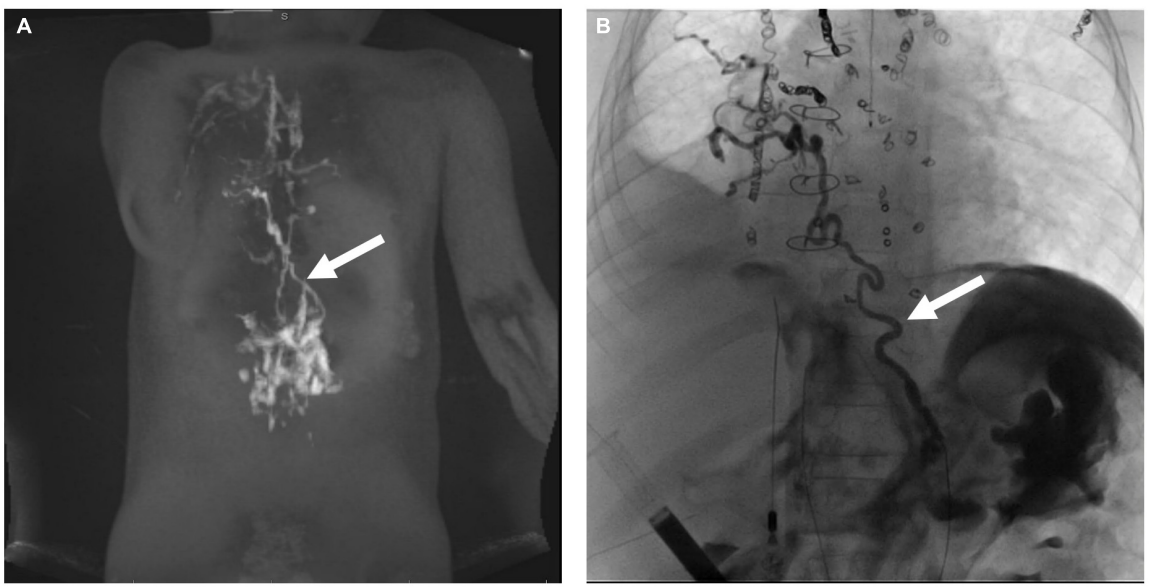

FIGURE 7 | (A) MIP coronal projection of IH-DCMRL demonstrating hepatopulmonary connection (arrow). **(B)** AP fluoroscopic image showing the hepatopulmonary connection after selective embolization (arrow).

of conservative management with a low-fat diet or nothing be mouth (NPO) (**Figure 5**) (8). Cardiac catheterization and medical optimization are also performed. Octreotide can also be tried but in many cases is ineffective. If conservative management fails, patients undergo IN and IH-DCMRL to visualize the central conducting lymphatic networks as well as screen for the potential development of PLE. In single ventricle patients and in babies, SLDE is the first line of therapy. When this is not possible and ascites and PLE are not a concern, TDE or TDL is an option. Other procedures, such as pleurodesis, are rarely used in our institution and are almost always not needed.

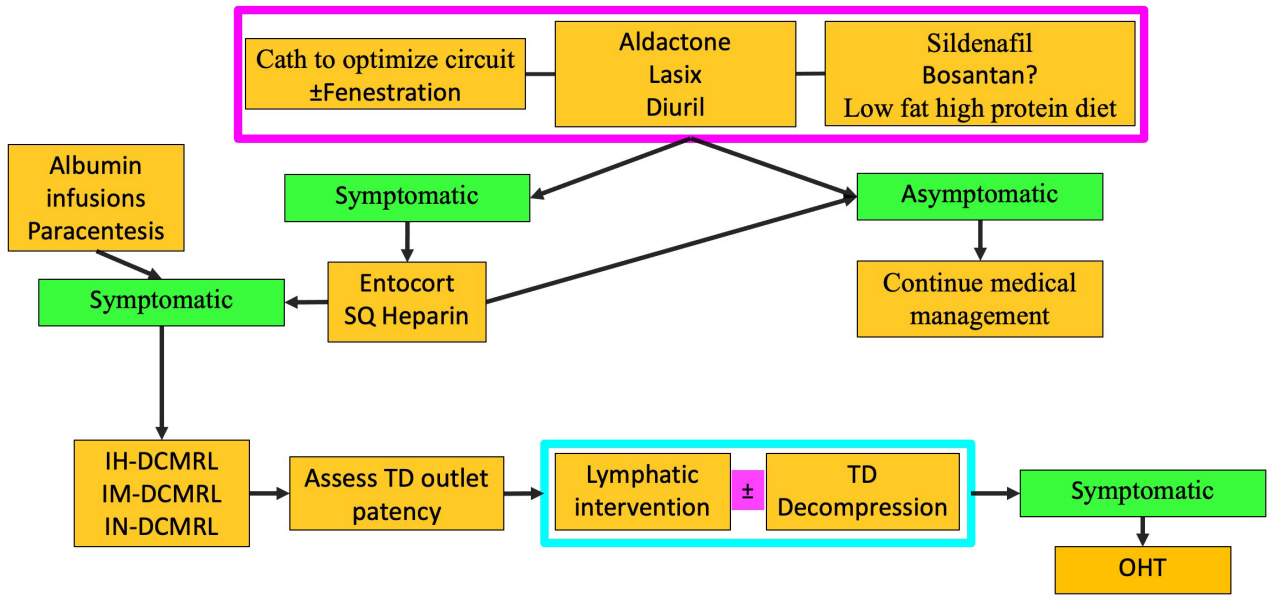

FIGURE 8 | Algorithm for PLE treatment (TD-thoracic duct, DCMRL-dynamic contrast lymphangiography, IN-intranodal, IH-intrahepatic, IM-intramesenteric, SQ-subcutaneous, OHT-orthotopic heart transplant).

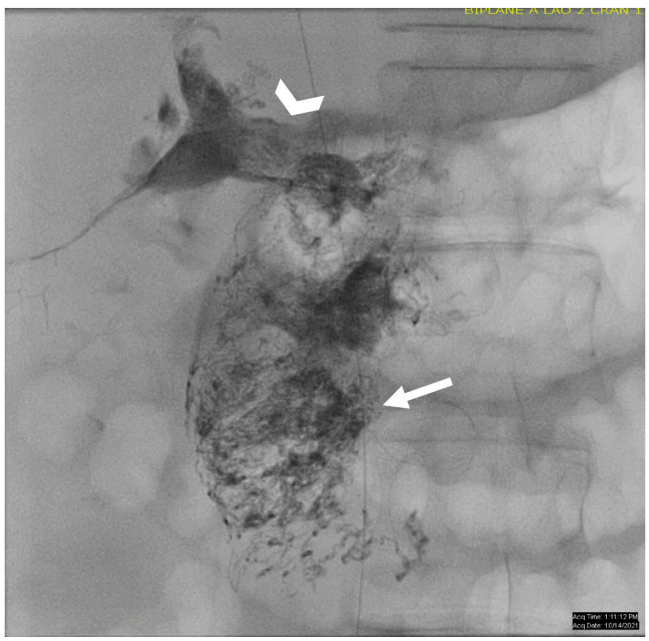

FIGURE 9 | AP fluoroscopic image of the duodenum after periduodenal (arrow) and hepatoduodenal (arrowhead) lymphatic embolization.

PLASTIC BRONCHITIS

The PB occurs most often in patients with single ventricle CHD. However, it can occur in other settings. In the current era, the mortality of this disease is low with most patients living free of symptoms after a lymphatic intervention. This disease should be considered in any single ventricle patient presenting with a chronic cough or diagnosis of asthma not responsive to medication. The etiology of PB is retrograde perfusion of the peribronchial lymphatic networks leading to inflammation and edema of the airway mucosa (13, 27). When the barrier for protein leak is overcome, lymphatic fluid containing proteinaceous material is instilled into the airway. Proteinaceous material, including fibrinogen, becomes sticky in

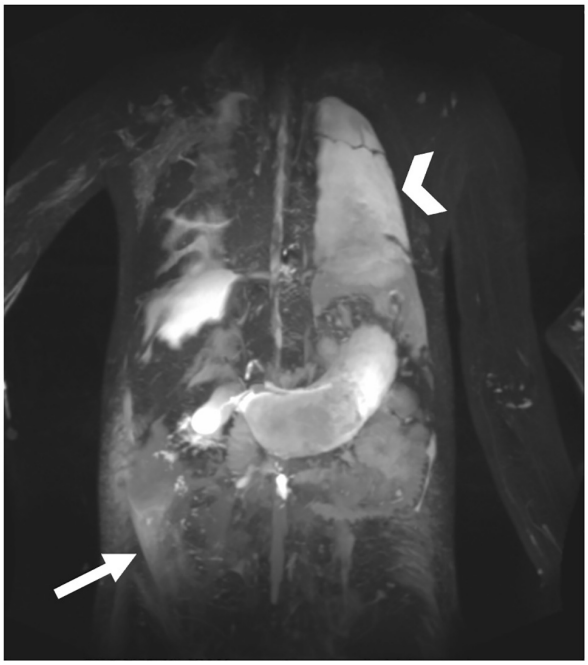

FIGURE 10 | MIP coronal projection of T2 imaging in patient with multicompartment lymphatic failure including ascites (arrow), PLE, edema, and chylothorax (arrowhead).

contact with a rare-forming gel-like material that can fill the airway forming the cast. Larger casts can put the patient at risk for respiratory failure from asphyxiation. Conservative management of PB involves inhaled bronchodilators, inhaled steroids, and pulmonary vasodilators (**Figure 6**). Cardiac catheterization is performed as well. If symptoms persist, medications aimed at breaking down the casts are used, including inhaled tissue plasminogen activator. However, if fibrinolytics are needed to improve symptoms, there is active lymph leaking into the airway and lymphatic imaging and intervention are needed. After IN and IH-DCMRL, SLDE is the first line of treatment.

If pleural effusion or PB symptoms persist despite lymphatic intervention, then TDD or orthotopic heart transplant (OHT) should be considered. In addition, it is reasonable to consider surgical TDD as the fenestration technique during the Fontan procedure in patients with high-grade thoracic lymphatic abnormalities as determined by T2 imaging.

Irrespective of clinical presentation in patients with thoracic lymphatic flow disorders, if central lymphatic imaging demonstrates a normal thoracic duct flow pattern without perfusion of the mediastinum or the lungs, then TDE or TDL should not be performed as it can lead to worsening of symptoms. In these cases, the etiology is most often hepatopulmonary connections that bypass the central lymphatic conduction system, including the thoracic duct (**Figure 7**) (16). Selective embolization of hepatopulmonary connections will lead to a resolution of symptoms in most cases while maintaining central lymphatic flow.

LYMPHATIC ABNORMALITIES IN THE ABDOMEN

Protein-Losing Enteropathy

The PLE is the most commonly encountered lymphatic flow abnormality in the abdomen, especially in patients with single ventricle physiology. PLE is defined as the loss of albumin and other proteins in the intestinal tract. This is a potentially life-threatening disease affecting approximately 5–15% of single ventricle patients (28, 29). Patients present with low albumin

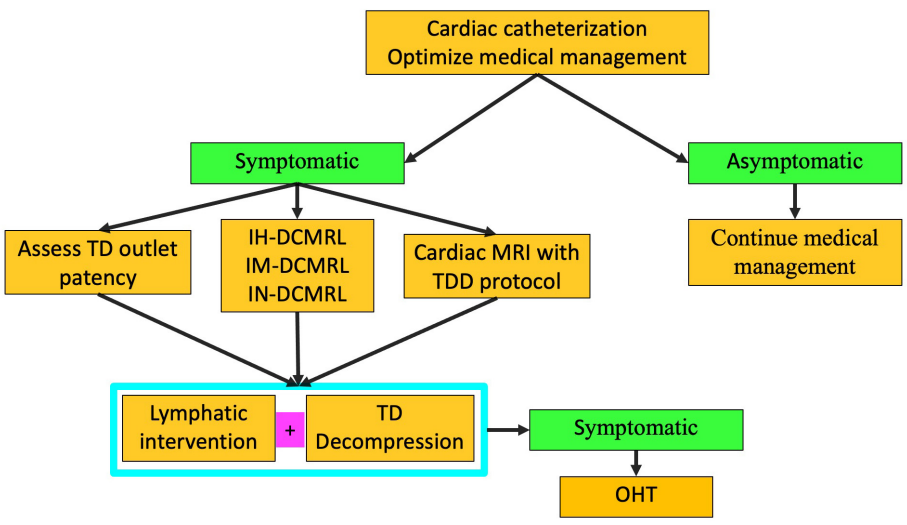

FIGURE 11 | Algorithm for multicompartment failure (TD-thoracic duct, DCMRL-dynamic contrast lymphangiography, IN-intranodal, IH-intrahepatic, IM-intramesenteric, TDD-thoracic duct decompression, OHT-orthotopic heart transplant).

and other common symptoms include diarrhea, edema, ascites, weight loss, and malabsorption. Diagnosis can often be confirmed with a stool alpha-1 antitrypsin. The etiology of PLE in all patients with single ventricle physiology is abnormal perfusion of the duodenum by increased liver lymphatic production and, in some cases, increased mesenteric production as well (30). This leads to duodenal wall edema, inflammation, and lymphangiectasia. When the barrier to protein leak is broken, lymphatic fluid will leak into the duodenal lumen leading to symptoms. In the later stages of the disease, endoscopy has demonstrated holes formed in the duodenal wall (**Figure 4c**).

Conservative management of PLE involves diuretics, including high-dose Aldactone and sildenafil (**Figure 8**) (8). The role of a low-fat high-protein diet is not clear but has also been tried. Cardiac catheterization must be performed to determine hemodynamics and any reversible Fontan pathway obstruction. Fenestration creation or recreation can also be attempted. Those who are asymptomatic with conservative management are continued to be monitored. However, those that remain symptomatic are then started on enteric steroids. If steroids fail to control symptoms, lymphatic imaging with IN and IH-DCMRL and intervention are warranted (**Figure 4d**). Interventions for PLE include embolization of hepatoduodenal and periduodenal lymphatic networks and procedures to lower pressure in the lymphatic system, such as TDD (**Figure 9**). When treatments fail Fontan takedown, VAD placement or OHT is considered.

Ascites

Chylous ascites can occur as a result of traumatic lymphatic leaks. However, most often in patients with CHD, ascites are non-chylous as a result of mesenteric lymphatic congestion. Paracentesis can be helpful for diagnostic purposes and to relieve symptoms. Imaging with DCMRL in patients with chylous ascites can help localize the leak which then can be glue embolized. In patients with non-chylous ascites, TDD should be considered.

Multicompartment Lymphatic Failure

Multicompartment lymphatic failure is defined as lymphatic perfusion abnormality involving at least two compartments, including thorax, abdomen, and soft tissue (**Figure 10**) (8). In both neonates and older patients, this is a difficult condition to manage. Irrespective of age, TDE or TDL should never be performed in these patients. Multicompartment lymphatic imaging should be performed in all cases (**Figure 11**). Selective embolization procedures in some cases can be performed but careful consideration should be paid to the consequences that these procedures can have on the other compartments. Normally, a combination of conservative management and TDD procedures, such as LVA, can resolve symptoms in neonates. In adults, selective embolization procedures and TDD can also lead to a resolution of symptoms. If, however, symptoms persist in most cases, OHT or assist device is needed.

CONCLUSION

Patients with CHD especially after single ventricle palliation are susceptible to a variety of lymphatic abnormalities of both the thorax and the abdomen. Imaging is the key step in the diagnosis of the ideology as well as for planning interventions. Imaging should be used to screen all patients with single ventricle physiology prior to undergoing Fontan palliation. Selective lymphatic interventions are the procedures of choice when possible.

AUTHOR CONTRIBUTIONS

Both authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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