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Case reports in heart failure and transplantation 2022

Edited by
Matteo Cameli and Emma Birks

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Case reports in heart failure and transplantation: 2022

Topic editors

Matteo Cameli — University of Siena, Italy

Emma Birks — University of Kentucky, United States

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Table of contents

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EDITED AND REVIEWED BY
Syamal K. Bhattacharya,
University of Tennessee Health Science Center (UTHSC), United States

*CORRESPONDENCE
Matteo Cameli
matteo.cameli@yahoo.com
Federico Landra
f.landra@student.unisi.it

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Editorial: Case reports in heart failure and transplantation: 2022

Matteo Cameli* and Federico Landra*

Department of Medical Biotechnologies, Division of Cardiology, University of Siena, Siena, Italy

In this editorial we summarize the most viewed and downloaded contributing articles to the Research Topic "Case Reports in Heart Failure and Transplantation: 2022" of the journal Frontiers in Cardiovascular Medicine.

KEYWORDS

heart failure, heart transplant, takotsubo, genetic, devices, advanced heart failure

Editorial on the Research Topic
Case reports in heart failure and transplantation: 2022

The adjunctive value of genetic testing

Even though it may be difficult to glean interpretable results in the absence of a specific clinical suspicion, nowadays genetic testing has largely established as a fundamental tool both in the diagnostic workflow and risk stratification of a great variety of cardiac diseases. A similar revolution in the cardiovascular field has been recognized with the introduction of cardiac magnetic resonance, which brought the possibility to unveil structural abnormalities without the need of a histological specimen. However, tissue alterations are only the epiphenomenon of an underlying pathological process and we sometimes fail to go beyond the ultrastructural understanding. In this context, genetic testing may help identifying the missing link piece, finally leading to a comprehensive characterization of the pathological process. This is the case of the patient reported by Liu X et al. which eventually appeared to be affected by a rare desmin myopathy. Diagnosis was only possible with the aid of genetic testing, which identified a missense mutation (c.1366G > A) in the desmin gene, and immunohistochemical staining confirmed desmin deficiency. Clearly, we are still far from tailored therapies for each genetic disease, so one could argue what is the adjunctive value of such pathological understanding. Heart failure and arrhythmia treatments would have been initiated irrespective of the diagnosis of desmin myopathy. However, being able to call a pathological entity by its name and its genetic underpinning give us the chance not only to focus more specifically on its peculiar characteristics, such as, for instance, conduction disturbances occurrence in the case of desmin myopathy, but also to diagnose the disease in a preclinical form in patient's relatives. In addition, the well-known advent of the precision medicine can cast the light of hope on the future of these progressive diseases.

Increasing knowledge in Takotsubo cardiomyopathy pathophysiology

Recently, growing evidence is forming around the mysterious pathophysiology of Takotsubo stress cardiomyopathy. As a proof of that, only in this Research Topic as much as three articles out of seventeen take into account this specific nosological entity. Takotsubo is known to be triggered by emotional or physical stress, and acute cathecolamine release is considered to be the causative event leading to cardiac dysfunction. Wei et al. presented an interesting case of an iatrogenic Takotsubo cardiomyopathy, occurred after injection of high doses of epinephrine infusion for cardiopulmonary resuscitation. This case confirms the central role of cathecolamines and poses the problem of treating those patients presenting with cardiogenic shock, since the much needed cathecolamines may paradoxically deteriorate the hemodynamic status. In contrast, beta blockers are usually beneficial, but overt heart failure is a clear contraindication, and levosimendan may be a reasonable option. Lastly, a potential common pathological substrate has been reported between cancer and Takotsubo cardiomyopathy, namely an individually high catecholaminergic state, underlying the need for careful investigation in that sense.

In addition to catecholamine excess, the pathogenesis could be linked also to other factors such as inflammatory responses and endothelial dysfunctions. Gudenkauf et al. nicely described a case of cytokine storm triggering Takotsubo cardiomyopathy. Cytokine storm is a clinically diagnosed condition presenting with fever, absence of signs of infections and elevated inflammatory biomarkers. In this case, cytokine storm was also associated with rapid development of lactic acidosis and hemodynamic compromise. Even though treatment of cytokine storm has not been clearly defined so far, and much interest is directed towards molecules specifically targeting single cytokines, the Authors showed the beneficial role of pulse dose steroids for the treatment of inflammation associated with Takotsubo syndrome. Further research will clarify in more detail an integrated pathophysiological process and better characterize treatment rationale and implementation depending on the specific phenotype of the disease.

New device options for advanced heart failure

We are now familiar with the implementation of devices in the treatment of heart failure, ranging from cardiac resynchronization therapy to mechanical circulatory support systems such as left ventricular assist devices. The improvements in medical and device therapy for chronic heart failure are dramatically increasing the number of patients worldwide living with this disease. A significant portion of these patients face a progressive decline in heart function and functional capacity, moving towards an advanced stage of the disease. At this point of the natural history of heart failure, patients may no longer tolerate full dose of medical treatments, therefore prognosis consequently worsen as witnessed by the higher number of heart failure-related hospitalizations. Heart transplant is the most effective treatment for these patients, but strict contraindications and the reduced number of organ availability limit the feasibility for most of the patients with advanced heart failure. Fortunately, many device therapies are available and play a major role at this stage, bringing prognostic benefit and improving quality of life. Cardiac contractility modulation is a novel device-based therapy for patients with heart failure with reduced ejection fraction and may be considered a valuable treatment option also for those patients in advanced stage in whom no other therapeutic strategies may be pursued. Cardiac contractility modulation has been shown to improve functional class, reverse left ventricular remodeling and reduce hospitalization in patients with reduced ejection fraction. In the case presented by Masarone et al. cardiac contractility modulation has been successfully used as a bridge to transplant strategy for an obese patient in whom no other viable options were available. In the follow-up, patient's quality of life improved, along with reduction of left ventricular filling pressure and level of N-terminal prohormone of brain natriuretic peptide. In another case by Visco et al. the hemodynamic improvement achieved by cardiac contractility modulation was elegantly demonstrated by data collected from the CardioMEMS device. CardioMEMS is another device which may be used for symptomatic patients with heart failure and recent hospitalization, placed at pulmonary artery level with the purpose of monitoring cardiac filling pressure. Having an invasive hemodynamic monitoring system allows prompt identification of congestion and treatment. In this case, for the first time the usefulness of cardiac contractility modulation was objectively proven by continuous invasive monitoring of pulmonary arterial pressures.

Final considerations

Generally speaking, research has the role to improve both diseases understanding and diseases treatment. This Research topic homogeneously included case reports which brought additional insights into these two directions. Aside from the papers highlighted herein, many other high-quality works have been published in this topic which well deserve a lecture. From heart transplant-related infections to rare cardiomyopathies, from mechanical circulatory support to cardiac rehabilitation, this series of clinical cases spans over a wide range of subjects concerning heart failure.

Author contributions

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CASE REPORT
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Case Report: "Gourd-Shaped" Heart Strangled by Localized Annular Calcification of the Left Ventricle: A Rare Case of Constrictive Pericarditis

Zhiyun Yang[1,2], *Hui Wang*[3], *Qiang Lv*[1,2], *Xin Du*[1,2], *Junming Zhu*[4] *and Jianzeng Dong*[1,2,5]*

[1] Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China, [2] National Clinical Research Center for Cardiovascular Diseases, Beijing, China, [3] Department of Radiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China, [4] Department of Cardiac Surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing, China, [5] Department of Cardiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, China

We report a rare case of a 43-year-old woman with calcific annular constrictive pericarditis (CP) encircling the basal segment of the right ventricle and the mid-segment of the left ventricle (LV) lateral wall. Over time, localized calcification has caused LV to be tightly strangled and shaped like a gourd. However, multimodality imaging confirmed no significantly clinical constriction associated with decreased cardiac movement and function. Additionally, cardiac magnetic resonance feature tracking confirmed the relatively preserved diastolic function and the characteristic "plateau" pattern of CP. The treatment strategy of this case is challenging and dialectical.

Keywords: multimodality imaging, heart failure, cardiac magnetic resonance feature tracking, pericardial calcification, constrictive pericarditis

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Emmanuel Androulakis, Royal Brompton and Harefield NHS Foundation Trust, United Kingdom

Reviewed by:
George Lazaros, Hippokration General Hospital, Greece
Kensuke Matsumoto, Kobe University, Japan

***Correspondence:**
Jianzeng Dong
jzdong@ccmu.edu.cn

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INTRODUCTION

Constrictive pericarditis (CP), caused by primary (idiopathic, posterior pericarditis or linked to rheumatism) or secondary factors (after heart surgery or radiation therapy), is characterized by pericardial adhesions, thickening, or calcification. The inelastic pericardium inhibits cardiac filling, causing cardiac diastolic filling dysfunction and diastolic heart failure (1). CP diagnosis may be challenging and requires multimodality imaging assessment: echocardiography, computed tomography (CT), and cardiac magnetic resonance (CMR) for structural and movement evaluation; catheterization to evaluate hemodynamics; myocardial strain rate analysis to assess myocardial deformation and function, etc. (2, 3). For patients with thickened and calcified pericardium, pericardiectomy is a potentially curable intervention that can improve prognosis. Most pericardial calcifications removed by pericardiectomy were found on the inferior and diaphragmatic surface, anterior right ventricular surface area, and atrioventricular groove posteriorly and over the infundibulum anteriorly (4, 5). While a few cases of pericardial calcification in localized areas have not undergone surgery, lesions of fibrotic or calcified pericardium have been retained *in situ* (6–8). Here, we present a rare case of a middle-aged woman who had calcified annular constrictive pericarditis with localized strangulation in the mid-segment of the left ventricle (LV) lateral wall and a "gourd-shaped" heart.

CASE REPORT

A 43-year-old woman was referred to Anzhen Hospital (Capital Medical University of Beijing, China) for a definite diagnosis and diastolic function evaluation. With a 7-year history of discovering pericardial calcification, she had no obvious symptoms or signs of systemic congestion and heart failure, only intermittent mild edema of both lower limbs. Laboratory examination showed that she had normal inflammatory marker levels, liver and renal function levels and plasma B-type natriuretic peptide level, and laboratory examination also excluded tuberculosis and rheumatism. Electrocardiogram showed sinus rhythm and secondary ST-segment and T-wave changes caused by pericardial calcification, and chest radiogram demonstrated pericardial calcification was not observed obviously (**Figure 1**). Transthoracic echocardiography revealed localized cardiac constriction for the right atrioventricular groove and LV lateral wall due to nodular masses (**Figure 2A**). Additionally, echocardiography indicated that normal size and systolic function of LV; bi-atrial enlargement; paradoxical septal motion with ventricular septal shift during respiration; early to late diastolic transmitral flow velocity (E/A) >1; mitral medial annulus e' velocity >8 cm/s; and mitral lateral annulus e' velocity (14 cm/s)<mitral medial annulus e' velocity (17 cm/s). Pulsed-wave Doppler showed respiratory variation in transmitral flow and the inferior vena cava was dilated (3 cm) without inspiratory collapse. All the above findings were consistent with the diagnosis of pericardial constriction. CT images clearly indicated calcified annular constrictive pericarditis encircling the basal segment of the right ventricle (RV) and the mid-segment of LV. As a result, the heart was tightly strangled and shaped like a gourd in CT imaging (**Figure 2B**) and 3D volume rendering view (**Figure 2C**). CMR revealed localized strangulation at the mid-segment of LV lateral wall, consistent with echocardiography and computed tomography findings. There was no significant reduction in the movement of each LV segment in cine imaging; no obvious abnormal findings in delayed enhanced imaging; and LVEF remained at 58% in CMR (**Figures 2D,E**).

To provide a more accurate assessment of myocardial deformation and LV diastolic function, we performed cardiac magnetic resonance feature tracking (CMR-FT) strain rate analysis for this patient. We analyzed LV global myocardial strain rate and LV global and regional basal-mid-apical segment time-strain curves, and obtained a three-dimensional LV feature tracking model. CMR-FT analysis indicated that the peak global longitudinal strain (GLS) was −11.9%, the peak global circumferential strain (GCS) was −19.1%, and the peak global radial strain (GRS) was 32.3%. Additionally, the characteristic "plateau" pattern of CP could be observed in LV global and regional mid-segment time-strain curves (**Figure 3**). In addition, there was localized strangulation in the mid-segment of LV lateral wall and a "gourd-shaped" heart in LV feature tracking model (**Figure 2F**). Hemodynamic evaluation elucidated and corroborated the effect of constrictive pericarditis on left ventricular filling. Multimodality imaging confirmed that the patient was definitely diagnosed with calcified annular constrictive pericarditis caused by constriction due to ring-shaped and localized calcified pericardium. Due to the location and shape of the calcification, relatively preserved diastolic function, and patient's desires, pericardiectomy has not yet been performed, and diuretic therapy (temporary oral torasemide 20 mg) has been prudently permitted when lower limbs edema occurs. Regular visits will follow up with this patient, and surgical treatment will be performed if necessary.

DISCUSSION

The uniqueness of this case is that calcified annular constrictive pericarditis is an extremely rare form of localized constrictive pericarditis. More precisely, the calcification, in this case, surrounds the right atrioventricular groove and the mid-segment of the LV lateral wall, rather than typically encircling the bilateral atrioventricular groove as reported by Carabelli et al. (9). Gradually, localized pericardial calcification, in this case, has resulted in an obvious stranglehold and altered shape of LV, but did not cause significant clinical constriction with decreased cardiac movement and function. For most patients with chronic and progressive CP, the radical treatment is surgical pericardiectomy. In ESC Guidelines, pericardiectomy is recommended for highly symptomatic patients of CP [New York Heart Association (NYHA) functional class III-IV] (recommendation I-C) and should be cautiously considered in patients of CP with mild symptoms or those with an advanced stage of the disease (cachexia, atrial fibrillation, low cardiac output, hypoalbuminemia, liver dysfunction), those showing myocardial dysfunction or significant kidney failure, and those with a disease secondary to radiotherapy (10). Pericardiectomy is a relatively safe procedure and a potentially curative treatment with an average perioperative mortality rate of 6% (11) and a reported 5–7 years survival rate over 80% (12). The best surgical procedure for pericardiectomy is median sternotomy which allows for easy dissection of diaphragmatic, posterior pericardium to the left phrenic nerve, vena cava, right atrium, and ventricle (13). Although anterior pericardiectomy makes dissecting LV easier than median sternotomy, it is not recommended yet (14). Unfortunately, this patient's LV calcification is as narrow as a ring, tightly attached to LV lateral wall and straddling the coronary arteries. The above-mentioned factors may increase the difficulty and risk of the operation, such as difficulty in peeling off pericardial calcification, bleeding, coronary artery damage, and myocardial atrophy following prolonged constriction.

On the other hand, multimodality imaging evaluation of this patient confirmed that LVEF and myocardial movement were not significantly reduced, and no evidence of necrosis or fibrosis was observed in the myocardium. Through CMR-FT strain rate analysis, we found that LV global strain rate of the patient demonstrated the relatively preserved diastolic function (the patient vs. age- and sex-matched healthy volunteers: peak GLS: −11.9 vs. −15.2 ± 3.7%; peak GCS: −19.1 vs. −23.4 ± 2.27%; peak GRS: 32.3 vs. 43.5 ± 9.8%). For most cases of CP, during the process of diastolic filling, LV stiffness and

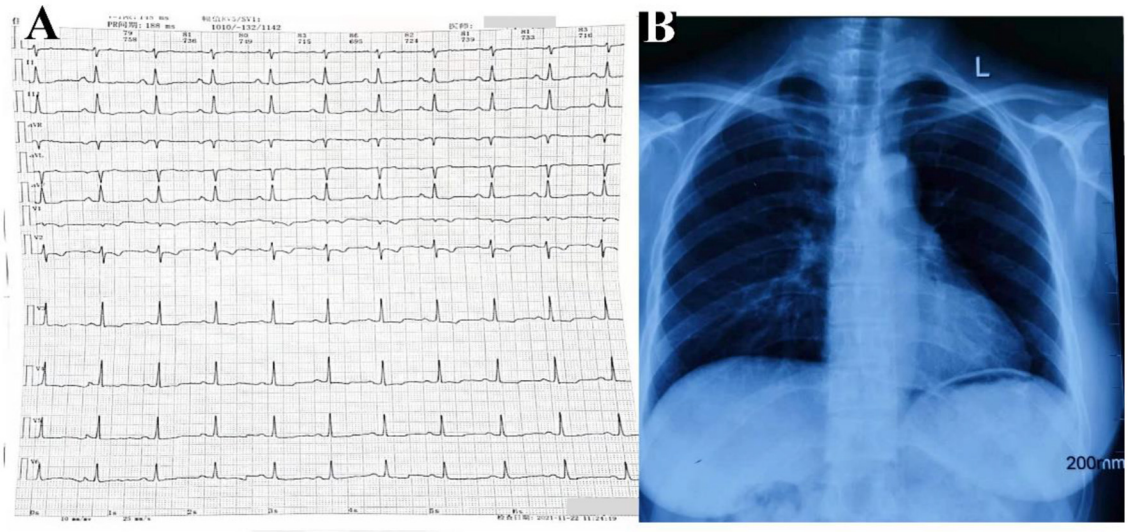

FIGURE 1 | Electrocardiogram **(A)** and chest radiogram **(B)** of calcific annular constrictive pericarditis. Electrocardiogram **(A)** showed sinus rhythm and secondary ST-segment and T-wave changes caused by pericardial calcification, and chest radiogram **(B)** demonstrated pericardial calcification was not observed obviously.

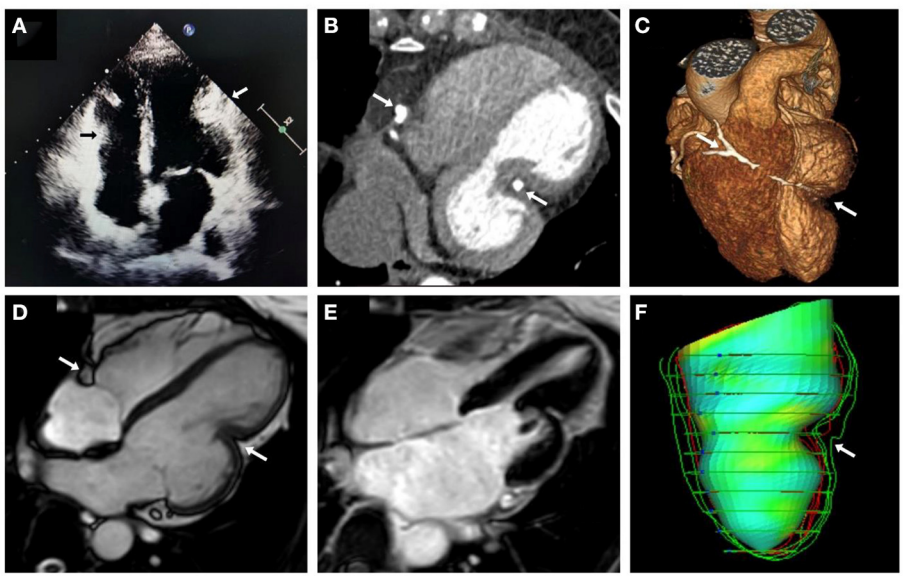

FIGURE 2 | Multimodality imaging of calcific annular constrictive pericarditis. Echocardiographic in apical 4-chamber view **(A)**, CT in 4-chambers view **(B)**, 3D volume rendering view **(C)**, and CMR cine imaging in 4-chambers view **(D)** revealed calcific annular constrictive pericarditis trapping in the right atrioventricular groove and the mid-segment of LV lateral wall (arrows) and the altered shape of "gourd-shaped" heart. CMR delayed enhanced imaging **(E)** showed no obvious abnormal findings. LV feature tracking model **(F)** also showed localized strangulation in LV and abnormal heart shape changes. CMR, cardiac magnetic resonance; CT, computed tomography; LV, left ventricle.

pericardial restraint will lead to increased LV afterload and impaired motor function, which ultimately leads to a significant reduction in circumferential deformation (presented as GCS, reflects subepicardial myofibres). However, due to the relatively preserved myocardial motion and function, this patient did not have a significant decrease in global strain rate. In addition, the characteristic "plateau" pattern of CP in LV global and regional mid-segment time-strain curves corresponded to the location of calcified pericardium (15). Balancing risks and benefits of this patient, we decided to postpone the operation, follow up the patient regularly, and pay close attention to the progressive course.

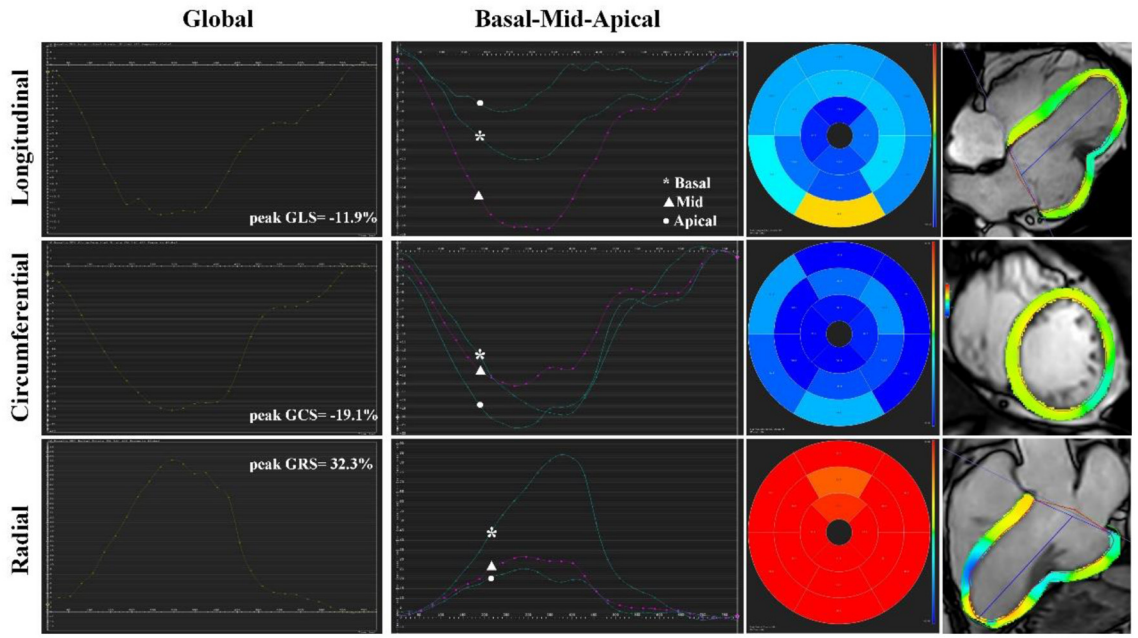

FIGURE 3 | Cardiac magnetic resonance feature tracking strain rate analysis of calcific annular constrictive pericarditis. CMR-FT revealed LV global myocardial strain rate, LV global and regional basal-mid-apical segment time-strain curves, and bull's-eye plots in longitudinal, circumferential, and radial direction. The characteristic "plateau" pattern of CP could be observed in LV global and regional mid-segment time-strain curves. CMR-FT, cardiac magnetic resonance feature tracking; CP, constrictive pericarditis; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LV, left ventricle.

CONCLUSIONS

Our case highlights the critical role of multimodality imaging in CP definite diagnosis, observation of the location and shape of pericardial calcification, and evaluation of myocardial movement and function. In addition, for chronic CP patients with a rare location of calcification and relatively preserved diastolic function, the timing and postoperative prognosis of pericardiectomy are unclear, which requires additional research to confirm.

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 Institutional Ethics Committee of Anzhen Hospital, Capital Medical University of Beijing, China (Approval No. 2006003x). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JD was the guarantors of the integrity of the entire study. HW and QL are responsible for the study concepts and design. ZY prepared the first draft of the manuscript, which was critically revised by XD, JZ, and JD. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Use of Cardiac Contractility Modulation as Bridge to Transplant in an Obese Patient With Advanced Heart Failure: A Case Report

Daniele Masarone[1], Andrea Petraio[2], Antonio Fiorentino[3], Santo Dellegrottaglie[4,5], Fabio Valente[1], Ernesto Ammendola[1], Gerardo Nigro[6] and Giuseppe Pacileo[1]*

[1] Heart Failure Unit, Department of Cardiology, AORN dei Colli, Monaldi Hospital, Naples, Italy, [2] Heart Transplant Unit, Department of Cardiac Surgery and Transplants, AORN dei Colli, Monaldi Hospital, Naples, Italy, [3] Impulse Dynamics Germany, Frankfurt, Germany, [4] Division of Cardiology, Ospedale Accreditato Villa dei Fiori, Naples, Italy, [5] Marie-Josee and Henry R. Kravis Center for Cardiovascular Health, Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, United States, [6] Department of Medical Translational Sciences, Monaldi Hospital, University of Campania "Luigi Vanvitelli," Naples, Italy

Cardiac contractility modulation (CCM) is a novel device-based therapy in patients with heart failure with reduced ejection fraction (HFrEF). In randomized clinical trials and real-life studies, CCM has been shown to improve exercise tolerance and quality of life, reverse left ventricular remodeling and reduce hospitalization in patients with HFrEF. In this case report, we describe for the first time the use of CCM as a "bridge to transplant" in a young obese patient with advanced heart failure due to non-ischemic dilated cardiomyopathy. The patient had a poor quality of life and frequent heart failure-related hospitalizations despite the optimal medical therapy and, due to obesity, a suitable heart donor was unlikely to be identified in the short term and due to severe obesity risk of complications after implantation of a left ventricular assist device (LVAD) was very high.

Keywords: heart failure reduced ejection fraction, advanced heart failure, cardiac contractility modulation, obesity, dilated cardiomyopathy

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Marco Di Maio,
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Michele Ciccarelli,
University of Salerno, Italy
Hiroyuki Kamiya,
Asahikawa Medical University, Japan

****Correspondence:***
Daniele Masarone
danielemasarone@gmail.com

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INTRODUCTION

Most patients with heart failure (HF) with reduced ejection fraction (HFrEF) respond well to evidence-based pharmacological treatments and enjoy a good quality of life, with a significant prolongation of life (1). However, for reasons that are as yet unexplained, up to 10% of patients do not respond to pharmacological or non-pharmacological approaches, resulting in disease progression to the most advanced stage of HF (2, 3).

The gold standard treatment option for patients with advanced HF is heart transplantation, or alternatively left ventricular assist system (LVAD) implantation as a bridge to transplant or as a destination therapy if a heart transplant is not feasible (2).

Obesity is one of the most significant factors that strongly influence the management of patients with advanced HF (4). Indeed, for patients with end-stage HFrEF, obesity has been associated with modestly reduced survival after heart transplantation (5).

Therefore, the International Society for Heart and Lung Transplantation (ISHLT) guidelines consider BMI $\geq$35 kg/m^2 to be a relative contraindication to heart transplant (6).

In addition, obese patients are more vulnerable to LVAD implantation due to their increased risks of post-procedural complications. In fact, in an analysis of 17,095 INTERMACS (Interagency

TABLE 1 | Demographic, clinical and echocardiographic characteristic of patient at admission.

Age	26 years
Weight	128 kg
Height	175 cm
BMI (Deveraux)	41.8
BSA (Dubois)	2.39 m^2
BP	130/80 mmHg
HR	105 b/m
LVEDD	88 mm
LVESD	71 mm
LVEDVI	123.9 ml/m^2
LVESVI	99,1 ml/m^2
EF (Simplon biplane)	20%
E/e'average	14
LAVI	47 ml/m^2
PASP	60 mmHg
IVC diameter	24
IVC collapsibility index	29,1%

BMI, body mass index; BSA, body surface area; BP, Blood pressure; HR, heart rate; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDVI, left ventricular end diastolic volume index; LVESI, left ventricular end systolic volume index; EF, ejection fraction; E/e' average, ratio between Peak velocity of early diastolic transmitral flow and peak velocity of early diastolic mitral septal and lateral annular motion; LAVI, left atrium volume index; PASP, Pulmonary Artery Systolic Pressure; IVC, inferior vena cava.

Registry for Mechanically Assisted Circulatory Support) registry participants who received LVADs between 2006 and 2014, obesity was associated with higher risks of infection, device malfunction/thrombosis, cardiac arrhythmias, and hospital readmissions (7).

Cardiac contractility modulation (CCM) is a new therapy for treating patients with HF that improves the performance of the failing myocardium by delivering biphasic electrical pulses during the refractory period (8).

Here, we describe a case of advanced HF in a young obese patient in which CCM was successfully used as a bridge to transplant option, highlighting the efficacy and safety of this approach in selected patients with advanced HF.

CASE PRESENTATION

A 26-year-old male obese (height 175 cm, weight 128 Kg, body mass index 41.8 kg/m^2, body surface area 2.39 m^2) patient was admitted to the Heart Failure Unit of AORN dei Colli-Monaldi Hospital in August 2019 for marked dyspnea and asthenia. The clinical and demographic parameters at admission are shown in **Table 1**.

After adequate therapy with diuretics and inodilators (levosimendan), which made it possible to reach a state of euvolemia and restoration of end-organ perfusion, an echocardiogram was performed with evidence of a severe reduction in left ventricular systolic function (left ventricular ejection fraction 20%), severe diastolic dysfunction and severe mitral regurgitation (**Figures 1A,B**; **Supplementary Videos 1, 2**).

To clarify the etiology of the HFrEF, coronary angiography was performed, which showed the absence of hemodynamically significant coronary lesions. Subsequently, the patient was referred for cardiac magnetic resonance imaging that confirmed the severe reduction of left ventricular ejection fraction (**Supplementary Videos 3, 4**) with evidence of a small area of fibrosis at the basal level of the interventricular septum (**Figures 1C,D**).

The patient was discharged in September 2019 and had regular outpatient check-ups in the following months to optimize therapy with the disease-modifying drugs.

As of October 2019, the patient had undergone optimized drug therapy (sacubitril/valsartan 97/103 mg bis in die, bisoprolol 10 mg once a day, eplerenone 50 mg daily), but despite this, severe left ventricular systolic dysfunction and NYHA class III persisted, and a subcutaneous ICD was implanted.

During hospitalization for ICD implantation, a cardiopulmonary test was performed to objectively evaluate his functional capacity, which indicated a severe reduction in functional capacity even after correction of the peak VO_2 for obesity (VO_2 peak 13.8 ml/kg/min).

Given the severe reduction in functional capacity despite optimized therapy, the patient was listed for cardiac transplantation in November 2019.

However, during follow-up, the patient experienced three episodes of acutely decompensated heart failure, requiring increased home diuretic therapy and, in one case, hospitalization for levosimendan infusion (**Supplementary Figure 1**).

Therefore, given the limited possibility of receiving a compatible heart within a short period, and considering the high risk of infection, device malfunction and pump thrombosis that LVAD implantation poses in obese patients, other therapeutic strategies were considered.

Mitraclip could be a viable therapeutic option for treating functional mitral regurgitation. However, the patient did not have a COAPT-like profile, and therefore this strategy would be unlikely to affect the patient's prognosis. Pulsed ambulatory infusion of levosimendan is another treatment possibility for patients with advanced HFrEF; however, this option has not been taken into account due to the severe obesity that may affect the drug efficacy.

Therefore, the only feasible therapeutic option as a bridge to transplant strategy was the off-label implantation of an Optimizer Smart® (Impulse Dynamics Inc. Orangeburg, NY, USA) device to deliver CCM therapy.

The implant was performed in March 2021 (**Supplementary Figure 2**), and in the first 3 months after implantation, the patient showed progressive improvement in symptoms, NYHA class, quality of life (as assessed by the Minnesota Living with Heart Failure Questionnaire), echocardiographic parameters and of N-terminal brain natriuretic peptide plasma levels (**Table 2**).

Six months after implantation, the patient repeated the cardiopulmonary test, which showed an increase of VO_2 peak and a reduction in the VE/VCO_2 ratio (**Table 3**).

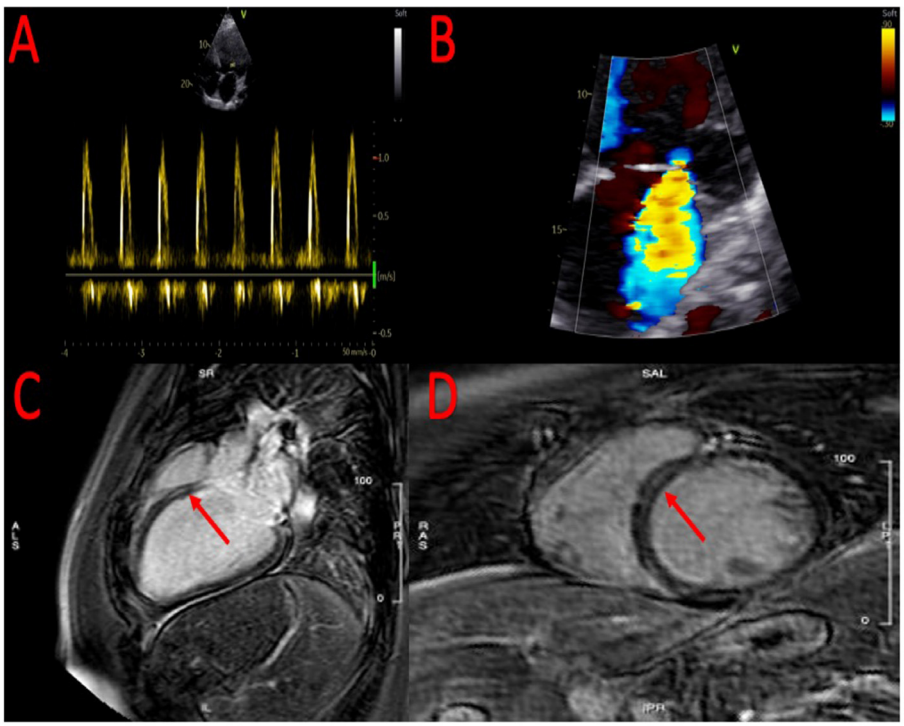

FIGURE 1 | Echocardiographic evidence of severe diastolic dysfunction **(A)** and severe mitral regurgitation **(B)**. At cardiac magnetic resonance, evidence of small area of fibrosis at the basal level of the interventricular septum **(C,D)**.

Through November 2021, the patient is in stable NYHA class II, following a diet to improve the possibility of a heart transplant. No further episodes of acutely decompensated heart failure occurred during follow-up.

DISCUSSION

Advanced HF is a clinical syndrome that is challenging to manage.

Intolerance to disease-modifying drugs is a hallmark of the end-stage phase of HFrEF, and electrical therapy such as cardiac resynchronization therapy is only indicated in patients with specific electrocardiographic characteristics (wide QRS interval, preferably with left bundle-branch block morphology), which are found in no more than 30% of all patients.

Cardiac transplantation is the gold standard therapy for these patients, and LVAD implantation is a valid treatment option, but both are limited by the presence of co-morbidities such as obesity.

In fact, a BMI >35 is related to a high risk of post-implant LVAD complications, such as drive-line infections, pump malfunction and pump thrombosis.

CCM is a new therapy for the treatment of patients with HF and severe-moderate systolic dysfunction. By delivering non-excitatory impulses to the myocardium, a series of long-term biochemical and molecular effects are induced, such as reduced expression of fetal genes (overexpressed in failing myocardium), improved calcium cycling and, finally, myocardial contraction (9, 10).

In randomized clinical trials, CCM reduces hospitalization and improves functional capacity and quality of life in patients with HFrEF (11, 12).

In a retrospective study of 68 patients who underwent CCM therapy at a follow-up after 4.5 years, the mortality of the enrolled patients was lower than predicted by the Seattle Heart Failure Model (SHFM) (13). In a retrospective single-center study, 81 patients with CCM demonstrated improvements in left ventricular ejection fraction, quality of life as measured by the Minnesota living with Heart Failure Questionnaire and a reduction in symptoms during a mean follow-up of 3 years (14). These patients had lower mortality rates than predicted by the Meta-Analysis Global Group in Chronic Heart Failure scores.

Recent results from the largest published registry to date, CCM-REG25-45, showed that the survival rates of patients with LVEF <35% were significantly higher than the survival predicted by the SHFM ($p = 0.46$) (15).

In our patient, when the advanced stage of HF was overt (documented by the frequent episodes of acutely decompensated heart failure despite optimal medical therapy), the obvious choice would have been an LVAD as a bridge to transplant, but due to the presence of severe obesity (BMI 41) the risk of complications was very high, so other therapeutic options were considered.

The MitraClip System (Abbott, Abbott Park, IL, USA), which provides transcatheter edge-to-edge repair of the mitral valve, is the most widely used device for treating functional mitral regurgitation in patients with HFrEF (16). In addition, the recent Mitrabridge registry showed that Mitraclip is a safe and

TABLE 2 | Comparison on demographic, clinical, echocardiographic and laboratory parameters between admission and 6 months follow-up.

Parameter	Baseline	6 months follow-up
Weight	128 kg	124
Height	175 cm	175
BMI (Deveraux)	41.8	40.4
BSA (Dubois)	2.39 m^2	2.36 m^2
BP	130/80 mmHg	120/70 mmHg
HR	105 b/m	88 b/m
LVEDVI	123.9 ml/m^2	119.8 ml/m^2
LVESVI	99.1 ml/m^2	85.3 ml/m^2
EF (Simplon biplane)	20%	28%
E/e'average	14	9
LAVI	47 ml/m^2	43 ml/m^2
PASP	60 mmHg	35
IVC diameter	24	18
IVC collapsibility index	29.1%	37.4%
NT-proBNP	3,569 pg/ml	2,256 pg/ml
MLWHFQ score	43	14

BMI, body mass index; BSA, body surface area; BP, Blood pressure; HR, heart rate; LVEDVI, left ventricular end diastolic volume index; LVESI, left ventricular end systolic volume index; EF, ejection fraction; E/e' average, ratio between Peak velocity of early diastolic transmitral flow and peak velocity of early diastolic mitral septal and lateral annular motion; LAVI, left atrium volume index; PASP, Pulmonary Artery Systolic Pressure; IVC, inferior vena cava; NT-proBNP, N terminal pro Brian Natriuretic Peptide; MLWHFQ, Minnesota Living With Heart Failure Questionnaire.

TABLE 3 | Comparison on cardiopulmonary exercise test derived data between baseline and 6 months follow-up.

Parameter	Baseline	6 months follow-up
RER	1.07	1.12
HR	155 b/m	166 b/m
Work	88 watts	112 watts
VO_2 peak	13.8 ml/kg/min	16.7 ml/kg/min
Oxygen pulse (VO2 peak/HR)	8.9 ml/beat	10 ml/beat
VE/VCO_2	34	25

RER, respiratory exchange ratio; HR, heart rate; VCO2, carbon dioxide output; VE, ventilation; VO2, oxygen uptake.

effective bridge to transplant strategy for patients with advanced HFrEF (17).

However, the COAPT criteria were not met in our patient (left ventricular end-systolic diameter >70 mm, left ventricular ejection fraction ≤20%); therefore, Mitraclip implant would probably not have improved our patient's prognosis (18).

Another strategy used in patients with advanced heart failure is the periodic infusion of levosimendan (19), which can lead to an improvement in the hemodynamic profile (20) and quality of life as well as reduction of acutely decompensated heart failure episodes in patients with advanced HFrEF (21). Pulsed levosimendan infusion can be performed at fixed intervals or by assessing changes in hemodynamic parameters (22), leading to a clear clinical benefit in both cases. However, little data are available on the efficacy of this therapeutic approach in obese patients (body weight > 120 kg); therefor this therapeutic option has not been performed.

According to Federal and Drugs Administration approved physician labeling, CCM is indicated in patients with heart failure in NYHA class III-IV despite optimal medical therapy; however, no data exists regarding their use as a bridge to transplant strategy.

The above treatment strategies were thoroughly discussed in terms of expected outcomes and possible complications with the patient, who decided for CCM therapy.

Thus, in our patient for the first time, an "off-label" implant of an Optimizer Smart® as a bridge to transplant strategy was performed.

During follow-up, our patient experienced a reduction in NYHA class and an improvement in quality of life, according to the Minnesota Living with Heart Failure Questionnaire. In addition, a reduced left ventricular filling pressure occurred, as documented by a reduction in the level of N-terminal prohormone of brain natriuretic peptide.

Furthermore, improvement of echocardiographic and cardiopulmonary exercise test data occurred during follow-up, indicating an increase in cardiac output (increase of VO2 peak) and a reduction of wedge pressure and pulmonary pressure (decreased VE/VCO2 slope).

CONCLUSION

In this case report, we described for the first time a case of advanced HFrEF treated with CCM therapy as a bridge to transplant strategy.

Based on our case, we believe that CCM could be used as a bridge to transplant strategy in selected patients with end-stage HFrEF, not adequately compensated by pharmacological therapy with contraindications to LVAD, such as patients with severe obesity.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DM, AP, AF, and GP: conceptualization. DM, EA, and FV: writing—original draft preparation. GN

and SD: writing—review and editing. All authors have read and agreed to the published 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.2022.833143/full#supplementary-material

Supplementary Figure 1 | Timeline of the clinical case.

Supplementary Figure 2 | Chest X ray showed evidence of Optimizer Smart generator (yellow line) and subcutaneous implantable cardioverter defibrillator generator (red line).

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Conflict of Interest: AF is a full-time employee of Impulse Dynamics®, where Optimizer Smart® was discovered and developed.

The remaining 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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CASE REPORT
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Case Report: Takotsubo Syndrome Induced by Severe Anaphylactic Reaction During Anesthesia Induction and Subsequent High-Dose Epinephrine Resuscitation

Jiaojiao Wei[1,2†], *Le Zhang*[1†], *Xia Ruan*[1], *Kai He*[1], *Chunhua Yu*[1] *and Le Shen*[1,3*]

[1] *Department of Anesthesiology, Peking Union Medical College, Peking Union Medical College Hospital, Chinese Academy of Medicine Science, Beijing, China,* [2] *Department of Anesthesiology, Civil Aviation General Hospital, Beijing, China,* [3] *State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Beijing, China*

Takotsubo syndrome (TTS) is a type of non-ischemic cardiomyopathy characterized by an acute reversible left ventricular dysfunction with typical apical ballooning, usually with subsequent complete recovery. Early diagnosis and prompt treatment are of great essence. Herein, we described a case of TTS of a patient who was scheduled initially for laparoscopic endometrial cancer staging. The 69-year-old woman presented with cardiogenic shock induced by the severe anaphylactic reaction to the antibiotics during anesthesia induction. Cardiopulmonary resuscitation (CPR) was implemented while several boluses of 1 mg epinephrine were injected. After the return of spontaneous circulation, a large number of orange peel-like rash appeared on the head, face, neck, and trunk of the patient. Transesophageal echocardiography (TEE) revealed diffused decreased left ventricular systolic function. Therefore, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and intra-aortic balloon pump (IABP) were applied in the intensive care unit. Biomarkers like cardiac troponin I (cTnI) subsequently decreased with improved cardiac insufficiency. Finally, the patient was discharged in good condition. This case demonstrated that TTS could be secondary to severe anaphylactic shock and exogenous catecholamines. With the consideration of the reversible condition and predictable recovery of TTS, early vigilance and advanced life support devices should be necessary.

Keywords: takotsubo syndrome, anaphylaxis, cardiogenic shock, cardiopulmonary resuscitation, epinephrine, extracorporeal membrane oxygenation

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****Correspondence:***
Le Shen
pumchshenle@163.com

† These authors have contributed equally to this work

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INTRODUCTION

A severe perioperative anaphylactic reaction is a rare, but life-threatening, condition with an incidence of ∼1:7,000–10,000. Possible exposures include antibiotics, anesthetics, colloids, disinfectants, latex, and so on (1). Meanwhile, life-threatening hypotension, bronchospasm, and even cardiopulmonary arrest could be the manifestations in most cases of a severe perioperative anaphylactic reaction, because skin signs might often be absent or neglected during general anesthesia. Immediate administration of low-dose epinephrine is the mainstay of severe

anaphylactic reaction treatment. If cardiopulmonary arrest occurred, advanced life support, including cardiopulmonary resuscitation (CPR) and 1 mg boluses of epinephrine, are necessary. Either severe anaphylactic reaction or high-dose epinephrine administration could activate the immune system and result in stress and inflammation storms, which may be associated with significant cardiovascular complications.

Takotsubo syndrome (TTS), also known as Takotsubo cardiomyopathy or stress cardiomyopathy, is a severe syndrome characterized by acute transient left ventricular systolic dysfunction and electrocardiogram changes in the absence of obstructive coronary artery disease (2). TTS could be induced by the acute endogenous release of catecholamines as well as the exogenous administration of large amounts of catecholamines. In addition to catecholamine excess, the pathogenesis of the disorder possibly involves low estradiol level, inflammation response, endothelial dysfunction, and thyroid dysfunction (3–6). Inflammation has been extensively studied, and both myocardial and systemic inflammation are associated with TTS (7). For patients with TTS, higher serum levels of IL-6 and IL-10 at admission could predict an increased risk of adverse events at follow-up (8). Different complications have been reported in TTS, including atrial fibrillation, cardiogenic shock, and thromboembolic events (9, 10). Atrial fibrillation in TTS is not uncommon. The mortality rate is significantly higher in TTS, accompanied by atrial fibrillation, and long-term prognosis decreased in these patients (11). A recent study has shown that patients with TTS suffered more often from thromboembolic events compared with patients with acute coronary syndrome (ACS), and an elevated C-reactive protein (CRP) level might be a predictor of thromboembolic events (12). In this report, we presented a rare case of TTS induced by catecholamine excess and it was accompanied by cardiogenic shock.

CASE PRESENTATION

A 69-year-old woman (height: 156 cm; weight: 105 kg) was scheduled for laparoscopic staging of endometrial cancer under general anesthesia. Her past medical history included hypertension (grade III, very high risk), type II diabetes, fatty liver, and breast nodules. She had an allergy to a traditional Chinese medicine, Red Flower Oil. The routine preoperative evaluation showed that her ECG with grade III hypertension and lead aVF was labeled as RS type (**Figure 1A**), her echocardiography showed reduced left ventricular diastolic function and a left ventricular ejection fraction (LVEF) of 63%, and her coronary artery CT showed mild to moderate coronary atherosclerosis.

Upon arrival in the operating room, routine monitoring, including ECG, noninvasive blood pressure (NBP), and pulse oximetry (SpO_2), was applied. Lactated Ringer's solution (500 ml) was rapidly infused intravenously during the induction of anesthesia, followed by 1 g of cefmetazole sodium injection. The patient was induced with mask oxygenation, lidocaine (70 mg), fentanyl (150 ug), parecoxib (40 mg), propofol (170 mg), and rocuronium (65 mg IV). Then, endotracheal intubation was performed successfully. Soon after the induction, NBP decreased quickly, and intravenous injection ephedrine or phenylephrine showed no effect. In 10 min, the carotid artery became very weak and could not be palpated; hence, CPR was started while several boluses of 1 mg epinephrine were injected. The NBP returned to 100–130/60–80 mmHg. Within 10 min, a large number of orange peel-like rash appeared on the head, face, neck, and trunk of the patient. To maintain enough circulation, epinephrine was infused with 1 mg/min. Transesophageal echocardiography (TEE) revealed diffused decreased left ventricular systolic function and poor left ventricular lower and posterior wall contraction. Contraction of the posterior interventricular septum, which is the area supplied by the right coronary artery, was generally normal (**Supplementary Videos 1, 2**). After the return of spontaneous circulation (ROSC), a 12-lead ECG indicated that the R wave of V1-V6 disappeared, and no elevation of the ST-segment was captured (**Figure 1B**). However, the bilateral pupils of the patient were found dilated to the diameter of 6–7 mm, with weakened light reflectance.

Due to the condition of the patient, the diagnosis was most likely a severe anaphylactic reaction to the antibiotics. After the patient was transferred to the intensive care unit, her spontaneous circulation needed high dose epinephrine, amounting to 0.6–1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and norepinephrine, amounting to 0.2–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Levosimendan was used for potential cardiogenic shock. However, the shock status deteriorated with continuously increasing demands of epinephrine and norepinephrine, as well as lactic acid levels. TEE showed reduced systolic function and poor anterior interval contraction. In addition, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was applied.

On a postoperative day one (POD1), the ECG of the patient manifested II, III, AVF, and V1-V6 leads as QS type, and her lactate was raised to 19.1 mmol/L, blood glucose to 28.7 mmol/L, WBC to 35.12×10^9/L, and cTnI raised from 11.038 to 27.68 ug/L. Upon these conditions, the diagnosis was most likely TTS. Afterward, the IABP was placed. With the support of VA-ECMO and IABP, epinephrine was discontinued on POD3. The VA-ECMO was removed on POD4. IABP was removed on POD5. cTnI became normal on POD6. The patient was successfully extubated on POD10, followed by the additional one-day non-invasive ventilator. On POD12, norepinephrine was discontinued. On POD14, the patient was transferred back to the general ward, and on POD17, she was discharged in good condition and had continued to use aspirin after discharge.

DISCUSSION

The reported patient finally recovered successfully from a severe cardiogenic shock due to severe anaphylactic reaction, CPR, and TTS sequentially. TTS is usually caused by the acute endogenous release of catecholamines with emotional or physical triggers. Occasionally, TTS could also be caused by exogenous administration of a large number of catecholamines. TTS always leads to myocardial inflammation and short-term left ventricular insufficiency (13). As an important and necessary protective

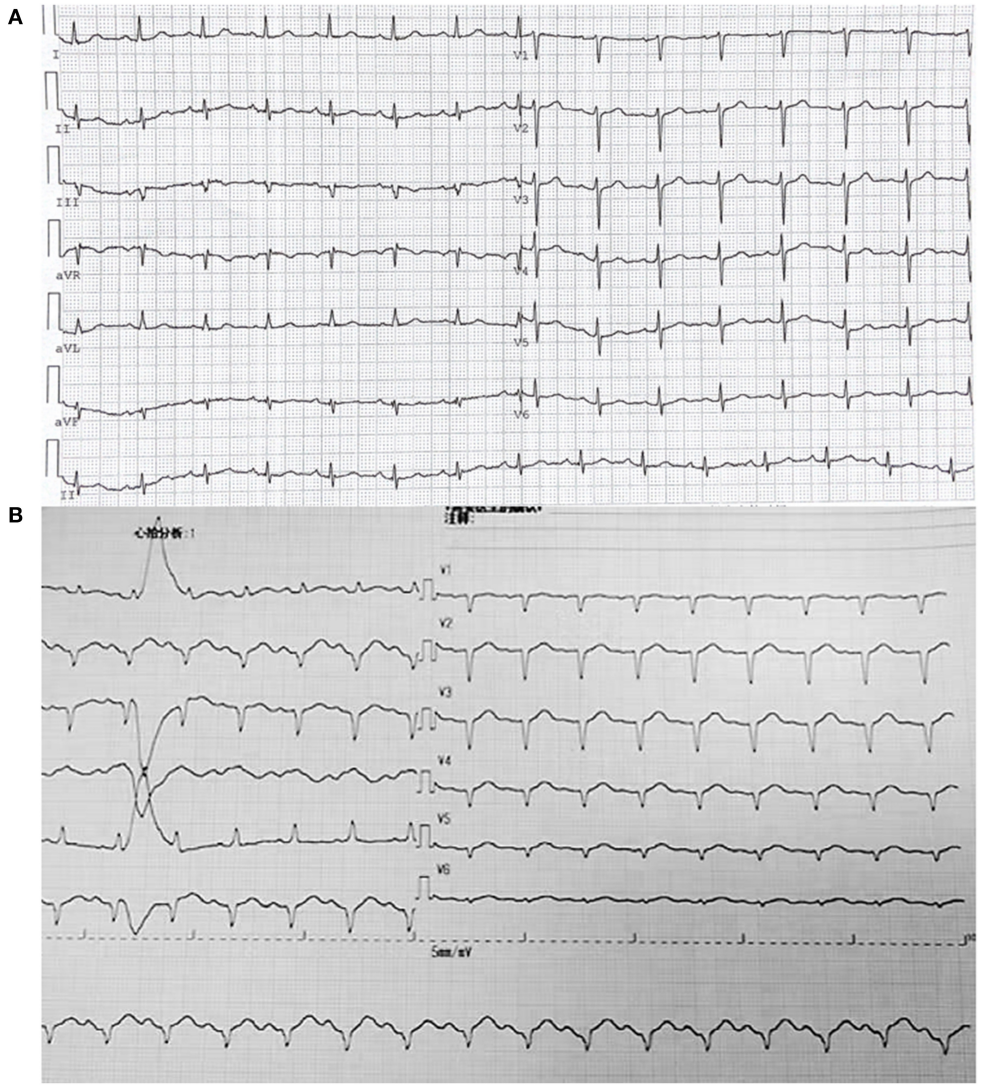

FIGURE 1 | Electrocardiogram **(A)** Before the surgery; Electrocardiogram **(B)** After return of spontaneous circulation (ROSC).

mechanism, the heart needs to "have a rest" to maintain myocardial integrity that displayed as symmetric regional wall motion abnormalities (RWMAs).

However, TTS is generally a benign and reversible condition with predictable recovery, and the RWMAs are usually transient. During the TTS progressing, excessive endogenous or exogenous epinephrine triggers the conversion of the β2-epinephrine receptor from GS to GI coupling, resulting in a negative inotropic response that limits the severity of acute myocardial injury caused by catecholamines. Secondarily, the activation of the phosphoinositol 3-kinase/protein kinase B (Akt) pathway and induced angiogenesis are essential for the improvement of left ventricular function after myocardial injury (14).

The diagnostic algorithm for TTS consists of electrocardiogram, InterTAK Diagnostic Score, biomarkers (markers of myocardial necrosis, B-type natriuretic peptide, and N-terminal prohormone of brain natriuretic peptide), and imagings (coronary angiography and ventriculography, echocardiography, cardiac CT angiography, cardiac MRI, cardiac nuclear imaging, perfusion imaging, metabolic imaging, and sympathetic nervous imaging). This patient received more than 10 mg epinephrine in a short time, which was combined with endogenous catecholamine release during the severe anaphylactic reaction, thereby causing TTS and cardiogenic shock (15). She displayed non-ST-segment elevation, with the InterTAK Diagnostic criteria partially met (**Table 1**). The biomarkers were all lately reported to be elevated significantly. cTnI and creatine kinase (CK)-MB peaked after applying VA-ECMO, while CK and myoglobin reached the top 2 or 3 days later. These biomarkers dropped as her left ventricular systolic function improved (**Figure 2**). There is another concern that obesity prompted the risk of perioperative rhabdomyolysis,

TABLE 1 | InterTAK Diagnostic Criteria for the case.

International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria)	This case
1. Patients show transient left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTS).b	√
2. An emotional, physical, or combined trigger can precede the takotsubo syndrome event, but this is not obligatory.	√
3. Neurologic disorders (e.g., subarachnoid hemorrhage, stroke/transient ischaemic attack, or seizures) as well as pheochromocytoma may serve as triggers for takotsubo syndrome.	N/A
4. New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.	√
5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common.	√
6. Significant coronary artery disease is not a contradiction in takotsubo syndrome.	N/A
7. Patients have no evidence of infectious myocarditis.	√
8. Postmenopausal women are predominantly affected.	√

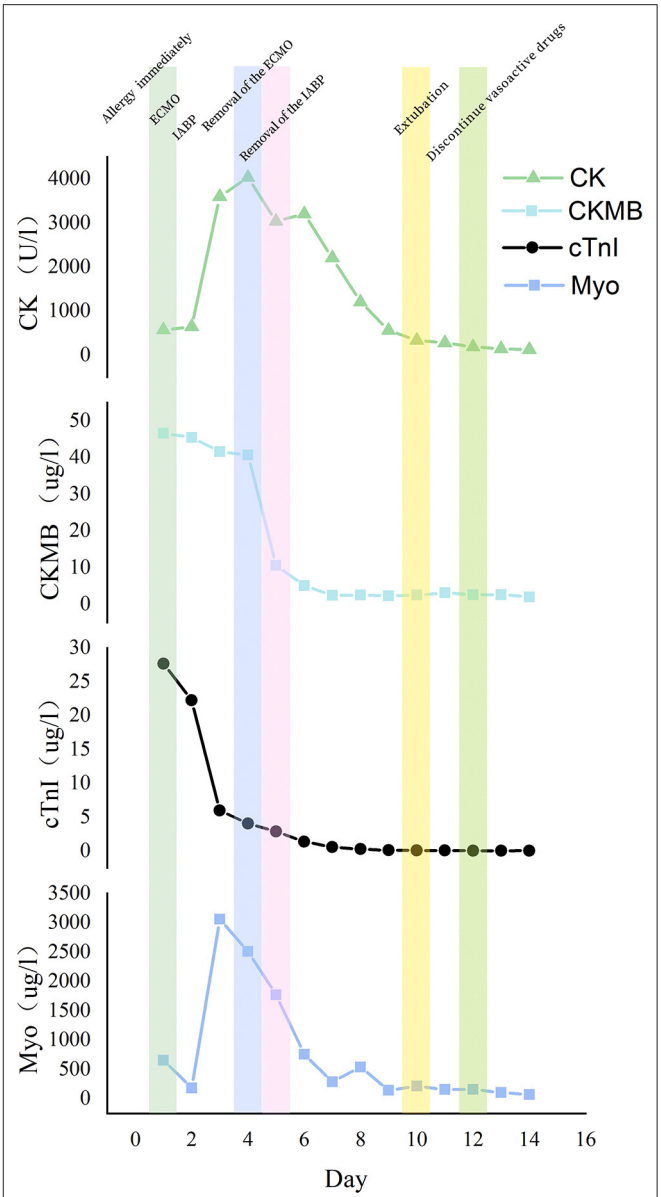

FIGURE 2 | The variation of biomarkers during hospital course. CK, creatine kinase; CKMB, creatine kinase-MB; cTnI, cardiac troponin I; Myo, myoglobin.

which is characterized by elevated serum muscle proteins, including CK and myoglobin (16). The theory could explain why CK and myoglobin peaked later than cTnI and decreased with advanced life support, as well as early bedside exercise. Because of low-quality TTE imaging, an immediate point-of-care TEE is of great necessity for the differential diagnosis of such a sudden collapse of the cardiovascular system, especially for the ruling out of acute myocardial infarction. Her left ventricular wall motion abnormalities extend beyond the distribution of a single coronary artery territory, as is featured in TTS (17). As for imaging, the following 4 different TTS forms have been reported to date: apical form, midventricular form, basal form, and rare focal form. This case belongs to the midventricular form according to the manifestation of TEE (18, 19). El-Battrawy et al. reported that the incidence of RV involvement in TTS was 11%. Furthermore, patients with RV involvement had a higher incidence of in-hospital cardiogenic shock, which helped explain the progression of this case (20).

When TTS is combined with cardiogenic shock, the Ca^{2+} sensitizer levosimendan has been suggested as being used safely and effectively as an alternative inotrope to catecholamine agents. Beta-blockers may also improve left ventricular outflow tract obstruction (LVOTO) but are contraindicated in acute and severe heart failure with low LVEF, hypotension, and bradycardia when the I_f channel inhibitor, ivabradine, may be beneficial. The left ventricular assist device (LVAD) and VA-ECMO are effective for patients with TTS during primary pump failure conditions. As a thrombogenic state may arise as a consequence of catecholamine-dependent ventricular dysfunction, platelet activation, and vasoconstriction during the acute phase of TTS, antiplatelet therapy during hospitalization seems to be an appropriate choice for patients with TTS. However, a recent study found that aspirin at discharge did not relate to a reduced risk of major adverse cardiac and cerebrovascular events in patients with TTS (21).

The primary diagnosis of the patient was endometrial cancer. A current study has presented a strong association between TTC and malignant diseases, and the association may be due to a common pathway, namely an individually high catecholaminergic state (22). Either the history of or the current cancer are associated with an increased risk of adverse events in patients with TTS. Therefore, a careful follow-up after an episode of TTS in patients with cancer counts a lot.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JW looked after the patient and wrote the report. LZ was involved in editing and writing assistance. XR assisted in the CPR of the case. KH and CY did the TEE examination for the case. LS supervised the patient's anesthesia and case report writing. All authors have read and 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.2022.842440/full#supplementary-material

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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.

frontiers in Cardiovascular Medicine

CASE REPORT
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Case Report: Early Resection of Pheochromocytoma in a Patient With Cardiogenic Shock Due to Pheochromocytoma-Induced Cardiomyopathy With Extracorporeal Life Support

Ting Lyu†, *Jianhua Niu*†, *Zhihai Liu and Tong Li**

Department of Intensive Care Medicine, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

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Leonardo Roever, Federal University of Uberlandia, Brazil

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***Correspondence:**
Tong Li
drli@mail.zju.edu.cn

†*These authors have contributed equally to this work*

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Background: Pheochromocytoma-induced cardiomyopathy is a rare but potentially life-threatening complication of pheochromocytoma. It mimics the patterns of stress-induced cardiomyopathy. In severe cases, patients can develop refractory cardiogenic shock, which might require mechanical circulatory support.

Case Presentation: We presented a case of 54-year-old female who developed refractory cardiogenic shock, following an elective orthopaedic surgery complicated by cardiac arrest, requiring veno-arterial extracorporeal membrane oxygenation (VA-ECMO) support. After urgent coronary catheterisation revealed normal coronary arteries, further evaluation of the aetiology of cardiogenic shock revealed pheochromocytoma. With a diagnosis of pheochromocytoma-induced cardiomyopathy, the patient had accelerated preoperative alpha adrenergic blockade preparation for a total of 6 days and subsequently had the tumour removed under VA-ECMO support. Postoperatively, the patient recovered well and was off ECMO support and extubated a few days later.

The optimal management of pheochromocytoma-induced cardiomyopathy, especially for severe cases, is still unclear. Indeed, some cases will require mechanical circulatory support to allow left ventricular function recovery. But our case also showed that it was possible to introduce alpha blockade safely whilst the patient is on VA-ECMO and has the pheochromocytoma removed with VA-ECMO support after accelerated preoperative preparation.

Keywords: pheochromocytoma-induced cardiomyopathy, cardiogenic shock, veno-arterial extracorporeal membrane oxygenation, case report, cardiac arrest

BACKGROUND

Pheochromocytomas are rare but potentially life-threatening tumours, arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia. Most patients present with common symptoms, such as episodic headache, sweating, and tachycardia, whilst, occasionally, some patients present with a pheochromocytoma crisis. Uncontrolled catecholamine release can lead

to catastrophic consequences, such as myocardial dysfunction. With a pattern similar to stress-induced cardiomyopathy, which is characterised by transient regional systolic dysfunction of the left ventricle (commonly apical and midventricular aknesis or dyskinesis and hyperkinesis of the base) without angiographic evidence of obstructive coronary artery disease or acute plaque rupture, pheochromocytoma-induced cardiomyopathy can be misdiagnosed as stress-induced cardiomyopathy (1, 2). Here, we present a case of a middle-age female with pheochromocytoma-developed refractory cardiogenic shock required veno-arterial extracorporeal membrane oxygenation (VA-ECMO) support, following an elective orthopaedic surgery. Subsequently, the patient successfully underwent urgent pheochromacytoma resection under VA-ECMO support.

CASE PRESENTATION

A 54-year-old Chinese female without significant past medical history underwent an elective right shoulder arthroscope under general anaesthesia on the 3rd of June 2021 in a rural hospital. During her outpatient orthopaedic follow-up, her blood pressure was 128/68 mmHg with a heart rate of 78 beats per minute. Intra-operatively and immediate post-operatively, she had stable hemodynamic status. However, she developed symptoms including palpitation, chest pain, and sweating the same night; the vital signs check revealed asystolic blood pressure of 170 mmHg with a heart rate of 100 beats per minute. On physical examination, the patient was still alert and conscious, but diaphoretic and tachypneic with a respiratory rate of 35 per minute. There were bilateral crepitations on auscultation. Her heart sounds were normal; extremities were cool. Abdominal examination was unremarkable. There was no pedal oedema. The electrocardiogram (ECG) revealed right bundle branch block and widespread ST-segment elevation at inferior and lateral leads (**Figure 1**). Urgent cardiology consultation was made. The impression from cardiologist was ST-segment elevated myocardial infarction (STEMI). Whilst preparing for urgent coronary angiogram, the patient rapidly deteriorated. She became cyanotic and hypotensive. She was intubated and supported with a high dose of inotropes. Bedside echocardiogram showed depressed left ventricular systolic function with left ventricular ejection fraction (LVEF) of 20%, but preserved right ventricular function with tricuspid annular plane systolic excursion (TAPSE) of 18 mm. Despite all support, the patient developed ventricular fibrillation and had return of spontaneous circulation (ROSC) after 3 min of resuscitation. The patient was reassessed by a cardiologist in the local hospital after the rapid deterioration and was deemed too unstable for coronary intervention without mechanical circulatory support. Hence, she was referred to our hospital for consideration of urgent revival with VA-ECMO for refractory cardiogenic shock. After tele-consultation by the ECMO specialist in our hospital, the patient was accepted for VA-ECMO support. The patient was supported by 1.5 μg/kg/min of noradrenaline and 0.5 μg/kg/min of adrenaline by the time our ECMO retrieval team arrived. She was then put on VA-ECMO support with adrenaline weaned off and noradrenaline decreased down to 0.3 μg/kg/min and subsequently transferred to our hospital for further management.

The patient underwent an urgent coronary angiography on arrival to our hospital, which, surprisingly, was normal, notwithstanding the typical ECG changes and raised troponins. Given the severe myocardial dysfunction with a normal coronary angiogram, we had a detailed review of her past medical history with the patient's daughter. The patient's daughter denied any significant medical condition including any cardiac issues and hypertension and confirmed that the patient had normal effort tolerance pre-operatively. But she mentioned that the patient had a cardiac workup done in June of last year due to palpitations and breathlessness, which included a normal echocardiogram and normal coronary angiogram. Also, the patient forgot to follow up her adrenal nodule, which was picked up incidentally during a previous health screening. Based on the new information, together with the patient's acute history and past investigations, suspicion of pheochromocytoma-induced cardiomyopathy was raised. The vasopressor strategy was changed to non-catecholamine-based drugs, including vasopressin and levosemendan. As the patient was anuric and still on noradrenaline infusion when pheochromocytoma-induced cardiomyopathy was suspected, serial serum samples for the metanephrine level were sent (**Figure 2**). Contrast adrenal CT was done, showing a 21 mm × 16 mm × 10 mm heterogeneous mass with regular spherical, smooth margins, and enhancement during the arterial phase (**Figure 3A**). Also, the patient had episodes of a sudden onset of hypertension and tachycardia without any stimulus and spontaneously resolved minutes later. The plasma metanephrine level was measured during these episodes also (**Figure 2**).

Subsequently, a multidisciplinary team (MDT) discussion, including an endocrinologist, a cardiologist, a urologist, and an intensivist, was held. The patient's clinical history and investigations were reviewed, and diagnosis of pheochromocytoma-induced cardiomyopathy was made during the MDT discussion. There was also detailed discussion about the timing of pheochromocytoma resection. The consensus was to start an alpha adrenergic blocker gradually and aim for an early surgery. Prazosin was started at a dosage of 0.5 mg two times a day, and increased daily by 1 mg. After 6 days of alpha blockade preparation, with prazosin of 3 mg two times a day, the patient underwent an uneventful open right pheochromocytoma resection with ongoing VA-ECMO support. Heparin was ceased 6 h prior to surgery with activated clotting time at 110 s prior to the surgery and was resumed 12 h post-operatively. ECMO was removed 1 day later, and the patient was extubated successfully on post-operative Day 5. **Figure 3B** is the histological image of the adrenal tumour. The sample was well-circumscribed and unencapsulated, was a size of 2 cm × 1.5 cm × 1 cm, and it showed a vaguely nested architecture and vesicular overlapping nuclei. The immunohistochemical examination of the specimen showed appearance typical of

Abbreviations: VA-ECMO, veno-arterial extracorporeal membrane oxygenation; ECG, electrocardiogram; STEMI, ST-segment-elevated myocardial infarction; LVEF, left ventricular ejection fraction; ROSC, return of spontaneous circulation; MDT, multidisciplinary team.

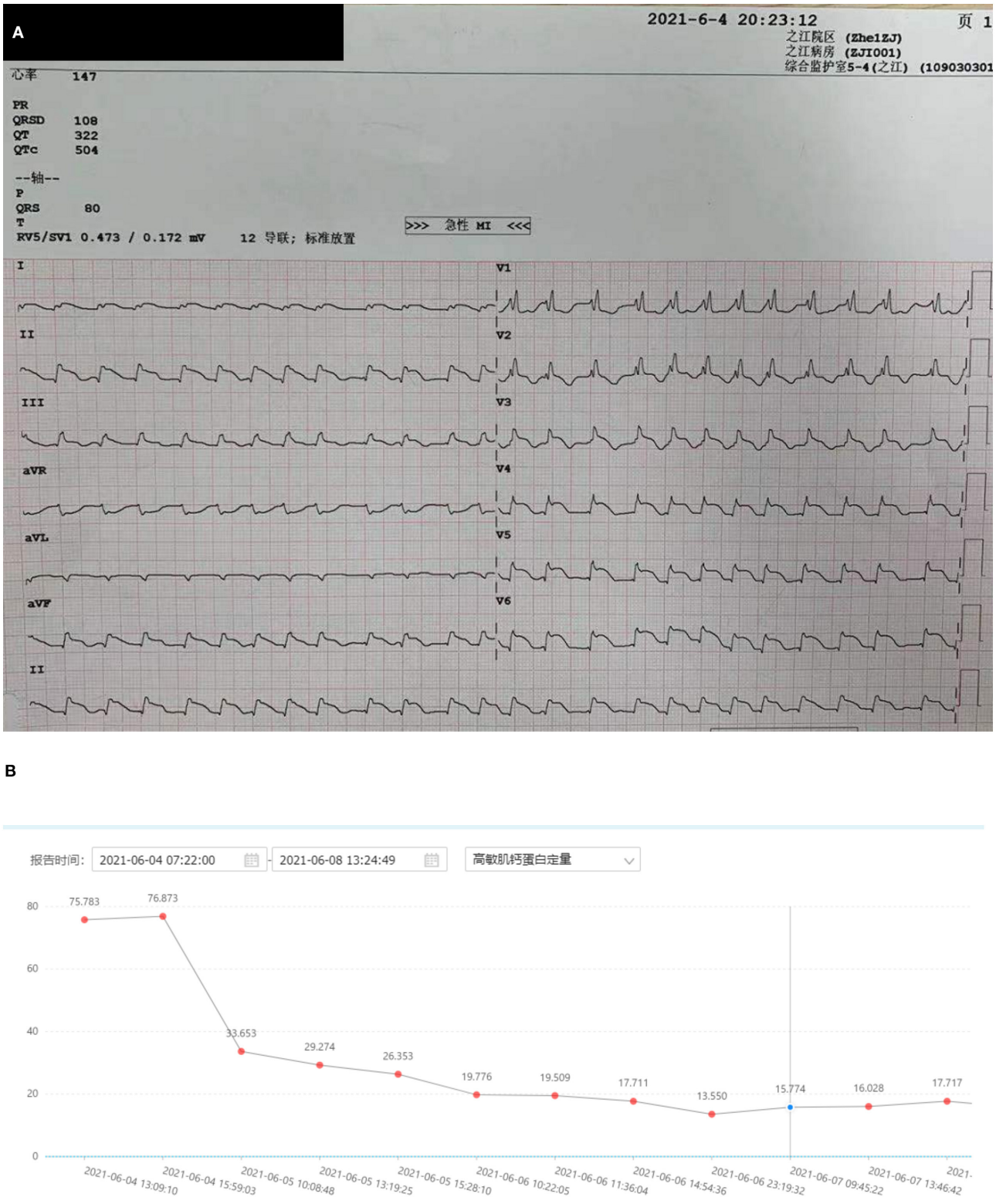

FIGURE 1 | Electrocardiogram of the patient. **(A)** Electrocardiogram of the patient (arrow: ST segment elevation). **(B)** A trend of troponin I (nanograms per litre).

pheochromocytoma, with specific neuroendocrine markers, including chromogranin A, a neural cell adhesion molecule, and synaotophysin, all returned positive. She was transferred to a rehabilitation centre after 24 days of stay in the intensive care unit (ICU). Upon transfer, her LVEF recovered to 55% as compared to 20% on admission. **Figure 4** is a timeline of

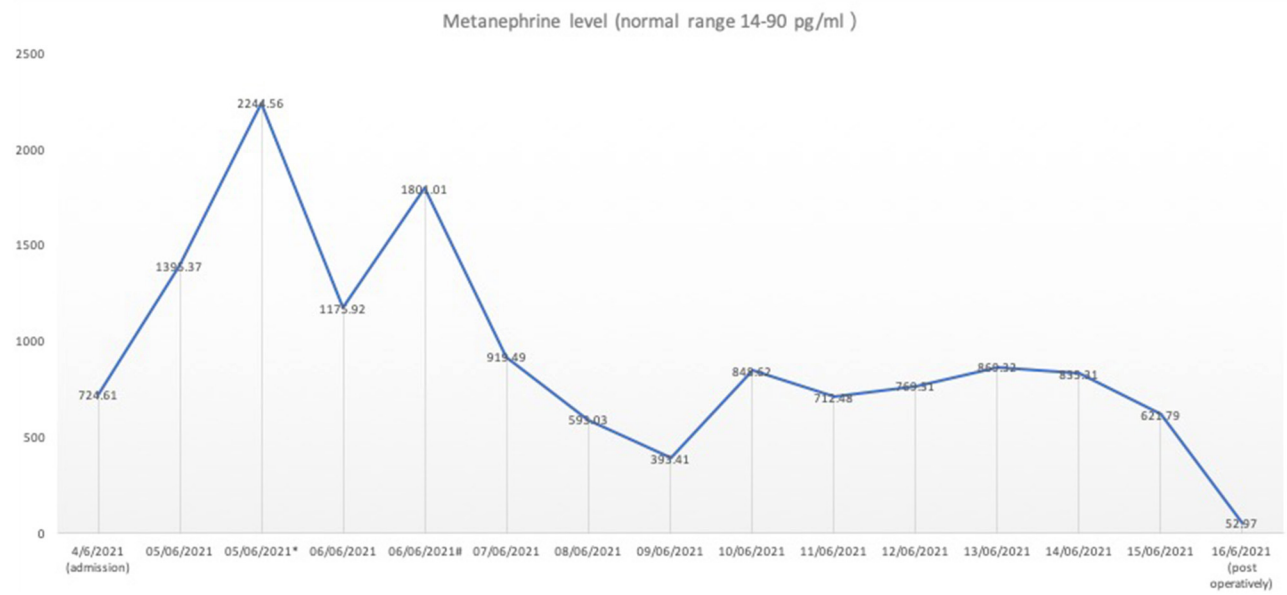

FIGURE 2 | The serum metanephrine level pre-operatively and post-operatively. The serum metanephrine level was measured continuously at 6 a.m. from 5th June 2021 onwards. *The metanephrine level during the first episode of the sudden onset of hypertension and tarchycardia. #The metanephrine level during the second episode of the sudden onset of hypertension and tarchycardia. On 16th June 2021, the metanephrine level dropped back to the reference range post-operatively on Day 1.

the clinical condition progress and major management of the patient.

DISCUSSION

According to the guideline, pheochromocytoma should be excluded before making the diagnosis of stress-induced cardiomyopathy (3). A large registry study demonstrated that more than 90% of patients with stress-induced cardiomyopathy were female at the age of 50s or older with neurologic disorder and emotional stress as common triggers (4). After a normal coronary angiogram, our patient seemed to well-fit in the diagnosis of stress-induced cardiomyopathy, given her age and possible stress from the surgery. However, the exclusion criteria of stress-induced cardiomyopathy reminded us to rule out pheochromocytoma before making a diagnosis of stress-induced cardiomyopathy. Indeed, further history of adrenal mass raised up the suspicion for pheochromocytoma-induced cardiomyopathy, which later proved to be the case. In the review paper by Agarwal et al. (1), they compared patients with pheochromocytoma-induced cardiomyopathy and stress-induced cardiomyopathy. The results showed that the patients with pheochromocytoma-induced cardiomyopathy were at higher risk of developing cardiogenic shock. They proposed that, in patients diagnosed with stress-induced cardiomyopathy, even in the absence of signs and symptoms of pheochromocytoma, a workup of pheochromocytoma should be strongly considered. This case again reminds us that every effort should be made to exclude pheochromocytoma in patients who present with features of stress-induced cardiomyopathy, especially those who present with cardiogenic shock.

A new diagnosis of pheochromocytoma in critically ill patients can be challenging. The usual diagnosis of pheochromocytoma includes biochemical testing as well as imaging (3). A previous study has shown that the plasma-free metanephrine level is a reliable test for confirming pheochromocytoma (5). In the critical care setting, the interpretation of catecholamines is more challenging due to the use of adrenergic agents as well as endogenous (physiological) release. A retrospective study comparing urine metanephrine levels from inpatient patients (including 132 patients from ICU) without pheochromocytoma with those with confirmed pheochromocytoma showed that there was a significant overlap of urine normetanephrine and metanephrine levels between hospitalised patients and patients with pheochromocytoma (6). The study concluded that for, ICU patients, cathecholamine levels more than five-fold above the upper reference limit had 98% specificity for the diagnosis of pheochromocytoma, but still had poor positive predictive value. As our patient was still on noradrenaline, the normetanephrine level was possibly affected by exogenous infusion, but no adrenaline was used since admission to our hospital, so the metanephrine level was unlikely affected by exogenous factors. As the patient was anuric, urine measurement of normetanephrine and metanephrine was deemed impossible; hence, the biochemical diagnosis, in this case, was based on the serum metanephrine level. The result showed that the baseline level of metanephrine level for this patient was already at least five times over the upper limit of the reference range. And, during the two episodes of the sudden onset of hypertension

and tachycardia, the metanephrine level was near 20 times over the upper limit. This was the biochemical basis of diagnosis for pheochromocytoma in this patient. Together with the typical contrast CT findings, the diagnosis of pheochromocytoma-induced cardiomyopathy was made during the MDT discussion.

In our case, the patient was initiated on VA-ECMO support for isolated left ventricular failure with preserved right ventricular function. As we have known, VA-ECMO support can provide circulatory support, but it is unlikely to improve left ventricular function (7). In fact, it can cause detrimental effects to the left ventricle as they increase left ventricle after load and stress. From this perspective, axial left ventricle-assisted devices, such as IMPELLA or TandemHeart would be more favourable. However, from practical aspects, axial left ventricle assisted-devices are not available in our institution unfortunately. For our case, the patient had cardiac arrest before VA-ECMO initiation; the preference for a mechanical circulatory support device would be one can provide biventricular support as there was still high risk of recurrence of cardiac arrest, especially with an unclear primary pathology causing cardiogenic shock. An axial left ventricle device will not be sufficient if the patient went into cardiac arrest again.

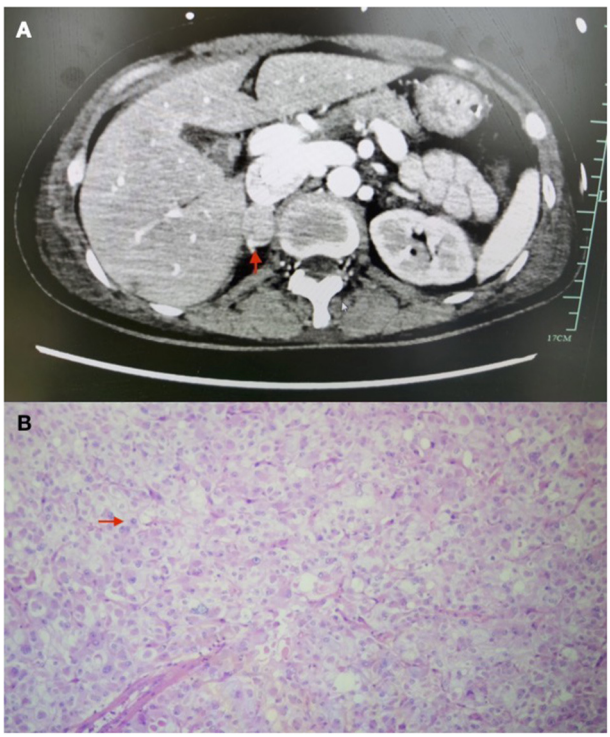

FIGURE 3 | Images of adrenal tumour. **(A)** CT images of adrenal tumour (arrow). **(B)** Histology image of adrenal tumour (arrow: characteristic-stippled chromatin).

Another challenge of managing this case was the timing of surgery. Guidelines recommend that all patients with pheochromocytoma should receive adequate alpha- and beta-blockade pre-operatively to prevent perioperative cardiovascular complications (3). While this fits well for elective resection of pheochromocytoma in stable patients, it was difficult to apply to our patient who suffered refractory cardiogenic shock and cardiac arrest, requiring mechanical circulatory support due to pheochromocytoma. Whilst all specialists including the anaesthetist agreed that the surgery should be done early, there were a few concerns of performing surgery for this patient. The first was whether to have the surgery done whilst the patient was still on VA-ECMO support. The benefit of performing pheochromocytoma resection surgery whilst on VA-ECMO support was ECMO can provide cardiac support in case the patient developed worsening cardiogenic shock or cardiac arrest during surgery due to a possible catecholamine surge during surgery. However, anticoagulation had to be ceased peri-operatively, which can increase the risk of ECMO-related complications, such as thrombotic events and oxygenator failure. Another concern was, without gradual and adequate adrenoreceptor blockade, the patient

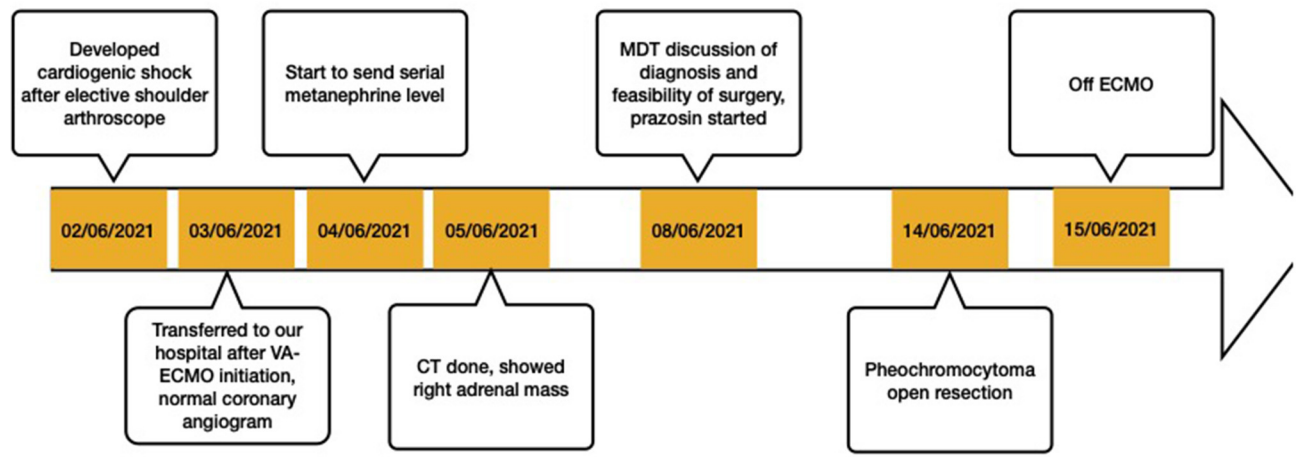

FIGURE 4 | The timeline of case progression.

might develop hypertensive crisis from a catecholamine surge, which could result in complications, such as cerebrovascular accidents. Also, without letting the body gradually adapt to the "decreased" catecholamine levels by adrenoreceptor blockade, the patient might develop severe vasoplegic shock due to sudden decreased catecholamine levels post-operatively, compounded by pharmacological adreno-receptor blockade. In this patient, we successfully introduced a short-acting alpha blocker, whilst the patient was still on VA-ECMO support. The patient subsequently underwent surgery uneventfully 6 days later, whilst most case series and case reports proposed that it might be safer to introduce alpha and beta blockers and perform adrenalectomy several weeks after the initial catastrophic presentation for pheochromocytoma-induced cardiogenic shock managed on VA-ECMO (8, 9). We managed to safely introduce alpha blockers in pheochromocytoma-induced cardiomyopathy whilst patient was in cardiogenic shock requiring ECMO and subsequently performed early pheochromocytoma resection with VA-ECMO support.

There are a few limitations of our case report. First, this is a single case report of pheochromocytoma resection under VA-ECMO support after an accelerated preparation. Second, we were unable to perform MIBG (Metaiodobenzylguanidine) scintigraphy pre-operatively to further confirm the diagnosis and rule out possibility of metastatic pheochromocytoma/paraganglioma, whilst the patient is on VA-ECMO support. And we did not follow up the patient further after she was transferred to the rehabilitation facility. The future direction would be further exploration of optimal duration of alpha and beta-adrenergic blockade therapy if patient is deemed requiring for an accelerated pre-operative preparation.

In conclusion, we presented a unique case with refractory cardiogenic shock due to pheochromocytoma-induced cardiomyopathy without a known history. Although rare, this case highlighted the importance of excluding patients with pheochromocytoma with features of stress-induced cardiomyopathy, especially those with cardiogenic shock. And early removal of pheochromocytoma after an accelerated preparation pre-operatively was feasible with VA-ECMO support.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Written informed consent was obtained from the relevant individual's legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TiL and JN collected the data and participated in manuscript writing. ZL and ToL participated in manuscript writing. All authors read and approved the final manuscript.

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CASE REPORT
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A Multistep Approach to Deal With Advanced Heart Failure: A Case Report on the Positive Effect of Cardiac Contractility Modulation Therapy on Pulmonary Pressure Measured by CardioMEMS

Valeria Visco[1], *Cristina Esposito*[2], *Michele Manzo*[2], *Antonio Fiorentino*[3], *Gennaro Galasso*[1], *Carmine Vecchione*[1,4] *and Michele Ciccarelli*[1]*

[1] Department of Medicine, Surgery and Dentistry, University of Salerno, Fisciano, Italy, [2] Cardiology Unit, University Hospital "San Giovanni di Dio e Ruggi D'Aragona", Salerno, Italy, [3] Impulse Dynamics Germany GmbH, Frankfurt Am Main, Germany, [4] Vascular Physiopathology Unit, IRCCS Neuromed, Pozzilli, Italy

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Daniele Masarone,
Azienda Ospedaliera dei Colli, Italy

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Michele Correale,
Azienda Ospedaliero-Universitaria Ospedali Riuniti di Foggia, Italy
Giuseppe Pacileo,
Azienda Ospedaliera dei Colli, Italy

***Correspondence:**
Michele Ciccarelli
mciccarelli@unisa.it

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During the last years, the management of heart failure (HF) made substantial progress, focusing on device-based therapies to meet the demands of this complex syndrome. In this case report, we present a multistep approach to deal with HF. Specifically, we report the first patient subjected to the implantation of both Optimizer Smart® (Impulse Dynamics Inc., Marlton, NJ, USA) and CardioMEMS devices. A 72-year-old male patient with HF and reduced ejection fraction (HFrEF) was admitted to our cardiology department in January 2021, following a progressive shortening of the time between hospitalizations for levosimendan infusions. Specifically, the patient was monitored daily by CardioMEMS, and a strategy of levosimendan infusions guided by the device had been adopted. He was also a carrier of MitraClips and cardiac resynchronization therapy defibrillator (CRT-D) and had optimized HF medical therapy. In January 2021, the patient implanted Optimizer Smart® device for cardiac contractility modulation (CCM) therapy because of poor response to therapy and elevated pulmonary artery pressure (PAP). CCM significantly reduced PAP values following discharge (systolic PAP 33.67 ± 2.92 vs. 40.6 ± 3.37 mmHg, diastolic PAP 14.5 ± 2.01 vs. 22.5 ± 2.53 mmHg, mean PAP 22.87 ± 2.20 vs. 30.9 ± 2.99 mmHg, HR 60.93 ± 1.53 vs. 80.83 ± 3.66 bpm; $p < 0.0001$), with persisting effect at 9 months. The usefulness of CCM is objectively demonstrated for the first time by continuous invasive monitoring of PAP by CardioMEMS, which can suggest the correct timing for CCM implantation.

Keywords: heart failure, case report, Optimizer Smart®, cardiac contractility modulation, CardioMEMS, telemonitoring, medical devices, levosimendan

INTRODUCTION

Heart failure (HF) shows phases of exacerbation interrupted by periods of clinical stability. Despite many pharmacological advances, morbidity and mortality in HF remain an important burden to patients, caregivers, and national healthcare systems (1–3). Advanced HF, defined as severe symptoms despite optimal medical therapy (OMT) and device, affects up to 25% of patients with HF (4). Treatments for such patients are limited. Consequently, during the last years, the management of HF made substantial progress, focusing on device-based therapies to meet the demands of this complex syndrome. Specifically, in the management of this syndrome, therapeutic strategies usually aim for improved outcomes in terms of reduced mortality and fewer unplanned HF hospitalizations (5).

On the one hand, the CardioMEMS (Abbott Medical, Inc., Abbott Park, Illinois, USA) is an implantable device positioned in the pulmonary artery and is able to detect higher cardiac filling pressures, an objective measure of "hemodynamic congestion," estimated to rise more than 2 weeks before the onset of symptomatic congestion (6, 7); this device is applicable in patients with chronic HF in functional New York Heart Association (NYHA) Class III with at least one admission for HF in the past year (class of recommendation IIb according to HF ESC Guideline 2021) (2). On the other hand, cardiac contractility modulation (CCM) therapy has emerged as a hopeful device treatment in patients with HF not indicated for cardiac resynchronization therapy (5). Specifically, CCM is an electrical therapy that consists of biphasic pulses of relatively high voltage being delivered to the right ventricular (RV) septum *via* a small implantable pulse generator in the absolute refractory period of the myocardium (8–10) (**Figure 1**). In this report, we present a multistep approach to deal with HF.

CASE PRESENTATION

A 72-year-old Caucasian male patient with HF and reduced ejection fraction (HFrEF) was admitted to our cardiology department in January 2021, following a progressive shortening of the time between hospitalizations for levosimendan infusions. Specifically, the patient had no symptoms or signs of HF exacerbation; however, he had a reduction in exercise tolerance (symptoms graded as Class III of the NYHA Functional Classification). Physical examination showed vesicular breath sounds, no peripheral edema, normal peripheral pulses, and systolic murmur in the mitral area. Moreover, blood tests showed brain natriuretic peptide (BNP) 1,093 pg/ml, hemoglobin 10 g/dl, and estimated glomerular filtration rate (eGFR) 25 ml/min/1.73 m^2. The patient's comorbidities comprised chronic kidney disease stage 4 with secondary anemia, dyslipidemia, carotid atheromasia, paroxysmal atrial fibrillation, hypothyroidism, chronic obstructive pulmonary disease, sizeable inguinal hernia, arterial hypertension, and obesity.

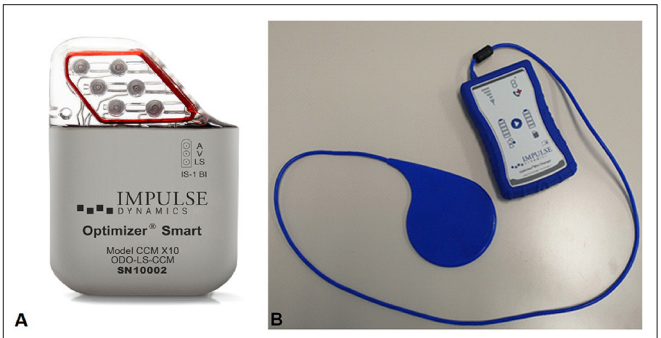

FIGURE 1 | Optimizer Smart® system. **(A)** The Optimizer Smart® Implantable Pulse Generator (IPG) unit. **(B)** Optimizer Smart Charger System. Patients can recharge the IPG unit using a portable, home-based charger system, without supervision. Charging the device on a weekly basis assures it has enough energy to provide the prescribed dose of CCM therapy.

PAST MEDICAL HISTORY

His medical history started in 2004, when he was diagnosed with primary hypokinetic dilated cardiomyopathy (EF 42%) in the absence of significant coronary artery disease. Despite the OMT, from 2004 to 2015, he had more than 20 hospitalizations for HF exacerbation with a gradual reduction of EF. In 2015, he underwent biventricular implantable cardioverter defibrillator (CRT-D) implantation for the evidence of EF <35%, while in 2017, he was treated by positioning of MitraClips (Abbott Laboratories, Menlo Park, California, USA) for severe mitral regurgitation. In the same year, the patient was enrolled in our HF clinic and further optimized HF therapy with the addition of Sacubitril/Valsartan 24/26 mg b.i.d. However, despite the OMT, from October 2017 to 2019, the patient underwent numerous hospitalizations. Then, in June 2019, a strategy of levosimendan infusions guided by CardioMEMS was implemented to obtain hemodynamic stability in the patient for a more extended period. Consequently, the patient was monitored daily by the device, and when home therapeutic changes were not sufficient, the patient was contacted for hospitalization and levosimendan infusion. From June 2019 to January 2021, the patient had only 5 hospitalizations scheduled for levosimendan infusion and only one for HF exacerbation. In January 2021, following a progressive shortening of the time between hospitalizations for levosimendan infusions, the patient was hospitalized in our Cardiology Unit to change the management strategy.

INVESTIGATIONS

An echocardiogram (January 2021) showed a dilated left ventricle (LV end-diastolic volume 197 ml) with impaired LV systolic function (EF 25%) and global hypokinesia, LV diastolic dysfunction with elevation in LV filling pressure, moderate mitral regurgitation and presence of MitraClips, dilated left atrium (volume 54 ml/m^2), a dilated right ventricle (RVD 57 mm) with preserved function (TAPSE 18 mm), increased pulmonary artery systolic pressure (41 mmHg), dilated inferior vena cava

(IVC), and no collapse. Normal sinus rhythm was observed on the electrocardiogram.

MANAGEMENT

Procedure

The patient received the typical 24-h intravenous infusion of levosimendan (0.1 μg/kg/min); subsequently, to reduce HF-related hospitalizations and to improve quality of life, we decided to implant a CCM therapy device. After signing informed consent, the Optimizer Smart (Impulse Dynamics Inc., Marlton, NJ, USA) for the delivery of CCM therapy was implanted with fluoroscopic guidance.

Because a CRT-D was already present in the left prepectoral area, Optimizer Smart implant was performed *via* a contralateral right-sided access. Current devices require the implantation of two standard pacing leads in the RV. Therefore, a device pocket was fashioned in the prepectoral area, and the leads (Tendril 2088TC – 58, Abbott) were sequentially implanted using two peel-away sheaths introduced over the guide wires. For each lead, mapping to optimize location was performed; particularly, the RV lead tips were placed along the septal wall at 2 cm apart (8). Finally, the septal position of the lead was confirmed by oblique fluoroscopy views and pacing ECG patterns. A testing for device–device interactions was performed to ascertain oversensing of the previously implanted CRT-D, given the large voltage signal (7.5 V/22-ms duration) produced by CCM (8). The Optimizer unit was then attached to the leads and located in the pocket (**Figure 2**). The Optimizer pulse generator needs manual transcutaneous recharging by the patient: routine recharging is done weekly and needs about 1 h to complete (11). In our case, the CCM therapy was scheduled for 10 h/day (**Figure 3**).

Follow-Up

The PA pressure values on monitoring in the 30 days following discharge were significantly lower than in the previous hospitalization (PAPs 33.67 ± 2.92 vs. 40.6 ± 3.37 mmHg, PAPd 14.5 ± 2.01 vs. 22.5 ± 2.53 mmHg, PAPm 22.87 ± 2.20 vs. 30.9 ± 2.99 mmHg, HR 60.93 ± 1.53 vs. 80.83 ± 3.66 bpm; $p < 0.0001$), and this effect persisted even after 9 months (**Figure 4**).

Specifically, after January 2021, the cardiologist continued to monitor the patient, making therapy adjustments according to PAPd, and no further levosimendan infusions or hospitalizations were made between January 2021 and June 2021. The patient was evaluated 4 weeks after implantation; at that visit, the pulse generator was interrogated to assess the percentage of beats receiving CCM impulse delivery to ensure the adequacy of CCM parameter programming (**Supplementary Figure 1**). Moreover, a 5-level EQ-5D version (EQ-5D-5L) questionnaire about quality of life was performed: the score increased from 79 (before) to 91 (4 weeks after implantation of Optimizer Smart®).

DISCUSSION

In this study, we report the case of a patient with advanced HF, whose quality of life was strictly invalidated by the multiple HF exacerbations. Our case supports a step-by-step approach to treat heart problems, with the help of innovative devices.

The CCM has been studied in preclinical and clinical studies over the past years and has now been found to benefit a population of patients characterized as having: NYHA Class III–IV despite the OMT, EF 25–45%, and electrocardiogram QRS complex duration < 130 ms (2, 12, 13). Moreover, some publications have verified the safety and effectiveness of the CCM in CRT nonresponder patients: the implants are justified in those patients where symptoms persist despite OMT (14, 15).

Specifically, in this report, we present the first patient experience with levosimendan infusion led by CardioMEMS and the subsequent Optimizer Smart® device implantation; consequently, the usefulness of CCM is objectively demonstrated for the first time by continuous invasive monitoring of pulmonary arterial pressures.

The CCM is a novel HF device therapy that acts through a high-energy, nonexcitatory biphasic signal in the absolute

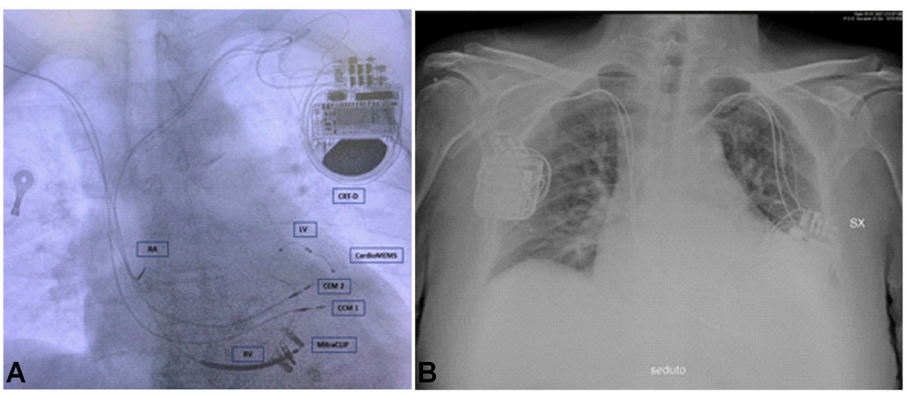

FIGURE 2 | Chest X-ray of the patient. **(A)** The figure shows two CCM leads, three CRT-D leads, CardioMEMS, and MitraClips. **(B)** The figure shows CCM device on the right and CRT-D on the left. CRT-D, cardiac resynchronization therapy – defibrillator device; CCM 1, lead 1 CCM; CCM 2, lead 2 CCM; RV, right ventricular lead for CRT-D; LV, left ventricular lead for CRT-D; RA, right atrial lead for CRT-D.

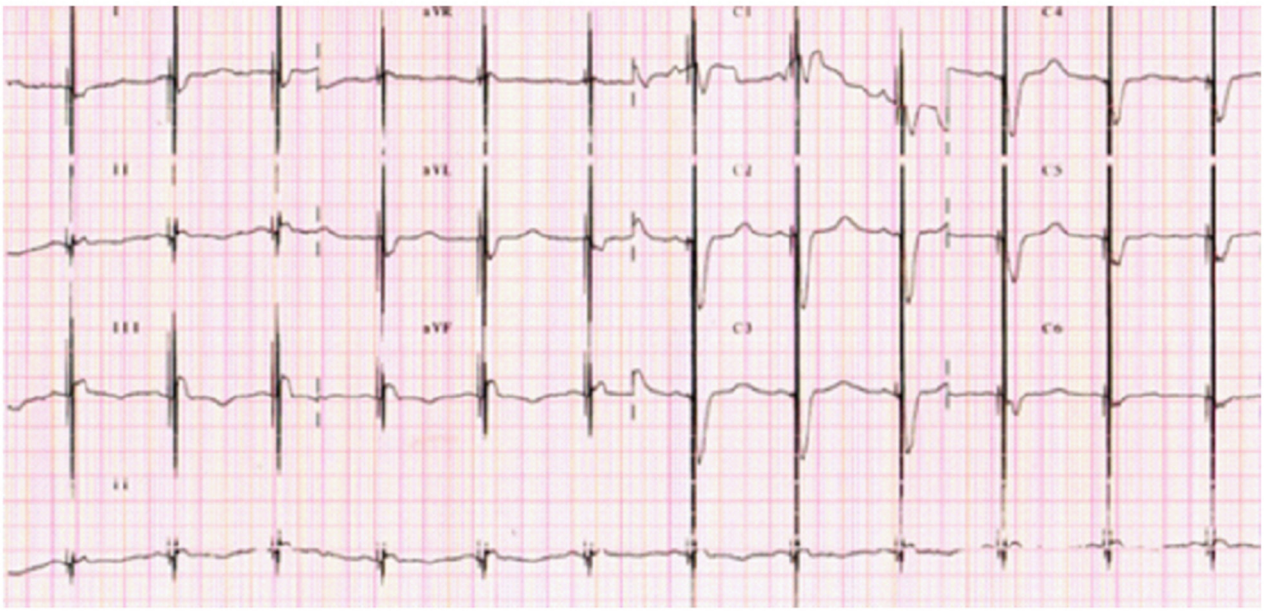

FIGURE 3 | A 12-lead ECG with visible spikes of high-energy impulses from CCM therapy.

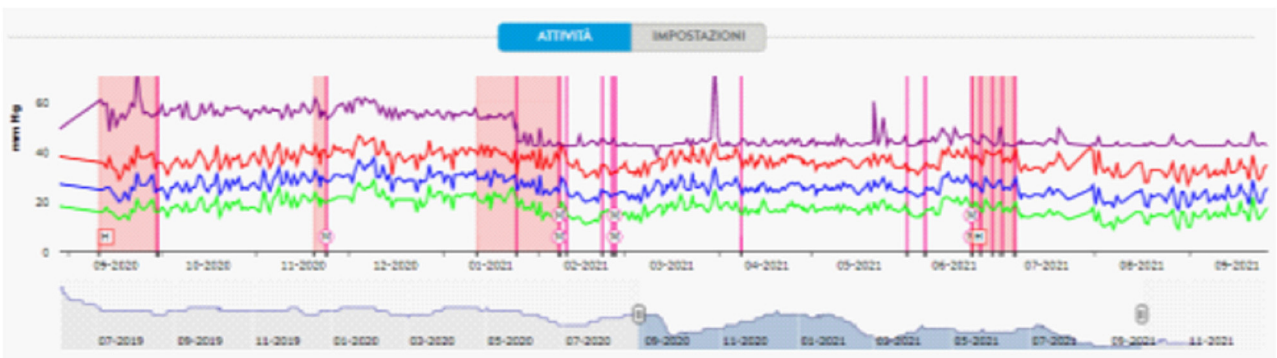

FIGURE 4 | Pulmonary artery pressure tracing detected by CardioMEMS. Starting from September 2020, there was a progressive shortening of the time between hospitalizations (pink squares) for levosimendan infusions. Pulmonary artery pressure tracing showing a mean diastolic PA drop after Optimizer Smart® implantation (January 2021). M and/or purple lines, remote therapy modifications; H, hospitalization.

ventricular refractory period of the heart cycle supplied by two leads placed on the RV septum (5). Contrary to other electrical stimulation, such as pacemaker therapy (CRT-P) or implantable cardioverter defibrillators (CRT-D), CCM does not affect the cardiac rhythm directly.

In particular, CCM improves calcium handling, reverses the fetal myocyte gene program associated with HF, and fosters reverse remodeling (5, 9, 16), through molecular remodeling and restoration of intracellular Ca2+ regulatory proteins, such as SERCA2a, phospholamban, and RyR2 (17). Furthermore, the HF gene expression profile was found to be reversed (toward normality) in patients who received the device (17). Moreover, the CCM therapy does not increase myocardial oxygen consumption but instead improves functional capacity (as measured by peak VO2 and 6MWT distance) and quality of life (as measured by MLWHFQ score) in patients with HF (5). In addition, the beneficial effects of CCM appear to be independent of HF etiology and QRS duration (18–21). These positive effects of CCM retain up to 3 years of follow-up, with a reduction in HF hospitalizations and improvements in functional status and quality of life extended at least through 24 months (22).

Finally, the FIX-HF-5C study showed an 89.7% complication-free rate, which achieved the primary safety endpoint (20). Specifically, the safety/adverse events included 5 events of lead dislodgements, 1 deep vein thrombosis, and 1 generator erosion resulting in pocket stimulation that required pocket revision and replacement of pacemaker leads (20). Subsequently, in the FIX-HF-5C2 study, there were decreased Optimizer-related

adverse events with the 2-lead system compared with the previous 3-lead system (0% vs. 8%; $p = 0.03$) (23); specifically, complication rates mirror those of dual-chamber pacemaker procedures (13).

CONCLUSION

In our case report, following the Optimizer Smart® implantation, we observed a reduction of the HF hospitalizations (scheduled and not scheduled), reduction of the diuretic dosage, and reduction in pulmonary artery pressures. The effective decrease of pulmonary pressures brought by the Optimizer Smart® implantation was recorded and witnessed by the CardioMEMS device.

Consequently, our case supports the "real-world" effectiveness and feasibility of this multistep approach for the management of advanced HF.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

VV and MC: conceptualization, formal analysis, investigation, resources, writing–original draft, and writing–review and editing. VV, CE, MM, GG, CV, and MC: data curation. AF: writing–review and editing. All authors have discussed, read, and approved the submission of this manuscript for publication.

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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.2022.874433/full#supplementary-material

Supplementary Figure 1 | Optimizer Smart® interrogation after 4 weeks. The percentage of beats receiving CCM impulse delivery was 99.9%.

Supplementary Table 1 | Timeline of the case. HF, heart failure; EF, ejection fraction, CRT-D, biventricular ICD; OMT, optimal medical therapy; PAP, pulmonary artery pressure.

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Conflict of Interest: AF is a full-time employee of Impulse Dynamics where Optimizer Smart® was discovered and developed.

The remaining 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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CASE REPORT
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Sustained Hemodynamic and Clinical Improvements for a Patient With Idiopathic Pulmonary Arterial Hypertension Over 1.5 Years After Balloon Atrial Septostomy: A Case Report

Kae-Woei Liang[1,2,3] *and Kuo-Yang Wang*[4]*

[1] Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan, [2] School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, [3] School of Medicine and School of Life Science, National Chung Hsing University, Taichung, Taiwan, [4] Center for Pulmonary Arterial Hypertension and Pulmonary Vascular Disease, China Medical University Hospital, Taichung, Taiwan

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Edited by:
Xin Jiang,
Peking Union Medical College Hospital (CAMS), China

Reviewed by:
Dan Nistor,
Târgu Mureş Emergency Institute for Cardiovascular Diseases and Transplantation (IUBCVT), Romania
Xin Pan,
Shanghai Jiaotong University, China

***Correspondence:**
Kuo-Yang Wang
wky830@gmail.com

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Balloon atrial septostomy (BAS) is an indicated treatment for subjects with idiopathic pulmonary arterial hypertension (IPAH), particularly for those with advanced right heart failure before bridging to lung transplantation. The mid-term clinical and hemodynamic benefits of BAS are not well studied. Here, we present a young female patient with IPAH who received maximal target medication and was admitted to our hospital due to advanced right heart failure. She had transition of subcutaneous to intravenous (IV) prostacyclin analogs (PA) injection and was registered for lung transplantation. The baseline mean right atrium (RA) pressure was 14 mmHg. BAS was performed with a balloon of 6 mm under intracardiac echocardiography (ICE) guidance. Systemic cardiac output (CO) (2.9–3.5 L/min) and oxygen delivery (OD) (291–318 ml/min) both increased after the BAS. Right heart failure was alleviated to function class II. One and a half years later, she received cardiac catheterization again. The second baseline mean RA pressure was 5 mmHg, left atrium (LA) pressure was 2 mmHg, and systemic CO was 3.3 L/min. These data indicated sustained hemodynamic improvements. The second course of BAS was performed under ICE guidance with a balloon of 8 mm. After the second BAS, her RA pressure was 3 mmHg, LA pressure was 3 mmHg, and CO was 3.4 L/min. In conclusion, BAS and IV PA infusion were effective in maintaining mid-term hemodynamic benefits and in stabilizing the critical right heart failure in a patient with IPAH over a 1.5-year period.

Keywords: balloon atrial septostomy (BAS), idiopathic pulmonary arterial hypertension (IPAH), intracardiac echocardiography (ICE), prostacyclin analogs, case report

INTRODUCTION

Balloon atrial septostomy (BAS) in an indicated (class IIb) treatment option for patients with idiopathic pulmonary arterial hypertension (IPAH) with concurrent advanced right heart failure before bridging to lung transplantation (1). Lung transplantation has a higher mortality in IPAH compared to other conditions and is unavailable for majority of patients in many parts of the world

(2). Recent meta-analysis confirmed immediate hemodynamic benefits of BAS, including reduction of right atrium (RA) pressure and increases of systemic cardiac output (CO) and oxygen delivery (OD) (3). However, its mid-term clinical and hemodynamic benefits are rarely reported. Herein, we present a young female with IPAH having received maximal target medication and was admitted due to advanced right heart failure. She received conversion of continuous infusion of prostacyclin analogs (PA) from subcutaneous to intravenous (IV) route plus BAS to rescue her from severe right heart failure episode. One and a half years later, hemodynamic data from cardiac catheterization confirmed both well maintained reduction of RA pressure and increases of systemic CO and OD.

CASE PRESENTATION

A 37-year-old woman with IPAH had received maximal target medications including oral phosphodiesterase type-5 inhibitor, endothelin receptor antagonist, and subcutaneous PA (treprostinil) injection. Other than IPAH, she had no remarkable past medical history. In April 2020, she developed worsening right heart failure with peripheral edema, oliguria, and hypotension (1st index admission). Upon admission, her systolic blood pressure was 92/76 mmHg, pulse rate was 107 beats/min, pulse oximetry was 91% in room air, and respiratory rate 20/min. Physical examinations revealed a jugular venous giant V wave with estimated central venous pressure $\geq$ 20 cmH_2O, a grade II pansystolic murmur, and a palpable heave at the left lower sternal border. Laboratory data showed anemia with hemoglobin 7.8 g/dL, hypokalemia 3.0 mEq/L, and elevated NT-pro BNP of 4,138 g/dL. Trans-thoracic echocardiogram revealed a marked dilated RA and right ventricle (RV), in addition to a small and compressed left atrium (LA) and left ventricle (LV) (**Figure 1A**). She had a transition of subcutaneous to IV PA injection via a peripherally inserted central catheter (PICC) and was registered for a lung transplantation waiting list. On the 7th

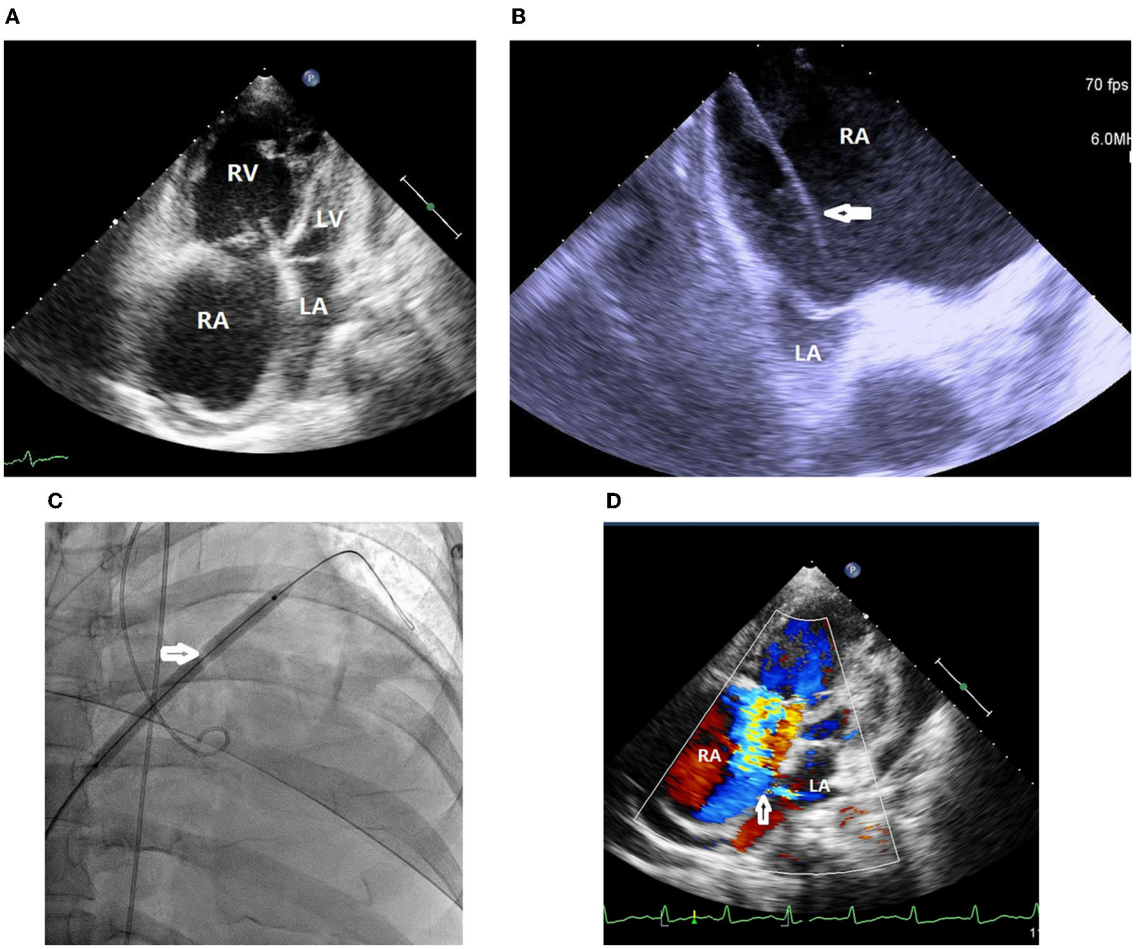

FIGURE 1 | (A) Trans-thoracic echocardiogram revealed marked dilated right atrium and right ventricle in addition to small and compressed left atrium and left ventricle. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle. **(B)** Intracardiac echocardiogram (ICE) showed marked dilated right atrium and small compressed left atrium. A transseptal Brockenbrough needle and a Mullins sheath (white arrow) was probing the inter-atrial septum with a tenting sign. RA, right atrium; LA, left atrium. **(C)** The atrial septum was dilated with a 6 mm $\times$ 8 cm balloon (white arrow). **(D)** Transthoracic echocardiogram confirmed the establishment of an inter-atrial shunt from right to left (white arrow). RA, right atrium; LA, left atrium.

day of admission, we performed standard right and left heart catheterization. The baseline mean RA pressure was 14 mmHg, aortic oximetry was 96% under oxygen supply at 3 L/min through a nasal cannula, systemic CO was 2.9 L/min, and systemic OD was 291 cc/min (**Table 1**). An intracardiac echocardiogram (ICE) catheter (AcuNac catheter, Siemens, Mountain View, CA, USA) was introduced via the left femoral vein into RA, and the image was displayed on an ACUSON SC 2000 System (Siemens, Mountain View, CA, USA). Using real-time ICE guidance, the inter-atrial septum and fossa ovalis were clearly visualized. We used a transseptal Brockenbrough needle and a Mullins sheath (Medtronic, Minneapolis, MN, USA) to probe the inter-atrial septum before entering the LA cavity under ICE guidance (**Figure 1B**). The atrial septum was subsequently dilated with a 5 mm × 8 cm and 6 mm × 8 cm Mustang balloon (Boston Scientific, MA, USA) (**Figure 1C**). After BAS, systemic CO was increased to 3.5 L/min and OD to 318 mL/min, while the systemic arterial oxygen saturation was dropped down to 87% (under nasal cannula 3 L/min oxygen supply) (**Table 1**). However, we observed no immediate fall of the RA pressure (**Table 1**). Transthoracic echocardiogram confirmed the establishment of an inter-atrial shunting from right to left (**Figure 1D**). After BAS in conjunction with continuous IV PA infusion, her heart failure symptoms were alleviated to function II. Her symptoms remained stable thereafter. One and a half years later, she was re-admitted for changing the PICC and to receive cardiac catheterization again as well. ICE confirmed the presence of an interatrial shunt created by previous BAS (**Figure 2A**). The second baseline hemodynamic data revealed mean RA pressure of 5 mmHg, LA pressure of 2 mmHg, and systemic CO of 3.3 L/min and OD of 403 mL/min. The findings were in support of the sustained hemodynamic improvements (**Table 1**). The second course of BAS was done with an 8 mm balloon (**Figure 2B**). ICE showed increased shunting from right to left after the second BAS (**Figure 2C**). Post second BAS catheterization measurements revealed mean RA pressure of 3 mmHg, LA pressure of 3 mmHg, systemic CO 3.4 L/min, and OD of 420 cc/min (**Table 1**). She was discharged with stable functional II symptoms.

TABLE 1 | Hemodynamic parameters before and after balloon atrial septostomy in a patient with idiopathic pulmonary arterial hypertension.

	Baseline (May 5, 2020)	Post-1st BAS (May 5, 2020)	2nd Baseline (Oct. 26, 2021)	Post 2nd BAS (Oct. 26, 2021)
Arterial O_2 saturation (%) under O_2 3 L/min	96%	87%	95%	96%
PA pressure (s/d/m, mmHg)	79/39/56	87/45/61	59/37/47	57/35/45
PVR (Wood unit)	17.5	19.2	15	14
Systemic cardiac output (L/min)	2.9	3.5	3.3	3.4
Qp/Qs	1	0.85	0.9	0.9
Hemoglobin (g/dL)	7.8	7.8	9.6	9.6
Systemic oxygen delivery (ml/min)	291	318	403	420
RA pressure (mean, mmHg)	14	14	5	3
LA pressure (mmHg)	6	4	2	3

BAS, balloon atrial septostomy; LA, left atrium, PA, pulmonary artery; PVR, pulmonary vascular resistance; Qp/Qs, pulmonary blood flow/systemic blood flow; RA, right atrium.

DISCUSSION

For IPAH with advanced right heart failure, the prognosis is poor (1). Regarding treatment options, continuous IV PA infusion is indicated (1). BAS creates a right-to-left inter-atrial shunt which decompresses the right heart and increases the preload of the left heart (4, 5). At the expense of reducing systemic arterial oxygen saturation, the systemic CO and OD are increased (4, 5). Case reports, case series, and meta-analysis reported immediate hemodynamic benefits of BAS (3–5). Fewer reports were published on the mid-term hemodynamic benefits of BAS (6). Our present case study found sustained hemodynamic improvements, including lower RA pressure and higher CO and OD, and also a sustained functional recovery to II at 1.5 years after the treatments of BAS and IV PA. This corroborates that BAS is a bridging treatment option before lung transplantation becomes available.

From the time of disease diagnosis of pulmonary arterial hypertension, the 5-year survival rate is very poor (57%) as revealed by historical data from the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL registry) (7). Subjects with IPAH and advanced right heart failure admitted to the intensive care unit (ICU) have a 41% mortality rate (1, 8). Chiu et al. (9) reported that patients with severe PAH receiving BAS had a 66% of 1-year transplant-free survival. Since there is no randomized control trial demonstrating survival benefits of BAS, the role of BAS in IPAH is limited and can serve as a bridging option before lung transplantation. This case showed a possible mid-term survival benefit conferred by BAS and IV PA infusion for a patient with IPAH who had been admitted to ICU due to advanced right heart failure while on a queue list for lung transplantation.

For this patient, we added procedural refinements to improve the safety and efficacy of BAS. First, we followed the existing guidelines and literature to perform a graded septum dilatation (1, 6, 10). Our patient received 5, 6 mm balloon dilatation in the first BAS session and 7, 8 mm balloon dilatation in the second BAS session at an inter-session interval of 1.5 years. Second, the current guidelines and literature suggest avoiding very high-risk scenarios, such as mean RA pressure > 20 mmHg or room air pulse oximetry < 85% (3, 6, 10). The patient was treated in line with the current recommendations. Third, we used ICE to guide the interatrial septum puncture, providing an instant clear view of the septum tenting sign (**Figure 1B**) and sparing the need for transesophageal echocardiogram and tracheal intubation (4, 5).

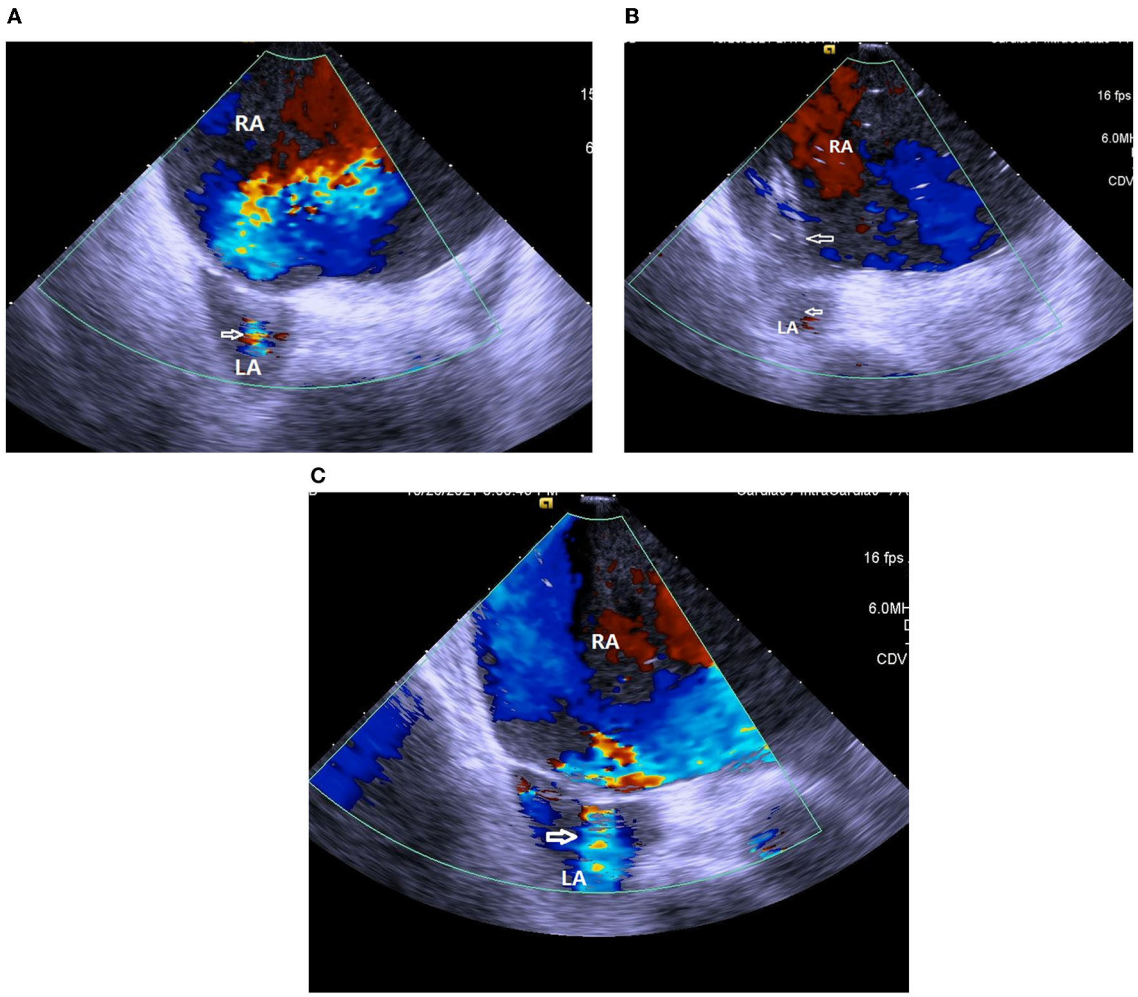

FIGURE 2 | (A) ICE confirmed the presence of interatrial shunting (white arrow) created by previous balloon atrial septostomy. RA, right atrium; LA, left atrium. **(B)** ICE showed inflation of an 8 mm balloon (white arrows) at the second session of balloon atrial septostomy. RA, right atrium; LA, left atrium. **(C)** ICE showed an increase of right to left shunting (white arrow) after second session of balloon atrial septostomy. RA, right atrium; LA, left atrium.

The cause of anemia in this patient could be multi-factorial. The first was a possible common side effect of fluid retention by endothelin receptor blocker (11). The second could be iron deficiency by menstruation blood loss. Her serum iron was low, around 20 μg/dl. She had received ferrous supplementation since 2017. Blood transfusion was done in the 1st index admission. The improvement of systemic oxygen delivery was in part due to correction of anemia.

We concluded that BAS and IV PA infusion are effective in maintaining mid-term hemodynamic benefits and stabilizing the critical right heart failure in IPAH patients over a 1.5-year interval. Such treatment is therefore a therapeutic option before lung transplantation.

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 patient signed informed consent for the publication of this report.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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CASE REPORT
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Benefits of a Supervised Ambulatory Outpatient Program in a Cardiovascular Rehabilitation Unit Prior to a Heart Transplant: A Case Study

*Antoine Poty[1,2], Florent Krim[3,4], Philippe Lopes[5], Yves Garaud[2] and Pierre-Marie Leprêtre[1,3,4]**

[1] Exercise Physiology and Rehabilitation Laboratory, Picardie Jules Verne University, Amiens, France, [2] Fundation Léopold Bellan, Chateau d'Ollencourt, Unit of Cardiac Rehabilitation, Tracy-le-Mont, France, [3] Service de Réadaptation Cardiovasculaire, Centre Hospitalier de Corbie, Corbie, France, [4] Association Picardie de Recherche en Réadaptation Cardiaque, Association Picardie de Recherche en Réadaptation Cardiaque, Corbie, France, [5] Laboratoire de Biologie de l'Exercice Pour la Performance et la Santé, Université d'Évry Val d'Essonne, Évry, France

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Edited by:
Martin Burtscher,
University of Innsbruck, Austria

Reviewed by:
Stephen C. Kolwicz Jr.,
Ursinus College, United States
Francesco Giallauria,
Federico II University Hospital, Italy
Prisca Eser,
University Children's Hospital Bern, Switzerland

***Correspondence:**
Pierre-Marie Leprêtre
pierre-marie.lepretre@u-picardie.fr

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Preoperative peak oxygen uptake ($\dot{V}O_{2peak}$) and ventilatory efficiency ($\dot{V}_E/\dot{V}CO_2$slope) are related to the vital prognosis after cardiac transplantation (HTx). The objective of our study was to evaluate the effects of exercise-based cardiac rehabilitation (ECR) program on the preoperative exercise capacity of a HTx candidate. A male patient, aged 50–55 years, with chronic heart failure was placed on the HTx list and performed 12 weeks of intensive ECR (5 sessions-a-week). Our results showed that the cardiac index continuously increased between the onset and the end of ECR (1.40 vs. 2.53 $L.min^{-1}.m^2$). The first 20 sessions of ECR induced a $\dot{V}O_{2peak}$ increase (15.0 vs. 19.3 $ml.min^{-1}.kg^{-1}$, corresponding to 42.0 and 53.0% of its maximal predicted values, respectively). The peak $\dot{V}O_2$ plateaued between the 20th and the 40th ECR session (19.3 vs. 19.4 $ml.min^{-1}.kg^{-1}$) then progressively increased until the 60th ECR session to reach 25.7 $ml.min^{-1}.kg^{-1}$, i.e., 71.0% of the maximal predicted values. The slope of $\dot{V}_E/\dot{V}CO_2$ showed a biphasic response during the ECR program, with an increase between the onset and the 20th ECR session (58.02 vs. 70.48) and a decrease between the 20th and the 40th ECR session (70.48 vs. 40.94) to reach its minimal value at the 60th ECR session (31.97). After the first 40 sessions of the ECR program, the Seattle Heart Failure Model score predicted median survival time was estimated at 7.2 years. In conclusion, the improvement in exercise capacity and cardiorespiratory function following the ECR helped delay the heart transplant surgery in our patient awaiting heart transplantation.

Keywords: transplant, preoperative aerobic capacity, rehabilitation, vital prognostic, cardiac patient

INTRODUCTION

Cardiac transplantation is the treatment of choice for many patients with end-stage heart failure who remain symptomatic despite optimal medical therapy. For carefully selected patients, heart transplantation offers markedly improved survival and quality of life (1). Khush et al. reported that the functional status after heart transplantation remained very good compared to living with advanced heart failure. Indeed, over 70% of recipients could perform normal daily life activities with no or minimal symptoms (2). Post-transplant survival also improved over time. The median survival time after adult heart transplants increased from 12.5 years in 2002 to 14.8 years in 2009 among 1-year survivors (2). However, comorbidities in patients with heart failure, like arterial high blood pressure, lung and kidney damage, or chronic obstructive pulmonary disease (COPD) raised the question of the transplantation procedure and the long-term patient's outcome. Additionally, heart transplantation requires a sufficient number of donors, the induction and the maintenance of immunosuppressants, lipid-lowering medication, and vasodilators used in cardiac disease, which diminish peak oxygen uptake ($\dot{V}O_{2peak}$) (3–5). The $\dot{V}O_{2peak}$, expressed in absolute or in% of the theoretical maximal value of the patient, is also used for heart transplantation referral (6, 7). Patients showing a $\dot{V}O_{2peak}$lower than 50% of predicted should be seriously considered for transplantation (8). Similarly, patients showing a $\dot{V}O_{2peak}$ greater than 60% of predicted should not warrant listing as transplant candidates in the absence of other significant risk factors, including unresponsiveness to drug therapy (8, 9).

Non-pharmacological strategies have been recommended to improve exercise capacity at the preoperative stage (10). Prior cardiac surgery and the use of implanted devices were associated with increased 1- and 5-year mortality (2). Fonarow et al. also found that the combination of optimized medical therapy and regular physical activity performed below the anaerobic threshold (AnTh) induced an increase in $\dot{V}O_{2peak}$ in heart transplant candidates (11). Namely, optimized medical therapy and regular physical activity reduced hospital admission rate in patients who led to complete 6 months of follow-up and a significant increase in functional capacity responses: 49% of 179 patients have been downgraded from New York Heart Association (NYHA) class III or IV before referral to I or II after 6 months of follow-up (11). This conclusion should be taken with caution because the results depended on the patient care model. Cardiac rehabilitation programs are aimed at limiting the psychological and physiological stresses of cardiovascular disease, optimizing cardiovascular risk reduction, reducing disability, and improving cardiovascular function to achieve the highest quality of life possible in patients (12). However, Leprêtre et al. (13) emphasized that the numerous models of care for heart disease could explain the low-level evidence for the beneficial effects of ECR (14). Moreover, ECR is, to our knowledge, mostly proposed in secondary prevention for heart transplant candidates (15). To our knowledge, only Gimeno-Santos et al. showed beneficial effects on functional and exercise capacity in patients waiting for heart transplantation (16).

It has been established that preoperative exercise capacity is a predictor of vital prognosis after transplantation in patients with cardiac insufficiency (17). Reduced exercise tolerance observed in chronic heart failure was mainly attributed to impaired skeletal muscle function (18, 19), which was indirectly evaluated by ventilatory efficiency, i.e., the slope of$\dot{V}_E/\dot{V}CO_2$ slope, during a cardiopulmonary exercise test (CPET) (20). Hence, the $\dot{V}_E/\dot{V}CO_2$ slope is an additional parameter that has to be considered together with $\dot{V}O_{2peak}$, for estimating the exercise capacity and patient outcome (21, 22). Thus, the objective of this study was to evaluate the effects of an exercise-based cardiac rehabilitation program on the preoperative exercise capacity of a heart transplant candidate, evaluated from $\dot{V}O_{2peak}$ and the ventilatory efficiency. We hypothesized that a short exercise program based on cardiac rehabilitation could delay heart transplantation by improving prognosis with an increased functional capacity in a patient with end-stage heart failure.

METHODS

Subject

A male patient, aged 50–55 years and placed on a heart transplantation list, was admitted for full hospitalization to perform a cardiac rehabilitation exercise program following seven heart failure relapses during the first half of 2018. This dyslipidemic patient with chronic obstructive pulmonary disease (NYHA class II dyspnea), had, at the beginning of the exercise-based cardiac rehabilitation program, severe ischemic heart disease with a dilated and hypertrophic left ventricle (LV), a bi-ventricular dysfunction (Tricuspid annular plane systolic excursion, i.e., TAPSE: 6.0 mm) with impaired right ventricular systolic function, moderate grade 2 mitral insufficiency, a significant grade 3 diastolic dysfunction, and a chronic tendency to hypotension (systolic blood pressure $\simeq$ 80–90 mmHg). These complications followed a myocardial infarction that occurred 5 years previously resulting in the insertion of a triple-chamber defibrillator, three stents, and a resynchronization. At presentation, he was a sedentary former smoker and former drinker. The Seattle Heart Failure Model (SHFM) score predicted a median survival time of 1.5 years. His height, weight, and body mass index (BMI) were 180 cm, 61.0 kg, and 18.8, respectively. His medication consisted of a diuretic (125 mg.day^{-1}), an aldosterone inhibitor (50 mg.day^{-1}), a beta-blocker (3.75 mg.day^{-1}), a hyper polarization-activated cyclic nucleotide-gated (HCN) inhibitor (5 mg, twice a day), and Entresto® (24/26 mg, two times daily). Before participation, the subject was informed of the risks and discomforts associated with the protocol and gave his written informed consent in accordance with the local ethics committee approval and the Ethical Standards in Sport and Exercise Science Research published in the International Journal of Sports Medicine (23). Written informed consent was obtained from the patient for the publication of any potentially identifiable data included in this article according to the CARE guidelines (24).

Protocol

A resting cardiac ultrasound (Vivid 9 Digital Ultrasound System Echocardiograph, General Electric Health Company, Boston, United States) and an incremental exercise test with gas exchange measurements were performed before (T_0), as well as after 20 (T_1), 40 (T_2), and 60 (T_3) sessions of exercise-based cardiac rehabilitation. LV volume and left ventricular ejection fraction (LVEF) were calculated using classical methods previously described by Shah et al. (25). The right ventricle contractile reserve was measured by changes in the tricuspid annular plane systolic excursion (TAPSE) (26). The cardiopulmonary exercise test (CPET) was performed on a bicycle ergometer (Ergoselect 200, Ergoline GmbH, Bitz, Germany) using a ramp protocol with increments of 10 w.min^{-1} which was followed by a 3-min loaded pedaling cool down and a 2-min passive recovery in sitting position. Oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}_E$) were measured using a breath-to-breath gas analyzer (Jaeger Vyntus® CPX, Carefusion, Hoechberg, Germany). The $\dot{V}O_2$peak was defined as the highest oxygen up takeover in any 15-s period, and the ventilatory efficiency was obtained from the $\dot{V}_E/\dot{V}CO_2$ slope (27). These values were expressed using the international unit system and as a percentage of maximal predictive values (28). Finally, the anaerobic threshold (AnTh) was determined as the breakpoint of the$\dot{V}CO_2$curve against $\dot{V}O_2$ plot (V-slope method) and expressed in absolute and in percentage of measured peak values (29). A 10-ml venous blood sample was drawn into an EDTA tube to assay plasma N-terminal fragment of the pro-brain natriuretic peptide (NT-proBNP) and to estimate natremia and glomerular filtration rate based on creatinine and patient characteristics (GFR by MDRD) (30, 31). The patient prognosis was assessed by the SHFM score (32).

Exercise-Based Cardiac Rehabilitation

The cardiac rehabilitation program followed the usual care recommendations (33, 34). The training sessions consisted of a 30-min continuous cycling exercise (Ergoselect 200, Ergoline GmbH, Bitz, Germany) at a steady power output equivalent to 100% of AnTh on 5 days per week. The patient was instructed to maintain a 60-rpm pedaling rate. Each cardiac rehabilitation session was complemented by a 30-min health therapy education, 30-min stretching exercises on the floor, and 60-min walking, 5 days a week, in accordance with current French society of cardiology standards (33). Exercise intensity was adjusted according to the CPET results conducted every 4 weeks.

RESULTS

Medical treatment did not change during the intervention period. **Table 1** presents the data on resting cardiac parameters and renal function. The baseline cardiac index was almost two times lower than the normal value. During the ECR program, the cardiac index increased from 1.40 to 2.53 L.min^{-1}.m^{-2}after 60 ECR sessions. However, LV remained dilated (92 vs. 88 mm) with an altered ejection fraction—visually assessed at 15 and 20%, at the onset and at the end of ECR program, respectively. TAPSE also increased from 6.0 to 17.8 mm, which approached the normal values in adults (i.e., 18.0 mm) at the end of the ECR program. NT-proBNP (T_0: 1,267 vs. T_3: 877 pg.ml^{-1}), GFR by MDRD (T_0: 100.59 vs. T_3: 92.04 ml.min^{-1}), and natremia (T_0: 136 vs. T_3: 140 mmol.L^{-1}) changes induced by the ECR program showed that the renal function was preserved throughout the whole ECR program. **Figure 1** illustrates the cardiorespiratory responses to the ECR. At baseline, $\dot{V}O_2$peak and maximal heart rate (HR) were 15.0 ml.min^{-1}.kg^{-1} and 95 beats.min^{-1}, which corresponded to 42.0 and 57.0% of the maximum predicted values, respectively. These peak values were reached at a maximal tolerated power (MTP) equal to 70 w (i.e., 42.0% of the predicted value). The first 20 sessions of ECR (between T_0 and T_1) induced an increase in MTP (70 vs. 90w), $\dot{V}O_{2peak}$ (15.0 vs. 19.3 ml.min^{-1}.kg^{-1}), and peak HR (95 vs. 106 beats.min^{-1}) reaching 54.0% of MTP and $\dot{V}O_{2peak}$ predicted values and 63.0% of maximal theoretical HR at T_1. Then, the cardiorespiratory measurements remained stable between the 20th and the 40th ECR session ($\dot{V}O_{2peak}$: 19.3 vs. 19.4 ml.min^{-1}.kg^{-1}, maximal HR: 106 vs. 106 beats.min^{-1} and MTP: 90 vs. 90 W, for T_1 and T_2, respectively). Thereafter, the$\dot{V}O_{2peak}$ progressively increased until the end of ECR to reach 25.7 ml.min^{-1}.kg^{-1} at T_3, corresponding to 71.0% of the predicted value. The MTP was 120 W, which was also consistent, reaching 71.0% of the maximal predicted power value. Additionally, the ECR program induced a decrease in resting HR and an improvement in cardiorespiratory parameters with a decrease in AnTh. Consequently, baseline $\dot{V}O_{2peak}$ and MTP were slightly lower than the $\dot{V}O_2$, and the mechanical power associated with AnTh was determined at the end of the ECR program. The slope of $\dot{V}_E/\dot{V}CO_2$ showed a biphasic response following the ECR program, with an increase between the baseline and the 20th ECR session (58.02 vs. 70.48 for T_0 and T_1, respectively) then the slope of $\dot{V}_E/\dot{V}CO_2$ decreased between T_1 and the 40th ECR session (70.48 vs. 40.94, T_1 and T_2, respectively) to show its lowest value after 60 ECR sessions (T_3: 31.97). Finally, the SHFM predicted median survival time increased from 1.5 to 7.2 years at the end of the 40 sessions of ECR (i.e., T_2).

DISCUSSION

Heart transplantation is an established therapy for end-stage heart failure that aims to improve the survival and quality of life of transplant recipients (1, 35). However, challenges still exist. First, the number of patients referred for heart transplantation continues to increase at a rate well beyond the number of available donors (9). Additionally, some complications such as impaired skeletal muscle function or organ rejection, occur (5, 35, 36). Some patients with heart transplant also present physical exercise intolerance. In their review, McMahon et al. (37) reported that $\dot{V}O_2$peak remained 70% lower in transplanted patients compared to age-matched controls. The reduced $\dot{V}O_2$peak may be related to heart and locomotion skeletal muscle dysfunction (metabolic abnormalities and atrophy) as a result of heart failure (36). Meta-analysis studies provided evidence that ECR benefits patients with heart failure (37). However, few studies, to our knowledge, described the effects of ECR programs on

exercise tolerance of end-stage heart failure patients awaiting heart transplantation (11, 16). The goal of our study was to evaluate the ECR program's effects on the preoperative exercise capacity of a heart transplant candidate. Our main result showed that the ECR program increased the exercise tolerance of our end-stage heart failure patient. We also found a disassociation in the training responses of$\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$ slope. First, we are going to discuss the effects of the ECR program on resting heart responses and NT-proBNP values.

Plasma NT-proBNP values are widely used in clinical practice to evaluate the severity of heart failure. While NT-proBNP may serve as an indicator of exercise tolerance in chronic heart failure (38), a previous systematic review reported beneficial effects of aerobic exercise training on NT-proBNP in patients with heart failure who performed a similar training to our subject (39). A tight relationship was found between NT-proBNP and resting HR in the elderly (40). In total, 60 sessions of our ECR program based on French national recommendations induced an improvement in NT-proBNP associated with a decrease in resting HR in our patient. It was established that the decrease in resting HR was inversely associated with cardiovascular morbidity and mortality (41). However, our finding should be considered with caution. It was recommended to measure resting HR in the supine position (42), but in our study, the resting HR measurement was carried out in a sitting position just before the CPET. Two important cardiac predictors of exercise capacity, i.e., the TAPSE and the cardiac index, were improved with the ECR program and approached normal values. A significant correlation was previously found between NT-proBNP and TAPSE in 60 patients with chronic heart failure (43). Furthermore, Nakano et al. observed a significant positive correlation between TAPSE and cardiac index in patients (44).

It was therefore not surprising to observe the $\dot{V}O_2$ peak improvement (+ 71.3%) and the increased $\dot{V}O_2$ at the anaerobic threshold in our patient. Gimeno-Santos et al. recently showed the beneficial effects of 16 exercise sessions (i.e., two times a week throughout an 8-week training program) on $\dot{V}O_2$ peak (+ 27.0 ± 45.0%) in 11 patients placed on a heart transplantation list (16). Troisi et al. (43) observed that chronic heart failure patients with TAPSE greater than 16.0 mm had higher $\dot{V}O_2$peak and $\dot{V}O_2$ at AnTh. TAPSE was independently and significantly associated with $\dot{V}O_2$peak, whereas resting LVEF was not (45). Together, these results suggested that the increase in exercise capacity with the ECR program, supported by the increased $\dot{V}O_2$peak and submaximal $\dot{V}O_2$ at AnTh, was partly due to structural and functional cardiac modifications without obvious improvements in resting LVEF. This could also explain the disassociation between $\dot{V}O_2$peak and ventilatory efficiency responses to the exercise-based cardiac rehabilitation in our patient. The cardiac index and TAPSE increase observed from T_0 to T_2 provide further evidence for the positive exercise training structural and functional effects on the cardiovascular system in our end-stage heart failure patient awaiting transplantation as previously observed (46, 47). Giallauria et al. previously showed a significant correlation between the changes in NT-proBNP at rest and LV volumes after 6 months of exercise training in cardiac patients with moderate LV dysfunction (48). Then, the improvement in cardiac function associated with a slight decrease in plasma NT-proBNP concentration would have later resulted in an increase in $\dot{V}O_2$peak associated with a delayed $\dot{V}_E/\dot{V}CO_2$ slope decrease (48, 49).

Finally, our results showed that the ECR program induced an increase in peak HR, which was associated with an HR decrease at rest. The difference between peak exercise and resting HR, called HR reserve (HRR), was classically used to evaluate chronotropic responses (50). It was recommended to measure resting HR in a supine position (42). The measurement of HR recovery could be an alternative solution. Defined as the difference between peak HR and HR obtained 1 min after exercise cessation (51), the HR recovery is however, dependent on post-exercise recovery modalities (52, 53). In the present study, HR recovery was probably affected

TABLE 1 | Changes in renal function and resting cardiac parameters induced by the ECR program.

	Normal values	T_0	T_1	T_2	T_3
Predicted median survival time (SHFM score)	15.2	1.5			7.2
Echocardiographic parameters					
Cardiac index, $L.min^{-1}.m^{-2}$	3.2–3.8	1.40	1.69	2.44	2.53
LVEF,%	62.8 ± 4.8	15	15	20	20
LV end-diastolic volume, mL	104.2 ± 25.1	240.0	309	366.7	222.7
LV end-systolic volume, mL	38.8 ± 11.2	204.0	262.7	290.4	179.4
LV dilatation, mm	42–58	92	120	87	88
LA area, cm^2	16.5 ± 3.2	51.2	36.3	29.5	36.0
LA volume, mL	52.5 ± 14.4	116	74.7	66.8	74.1
RA area, cm^2	14.5 ± 3.2	27.0	12.4	17.0	12.3
RA volume, mL	44.5 ± 15.6	61.2	28.2	38.6	38.0
RV end-diastolic area, cm^2	18.1 ± 3.9	–	–	–	–
RV end-systolic area, cm^2	10.1 ± 3.0	–	–	–	–
TAPSE, mm	>16	6.0	17.8	11.4	17.8
Blood data					
Hemoglobin, $g.dL^{-1}$	13–18	11.8	11.8	13.5	13.9
NT-proBNP, $pg.mL^{-1}$	<125	1,267	861	689	877
GFR by MDRD, $mL.min^{-1}.1.73\ m^2$	≥90	100.59	74.76	84.76	92.04
Natremia, $mmol.L^{-1}$	136–145	136	134	140	140

LV and RV are left and right ventricles, respectively. LA and RA are left and right atriums, respectively. LVEF is the acronym for the left ventricular ejection fraction, and TAPSE is the acronym for the tricuspid annular plane systolic excursion. NT-proBNP represents the N-terminal fragment of the pro-brain natriuretic peptide, and GFR by MDRD represents the estimated glomerular filtration rate based on creatinine and patient characteristics (age, race, gender, and plasma creatinine). SHFM is the acronym for the Seattle Heart Failure Model. Normal values corresponded to echocardiographic reference ranges published by Cohen and Soulat-Dufour (54) and in the NORRE study (55).

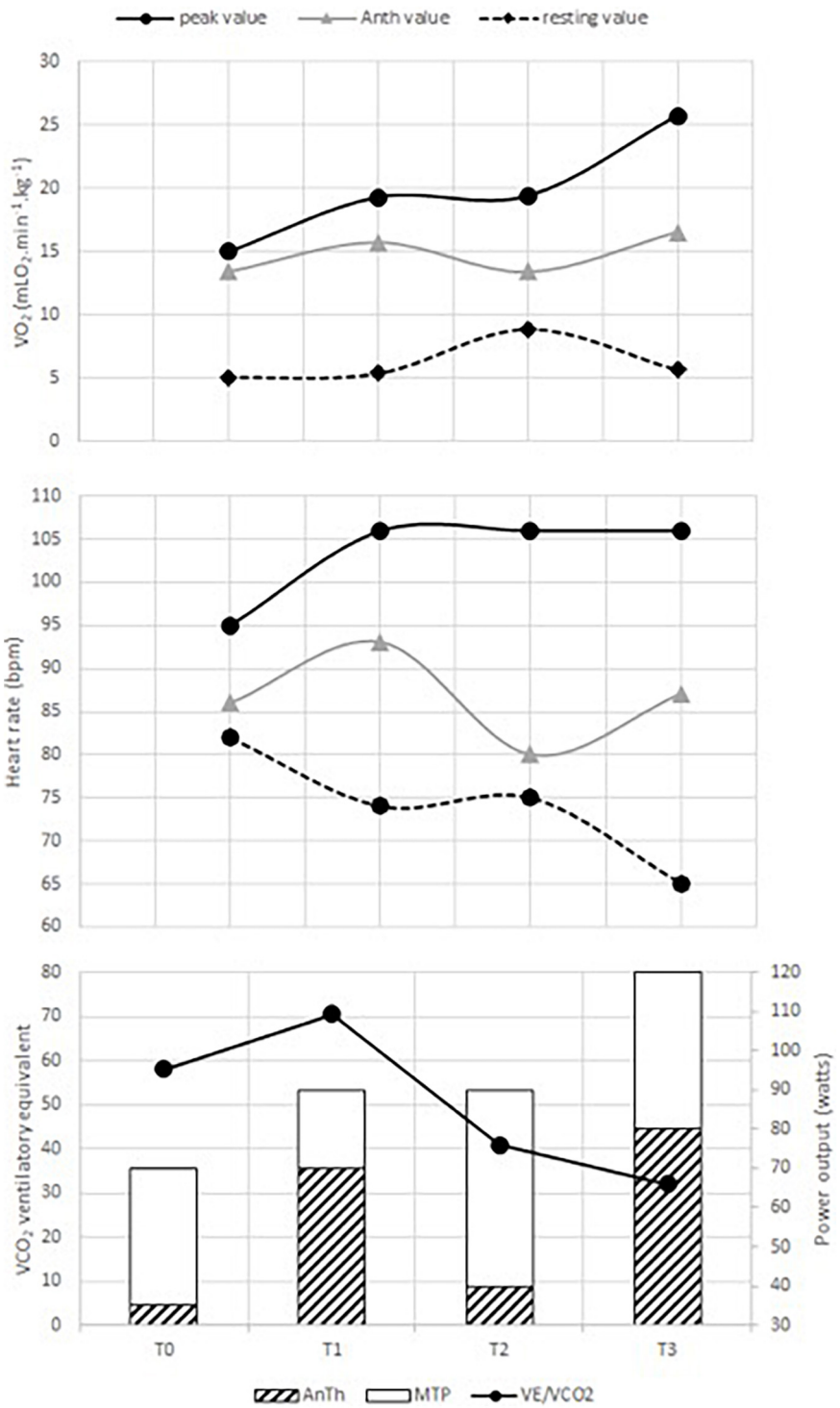

FIGURE 1 | Changes in cardiorespiratory responses induced by the exercise-based cardiac rehabilitation (ECR) program. AnTh is the acronym for anaerobic threshold. $\dot{V}O_2$, V_E/VCO_2, HR, and MTP represent oxygen uptake, ventilatory equivalent to CO_2, heart rate, and maximal tolerated power, respectively. T_0 is the time of the initial evaluation, T_1 and T_2, the times of the intermediate evaluation (after the first 20 and 40 sessions), and T_3, the time of the final evaluation.

by the 3-min unloaded pedaling of post-exercise recovery. Thus, it would be speculative in the current study to estimate HRR and HR recovery and conclude that the ECR program resulted in favorable changes in chronotropic function for our heart transplant candidate based simply on our HR measurements.

CONCLUSION

Despite some methodological limitations, our results, taken together, may explain the improvement in the Seattle Heart Failure Model score. Therefore, we can conclude that the improvement in exercise capacity and cardiorespiratory function following ECR helped delay the heart transplant surgery in our patient on the transplant waiting list.

Patient Outcome

Our patient continued to perform regular physical exercise until the first COVID19 lockdown when he completely stopped any form of physical activity. In January 2022, he was hospitalized for septic and cardiogenic shocks and died several days later.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Written informed consent was obtained from the relevant individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

P-ML, AP, YG, and FK contributed to conception and design of the study. FK and YG organized the database. AP and P-ML wrote the first draft of the manuscript. PL reviewed and edited all sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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CASE REPORT
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Case Report: Steroid-Responsive Takotsubo Cardiomyopathy Associated With Cytokine Storm and Obstructive Shock

Brent Gudenkauf[1], *Michael R. Goetsch*[1], *Rachit M. Vakil*[2], *Oscar Cingolani*[2] *and Luigi Adamo*[2]*

[1] Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2] Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, United States

A growing body of evidence suggests that inflammation may play a key role in the development of Takotsubo stress cardiomyopathy. Here, we report the case of a 63-year-old woman who presented with chest pain and was diagnosed with this cardiomyopathy. After an initial improvement, the patient experienced a systemic inflammatory response of unclear origin and deteriorated rapidly into obstructive shock. Her presentation was considered consistent with cytokine storm. She was, therefore, treated with steroids with rapid improvement in her clinical picture. She relapsed after the taper. Endomyocardial biopsy soon after initiation of pulse dose steroids showed macrophage and lymphocytic infiltration. This case highlights the potential intimate connection between systemic inflammatory response and Takotsubo stress cardiomyopathy and contributes to the evolving understanding of inflammation in the pathogenesis of this disease.

Keywords: stress cardiomyopathy, Takotsubo stress cardiomyopathy, heart failure, cytokine storm, obstructive shock

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Matteo Cameli,
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Jun Ren,
University of Washington, United States

****Correspondence:***
Luigi Adamo
ladamo2@jhmi.edu

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INTRODUCTION

Takotsubo stress cardiomyopathy is classically a transient, acute form of heart failure characterized by apical hypokinesis and hyperdynamic basal segments in the absence of coronary artery disease (1). It frequently occurs after an identifiable stressor, and it has been postulated that the pathogenic mechanism centers on catecholamine surge and resultant myocardial toxicity/dysfunction (2). However, one of the histologic hallmarks of stress cardiomyopathy is macrophage and lymphocytic infiltration of the myocardium (2, 3), and there are emerging data from both human studies and animal models indicating that inflammation plays a key role in the development of this syndrome (2–9). Recently, analysis of cardiotoxicity triggered by the rapid release of cytokines that occurs with cytokine release syndrome after CAR-T cell therapy has provided robust evidence that rapid elevation in the serum levels of inflammatory cytokines is associated with acute left ventricular dysfunction with Takotsubo features (10–12). The presence of a systemic inflammatory response at the time of diagnosis of Takotsubo stress cardiomyopathy has also been shown to be a negative prognostic factor. However, the role that systemic inflammation plays in the evolution of Takotsubo and the potential role of anti-inflammatory therapies in Takotsubo remain unknown (13). Here, we report a case of Takotsubo stress cardiomyopathy

that developed a systemic inflammatory response, cytokine storm, and hemodynamic collapse after initial presentation, which responded swiftly to pulse dose steroids. This case is unique as it provides insight into the role that systemic inflammation might play in the pathogenesis of this cardiomyopathy, and it highlights the potential role of anti-inflammatory drugs in the treatment of life-threatening hemodynamic compromise secondary to Takotsubo.

CASE DESCRIPTION

A 63-year-old woman presented to the emergency department with acute chest pain. The patient had well-controlled type 2 diabetes mellitus, hyperlipidemia, chronic migraines, anxiety, depression, gastroesophageal reflux disease, splenic and renal artery aneurysms, a right ovarian cyst, and ankylosing spondylitis (and she was on chronic immunosuppression for this). She was status post-cholecystectomy, bilateral saline breast implants, chin reduction, upper eye and facelift, and abdominoplasty.

She was in her usual state of health until that day when she developed aching deep chest pain, dyspnea, and migraine while at a grandchild's baseball game. She denied any strong emotions provoked by the baseball game itself and had no other current emotional stressors in her life. On arrival, she was tachycardic, with a regular rate at 148 beats/min, with a respiratory rate in the 20 s; blood pressure, 98/68 mmHg; and oxygen saturation, 98% breathing ambient air. Her jugular vein was distended, but examination of the cardiovascular, pulmonary, and other systems was otherwise normal.

Cross-sectional imaging excluded pulmonary embolism and aortic dissection. An electrocardiogram showed sinus tachycardia and ST-elevations in inferior leads. Troponin I was 14.1 ng/ml (reference range, RR, <0.4 ng/ml). The differential diagnosis of her presentation included takotsubo cardiomyopathy and acute coronary syndrome. She was, therefore, urgently transferred to the cardiac catheterization laboratory. A coronary angiogram showed no coronary disease. The left ventriculogram showed reduced ejection fraction (LVEF) to 20% and severe hypokinesis of the mid- and distal anterior, inferior, and apical walls with sparing of the base. Transthoracic echocardiogram showed normal left ventricular size; ejection fraction, 30%; and akinetic apical lateral/anterior/inferior and mid anterior septal/lateral wall segments with an aneurysmal appearance of the left ventricular apex. She was admitted to the cardiac care unit with a diagnosis of Takotsubo stress cardiomyopathy.

On admission, her white blood cell count (WBC) was 16,960/cubic mm, the erythrocyte sedimentation rate (ESR) was 8 mm/h (RR, 4–30 mm/h), and C-reactive protein (CRP) was 10.3 mg/dL (RR <0.5 mg/dL). The patient developed a fever on Hospital Day 1, which remained despite broad-spectrum antibiotics. Infectious workup was negative (**Table 1**).

TABLE 1 | Laboratory investigations.

Laboratory Study	Result	Reference range
Cardiac troponin	**14.1 ng/mL on admission, to 0.07 ng/mL**	<0.04 ng/mL
Pro-B-type natriuretic peptide	**3,327 pg/mL**	<125 pg/mL
White blood cell count	**16,960 cells/mL**	4,500–11,000 cells/mL
Hemoglobin	14.5 g/dL	12.0–15.0 g/dL
Creatinine	0.6 mg/dL	0.5–1.2 mg/dL
Antinuclear antibody	Negative	Negative
C3 complement	88.9 mg/dL	81–157 mg/dL
C4 complement	20.05 mg/dL	13–39 mg/dL
Interleukin 6	**94.8 downtrending to 5.1 pg/mL**	< 10 pg/mL
Interleukin 2 receptor	**2,344 pg/mL**	532–1,891 pg/mL
Serum IgA	181 mg/dL	61–348 mg/dL
Serum IgM	73 mg/dL	35–242 mg/dL
Serum IgE	110 kU/L	<114 kU/L
Serum IgG	557 mg/dL	610–1,616 mg/dL
Serum IgG_1	304 mg/dL	382–929 mg/dL
Serum IgG_2	129 mg/dL	242–700 mg/dL
Serum IgG_3	38.3 mg/dL	21.8–176.1 mg/dL
Serum IgG_4	2.3 mg/dL	3.9–86.4 mg/dL
Erythrocyte sedimentation rate	**57 downtrending to 30 mm/hr**	4–30 mm/hr
C-reactive protein	**10.3 mg/dL**	<0.5 mg/dL
Bacterial blood cultures	Negative	Negative
Fungal blood cultures	Negative	Negative
Urine cultures	Negative	Negative

Abnormal values are in bold.

She initially improved, but, on Hospital Day 5, she developed hypotension and recurrence of lactic acidosis (**Table 2**). Of note, the patient was not taking metformin prior to admission or while hospitalized. There was no significant left ventricular outflow tract (LVOT) gradient upon admission, but the patient developed a gradient of 61 mmHg at this time. A pulmonary artery catheter was placed and showed a mean right atrial pressure of 14 mmHg, mean pulmonary arterial pressure of 21 mmHg, mean pulmonary capillary wedge pressure of 18 mmHg, mixed venous oxygen saturation of 47%, cardiac output (CO) of 4.32 L/min, cardiac index (CI) of 2.5 L/min/m^2, pulmonary vascular resistance of 0.69 Woods units, and indexed systemic vascular resistance of 1,939 dynes-s/cm^5/m^2. She was started on phenylephrine to maintain cardiac output in the context of LVOT obstruction.

On the day of her decompensation, her ESR was 57 mm/h and CRP was 17.2 mg/dL. Ferritin was 1,691 ng/ml, serum interleukin-6 (IL-6) was 94.8 pg/ml (RR < 10 pg/ml), and soluble interleukin-2 (IL-2) receptor was 2,344 pg/ml (RR, 532–1,891 pg/ml).

MANAGEMENT

On Day 7 of presentation, the patient was clinically deteriorating rapidly. Interventional cardiology and cardiothoracic surgery

Abbreviations: CI, Cardiac index; CO, Cardiac output; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; IL-2, Interleukin-2; IL-6, Interleukin-6; LVEF, Left ventricular ejection fraction; LVOT, Left ventricular outflow tract; RR, Reference range.

TABLE 2 | Case timeline.

Time	Events
Day 1	Patient presented with chest pain. Electrocardiogram showed ST-segment elevation in the inferior leads.
Day 2	Coronary angiogram showed no obstructive coronary disease and left ventriculogram showed apical ballooning. Transthoracic echocardiogram showed EF 20%. The patient was admitted to the CCU. Due to newly developed fever and hypotension, infectious workup commenced, and antibiotics were started for presumed mixed shock.
Day 3	Lactic acidosis resolved. The pulmonary artery catheter was removed.
Day 5	Transthoracic echocardiogram showed new left ventricular outflow tract gradient of 30 mmHg. Hypotension developed, with recurrence of lactic acidosis.
Day 6	Transthoracic echocardiogram showed increased left ventricular outflow tract gradient to 61 mmHg.
Day 7	Right heart catheterization showed mildly elevated filling pressures and cardiac index of 2.5 L/min/m^2. Phenylephrine was started.
Day 7	Due to ongoing fevers and elevated inflammatory markers, methylprednisolone was initiated.
Day 8	Lactic acidosis resolved.
Day 9	Transthoracic echocardiogram showed resolution of left ventricular outflow tract gradient and EF 35%. Phenylephrine was weaned off.
Day 11	Endomyocardial biopsy was performed, compatible with Takotsubo cardiomyopathy. Right heart catheterization showed mildly elevated filling pressures and cardiac output of 5.5 L/min. Steroid taper commenced. Antibiotics were discontinued.
Day 12	Cardiac magnetic resonance imaging showed distal mid-cavity to apical hypokinesis with a hyperdynamic base, without edema or late gadolinium enhancement.
Day 15	Transthoracic echocardiogram showed EF 55–60%. The patient was discharged from the hospital on metoprolol and prednisone.
Day 28	The patient took her final dose of prednisone.
Day 29	The patient presented again with sharp, positional chest pain. She was admitted for pericarditis.
Day 31	Transthoracic echocardiogram showed recurrence of apical and apical-lateral segment hypokinesis, with EF 65%. Aspirin and colchicine were started.
Day 35	Pain remitted and the patient was discharged from the hospital.
4 months after initial admission	The patient was seen in the clinic and doing well, without further chest pain, or symptoms/signs of heart failure. NSAID was stopped and colchicine was continued.

were consulted to plan for possible impella or ECMO placement. Her blood vessels were deemed too small for impella or peripheral ECMO. Given the absence of evidence of infection and the lack of improvement with broad-spectrum antibiotics, a diagnosis of cytokine storm syndrome (14) was made, and she was given 1 gram of methylprednisolone daily. Over the ensuing 48 h, her fever resolved, the heart rate decreased from 130 to 90 bpm, CO improved to 4.7 L/min, CI improved to 2.7 L/min/m^2, SVRI improved to 1,528 dynes-s/cm^5/m^2, mixed venous oxygen saturation improved to 57%, and lactic acidosis resolved. ESR decreased to 30 mm/h, CRP decreased to 3.7 mg/dL, IL-6 decreased to 7.9 pg/ml, and IL-2 receptor decreased to 2,217 pg/ml. Her LVOT obstruction and phenylephrine requirement were resolved. Forty-eight hours after initiation of steroids, she underwent an endomyocardial biopsy that showed mild focal fibrosis, a diffuse mild infiltrate of macrophages, and a slight infiltrate of T lymphocytes, without necrosis (**Figure 1**). Cardiac MRI performed on Hospital Day 12, five days after steroids were initiated, and after LVOT obstruction resolved, showed circumferential hypokinesis of the distal mid-cavity to the apex of the left ventricle with hyperdynamic base maintaining normal function, without fibrosis or edema (**Supplementary Video 1**). After 3 days of high-dose steroids, she has transitioned to prednisone 40 mg daily, a beta-blocker, and was discharged with a 2-week steroid taper to null.

The patient represented one day after completing the taper with acute onset of pleuritic, left-sided chest and shoulder pain. She was hypotensive and febrile. CRP and soluble IL-2 receptor were again elevated (13.2 from 3.7 mg/dL at discharge and 2,643 from 2,217 pg/ml at discharge, respectively). An echocardiogram showed recrudescence of mild apical hypokinesis. She was treated with high-dose non-steroidal anti-inflammatory drugs and colchicine, with a resolution of her chest pain and improvement of LVEF to 60%.

Four months after her index hospitalization, she was tapered off NSAIDs and remained on colchicine. She was free of further hospitalization, without recurrence of symptoms, and her cardiac function and CRP had completely normalized. Ten months after her index hospitalization, she was taken off colchicine and remained stable, with normal cardiac function and serum CRP.

DISCUSSION

The case here presented is unique because it highlights the potential role of inflammation as a trigger for a biphasic presentation of Takotsubo cardiomyopathy, it highlights the potential role of pulse dose steroids for the treatment of cytokine storm with hemodynamic compromise, and it adds to the growing body of evidence implicating cytokine storm as a potential trigger for Takotsubo cardiomyopathy.

Cytokine storm is a clinical diagnosis with poorly defined parameters (14). However, the presentation of our patient with fevers, elevated ESR, CRP, and IL-6 in the context of rapid development of lactic acidosis and hemodynamic compromise clearly fits within this presentation. The literature reports several

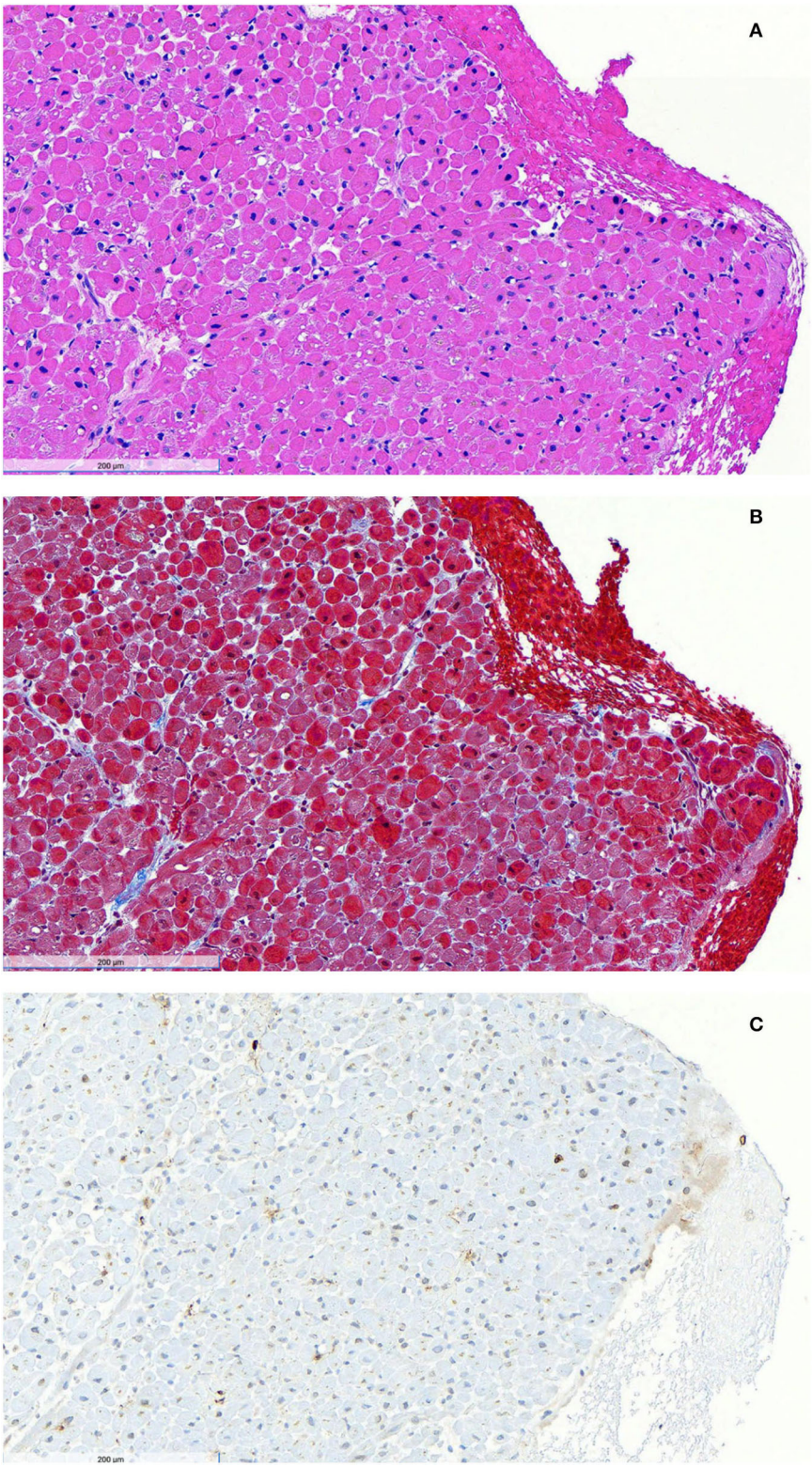

FIGURE 1 | Endomyocardial biopsy after initiation of steroid therapy. Hematoxylin and eosin staining **(A)** shows no acute myocyte necrosis and no significant interstitial expansion. No granulomas or giant cells were observed. Masson trichrome staining **(B)** shows focal mild blue-stained fibrosis. Immunoperoxidase staining for CD3 **(C)** reveals a slight infiltrate of brown CD3-positive T lymphocytes. Immunoperoxidase staining for CD68 demonstrated a diffuse mild infiltrate of CD68-positive macrophages. There was no evidence of amyloid on Congo red stain, no endocardial fibroelastosis on Movat stain, no iron deposition on Fe stain, and no excessive glycogen deposition on PAS stain. Toluidine blue-stained EM thick sections showed mild endocardial fibrosis and some endocardial lipid droplets.

cases of Takotsubo presenting in association with a systemic inflammatory response syndrome, (13) and it is well-known that patients with Takotsubo can have recurrences at variable times after the initial presentation (15). However, we are not aware of prior reports of a "back-to-back" recrudescence of Takotsubo associated with a systemic inflammatory response.

After making a diagnosis of cytokine storm, we decided to treat with pulse dose steroids. Treatment of cytokine storm has not been codified. Current trends point to the use of biologics targeting single cytokines (14). However, pulse-dose steroids are a safe, cheap, and accessible tool to rapidly suppress both the adaptive and innate immune response (16). Treatment response in a single patient cannot prove a cause-and-effect relationship between the administration of high-dose steroids and the rapid clinical improvement that we observed. However, our observation suggests that pulse-dose steroids might be a reasonable option for the treatment of cytokine storm-associated hemodynamic compromise. At least two other cases exist in the literature where steroids were used to treat Takotsubo cardiomyopathy, with good outcomes. One patient was treated for Takotsubo associated with acute demyelinating encephalomyelitis, with improvement in LVEF in 1 week (17), and another was treated for Takotsubo associated with an allergic reaction to dimethyl fumarate (used to treat relapsing-remitting multiple sclerosis), with improvement in LVEF by 3 months (18). While neither of these cases involved treatment of cytokine storm or associated obstructive shock as in our patient, they further support that steroid therapy might be a safe and effective means of treating inflammation-associated Takotsubo.

In our patient, we did not observe myocardial edema on cardiac MRI. This was somewhat unexpected because myocardial edema has been previously reported in Takotsubo (6). However, since our patient completed a cardiac MRI after the completion of 5 days of treatment with high-dose steroids, we speculate that myocardial edema might have subsided in response to treatment.

An additional interesting aspect of the presented case is that our patient developed recurrence of symptoms and pericarditis chest pain after completion of a slow steroid taper. Scally et al. have described systemic inflammation up to 5 months after initial presentation, with both symptoms and myocardial dysfunction up to 20 months after diagnosis (3, 5). Our patient was able to discontinue anti-inflammatory medications after a second slow taper of steroids associated with a prolonged treatment course with colchicine. This suggests that her initial presentation was associated with a degree of chronic inflammation that resolved over several months.

Interestingly, we were unable to find a definitive emotional stressor as the cause of this patient's Takotsubo syndrome. She denied any emotional disturbance during the grandchild's baseball game. However, she did have a preceding migraine, which has been reported as the trigger for the acute onset of Takotsubo stress cardiomyopathy in other patients (19).

In summary, the case here presented is unique insofar as it contributes to the growing appreciation for the role of systemic inflammation in the pathogenesis and evolution of Takotsubo stress cardiomyopathy, and it highlights the potential role of steroids in the treatment of life-threatening hemodynamic compromise secondary to Takotsubo, as well as the potential value of anti-inflammatory therapy to prevent relapse. Dedicated studies will be needed to understand whether the experience from this case can be generalized to a wider patient population.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

BG, MG, RV, OC, and LA contributed equally and substantially in the conception of the work, in the acquisition, analysis and interpretation of data, in drafting and revision, provided approval for publication of the content, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. 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.2022.931070/full#supplementary-material

Supplementary Video 1 | Apical 4-chamber cine cardiac magnetic resonance imaging after initiation of steroid therapy. Circumferential hypokinesis of the distal mid-cavity to apex of the left ventricle is observed with the hyperdynamic base maintaining normal function. LVEF, 64%. No fibrosis or edema was observed. Additionally, small pericardial and bilateral pleural effusions with compressive atelectasis are seen.

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The remaining 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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EDITED BY
Matteo Cameli,
University of Siena, Italy

REVIEWED BY
Giuseppe Mascia,
San Martino Hospital (IRCCS), Italy
Maria Concetta Pastore,
Università del Piemonte Orientale, Italy

*CORRESPONDENCE
Weihua Zhang
weihua@jlu.edu.cn

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Case report: An unusual case of desmin myopathy associated with heart failure and arrhythmia

Xuhan Liu, Yuan Liu, Bo Li, Lin Wang and Weihua Zhang*

Department of Cardiovascular Medicine, The First Hospital of Jilin University, Changchun, China

Introduction: Desmin myopathy is a novel desmin (DES) indel mutation that causes severe atypical cardiomyopathy as well as atrioventricular block and skeletal myopathy. The mutation of the gene of the nodal tail causes myocardial injury. Rarely does desmin myopathy cause bilateral ventricular changes.

Case presentation: We present a case of a 48-year-old man admitted with dyspnea and edema of both lower extremities. Due to bilateral lower limb weakness and calf muscle atrophy, gene sequencing was performed. The results showed that there was a pure missense mutation in the 8th exon region of the DES gene (c.1366G>A), encoding amino acid p.G456R (glycine>arginine). Supplementary examination suggests a high possibility of heart failure, atrial flutter, and desmin myopathy. Atrial flutter was treated by radiofrequency ablation. The clinical symptoms were stable after oral administration of rivaroxaban, coenzyme Q10, and ARNI.

Conclusion: In our case, mutation results are the gold standard for the diagnosis of desmin myopathy. Cardiac magnetic resonance can define the extent and degree of cardiomyopathy and quantitatively evaluate cardiac function. At present, there is a lack of specific treatment for proteolytic myopathy. Therefore, the treatment for heart failure proves effective. Due to the multiple systems involved, early diagnosis and multidisciplinary management are critical to improving patient outcomes.

KEYWORDS

heart failure, desmin (DES), arrhythmia, ARNI, cardiac conduction system

Keypoints

- Desmin myopathy is a novel desmin (DES) indel mutation. The condition is characterized by severe atypical cardiomyopathy combined with atrioventricular block and skeletal myopathy.
- Bilateral ventricular changes due to desmin myopathy are rare.
- Currently, there is a lack of specific treatments for desmin myopathy. But treatment regimens that correct arrhythmias and improve heart failure and myocardial metabolism have proven effective.

Introduction

Desmin myopathy is a subtype of myofibromyopathy in which the DES gene, the pathogenic gene, is located on chromosome 2q35 and contains nine exons (1). The age of onset of desmin myopathy is from 2 to 48 years old. Both men and women can be affected, with the autosomal dominant inheritance of family cases (2). Heart failure, severe arrhythmias, and respiratory muscle involvement with respiratory failure caused by cardiac damage in desmin myopathy are direct factors for poor prognosis. This paper shows a case of a man admitted with dyspnea and bilateral lower limb as the first symptoms of a severe desmin myopathy complicated by arrhythmia.

Case report

We present a case of a 41-year-old man who was admitted to the First Hospital of Jilin University on June 11, 2020, with intermittent dyspnea for 8 years and bilateral lower limb edema for 2 years, aggravated for 3 months. He had been suffering from bilateral lower limb weakness with calf muscle atrophy for 30 years, and electromyography suggested myogenic damage, and muscle biopsy showed myotonic changes. The results of sequencing suggested a pure missense mutation (c.1366G>A) in the exon eight regions of the desmin (Desmin, *DES*) gene, encoding amino acid p.G456R (glycine>arginine).The patient's muscle biopsy was performed with immunohistochemical staining. Muscle fibers were not stained by Desmin staining. Consider the possibility of desmin myopathy, only whole-exon DES testing was performed. The parents of the preexisting patient were non-consanguineous, both carriers of the heterozygous variant at the locus, and had no clinical manifestations such as myasthenia gravis. The parents were tested at the same time.

Diuretics and multifunctional monitoring were promptly administered. Laboratory findings are as followed: serum creatine kinase (CK) 223 U/L. N terminal-pro B type natriuretic peptide (NT-proBNP) 1,770 pg/mL. cTnI (cardiac troponin I) was in the normal range. Blood gas analysis showed: partial pressure of oxygen of 89 mmHg (1 mmHg = 0.133 kPa) and partial pressure of carbon dioxide of 34 mmHg. Electrocardiogram (ECG) showed: sinus rhythm, incomplete right bundle branch block, left anterior branch block, atrial premature beat, and ventricular premature beat (Figure 1). Radionuclide lung ventilation-perfusion imaging was not abnormal. Pulmonary function tests showed that exertional spirometry was 48% of the expected value, suggesting restrictive ventilatory dysfunction. The echocardiogram showed a left ventricular ejection fraction (LVEF) of 46% (M-type Teichholz method), a right ventricular internal diameter of 26 mm, a right atrial diameter of 54 × 64 mm, diffusely attenuated right ventricular wall pulsation, and the tricuspid plane systolic excursion (TAPSE) was 12 mm, and the tricuspid regurgitation was severe (Figure 2).

After controlling the patient's heart rate with medication, a cardiac magnetic resonance examination was performed. The result of magnetic resonance imaging (MRI) (Figure 3) showed

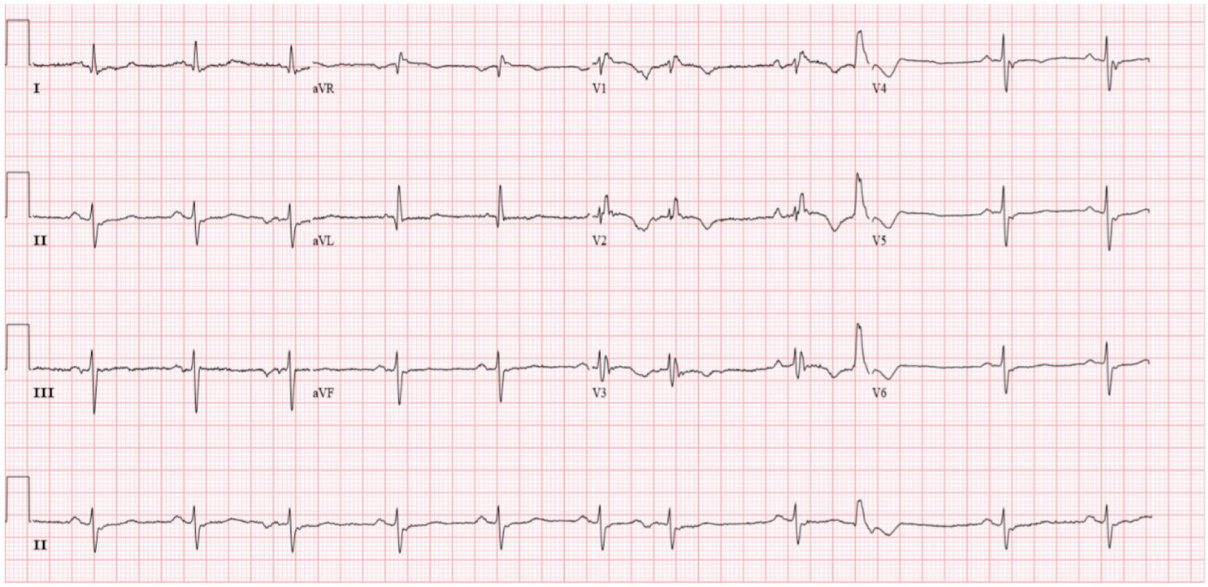

FIGURE 1
Patient's electrocardiogram (sinus rhythm, heart rate 66 beats/min, incomplete right bundle branch block, left anterior branch block, premature atrial, and ventricular beats).

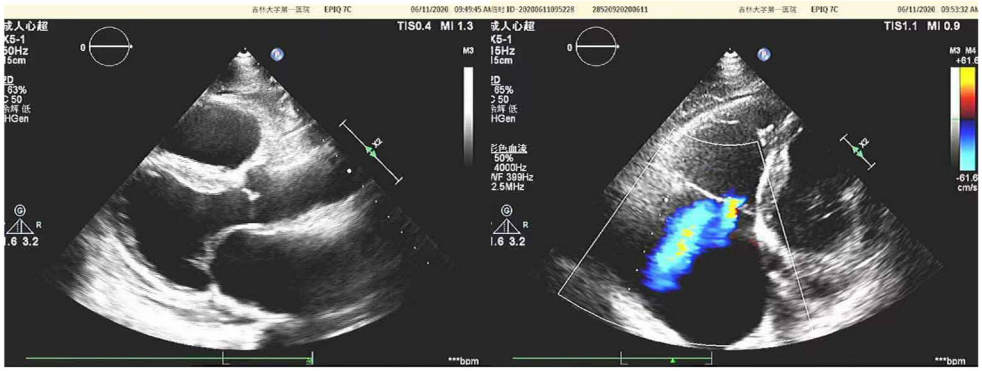

FIGURE 2
Echocardiographic of the patient's heart [a left ventricular ejection fraction (LVEF) of 46% (M-type Teichholz method), a right ventricular internal diameter of 26 mm, a right atrial diameter of 54 × 64 mm, diffusely attenuated right ventricular wall pulsation, and the tricuspid plane systolic excursion (TAPSE) was 12 mm, and the tricuspid regurgitation was severe].

that the left atrial and left ventricular internal diameters were normal, the right atrium was 61 mm anterior-posterior, and the right ventricular transverse diameter was 43 mm. The delayed scan showed diffuse striated enhancement of the left ventricular lateral wall, apex of heart, and right ventricular wall, with some transmural enhancement, LVEF 35%, and cardiac output 2.61 L/min.

In this patient, the diagnosis was clear: desmin myopathy caused myocardial injury, right heart dilatation, total heart failure, cardiac function class 3 (NYHA class), arrhythmia-RBBB, LAFB, atrial premature beat, ventricular premature beat. The patient was treated with a diuretic treatment (Furosemide, Spironolactone orally), cardiac stimulant (digoxin orally), and sacubitril/valsartan 50 mg 2 times/d orally, which relieved dyspnea, nocturnal paroxysmal dyspnea, and bilateral lower limb edema. Two months later, the patient's reexamination showed improvement: NT-proBNP 1,090 pg/mL.

Nevertheless, the patient was admitted to our hospital again on December 18, 2020, with palpitations for 1 day. Physical examination: pulse 98 times/min, respiration 19 times/min, blood pressure 112/70 mmHg. There is no distension of jugular veins, coarse breath sounds in both lungs, and no rales were heard. The heart rate was 98 beats/min with arrhythmias. A grade 2/6 systolic murmur could be heard under the xiphoid. The gastrocnemius muscles were atrophied bilaterally. Muscle strength examination: grade IV in the distal part of both lower limbs, grade II in the dorsal extension of both feet. Supplementary examination: B type natriuretic peptide (BNP) 934 pg/mL; digoxin concentration: 0.43 ng/mL; serum ion and cTnI levels normal range. The patient did not have an ECG at the time of the palpitations attack. Still, the ECG after admission showed ectopic rhythm, paroxysmal atrial flutter (2:1 conduction), non-specific intraventricular block, and prolonged QT interval (Figure 4). The echocardiogram showed an LVEF of 29% (M-type Teichholz method), an anterior-posterior right ventricular diameter of 34 mm, a right atrial diameter of 55 × 68 mm, and a TAPSE of 8 mm, a decreased right ventricular function, and moderate tricuspid regurgitation. The diagnosis of atrial flutter was clear, and the patient underwent cardiac radiofrequency ablation with temporary pacemaker implantation on the 5th day of admission. Preoperative esophageal echocardiography and left atrial computed tomographic angiography (CTA) did not show any left atrial or left atrial appendage thrombus.

To correct the arrhythmia, a star mapping electrode was applied, and the result was tricuspid isthmus reverse clock reentry atrial flutter. Linear radiofrequency ablation was performed along the tricuspid isthmus (Figure 5), which lead to atrial flutter terminating and recovering sinus rhythm, with intermittent borderline rhythm. After giving temporary cardiac pacing, the postoperative HV interval was 69 ms. The patient's postoperative ECG showed sinus rhythm with non-specific intraventricular block and prolonged QT interval. The temporary pacemaker was removed on the second postoperative day. After the discharge, the patient was given a diuretic (furosemide orally), anticoagulation (rivaroxaban orally), and coenzyme Q10 therapy. Due to low blood pressure, the dose of sacubitril/valsartan was reduced to 25 mg orally twice. The patient was followed up regularly (Figure 6).

Discussions

Desmin myopathy is a subtype of myogenic fibromyopathy with a causative gene, the *DES* gene, located on chromosome 2q35 and containing nine exons (1). The age of onset of desmin myopathy is 2–48 years, both sexes can be affected, and family cases are mainly autosomal dominant (2). In

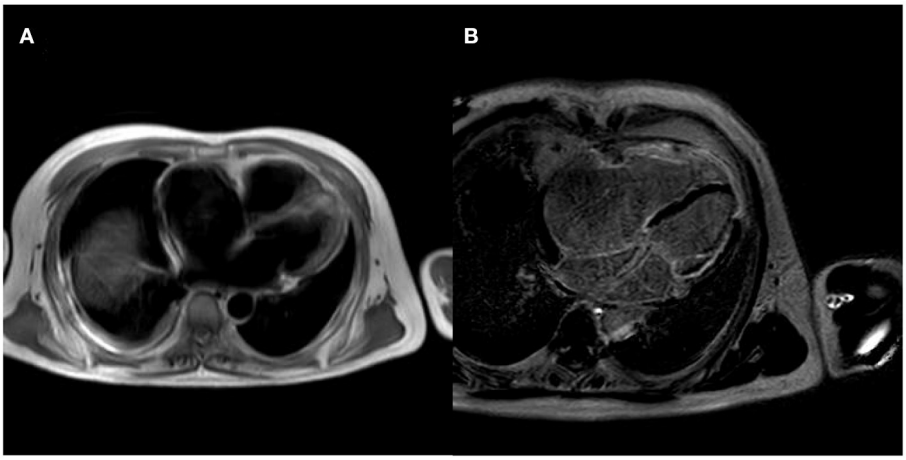

FIGURE 3
MRI of the patient's heart [**(A)** is a whole heart cross-sectional view, which shows a small left atrium and an enlarged right atrium; **(B)** is a delayed scan, which shows diffuse strip enhancement of the left ventricular lateral wall, apical region, and right ventricular wall, with some transmural-like enhancement].

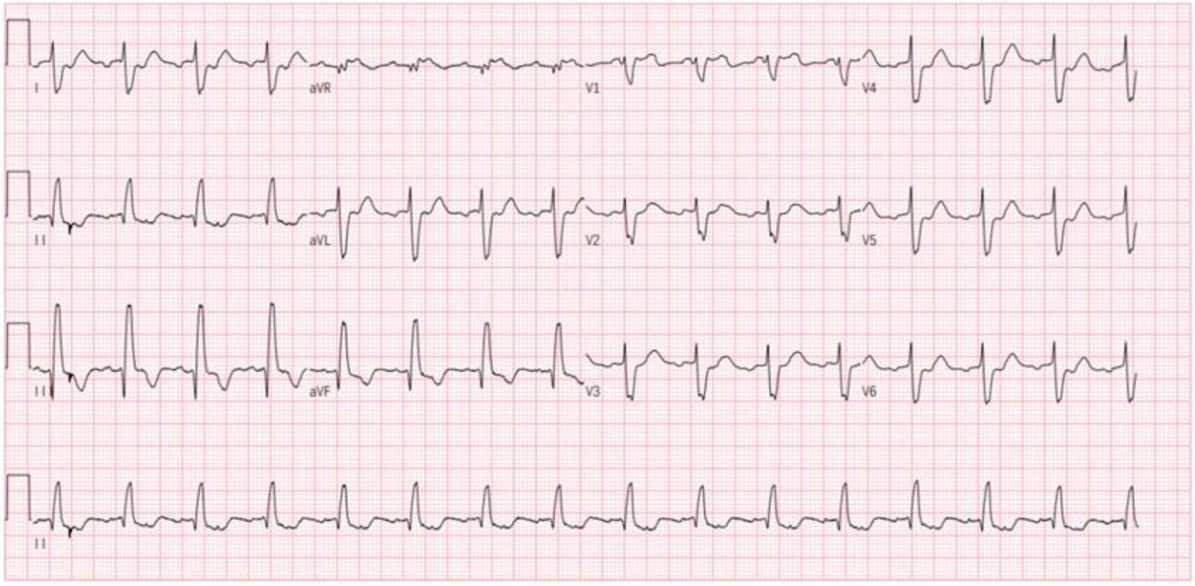

FIGURE 4
Patient's ECG after this admission (ectopic rhythm, heart rate 93 beats/min, paroxysmal atrial flutter 2:1 conduction, non-specific intraventricular conduction block, prolonged QT interval).

this case, both parents are carriers of the mutated gene. Neither of them has developed the disease; the preexisting patient is a homozygous, consistent with autosomal recessive inheritance. The disease mainly presents with symmetrical distal muscle weakness of the lower extremities, in some cases involving the myocardium and cardiac conduction system (1). A meta-analysis by Carvalho et al. showed that ∼15–50% of patients have restrictive respiratory insufficiency (3, 4). Van Spaendonck-Zwarts et al. (5) showed that most patients with DES mutations present with combined skeletal and cardiac myopathy, with ∼75% of patients with DES mutations presenting with cardiac symptoms, of which only 22% have

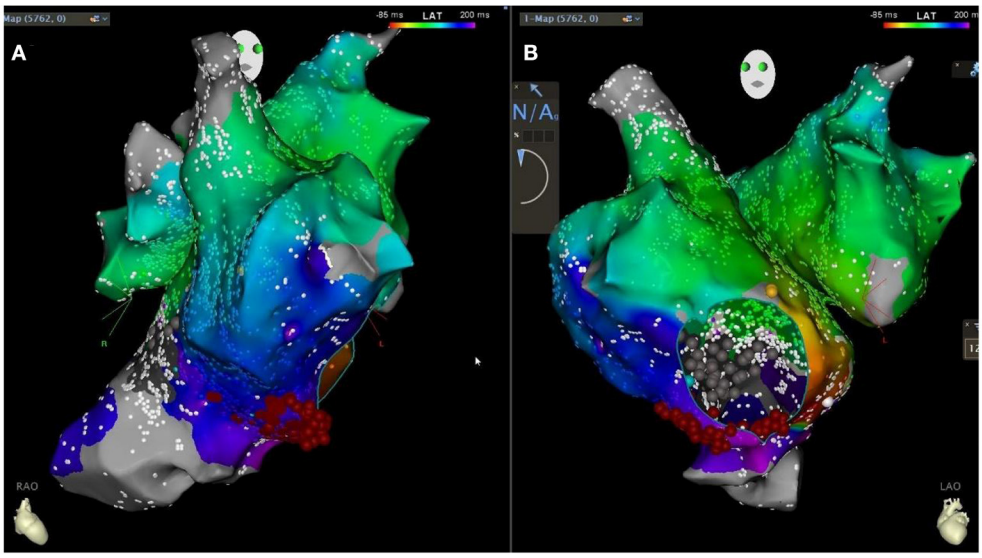

FIGURE 5
Patient's CARTO downstream agitation specimen [retrograde bell-like folding atrial flutter around the tricuspid annulus, tachycardia circumference 300ms, linear ablation along the tricuspid isthmus in the right anterior oblique 30 degrees in **(A)** and left anterior oblique 45 degrees in **(B)** position].

symptoms	date	treatment
• bilateral lower limb weakness with calf muscle atrophy	01/01/1990	
• Intermittent dyspnea	01/01/2012	
• bilateral lower limb edema	01/01/2018	
• bilateral lower limb edema aggravating for 3 months	06/06/2020	Echocardiogram showed a left ventricular ejection fraction (LVEF) of 46%
• bilateral lower limb edema	06/11/2020	digoxin (p.o.), diuretic(p.o.), amiodarone(p.o.), ARNI(p.o.)
	08/24/2020	MRI showed diffuse strip enhancement of the left ventricular lateral wall, apical region, and right ventricular wall, with some transmural-like enhancement
• Heart palpitations	12/18/2020	Diuretic (i.v.) ARNI(p.o.), beta blocker(p.o.) Rivaroxaban(p.o.)
• Heart palpitations	12/24/2020	Linear radiofrequency ablation
• Re-examination	03/25/2021	Echocardiogram showed a left ventricular ejection fraction (LVEF) of 48%

FIGURE 6
The patient's timeline of admission, diagnosis, and treatment.

an isolated cardiac phenotype (6). In this case, the patient's first symptom was myasthenia with myasthenia gravis, elevated serum CK, and electromyography, and muscle biopsy pathology confirmed the presence of myopathy, consistent with combined skeletal and cardiac diseases, and with pulmonary function suggesting restrictive respiratory insufficiency. It has been reported that the junctional protein tail is involved in the regulation of intermediate filament dynamics, and its mutation mainly causes myocardial damage. In our patient, the *DES* gene mutation site was in the region encoding the structure of the junctional protein tail (c.1366G>A), resulting in the substitution of glycine by arginine, leading to a conformational change in this structural domain and increased sensitivity of myocytes to mechanical forces associated with contraction, triggering contractile dysfunction in cardiac, and skeletal muscle and promoting myocardial remodeling.

Echocardiography and cardiac MRI can clarify the extent and degree of myocardial disease and quantitatively assess cardiac function. Desmin myopathy often presents as different types of cardiomyopathy, including dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and non-dense cardiomyopathy (7, 8). Arrhythmias include atrioventricular block, bundle branch block, atrial fibrillation, and ventricular tachycardia (9). CMR can differentiate between injured and normal myocardium. T2-weighted imaging sequences of myocardial hyper-signal reflect myocardial edema, and perfusion sequences can detect myocardial ischemia (10). The echocardiogram showed severe right heart damage, consistent with restrictive cardiomyopathy. Still, the cardiac MRI showed that the left ventricular myocardium was also involved, and the LVEF value was significantly reduced. In this case, the right atrium was dilated, resulting in right atrial remodeling, which facilitated the formation of a foldback loop, resulting in rapid atrial pulsation, and eventually atrial flutter.

On the contrary, the loss of atrial pump function and the desynchronization of atrial and ventricular motion during atrial flutter can further induce and aggravate heart failure, creating a vicious circle between the two, and significantly reducing activity tolerance. In addition, junctional proteins are also expressed in Purkinje fibers and intercalated discs; therefore, junctional protein myopathy often causes conduction block arrhythmias (11). In this case, the electrocardiogram shows a non-specific intraventricular block, suggesting an involvement of the cardiac conduction system. If the lesion worsens, a complete AV block at the branch level may occur, leading to syncope or sudden cardiac death.

In this case, the patient underwent linear ablation at the isthmus of tricuspid valve. During the ablation process, atrial flutter was terminated and sinus rhythm was restored, and borderline rhythm occurred intermittently. Temporary cardiac pacing was performed to verify the integrity of the ablation line. Low right atrium and coronary sinus pacing, PPI measurement of 200 ms, indicating tricuspid isthmus bidirectional block, indicating a successful operation. The amount of radiation in radiofrequency ablation surgery is used on-demand. In this radiofrequency ablation operation, we have tried to reduce the radiation dose of the patient, and the radiation dose of this patient is about 30–40 MGy. In addition to determining potential clinical benefits, zero X-ray also defines safe technical advantages in terms of lower ionizing radiation exposure. In surgery for the future, we should try to less rays, achieve zero ray of surgery, reduce the damage to the body (12).

There is a lack of specific treatment for myocardial damage in junctional protein myopathy. Medicine can only be based on the guidelines for heart failure (13). In patients with heart failure combined with atrial flutter, aggressive radiofrequency ablation is given to treat the atrial flutter and synchronize the atrial motion, which is beneficial to improving the prognosis of patients with heart failure. The patient, in this case, applied cardiotonic and diuretic drugs but not β-blockers, considering that their adverse inotropic effects may aggravate right heart failure. In this case, the patient's symptoms were relieved after applying anti-heart failure drugs, and the NT-proBNP level was reduced. However, the echocardiogram after the onset of atrial flutter indicated that the cardiac function was lower than before, suggesting that the atrioventricular desynchronization caused by atrial flutter may reduce the efficacy of anti-cardiac failure drugs. The long-term effectiveness of radiofrequency ablation in patients with heart failure combined with atrial flutter needs to be further observed. Heart transplantation may be considered in patients with advanced chronic heart failure (2). However, respiratory muscle damage due to myopathy can still lead to death, so the benefit of heart transplantation may be limited. Because of the abnormalities in mitochondrial function in Desmin myopathy, the administration of drugs such as coenzyme Q10 and trimetazidine to improve energy metabolism may be beneficial (14). Due to diffuse cardiac conduction system lesions, guidelines recommend implanting a permanent pacemaker if the patient develops severe bradyarrhythmias (15). As a result of gaining experience in developing muscle-specific synthetic promoters, scientists can develop constructs that mimic the distinctive expression profile of muscles-specific proteins and fully recover their lost functions (16). For those with inherited muscle metabolic diseases, this treatment may be particularly useful.

Heart failure due to myocardial damage in desmin myopathy, severe arrhythmias, and respiratory muscle involvement complicated by respiratory failure are direct factors in the poor prognosis of the patient. In this case, the patient presented with total heart failure, bundle branch block, atrial flutter, and restrictive ventilation dysfunction, suggesting the presence of respiratory muscle involvement, presumably with a poor long-term prognosis. CMR is an essential imaging test for detecting early cardiac involvement in desmin myopathy and predicting patient prognosis; therefore, early completion of CMR in patients with suspected desmin myopathy should be recommended to achieve earlier diagnosis, early treatment, reduce further myocardial injury, and improve patient survival. Most junctional protein myopathies are missense mutations or small deletion mutations, and in this case, the patient had a missense mutation. Since junctional proteins are scaffolding proteins that connect organelles, there are various secondary and tertiary molecular and cytopathological mechanisms *in vitro* and *in vivo* that affect different cellular compartments. There is no specific therapy yet. It is hoped that in the future new advances in molecular and cellular biology will allow the development of molecular treatments applied to patients with junctional protein myopathy.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XL, YL, BL, LW, and WZ: substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, drafting the work or

revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. YL: writing—review & editing. BL: conceptualization, methodology, and visualization. LW: investigation, formal analysis, and writing—review & editing. 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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EDITED BY
Matteo Cameli,
University of Siena, Italy

REVIEWED BY
Germán Cediel,
Hospital Germans Trias i Pujol, Spain

*CORRESPONDENCE
Weihua Zhang
weihua@jlu.edu.cn

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Corrigendum: Case report: An unusual case of desmin myopathy associated with heart failure and arrhythmia

Xuhan Liu, Yuan Liu, Bo Li, Lin Wang and Weihua Zhang*

Department of Cardiovascular Medicine, The First Hospital of Jilin University, Changchun, China

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heart failure, desmin (DES), arrhythmia, ARNI, cardiac conduction system

A corrigendum on

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In the published article, there were some errors.

A correction has been made to **Abstract**, *Conclusion*, Paragraph 1. This sentence previously stated "In our case, mutation results are the gold standard for the diagnosis of nodular myopathy." The corrected sentence is "In our case, mutation results are the gold standard for the diagnosis of desmin myopathy."

A correction has been made to **Introduction**, Paragraph 1. This sentence previously stated "…and respiratory muscle involvement with respiratory failure caused by cardiac damage in nodular myopathy are direct factors for poor prognosis." The corrected sentence is "…and respiratory muscle involvement with respiratory failure caused by cardiac damage in desmin myopathy are direct factors for poor prognosis".

A correction has been made to **Case report**, Paragraph 4. This sentence previously stated "So far, the patient's clinical diagnosis is clear, which is myocardial damage in desmin myopathy." The corrected sentence is "In this patient, the diagnosis was clear: desmin myopathy caused myocardial injury".

The authors apologize for these errors and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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EDITED BY
Matteo Cameli,
University of Siena, Italy

REVIEWED BY
Iacopo Fabiani,
Gabriele Monasterio Tuscany Foundation (CNR), Italy
Anna Eremkina,
Endocrinology Research Center, Russia

*CORRESPONDENCE
Xiaolin Luo
lwy920831@126.com

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Hypocalcemic cardiomyopathy: A case report

Yi Wen[1,2] and Xiaolin Luo[3]*

[1]West China School of Nursing/West China Hospital, Sichuan University, Chengdu, China, [2]Department of Cardiovascular Medicine, West China Hospital, Sichuan University, Chengdu, China, [3]Department of Cardiology, Xinqiao Hospital, Army Medical University, Chongqing, China

Hypocalcemia and its related symptoms are common manifestations in postsurgical hypoparathyroidism, but patients with hypocalcemia manifested as heart failure is rare and few cases are reported in the literature. Here we reported a 58-year-old female with hypoparathyroidism and uncontrolled hypocalcemia after thyroidectomy, presented with acute heart failure, accompanied with enlargement and reduced ejection fraction of left ventricle. She was refractory to guideline-directed medical therapy for heart failure including digitalis and diuretics. However, her symptoms resolved and cardiac function improved dramatically after normalization of serum calcium level. This rare case highlights the pivotal role of calcium in maintaining cardiac function and the importance of treating underlying reversible causes of heart failure. For patients with hypoparathyroidism, it is essential to get standard treatment to avoid development of heart failure and hypocalcemia related syndromes.

KEYWORDS

hypocalcemic cardiomyopathy, hypocalcemia, hypoparathyroidism, heart failure, thyroidectomy

Introduction

Thyroidectomy is one of the main reasons of hypoparathyroidism (HypoPT) (1). Manifestations of HypoPT include hypocalcemia, hyperphosphatemia, neuromuscular excitability, and ectopic tissue calcification (1, 2). However, hypocalcemia manifested as heart failure after thyroidectomy is quite rare (3). Besides, previous cases indicated that traditional therapy for heart failure, including diuretics and digitalis, is not effective in resolving these patients' symptoms (4). Here we reported a patient presented with left ventricular dysfunction induced by hypocalcemia after thyroidectomy, which recovered after normalization of serum calcium. Therefore, clinicians should seek and treat any underlying reversible causes of heart failure to improve the prognosis (5).

Case presentation

This is a 58-year-old female who was admitted to our hospital with the complaint of exertional dyspnea for 3 months. She underwent total thyroidectomy 2 years ago for papillary thyroid carcinoma in another tertiary hospital. Two days after surgery, laboratory tests showed a decreased serum concentration of parathyroid hormone (PTH) of 2.64 pg/ml [reference range (Ref): 15–65 pg/ml], concomitant with a total calcium

of 1.86 mmol/L (Ref: 2.2–2.65 mmol/L) and a phosphate of 1.54 mmol/L (Ref: 0.81–1.55 mmol/L). Then she was treated with Calcium Gluconate Oral Solution, Calcium Carbonate and Vitamin D3 Tablets and alfacalcidol. Meanwhile, levothyroxine (100 ug per day) was given for supplementation of thyroxine. After discharge, however, she did not come to hospital for test of serum calcium, phosphate and PTH level. What's worse, Calcium Carbonate, Vitamin D3 Tablets, and Alfacalcidol were withdrawn on her own. Six months after surgery, she started to suffered from paroxysmal tetany, which could be relieved by calcium supplementation. However, she did not seek for further medical intervention. Three months before admission, she began to experience exertional dyspnea and shortness of breath, accompanied by nocturnal paroxysmal dyspnea and orthopnea. Cardiac ultrasound at local hospital found an enlarged heart and a decreased left ventricular ejection fraction (LVEF). She was diagnosed with heart failure and treated with diuretics and guideline-directed medical therapy (GDMT) for heart failure with reduced EF, but her symptoms did not resolve. She has no history of hypertension, diabetes mellitus, coronary heart disease, valvular heart disease, congenital heart disease, no history of alcohol abuse and tobacco smoking, and no family history of cardiomyopathy. She underwent a laparoscopic cholecystectomy for gallbladder stones 6 months ago.

Physical examination revealed a blood pressure (BP) of 109/92 mmHg, a respiration rate of 24 breaths per minute, and a heart rate of 124 beats per minute. The jugular veins were normal. Pulmonary auscultation found fine rales at the base of both lungs. The cardiac auscultation found a diminished S1 and S2 without any murmurs. Mild pitting edema was found in lower limbs. Chvostek sign and Trousseau sign were negative.

On admission, laboratory tests revealed brain natriuretic peptide (BNP) was 1200 pg/ml and cardiac troponin I was negative. Serum total albumin-corrected and ironized calcium concentration was decreased, and phosphate concentration was increased. PTH was 44.30 pg/ml. Thyroid hormones concentrations were within normal range (summarized in Table 1). Electrocardiogram (ECG) showed sinus tachycardia and prolonged corrected QT interval (QTc) of 502 ms (Figure 1A). The chest X-radiography found enlargement of the heart (Figure 1B). Echocardiography found dilated left ventricular diameter of 50 mm, accompanied by moderate mitral regurgitation, severe tricuspid regurgitation and global hypokinesis of left ventricular wall with LVEF of 43% (Table 1; Figures 1C,D). Coronary computed tomography angiography showed no abnormalities of coronary arteries. Cardiac magnetic resonance imaging was planned but the patient refused. Other causes of hypocalcemia besides HypoPT were not identified.

Based on these findings, acute heart failure resulting from hypocalcemia and chronic HypoPT were diagnosed. Since loop diuretics may exacerbate the loss of calcium from urine (2), hydrochlorothiazide (25 mg per day) and spironolactone (20 mg per day) were prescribed instead to relieve heart failure syndrome. The 10% calcium gluconate injection was administered intravenously (10 ml per day, 3 days; 90 mg elemental calcium/10 ml) and calcium gluconate oral solution (20 ml, three times per day; 90 mg elemental calcium/10 ml) was given, accompanied by alfacalcidol (0.5 ug per day) to correct hypocalcemia. According to the guidelines for heart failure, Sacubitril Valsartan Sodium Tablets and Metoprolol Succinate Sustained-release Tablets were also given and dosages were titrated to the most tolerance (5, 6). From the time of discharge till 1 month after discharge, the drugs contained calcium gluconate oral solution (20 ml, three times per day), alfacalcidol (0.5 ug per day), sacubitril valsartan (titrated to 100 mg, twice a day), metoprolol (titrated to 142.5 mg per day), hydrochlorothiazide (25 mg per day) and spironolactone (20 mg per day). Since the patient still experienced sinus tachycardia during the titration of metoprolol, ivabradine (7.5 mg, twice a day) was initially combined, and the dosage of levothyroxine (initially 100 ug per day) was simultaneously reduced (75 ug per day). Before discharge, dyspnea and other heart failure syndromes were relieved, albumin adjusted calcium increased to 2.44 mmol/L and BNP decreased to 544 pg/ml.

One month after discharge, the patient experienced an episode of sinus bradycardia, ivabradine was withdrawn and heart rate returned to 70–80 beats per min. She underwent regular monitoring of serum calcium and phosphate. Six months after discharge, she was asymptomatic and could tolerate daily activities. Moreover, she had no longer suffered from episode of tetany. Hypocalcemia and hyperphosphatemia were corrected, the albumin-adjusted calcium was 2.21 mmol/L and serum phosphate was 1.45 mmol/L. ECG showed sinus rhythm with normalized QTc interval of 440 ms. Echocardiography revealed normalization of left ventricular diameter to 40 mm, no mitral and tricuspid regurgitation, improvement of LVEF to 53%, and mild hypokinesis of left ventricular wall. Sonography of urinary tract was performed and no kidney stones were found. Now, the patient is still taking the medications at the time of discharge except hydrochlorothiazide and ivabradine and is being closely followed up.

Discussion

Although prognosis of patients with heart failure has been improved with novel evidence-based therapy, many patients still died of advanced heart failure. Early intervention of reversible factors of heart failure, like ischemia and valvular heart disease, could greatly improve the prognosis. Therefore, it should always be emphasized to assess and treat reversible causes for each individual with heart failure (5, 6). In the present case, the patient suffered from serious heart failure symptoms but was initially refractory to traditional therapy (e.g., digitalis and diuretics). Considering the history of total thyroidectomy, episode of paroxysmal tetany, hypocalcemia,

TABLE 1 Laboratory values and echocardiography parameters.

	At admission	During admission	Before discharge	2021.9.5	2022.1.17	2022.3.17	2022.8.1	Reference range
Calcium total, mmol/L	1.84	1.93	2.38	2.19	2.08	2.33	2.27	2.02–2.6
Calcium ionized, mmol/L	0.92	-	1.07	1.10	-	1.16	-	1.12–1.23
Albumin adjusted calcium, mmol/L[#]	1.87	-	2.44	2.03	1.93	2.13	2.21	-
Phosphate, mmol/L	1.98	2.16	2.15	-	1.74	-	1.45	0.9–1.34
Magnesium, mmol/L	0.74	0.92	1.10	-	0.99	-	-	0.65–1.05
PTH, pg/ml	44.30	35.80	8.20	-	4.50	-	-	12–65
25-OH vitamin D, ng/ml	22.10	21.80	17.90	-	-	-	-	30–40
Calcitonin	<2.0	<2.0	<2.0	-	-	-	-	0–5
BNP, pg/ml	1,200	-	544	200	46.54*	-	46.6*	5–100
ALT, IU/L	104.1	-	33.7	23	13.6	18	23	7–40
AST, IU/L	62.31	-	33.2	33	17.6	16	23	13–35
Albumin, g/L	38.5	-	37.1	47.9	47.5	49.8	43.1	40–55
Creatine, umol/L	91.1	-	80.4	77.0	73.0	62.0	62.6	45–105
FT3, pmol/L	2.74	-	-	2.36	3.53	2.153	-	2.43–6.01
FT4, pmol/L	19.04	-	-	20.28	23.12	15.94	-	9.01–19.05
TSH, mIU/L	2.635	-	-	4.16	14.90	13.32	-	0.35–4.94
T3, nmol/L	0.83	-	-	0.99	-	0.979	-	0.98–2.33
T4, nmol/L	138.37	-	-	93.63	-	99.21	-	62.68–150.84
Echocardiography								
EDD, mm	50	52	-	51	40	-	-	-
LVEF, %	43	38	-	41	53	-	-	-
MR	Moderate	Moderate	-	Mild	None	-	-	-
TR	Severe	Mild	-	Mild	None	-	-	-

PTH, parathyroid hormone; BNP, brain natriuretic peptides; ALT, alanine transaminase; AST, aspartate transaminase; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; EDD, end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TR, tricuspid regurgitation.

*NT-proBNP.

[#]Adjusted calcium concentration (mmol/L) = total calcium (mmol/L) +0.02*(40-albumin in g/L).

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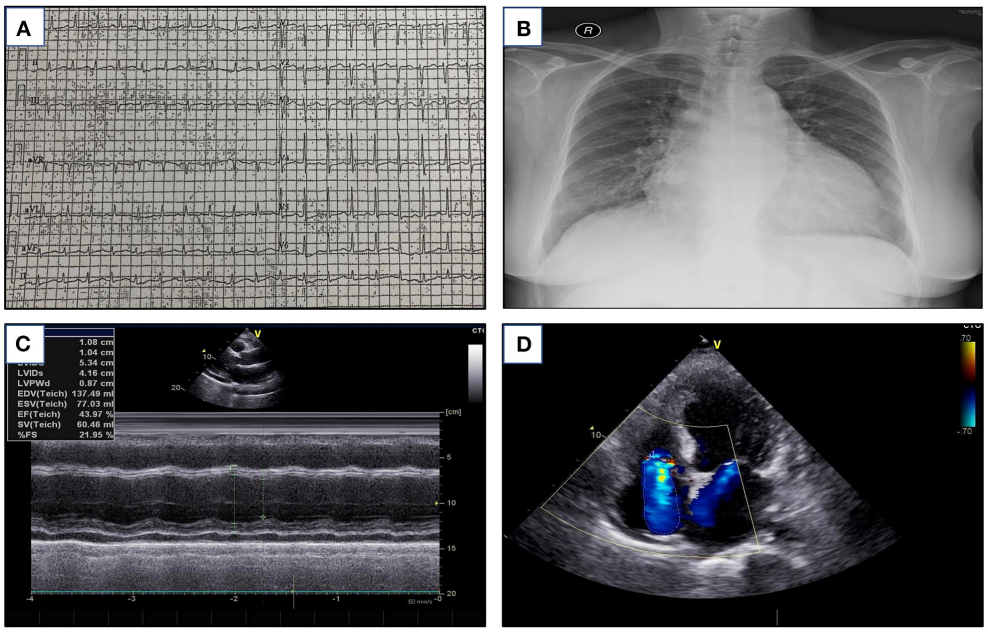

FIGURE 1
(A) The ECG at admission (speed 25 mm/s, 10 mm/mV) with HR 128 beats/min and QTc interval of 502 ms. **(B)** The chest radiography shows cardiac enlargement and signs of pulmonary congestion. **(C)** The echocardiography in the long-axis, M mode shows an increased left ventricular end-diastolic diameter (5.0 cm) and reduced EF (43%). **(D)** Doppler ultrasound shows moderate mitral regurgitation and severe tricuspid regurgitation.

hyperphosphatemia and inappropriate "normal" PTH level on admission, chronic HypoPT was diagnosed (2, 7). Dramatically, symptoms of heart failure and LVEF improved gradually and restored to normal with the correction of hypocalcemia. Therefore, the diagnosis of hypocalcemic cardiomyopathy of our patient was made according to the criteria proposed previously (4, 8).

In most cases, hypocalcemic cardiomyopathy manifests as a treatable cause of heart failure as normalization of calcium concentration could lead to complete recovery of cardiac function (3, 4, 9–12). However, prolonged and profound hypocalcemia may cause irreversible myocardial damage and extensive interstitial fibrosis in rare cases, in which complete recovery of cardiac function could not be reached (13, 14). In addition, discontinuation or poor compliance of calcium supplementation therapy can result in recurrence of the disease (3, 15).

The mechanism of hypocalcemic cardiomyopathy is thought to be related to the vital role of calcium in myocardial excitation-contraction coupling (16). Besides, hypomagnesemia, low PTH and vitamin D level in chronic HypoHT are also assumed to participant in the development of the disease (17–19). Thus, hypocalcemia may lead to left ventricular systolic dysfunction. It is reported that 98% of the cases present with reduced LVEF published in the literatures (3). On the other hand, calcium channel blockers may worsen heart failure or increase late onset congestive heart failure in postinfarction patients due to its negative inotropic effect (20, 21). Calcium is involved in cardiomyocyte repolarization and hypocalcemia is supposed to result in prolongation of QT interval and T-wave inversion (11). Therefore, it could explain the features of hypocalcemic cardiomyopathy that restoration of LVEF and QT interval could be reached with correction of hypocalcemia, and that single conventional therapy for heart failure (e.g., furosemide, which may even aggravate hypocalcemia) is not effective (13, 14). Although normalization of serum calcium concentration was quick, it took 6 months for the complete recovery of myocardial function of our patient. It is reported to take a much longer time for the recovery in some cases (22), indicating that restoring intracellular calcium level is more important.

Hypocalcemia cardiomyopathy in HypoPT is quite rare since most patients would seek for early intervention for hypocalcemia related syndromes. The median interval for development of the disease is reported to be 10 years, ranging from 1.5 months to 36 years (3). Our patient was found to have hypocalcemia, hyperphosphatemia and inappropriate "normal" PTH on admission, and chronic HypoPT was diagnosed. In fact, she developed HypoPT after thyroidectomy 2 years ago, but did not receive regular follow-up. Her symptom of recurrent tetany indicated there were fluctuations of serum calcium which resulted in the development of heart failure.

Besides, symptoms of HypoPT do not translate directly to the serum calcium levels and may vary from an asymptomatic state to severe manifestations, which often leads to missed diagnosis and delayed treatment of HypoPT (2). Therefore, it is crucial to monitor and maintain the homeostasis of calcium, phosphate and magnesium for patients with HypoPT, not only to reduce hypocalcemia related syndromes, but also to avoid complications from excessive calcium supplementation. Individuals with unexplained heart failure should be screened for HypoPT, especially for patients with history of neck surgery.

Conclusion

Hypocalcemic cardiomyopathy is a rare complication of HypoPT. Early correction of hypocalcemia has a dramatic effect in the therapy of heart failure, and cardiac function could recover after normalization of calcium level. Thus, it is indispensable to assess the underlying reversible etiology of each patient with heart failure, and it is pivotal to keep the balance of calcium in HypoPT to reduce the incidence of heart failure development and other complications.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YW contributed to the work of patients' follow up, data collection, and manuscript draft. XL is responsible for the manuscript revision. 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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EDITED BY
Andrew Richard Kolodziej,
University of Kentucky, United States

REVIEWED BY
Tomasz Urbanowicz,
Poznan University of Medical Sciences, Poland
Suguru Ohira,
Westchester Medical Center, United States

*CORRESPONDENCE
Hitoshi Hirose
hhirose@virtua.org

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Massive hemoptysis bridged with VV ECMO: A case report

Dylan Ryan, Kathleen Miller, Carly Capaldi, Claudine Pasquarello, Qiong Yang and Hitoshi Hirose*

Department of Surgery, Virtua Health, Our Lady of Lourdes Hospital, Camden, NJ, United States

Objective: Extracorporeal membrane oxygenation (ECMO) can provide full pulmonary support when a patient is completely apneic. The combination of veno-venous (VV) ECMO and induced apnea can be utilized to control significant hemoptysis. We present a case of massive hemoptysis that developed while on VV ECMO and was treated with temporary discontinuation of the ventilator and serial declotting bronchoscopies.

Methods: A 42-year-old male with recent acute ST elevation myocardial infarction status post cardiac stent developed aspiration pneumonia that progressed to acute respiratory distress syndrome. The patient's biventricular function was preserved. VV ECMO was placed for lung rescue on hospital day #7, and tracheostomy was performed for ventilator dependence on hospital day #12. On hospital day #18, the patient developed significant hemoptysis despite the discontinuation of anticoagulation. Bronchoscopy revealed massive bleeding from bilateral bronchi. To facilitate tamponade within the tracheobronchial tree, the ventilator was temporarily discontinued while VV ECMO provided full respiratory support. After 48 h, mechanical ventilation was resumed, and daily bronchoscopies were performed to remove clots from both bronchi until a chest x-ray showed improvement in bilateral opacifications. Bronchoscopy was performed a total of 14 times. There was no recurrence of bronchial bleeding, the patient's respiratory status improved, and VV ECMO was weaned off on hospital day #37. The patient was transferred to a long-term rehabilitation facility 36 days after successful VV ECMO decannulation on hospital day #73.

Conclusions: This patient's survival of massive hemoptysis was facilitated largely by the utilization of serial declotting bronchoscopies with VV ECMO providing full pulmonary support during temporary discontinuation of mechanical ventilation.

KEYWORDS

ECMO, hemoptysis, ventilator, respiratory failure, ST-elevation myocardial infarction (STEMI)

Background

The use of extracorporeal membrane oxygenation (ECMO) remains a common practice in the setting of both cardiac and respiratory emergencies (1). In patients with acute respiratory distress syndrome (ARDS), veno-venous ECMO (VV ECMO) combined with a lung-protective ventilation strategy can mitigate ventilator-associated lung injury and improve lung recovery (1, 2). In the event of substantial hemoptysis, the combination of VV ECMO and induced apnea can be utilized to control hemorrhage and

allow lung healing. The following is a case of massive hemoptysis that developed while on VV ECMO and was treated with temporary discontinuation of mechanical ventilation in addition to serial declotting bronchoscopies.

Case presentation

A 44-year-old male (weight 80 kg, height 167 cm, body surface area 1.9 m^2) with no significant past medical history aside from vaping presented to the emergency department with anterior ST-elevation myocardial infarction (STEMI). Hypoxemia was noted with concern for aspiration and the patient was intubated. Cardiac catheterization revealed total occlusion of the proximal left anterior descending artery (LAD). An intra-aortic balloon pump (IABP) was placed, inotropic therapy was initiated, and the patient underwent successful coronary intervention of the LAD with a drug-eluting stent. Aspirin 325 mg and Clopidogrel 300 mg were introduced immediately, followed by daily dose of Aspirin 81 mg and Clopidogrel 75 mg. IABP was removed on hospital day #4 following hemodynamic improvement. Inotropic support was successfully weaned off on hospital day #6. A follow-up echocardiogram demonstrated an ejection fraction (EF) of 50% with preserved right ventricular function.

Initially, the patient maintained oxygenation with minimum ventilator support (assist control respiratory rate (RR) 16, tidal volume (TV) 500 cc, FiO_2 70%, PEEP 8 cm H_2O, resulting in arterial blood gas [ABG] pH 7.32, $PaCO_2$ 38 mm Hg, PaO_2 97 mm Hg). However, the following day, the patient's respiratory status deteriorated and his ventilator requirements quickly increased (FiO_2 100%, PEEP 15 cm H_2O) after vomitus and aspiration event. On hospital day #7, the patient's hypoxia worsened (ABG: pH 7.36, $PaCO_2$ 69 mm Hg, PaO_2 76 mm Hg) despite initiation of inhaled epoprostenol, deep sedation, paralysis, and maximum ventilator support (FiO_2 100%, PEEP 20 cm H_2O, RR 26, and TV 550 cc). Repeat echocardiography showed preserved biventricular function. No

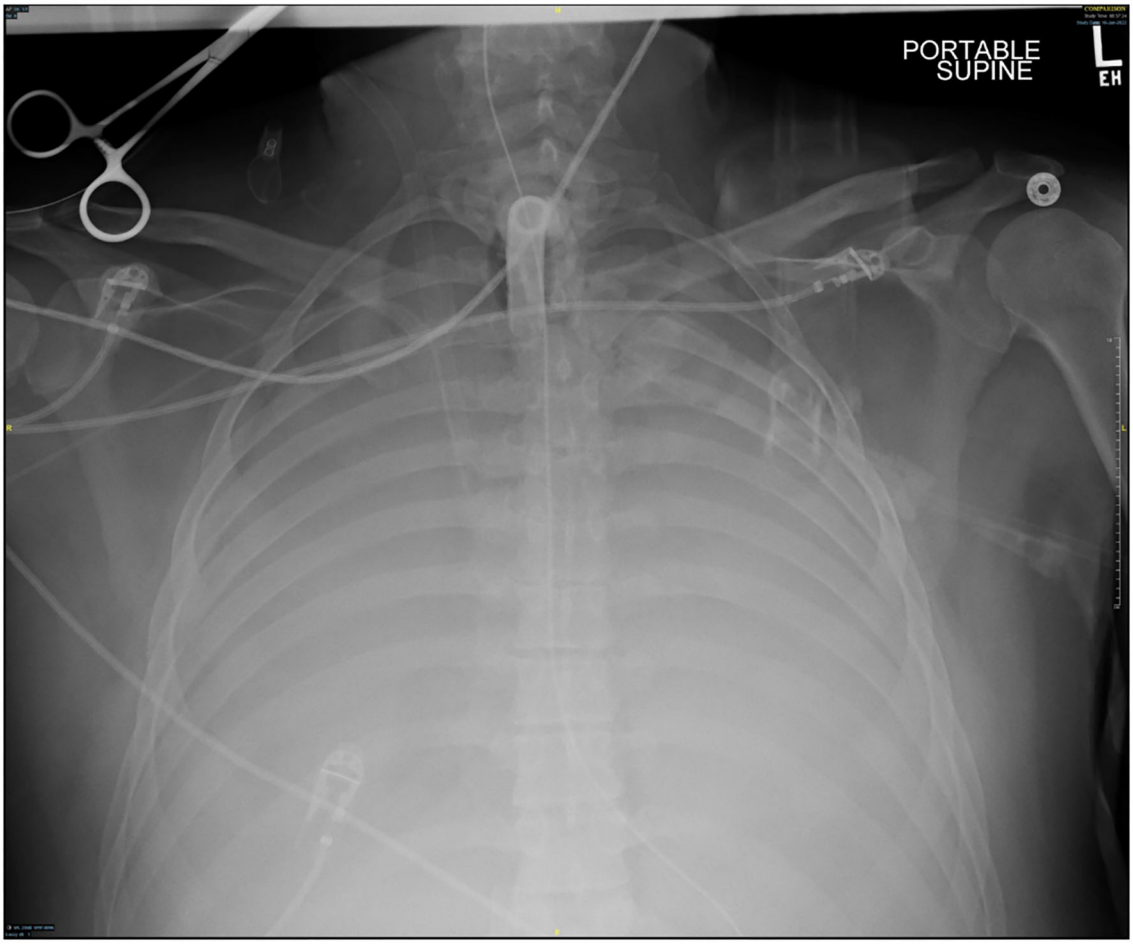

FIGURE 1
Chest x-ray at the time of hemoptysis.

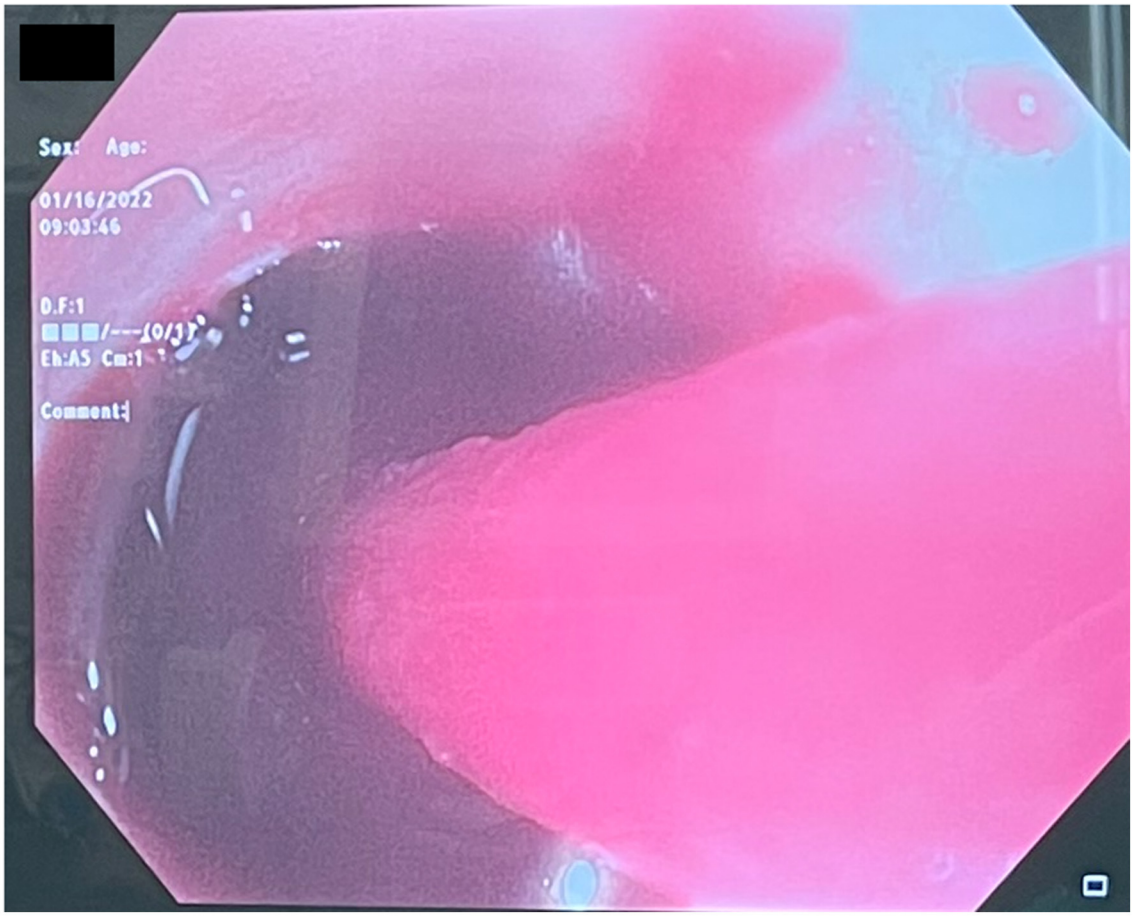

FIGURE 2
Bronchoscopy reveals massive hemoptysis.

inotropes or vasopressors were required to maintain adequeate hemodynamics; however, desaturation below 80% was noted by the bedside monitor. A multidisciplinary meeting was held regarding his severe hypoxia and hypercapnia, and decided to place ECMO. VV ECMO was chosen instead of venoarterial ECMO (VA ECMO) because cardiac function was preserved (2). The right femoral vein was cannulated with a 25-Fr cannula and the right internal jugular vein with a 20-Fr cannula, followed by a 5,000 unit heparin bolus (2). After VV ECMO was established, ventilator settings were adjusted to lung-protective setting (FiO_2 100%, PEEP 15 cm H_2O, RR 10, TV 315 cc (ideal body weight [IBW] x 5 cc). The VV ECMO circuit was flowing 4.5–5.0 L/min with FiO_2 100% and sweep 8 L/min. ABG on these settings demonstrated progress with pH 7.41, $PaCO_2$ 42 mm Hg, and PaO_2 86 mm Hg. PTT was maintained in the rage of 45–55 s with heparin per our protocol (2).

On hospital day #12 (VV ECMO day #5), tracheostomy was performed without complications. Paralytics were discontinued after tracheostomy, though lung-protective ventilator settings were maintained as FiO2 requirements began to decrease (FiO_2 50%, PEEP 8 cm H_2O, RR 10, and TV 315 cc). The VV ECMO circuit was flowing nearly 5 L/min with 100% FiO2 and sweep of 9.

Several days after tracheostomy (hospital day #18, VV ECMO day #11) hemoptysis developed and it persisted despite holding heparin drip and normal platelet counts. His chest x-ray demonstrated bilateral opacifications (Figure 1). Dark blood was suctioned continuously from the tracheostomy and hemoglobin repeatedly dropped requiring transfusions. VV ECMO settings were increased to 100% FiO_2 as the VV ECMO sweep was maximized to 11 L/min to maintain SpO2 >85%. Bedside bronchoscopy revealed massive bleeding in the left and right main bronchi. Ice cold saline and epinephrine lavage failed to control the bleeding, thus the site of bleeding was unable to be identified. Despite the evacuation of more than 500 cc of blood under bronchoscopy, there was continued hemorrhage from both main bronchi (Figure 2). The tracheostomy tube was

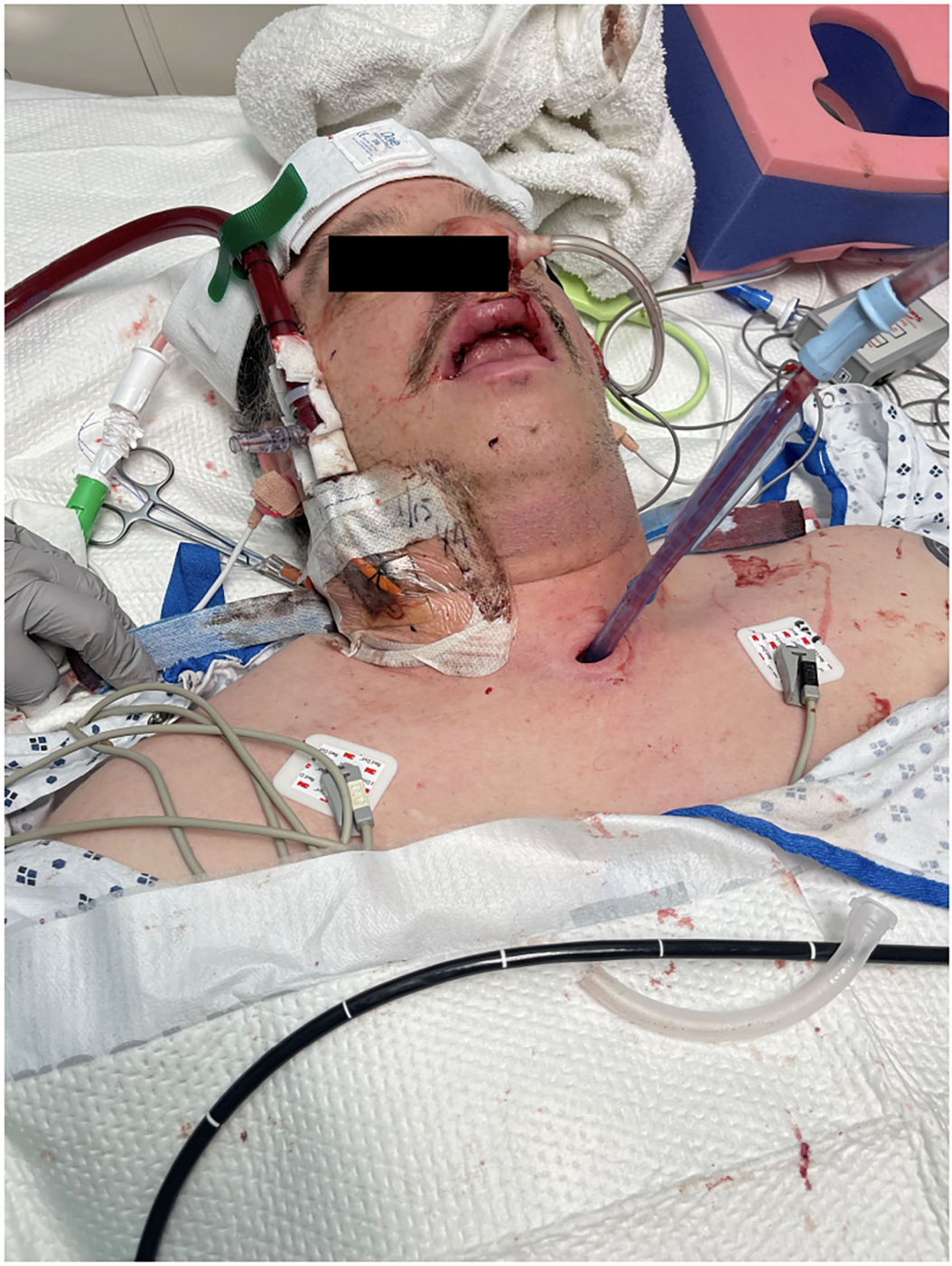

FIGURE 3
Tracheostomy tube was removed, and direct suction was performed from tracheal stoma using Yankauer catheter.

removed to examine the stoma, and no active bleeding was identified in that area. A direct suction was then attempted, inserting a Yankauer suction catheter into the trachea *via* the tracheostomy stoma (Figure 3). This was also unsuccessful in clearing the airway. In further attempts to control bleeding, continuous bronchoscopy was performed for 4 h with the maintenance of adequate SpO2 >85% despite discontinuation of the ventilator.

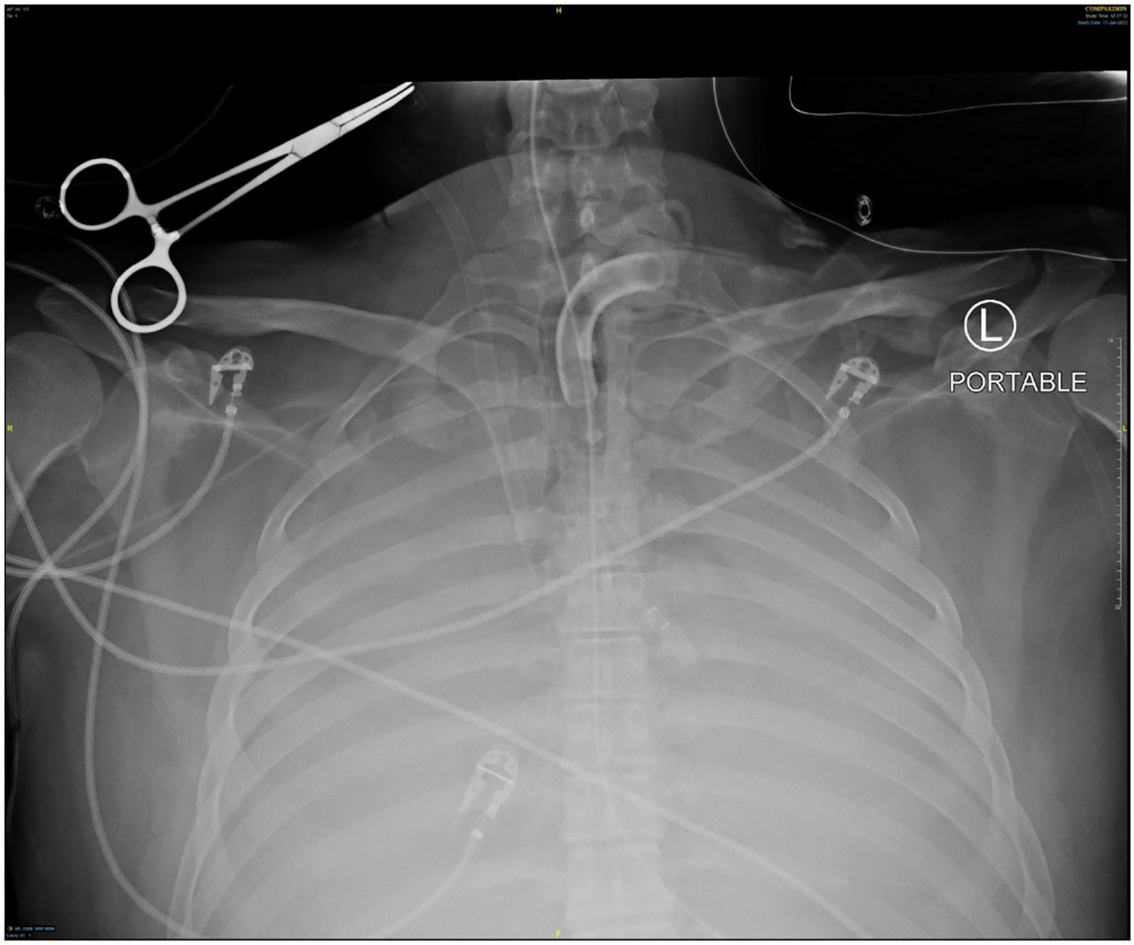

FIGURE 4
Chest x-ray off ventilator support.

Given adequate oxygenation, the decision was made to temporarily discontinue mechanical ventilation post-bronchoscopy to allow clot formation in the tracheobronchial tree. Paralysis was reinitiated to minimize oxygen consumption. Systemic anticoagulation and antiplatelet therapy were discontinued to promote clot formation. Due to the presence of VV ECMO, HemoSphere^{TM} (Edwards Lifesciences, Irvine, CA) technology with near-infrared tissue oximetry was utilized to sustain adequate cerebral and somatic saturation. Goals were set to maintain regional cerebral saturation >60% and somatic tissue saturation >50% for each lower extremity. Cardiac hemodynamics were evaluated non-invasively *via* FloTrac^{TM} (Edwards Lifesciences, Irvine, CA) monitoring system, with a goal cardiac index of 2.5 L/min/m^2.

Though active hemorrhage had ceased during this time of mechanical ventilation, the patient's chest x-ray continued to exhibit bilateral opacification (Figure 4). On hospital day #20 (VV ECMO day #13), a repeat bronchoscopy was performed to remove clot which had formed from the bilateral bronchi with some radiographic progress. Due to improvement in active hemoptysis, the ventilator was restarted with a minimum TV of 250 cc (IBW x 4 cc) after 48 hours of complete discontinuation of ventilator. Serial declotting bronchoscopies were then performed utilizing various bronchoscopic instruments including a basket, biopsy clamp, and brush to facilitate clot retrieval. This process was continued daily until all visible clot was removed and chest x-ray demonstrated decreased opacification (Figure 5). Bronchoscopy was performed a total of 14 times. Antiplatelet therapy was then resumed, and there was no recurrence of bronchial hemorrhage, although systemic heparin and anti-platelet agents were held.

Despite low tidal volumes, the patient's peak airway pressure remained elevated above 40 cm H_2O. Due to rising peak airway pressures, the ventilator mode was switched to pressure control ventilation (PCV) with 15 cm H_2O above PEEP 15 cm

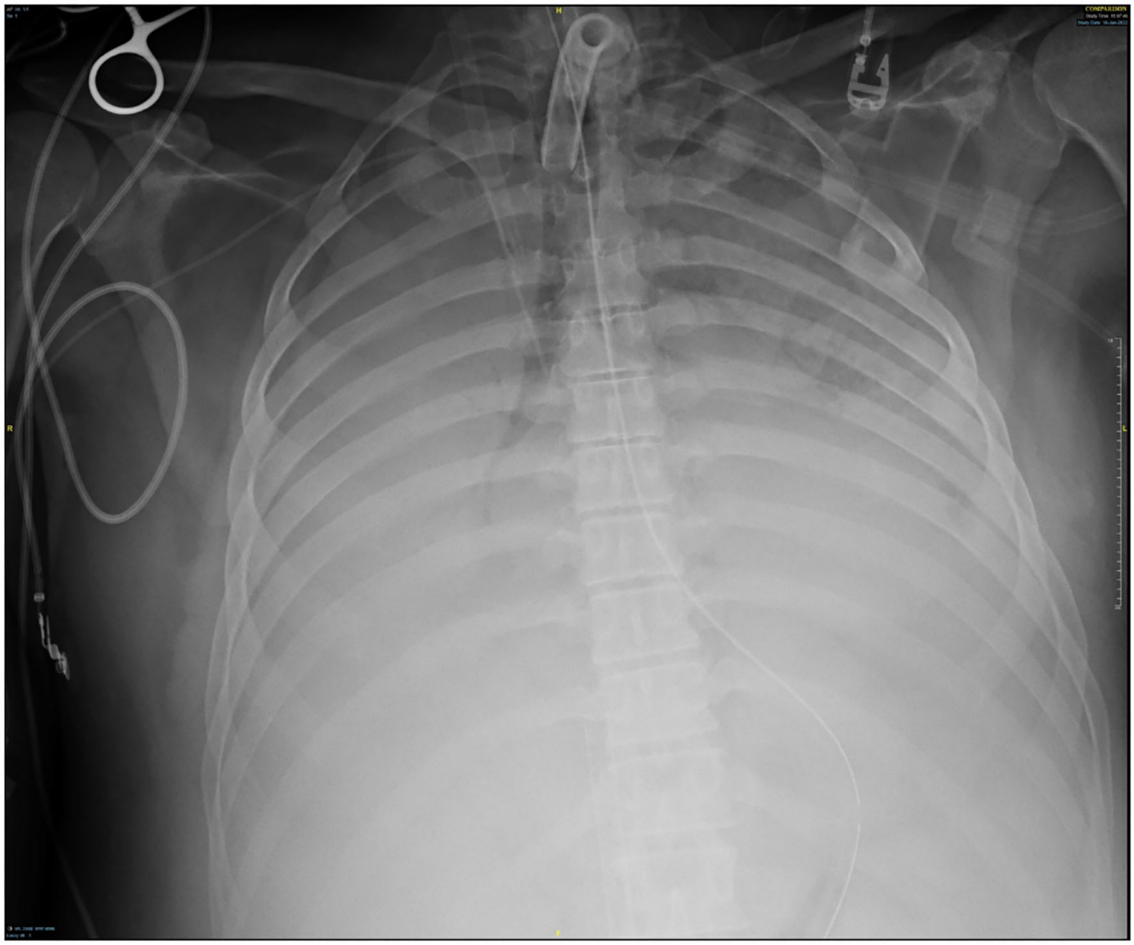

FIGURE 5
Chest x-ray 2 days after resuming ventilator.

H_2O. Over time, chest x-ray findings improved on these ventilator settings, with TV ∼50cc (Figure 6). Sweep gas was adjusted to meet a goal $PaCO_2$ ∼40 mm Hg, and TV was gradually increased. Once an appropriate TV of 300 cc was consistently achieved by PCV, paralysis was discontinued. At that time, the ventilator mode was changed from PCV to Volume Control (VC) with a tidal volume of 315 cc (IBW x 5cc).

Of note, the patient's hospital course was further complicated by acute renal failure requiring continuous veno-venous hemodialysis (CVVHD) and *Serratia* and *Klebsiella pneumonia* treated with the appropriate antibiotics.

As his respiratory status improved, VV ECMO FiO_2 and sweep were decreased as tolerated. VV ECMO sweep gas was eventually minimized and his ABG remained appropriate with standard ventilator support of 50% FiO_2, PEEP 10 cm H_2O, and TV 570 cc. With significant radiographic improvement (Figure 7), VV ECMO was successfully decannulated at the bedside on hospital day #37 (VV ECMO day #30). There was no thrombotic complication or pump thrombosis even though we held anticoagulation while VV ECMO run. CVVHD was converted to hemodialysis on hospital day #42 (VV ECMO removal day #5). The ventilator was eventually switched to pressure support ventilation (PSV) which the patient tolerated well. The patient was mobilized to the chair daily and was able to communicate without evidence of neurological compromise. On hospital day #73 (VV ECMO removal day #36), the patient was successfully discharged to an acute rehabilitation facility. The patient had an outpatient office visit 3 months after VV ECMO discontinuation without the need of tracheostomy or hemodialysis. At that time, his oxygen saturation was 98% with 2L nasal cannula supplemental oxygen and he was able to walk without assistance. There was no desaturation with 6 min walk test. He was eventually return to work without physical disability.

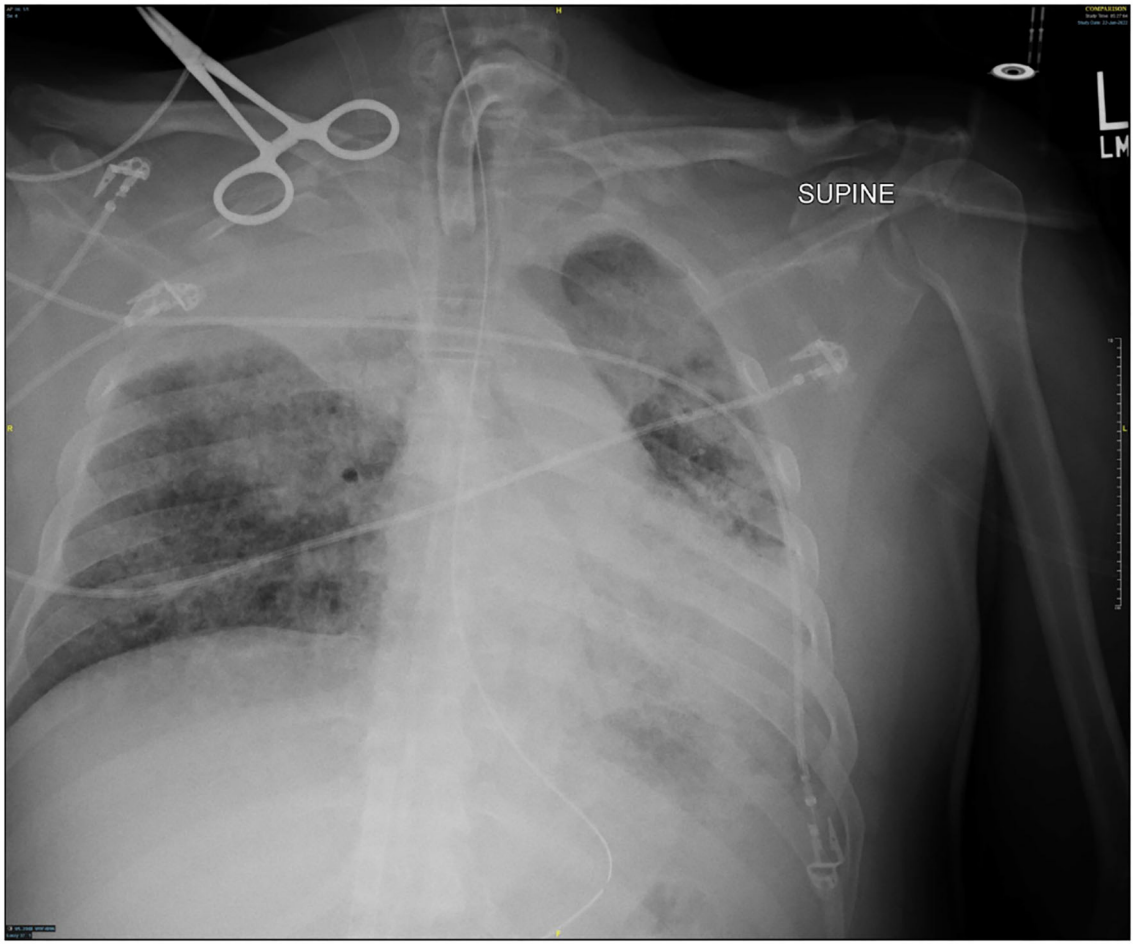

FIGURE 6
Chest x-ray 4 days after resuming ventilator.

Discussion

In the setting of massive hemoptysis, VV ECMO has been used for rescue oxygenation and ventilation support (3–5). In prior cases, ECMO was used as a bridge to definitive treatment but was not utilized in conjunction with prolonged induced apnea. A contributing author in this case study has previously reported VA ECMO support for massive hemoptysis (6). The case study reinforced discontinuation of mechanical ventilation under ECMO support, but was used, in conjunction with bronchial artery embolization by interventional radiology and subsequent serial bronchoscopies for clot removal.

Induced apnea *via* temporary ventilator cessation can be safely used to facilitate airway clot formation while using VV ECMO as primary support for adequate oxygenation and ventilation. This strategy can lead to eventual tamponade of bleeding sites. Alternatively, if the active bleeding can be localized to a single site, a bronchial blocker and one lung ventilation approach may be utilized (7). Bronchial blocker with one lung ventilation was not feasible in the case presented due to diffuse bilateral bleeding. Additionally, the use of bronchial artery embolization was not possible as with bilateral bleeding there was likely a need for multiple embolizations of the bronchial and/or pulmonary arteries.

Although ECMO provided sufficient oxygenation during ventilator cessation, systemic circulation was monitored by conventional pulse oximetry, arterial blood gases, cerebral/somatic tissue saturation, and cardiac output provided *via* FloTrac^{TM}. Near-infrared technology was essential to ensure appropriate cerebral oxygenation during deep sedation (5). With continuous cerebral saturation data, sedation was adjusted confidently to maintain adequate oxygenation and allow resting of brain activity (8).

While on VV ECMO, appropriate cardiac output must be maintained in order to circulate oxygenated blood from the right side of the heart *via* native cardiac ejection (9). This requires

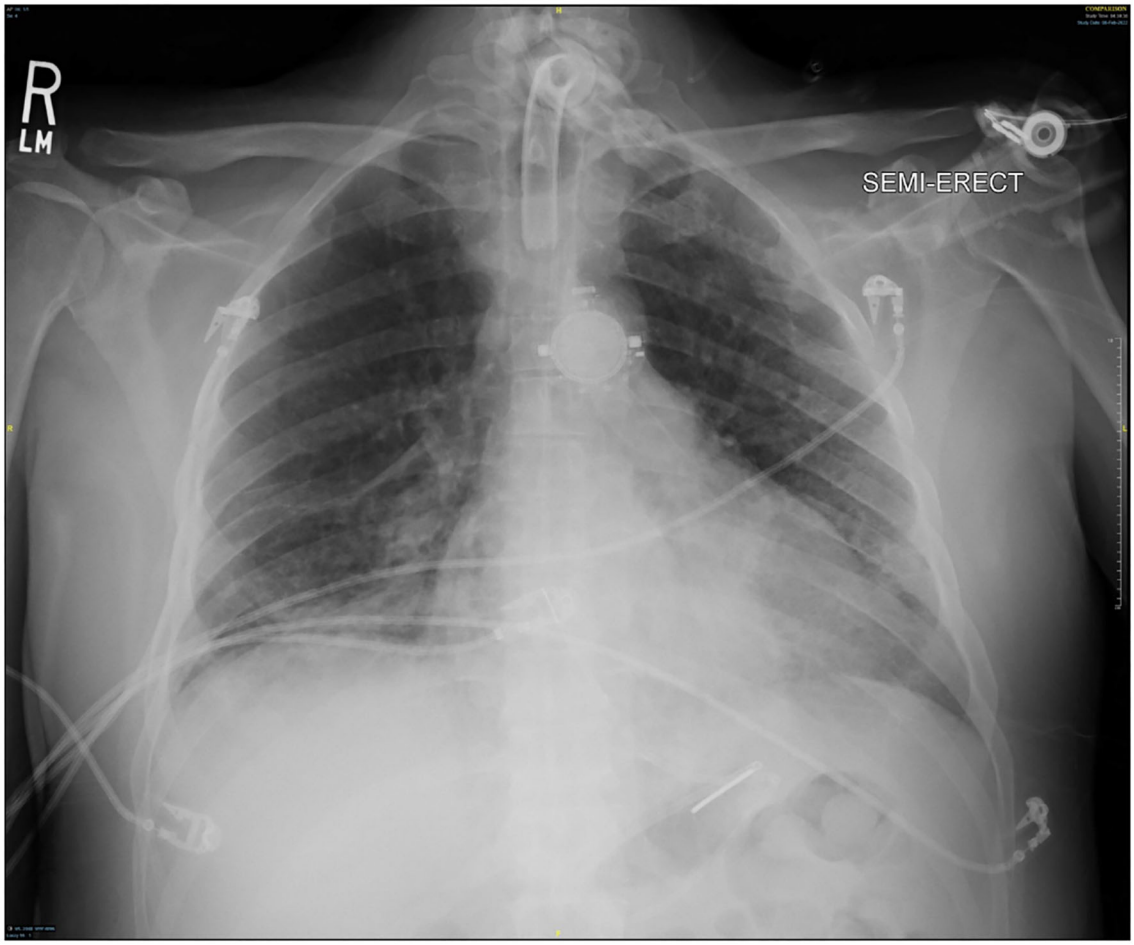

FIGURE 7
Chest x-ray after ECMO decannulation.

preserved cardiac function. If cardiac status is depressed, VA ECMO would be a more appropriate modaility for mechanical circulatory support, rather than VV ECMO. In this case, VV ECMO was selected because patient had preserved biventricular function.

Monitoring cardiac function in patients with massive hemoptysis is essential as some may develop cardiac dysfunction either from hypoxia or stress-induced cardiomyopathy. This was assessed intermittently *via* transthoracic echocardiography and continuously *via* FloTrac^{TM} technology throughout the patient's hospital course. New technology provided by FloTrac^{TM} uses an arterial pressure waveform to calculate left-sided cardiac output using the patient's arterial line (10). Non-invasive hemodynamic monitoring is preferred since thermodilution cardiac output assessments are not accurate in patients on VV ECMO due to the return of blood from the ECMO circuit to the right side of the heart. Mixed venous saturations are also falsely elevated for this reason. In this case, the non-invasive FloTrac^{TM} device was primarily utilized while on VV ECMO to ensure that sufficient cardiac output was maintained.

The etiology of massive hemoptysis in this patient remains unknown (7). The initial presumed cause was trauma to the tracheobronchial tree during tracheostomy; however, the tracheostomy stoma was without hemorrhage on multiple inspections. Additionally, the carina was evaluated and no injury was localized. Anticoagulation-induced bleeding is common in ECMO patients; however, it is less likely the source in this study as PTT was tightly controlled within the 45–55 range as per our protocol (11). Another etiology considered was medication induced platelet dysfunction given recent cardiac stenting after anterior STEMI. This was later deemed unlikely as bleeding did not recur upon reinitiation of antiplatelet therapy. Hemoptysis secondary to tracheo-innominate artery fistula is typically seen as a late complication following tracheostomy but has been reported to develop as early as 3 days post procedure (12). Bleeding from this type of fistula is classically

seen to the right of the 6–10th tracheal rings, located in close proximity to the innominate artery (13). Mortality from tracheo-innominate fistula without surgical or endovascular intervention is reported to be nearly 100% (13). In this case, bleeding ceased without surgical or endovascular involvement, suggesting the source of hemorrhage was more likely in the bilateral lower airways than from a tracheo-innominate fistula. Lastly, diffuse alveolar hemorrhage was considered. It can be seen in severe inflammatory lung disease and is diagnosed *via* lung biopsy. This cause cannot be confirmed here as a lung biopsy was not obtained; however, diffuse alveolar hemorrhage was ultimately suspected as the etiology of bleeding in this case.

We propose the following clinical pathway for a patient with massive hemoptysis: (1) appropriate selection of ECMO support, (2) discontinuation of anticoagulation and antiplatelet therapy, (3) bronchoscopy to identify bleeding sites, (4) bronchial blocker or one lung ventilation if bleeding is localized, (5) induced apnea with mechanical ventilation cessation and full respiratory support *via* VV ECMO to facilitate clot formation, (6) initiation of deep sedation and paralysis, (7) continuous cardiac output and cerebral saturation monitoring, (8) serial bronchoscopies for clot removal following successful tamponade *via* the above measures, and (9) progressive return to ventilator support.

Conclusion

Massive hemoptysis while on ECMO can be managed with induced apnea by temporarily discontinuing the ventilator and utilizing VV ECMO as primary support for oxygenation and ventilation. This combination is best used to provide full pulmonary support and safely allows tamponade of bleeding sites. Following hemorrhage cessation, serial bronchoscopies can be performed to remove formed clots from the airways. With time, mechanical ventilation can be gradually resumed and VV ECMO support decreased. In successful cases, there will be a reduction in oxygen requirements and radiographic improvement of the lungs with the resolution of lung opacification. Because of this, mechanical pulmonary support with VV ECMO can be successfully weaned while maintaining satisfactory gas exchange as hemoptysis resolves.

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 Virtua Health. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

Author DR serves as a clinical consultant of Edwards Lifesciences.

The remaining 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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EDITED BY
Matteo Cameli,
University of Siena, Italy

REVIEWED BY
Suguru Ohira,
Westchester Medical Center,
United States
Diego Chemello,
Federal University of Santa Maria, Brazil

*CORRESPONDENCE
Baudouin Bourlond
baudouin-philippe.bourlond@chuv.ch

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Case report: Disseminated *Scedosporium apiospermum* infection with invasive right atrial mass in a heart transplant patient

Baudouin Bourlond[1]*, Ana Cipriano[2], Julien Regamey[1], Matthaios Papadimitriou-Olivgeris[2], Christel Kamani[1,3], Danila Seidel[4,5,6,7], Frederic Lamoth[2,8], Olivier Muller[1] and Patrick Yerly[1]

[1]Department of Cardiology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [2]Infectious Diseases Service, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [3]Department of Nuclear Medicine and Molecular Imaging, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [4]Department I of Internal Medicine, Faculty of Medicine, University Hospital Cologne, University of Cologne, Cologne, Germany, [5]Center for Integrated Oncology Aachen Bonn Cologne Dusseldorf (CIO ABCD), University of Cologne, Cologne, Germany, [6]Excellence Center for Medical Mycology (ECMM), University of Cologne, Cologne, Germany, [7]Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany, [8]Department of Laboratories, Institute of Microbiology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Scedosporium apiospermum associated endocarditis is extremely rare. We report a case of a disseminated *S. apiospermum* infection with an invasive right atrial mass in a 52-year-old male, 11 months after heart transplantation, referred to our institution for an endogenous endophthalmitis with a one-month history of diffuse myalgias and fatigue. The patient had been supported two times with extracorporeal membrane oxygenation (ECMO) during the first three postoperative months. The echocardiography on admission revealed a mass in the right atrium attached to a thickened lateral wall. The whole-body [^{18}F]FDG PET/CT revealed systemic dissemination in the lungs, muscles, and subcutaneous tissue. Blood cultures were positive on day three for filamentous fungi later identified as *S. apiospermum*. The disease was refractory to a 3-week dual antifungal therapy with voriconazole and anidulafungin in addition to reduced immunosuppression, and palliative care was implemented.

KEYWORDS

***Scedosporium apiospermum*, *Lomentospora prolificans*, PET/CT, infective endocarditis, mycoses, heart tranplantation, heart failure**

Introduction

Fungal infective endocarditis (FE) remains the most serious form of infective endocarditis, associated to a high mortality rate (∼50%) (1). In about half of the cases, *Candida* species account for FE, *Aspergillus* spp., account for one fourth of the cases (2). Non-*Aspergillus* molds infective endocarditis account for the remaining of cases, with *Scedosporium* spp. being seldom identified.

Scedosporium spp. are filamentous fungi, ubiquitous in the environment and commonly found in temperate climates. *Scedosporium apiospermum* and *Lomentospora prolificans* (formerly *S. prolificans*) (S/L) are the major pathogens in humans (3). Infection occurs after inhalation of spores into the lungs or paranasal sinuses or through direct skin inoculation after traumatic injuries or during surgery. Medical care advances increased the number of immunocompromised patients with non-*Aspergillus* mold infections (NAIMI). In solid organ transplant (SOT) recipients, approximately 25% of NAIMI are caused by S/L, representing 1% of all fungal infections in these patients (4, 5). In this population, pretransplant colonization of the respiratory tract (lung transplant recipients), prior amphotericin B treatment, and enhanced immunosuppression, as a treatment for organ rejection, represent the major associated risk factors for NAIMI (6).

Scedosporiosis and lomentosporiosis are of particular concern due to intrinsic resistance to most available antifungal drugs. Outcomes seem to be better with *S. apiospermum* infection, which presents a better response to antifungal agents. Voriconazole appears to have the best *in vitro* activity and is considered the drug of choice by most international guidelines (7). Combined antifungal therapy with echinocandins may be used against *S. apiospermum*, as a synergistic effect has been described (6, 8, 9). Where possible, surgical debridement and immunosuppression reduction should be part of the treatment management (6, 9).

Case presentation

A 52-year-old male patient was referred to our hospital by the ophthalmologist for additional work-up in the context of endogenous endophthalmitis. He reported a one-month history of migratory myalgia without fever, one-week history of abdominal pain with vomiting, atraumatic eyes pain for two days, and an isolated cutaneous nodule on the right inferior limb (**Figure 1**, Panel A). He had received a heart transplantation for dilated cardiomyopathy 11 months prior to admission and had been on a left ventricular assist device (Heartmate 3TM) for three years before transplantation. His transplant operation had been complicated with primary graft failure necessitating eight days of mechanical support with veno-arterial ECMO. Moreover, he had suffered from a nosocomial SARS-CoV2 infection on the third post-operative month, with acute respiratory distress syndrome treated with tocilizumab, and refractory hypoxemia necessitating 18 days of venovenous ECMO. In both cases, peripheral cannulation of the right atrium was used.

At presentation (day 1), he was on immunosuppressive therapy with prednisolone 12.5 mg od, tacrolimus 3 mg bid, and mycophenolate mofetil 720 mg bid. On admission, blood pressure was 140/76 mmHg with a resting heart rate of 70 beats per minute and a temperature of 36.3°C. Physical examination was noteworthy for diffuse right eyelid edema, a painless purplish cutaneous nodule of the outer edge of the tibia (**Figure 1**, Panel A), and asymmetric erythema of the right ankle. Cardio-pulmonary, neurological and abdominal examinations were regular.

Diagnosis, management and follow-up

The cardiac workup included a transthoracic echocardiography revealing an atrial mass measuring 15 × 18 mm, with a thickened lateral wall without associated tricuspid valve anomalies (**Figure 2A**). These findings were confirmed with transoesophageal echocardiography, which showed an abscessed pattern in this mass and moving filaments (**Figure 2B**). The fundoscopy revealed bilateral endogenous endophthalmitis and Roth spots. Laboratory tests showed increased inflammatory parameters (CRP: 163 mg/L, procalcitonin: 0.66 mcg/L), with relatively low leucocyte count (4.8 G/L) and a KDIGO 1 acute kidney injury. Blood cultures were collected. In order to characterize the nature of the right atrial mass, a whole-body [^{18}F]FDG PET/CT after 24 h of dietary preparation and heparin pre-administration to suppress the physiological myocardial FDG uptake was performed (10). It showed an intense FDG accumulation of the right atrial mass with extension to the epicardium, which was suggestive of an active infectious process. Septic emboli in the lungs, muscles, and subcutaneous tissue were also evident (**Figure 3**). Brain magnetic resonance imaging (MRI) also highlighted multiple brain lesions.

The first suspected diagnosis was bacterial endocarditis with secondary endogenous endophthalmitis (*Staphylococcus aureus,* streptococci, or enterococci as the most likely pathogens). Therefore, intravenous empirical antibiotic therapy with vancomycin and co-amoxicillin was started while awaiting blood cultures and the culture of a vitreous sample. Twenty-four hours later, due to increased serum beta-D-glucan antigen (>500 pg/ml) and negative blood cultures a fungal infection was suspected and liposomal amphotericin B (5 mg/kg) was initiated. The immunosuppression was reduced to the minimum with prednisone 5 mg and tacrolimus for trough levels at 5–7 ug/L. Blood cultures were positive for filamentous fungi on day 3. *S. apiospermum* was identified as the causative pathogen three days later (day 6) and liposomal amphotericin B

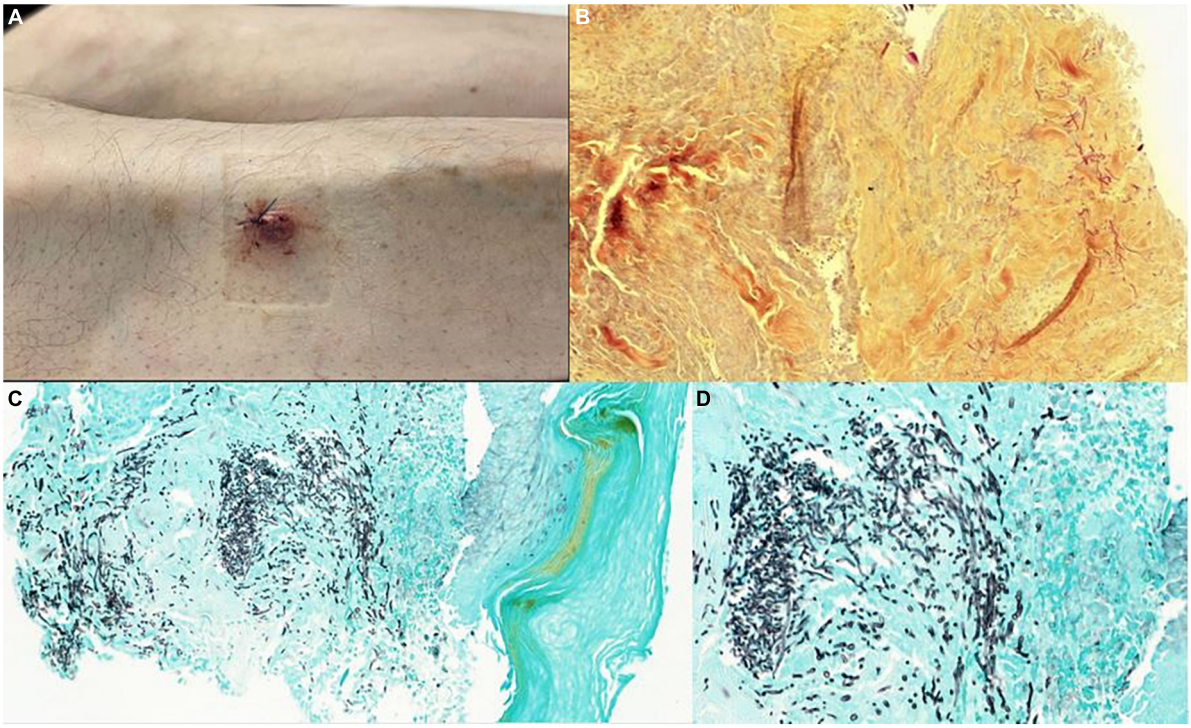

FIGURE 1
Painful purplish cutaneous nodules **(A)**, pathology examination with Periodic Acid Schiff coloration 10x **(B)**, and colorations with GROCOTT stain of cutaneous nodules showing regular septate filaments connected with 45-degree divisions 10x **(C)** and 40x **(D)**.

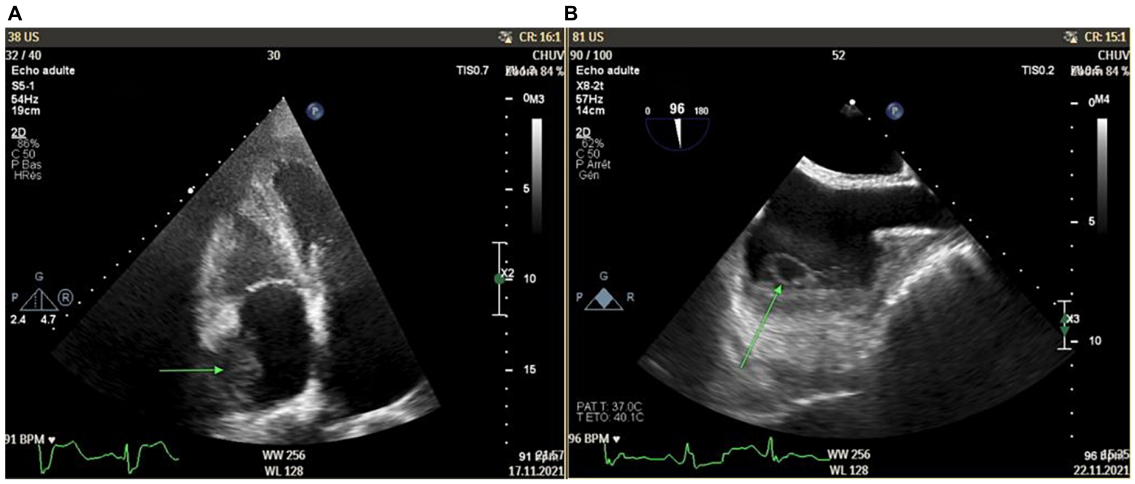

FIGURE 2
Right atrium mass (15 × 18 mm) with thickened lateral wall without associated tricuspid valve anomalies as shown in transthoracic echocardiography [green arrow, Panel **(A)**] and transesophageal echocardiography [green arrow, Panel **(B)**].

(minimum inhibitory concentration, – MIC 2.0 mg/l) switched to combination therapy with voriconazole (6 mg/kg bid the first day and then 4 mg/kg bid; MIC 0.25 mg/l) and anidulafungin (200 mg the first day and then 100 mg/day; MIC 1 mg/l). The endophthalmitis was treated with an intravitreal injection of ceftazidime and vancomycin. After *S. apiospermum* was identified, two intravitreal injections of voriconazole 0.5 mg were performed. Surgical resection of the right atrial mass was early discussed but refrained considering the invasion of the atrial wall, the disseminated disease, and the patient's poor

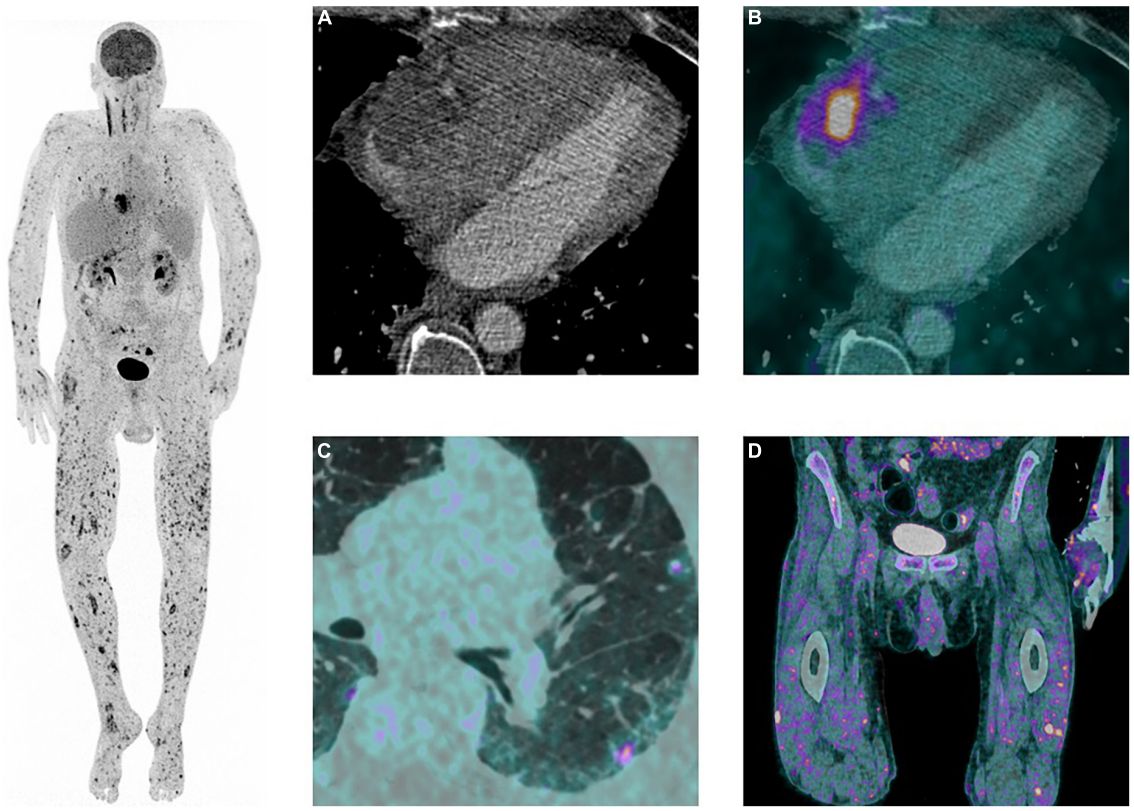

FIGURE 3
^{18}F-fluodeoxyglucose ([^{18}F]FDG) Positron emission tomography (PET)/computed tomography angiography (CTA) findings. Left: Maximum intensity projection image of the whole body showing pathological focal diffuse [^{18}F]FDG uptake of the trunk as well as the upper and lower extremities. Right: **(A)** Cardiac CTA showing an heterogeneous mass with irregular margins, in contact with the lateral wall of the right atrium with extension in the pericardial space. **(B)** Transaxial view of [^{18}F]FDG PET/CTA showing pathological [^{18}F]FDG accumulation of the right atrial mass, suggestive of an active infectious process. **(C)** Transaxial view of [^{18}F]FDG PET/CTA showing focal subpleural nodules with increase [^{18}F]FDG accumulation in the left lung, suggestive of septic emboli. **(D)** Coronal view of [^{18}F]FDG PET/CT showing focal increased cutaneous and subcutaneous [^{18}F]FDG accumulation in the proximal part of the lower limbs, suggestive of septic emboli.

general condition with worsening asthenia and daily loss of weight despite enteral and then parenteral nutrition.

Despite dual antifungal therapy and reduced immunosuppression, the patient presented with ongoing fever, declining general condition, and a confusional state favored by brain abscesses and severely impaired vision. During this time, cardiac function remained stable, and no local complications of the atrial mass such as atrial obstruction, wall rupture with pericardial effusion, or invasion of the tricuspid valve were observed during serial echocardiographic assessments. Nevertheless, he developed multiple painful purplish cutaneous nodules, two of whom were biopsied and revealed regular septate filaments connected with 45-degree divisions on the Periodic Acid Schiff (PAS) and GROCOTT coloration (**Figure 1**). These lesions were extremely painful, and pain management was a true challenge in the context of severe renal impairment and worsening liver function related to the toxicity of antifungal therapies. A high dose of intravenous fentanyl was necessary in addition to anxiolytic treatment.

After three weeks of optimal medical treatment, cerebral MRI and [^{18}F]FDG PET/CT were performed and showed no regression of the multiple lesions. The clinical course continued to be unfavorable, with the patient's general condition declining rapidly. At his request, palliative care was started. He was transferred to a palliative institution, where he deceased a few days later.

Discussion/Conclusion

Scedosporiosis/lomentosporiosis, even though rare, is of particular concern due to intrinsic resistance to available antifungal drugs. Current clinical guidelines recommend voriconazole alone or in combination and surgical source control (7, 8).

By microscopy, the morphological characteristics of these fungi are well characterized and distinct with the presence of ovoid or pyriform conidia arising as a single terminal spore

TABLE 1 Literature review of infective endocarditis caused by *Scedosporium* spp. in solid transplant patients.

Case	Reference	Sex(M/F)/ age(years)	Organ transplanted	Year of transplant	Year of infection	Immunosuppression	Insolation site	Disseminated infection	Cardiac site	Treatment	Cardiac surgery	Outcome
1	(18)	F/37	Lung	2008	2008	T, M, P	Blood, bronchial secretion, cutaneous biopsy	Yes	Native mitral valve	Voriconazole, caspofungin, terbinafine	Yes	Deceased
2	(19)	M/35	Lungs and liver	2012	2012	B, T, M, P	Autopsy	Yes	No precision	Caspofungin, voriconazole	No	Deceased
3	(20)	M/19	Heart	2013	2013	B, T, M, P	Blood	Yes	Papillary muscle of both ventricles	Amphotericin-B	No	Deceased
4	(21)	M/70	Heart	2011	2014	T	Blood, valve culture, synovial fluid	Yes	Native tricuspid valve	Posaconazole, terbinafine	Yes	Deceased
5	(22)	M/62	Lung	2014	2014	Unknown	Bronchial aspirate, surgical incision, post-mortem analysis	Yes	Left ventricle	Amphotericin-B	No	Deceased
6	Present study	M/52	Heart	2020	2021	T, M, P	Blood	Yes	Right atrium	Liposomal amphotericin B, voriconazole, anidulafungin	No	Deceased

B: basiliximab for induction, M: mycophenolate mophetil, P: prednisone, T: tacrolimus.

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from a long tiny conidiophore (*S. apiospermum* complex) or in clusters from a short flask shaped conidiophore (*L. prolificans*).

Invasive scedosporiosis represents 13–33% of infections due to non-*Aspergillus* molds (11). Fifty-seven cases of scedosporiosis were described in the United States, while only 5 cases have been reported with heart involvement worldwide (12), as shown in **Table 1**. In these cases, despite antifungal treatments (itraconazole, voriconazole, amphotericin B), there was no survivor (6, 13).

Our patient was on tacrolimus, which was previously shown to have synergistic effect with azoles *in vitro* and in a *Galleria mellonella* larvae model (14). However, this synergistic effect is obtained at high concentrations of tacrolimus (i.e., beyond the therapeutic range) and is counterbalanced by the strong immunosuppressive effect of this calcineurin inhibitor which may favor invasive fungal infections. As previously shown, despite this synergistic effect, the outcome was unfavorable for our patient.

It is noteworthy that novel antifungal agents, such as fosmanogepix (inhibitor of the glycosylphosphatidylinositol biosynthesis) and olorofim (inhibitor of the dihydroorotate dehydrogenase), which are currently in phase II-III clinical trials, demonstrated potent *in vitro* activity and *in vivo* efficacy in murine models against *S. apiospermum* and *L. prolificans*, and therefore represent promising therapies for scedosporiosis/lomentosporosis in the future (9, 15, 16). Our case illustrates a unique presentation of this rare infection with an intra-cardiac mass in the right atrium infiltrating its lateral wall and the tricuspid annulus, with disseminated disease (bilateral endophthalmitis, lungs, brain, muscles, and subcutaneous tissue). The patient was supported with ECMO twice following heart transplantation, which suggests that the infection may have spread from the venous cannula of the ECMO in the right atrium. Moreover, in addition to his post-transplant immunosuppression, he received tocilizumab to treat his severe SARS-COV-2 infection. This IL-2 receptor inhibitor has been associated with an increased risk for fungal infections (17). This kind of infection can happen in transplant patients, especially if they previously had primary graft dysfunction (PGD) or veno-arterial ECMO.

Our case highlights the importance of early detection of the pathogen by fungal culture or indirect marker such as the beta-glucan test in serum (13). In addition to surgery and reduction of immunosuppression when possible, early identification and treatment may improve the chance of recovery and survival.

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

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors approved the manuscript, vouch for the accuracy, and completeness of the data.

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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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EDITED BY
Francesco Gentile,
Gabriele Monasterio Tuscany Foundation (CNR), Italy

REVIEWED BY
Francesco Negro,
University of Pisa, Italy
Nicolò Ghionzoli,
University of Siena, Italy

*CORRESPONDENCE
Yan Zhang
13611923471@163.com

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Case report: Takotsubo syndrome induced by severe hypoglycemia

Panpan Xia, Yan Zhang*, Yumin Sun and Jun Wang

Department of Cardiology, Jing'an District Central Hospital of Shanghai, Fudan University, Shanghai, China

Background: Takotsubo syndrome (TTS) is a disorder frequently characterized by transient dysfunction of the apical portion of the left ventricle with hyperkinesis in other parts of the heart walls. TTS is also called stress cardiomyopathy because it is known to be triggered by emotional or physical stress. We report a case of TTS associated with severe hypoglycemia.

Case summary: An 85-year-old female patient with a history of non-insulin-dependent diabetes mellitus and hypertension presented to the emergency department with hypoglycemia-induced unconsciousness. The patient regained consciousness after an intravenous glucose injection. The patient complained of chest discomfort after the correction of hypoglycemia. Electrocardiography (ECG) revealed ST-segment elevation in leads V_2-V_5, therefore, ST-segment elevation myocardial infarction was highly suspected. Echocardiography showed impaired left ventricular systolic function with an ejection fraction of 40% accompanied by hypokinesis of the apex. Percutaneous coronary angiography showed 30% stenosis of the left anterior descending coronary artery. Left ventricular angiography revealed apical dyskinesia, which is typical of the classic apical ballooning shape of takotsubo. The patient was diagnosed with TTS and managed with pharmacological therapy, including antiplatelet (i.e., aspirin), lipid-lowering, anti-heart failure, and hypoglycemic drugs. The patient was successfully discharged in a stable condition.

Conclusion: This is a representative case of TTS caused by hypoglycemia. Due to the self-limiting nature of TTS, diagnoses can be missed among hypoglycemic patients. Thus, echocardiography is required for patients with hypoglycemia to ensure an accurate TTS diagnosis in the emergency department.

KEYWORDS

takotsubo syndrome, stress, hypoglycemia, heart failure, case report

Introduction

Since its first description in Japan in 1990 (1), takotsubo syndrome (TTS), also known as stress cardiomyopathy, has emerged as a critical form of acute and transient regional left ventricular systolic dysfunction. Its pathogenesis is often related to emotional or physical stress (2, 3). Its prevalence is estimated to be 1–2% in patients with suspected acute coronary syndrome (ACS) (4, 5); however, it is often underestimated due to the self-limiting characteristic of the condition. Hypoglycemia is a physical stressor that can cause TTS (6–8); however, such cases are relatively rare. Here, we present a case of TTS associated with severe hypoglycemia.

Timeline

1-Day before presentation	The patient experienced repeated excretion of watery feces accompanied by nausea and vomited over 10 times after drinking iced soy milk.
Day 0	An 85-year-old female patient with a history of non-insulin-dependent diabetes mellitus and hypertension presented to the emergency department with hypoglycemia-induced unconsciousness.
Day 1	The patient was admitted to the cardiac care unit with suspected ST-segment elevation myocardial infarction (STEMI) and hypoglycemia. Echocardiography was performed.
Day 2	The patient underwent coronary and left ventricular angiography and was diagnosed with TTS.
Day 7	The patient experienced shortness of breath and mild edema of the lower limbs.
Day 14	Chest computed tomography (CT) was performed.
Day 21	Cardiac magnetic resonance (CMR) was performed.
Day 24	Echocardiography was performed again.
Day 26	The patient was discharged in a stable condition.
1-Month post-discharge	The patient remained asymptomatic. Echocardiography was performed again.

Case presentation

An 85-year-old female patient with a history of non-insulin-dependent diabetes mellitus treated with glimepiride and hypertension presented to the emergency department unconscious. The day before, the patient experienced repeated excretion of watery feces accompanied by nausea and vomited over 10 times after drinking iced soy milk. Rapid glucose testing revealed a blood glucose level of 0.3 mmol/L. Consciousness was regained after the administration of a 40-mL 50% glucose solution bolus. The blood glucose remeasurement level was 3.4 mmol/L. The next day, the patient experienced chest tightness and discomfort. Cardiac biomarkers were elevated: creatine kinase-MB, 21.1 ng/mL (reference range, < 4.90 ng/mL); myoglobin, 528 ng/mL (reference range, 28–72 ng/mL); troponin T, 1.120 ng/mL (reference range, 0–0.014 ng/mL); and N-terminal brain natriuretic peptide, 1,225 pg/mL (reference range, 0–300 pg/mL). Routine blood tests showed a C-reactive protein level of < 8 mg/L and a white blood cell count of 8.35×10^9/L. Electrocardiography (ECG) revealed sinus tachycardia, low limb lead voltage, and ST-segment elevation in leads V_2-V_5 of 0.1–0.3 mV (**Figure 1**). The patient was admitted to the cardiac care unit with suspected STEMI and hypoglycemia. Aspirin, clopidogrel, atorvastatin, and metoprolol were administered. The patient had a medical history of diabetes for the past 20 years and hypertension for 1 year. She had undergone a hysterectomy 30 years prior. She denied any familial diseases and smoking. Vital signs included a blood pressure of 122/68 mmHg, a heart rate of 102 beats/min, a respiratory rate of 18 breaths/min, and an oxygen saturation of 99% with a nasal tube.

Impaired left ventricular systolic function with an ejection fraction of 40% accompanied by hypokinetic apical movement, paradoxical movement of the myocardium from the papillary muscle to the apex, mild mitral regurgitation, and moderate-to-severe tricuspid regurgitation were detected using transthoracic echocardiography (UCG) (**Figures 2A,B**). The next day, percutaneous coronary angiography revealed 30% stenosis of the middle of the left anterior descending coronary artery (**Figure 3A**). Left anterior descending coronary artery intravascular ultrasonography showed partial intimal calcification of the coronary plaque but no plaque rupture or dissecting hematoma (**Figure 3A**). Left ventricular angiography revealed a takotsubo contractile pattern consisting of apical dyskinesis and basal hyperkinesis (**Figures 3B,C**). The patient was diagnosed with TTS potentially induced by hypoglycemia.

Shortness of breath and mild edema of the lower limbs were noted 1 week after admission, for which oral diuretics were administered. Follow-up ECG revealed a gradual decrease in the ST-segment elevation in leads V_2-V_5 with T-wave inversion appearing on the 8th day of admission (**Supplementary Figure 1**). Chest CT on day 14 showed minimal percolation from both lungs and bilateral pleural effusion (**Supplementary Figures 2A,B**). Intravenous diuretics were administered to relieve symptoms. Fortunately, repeated chest CT on day 21 revealed significantly reduced pleural fluid and pulmonary exudate (**Supplementary Figures 2C,D**). CMR examination performed 3 weeks after admission indicated that the heart apex was bulging toward the diaphragm with hypoactive contraction in the local left ventricle. Late gadolinium enhancement showed a weakly enhanced interventricular septum (**Figure 4**). UCG on day 24 revealed improvement in left ventricular systolic function with an ejection fraction of 54% (**Figures 2C,D**).

Eventually, the patient was discharged in a stable condition with oral heart medications, including metoprolol, sacubitril/valsartan, torsemide, antisterone, atorvastatin,

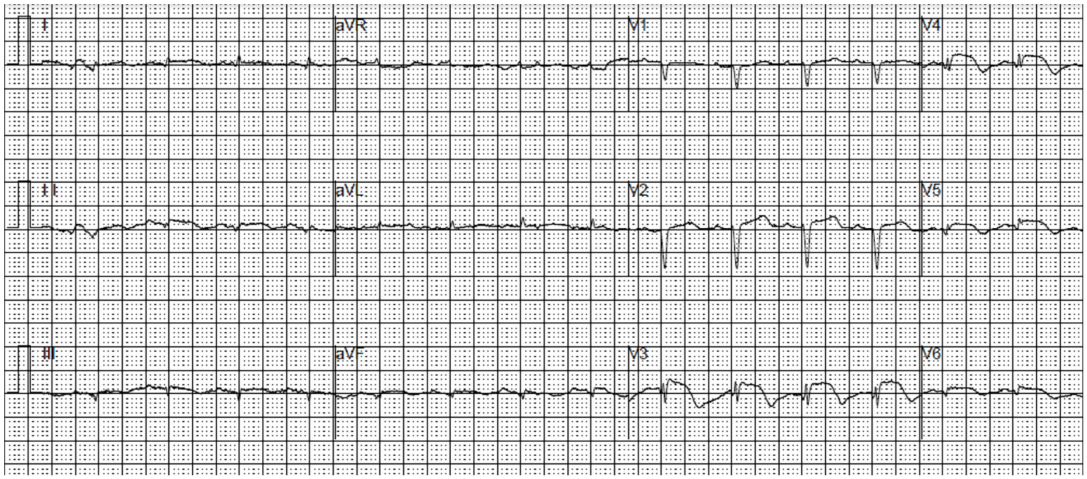

FIGURE 1
An electrocardiogram demonstrating sinus tachycardia, low limb lead voltage, and ST-segment elevation in leads V_2-V_5.

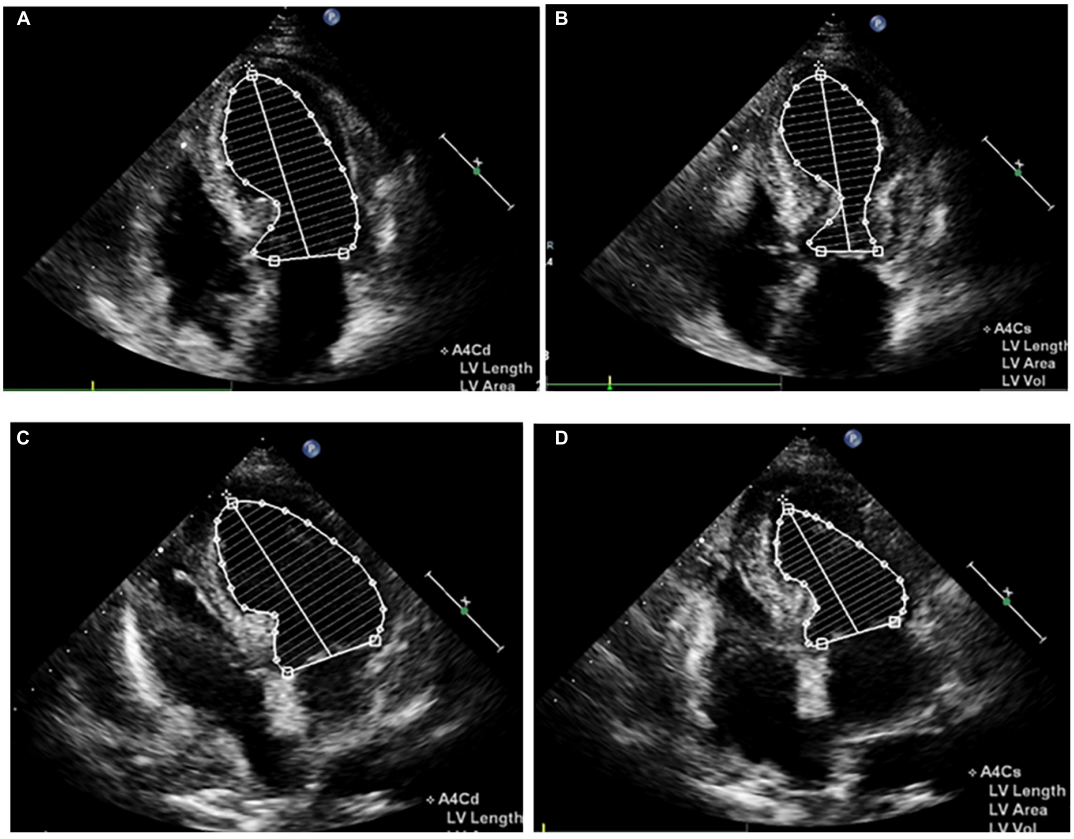

FIGURE 2
Apical four-chamber view echocardiogram reveals apical dyskinesis and basal to midventricular hyperkinesis **(A,B)**, as well as apex systolic function improvement **(C,D)**. **(A,C)** Diastole. **(B,D)** Systole.

empagliflozin, and alogliptin. Empagliflozin has been indicated for both diabetes and heart failure in such cases. Outpatient follow-ups and enrollment with a general practitioner were scheduled. At the 1-month follow-up, the patient remained in good condition with no symptoms and had been taking her medications regularly. UCG showed normal left ventricular

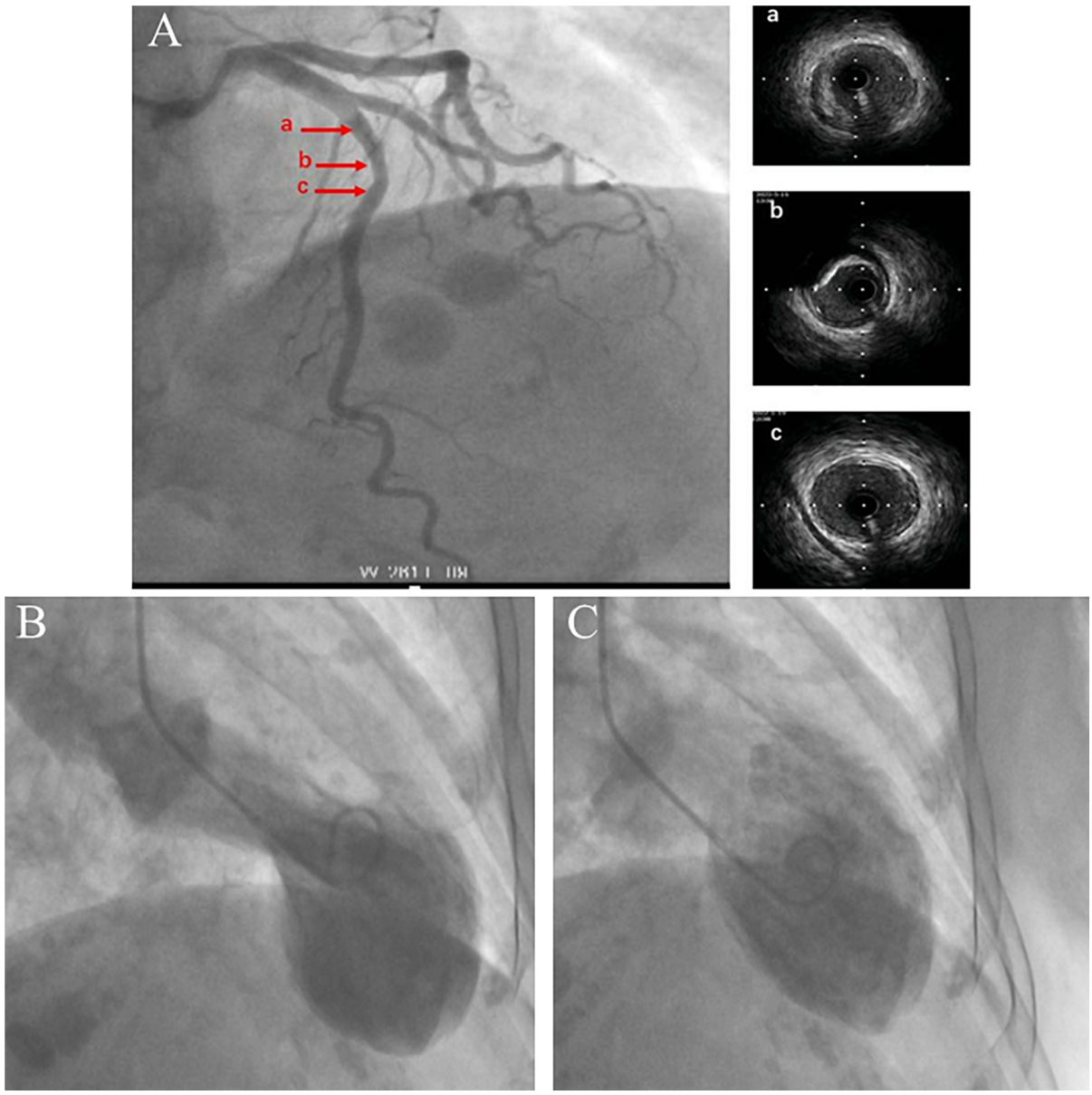

FIGURE 3
Coronary angiography and intravascular ultrasound show 30% stenosis of the left anterior descending coronary artery with no plaque rupture or dissecting hematoma. The a, b, and c arrows on the left correspond to the ultrasound positions labeled a–c on the right **(A)**. Left ventricular angiography shows a takotsubo contractile pattern with apical dyskinesis and basal hyperkinesis **(B,C)**. **(B)** Systole. **(C)** Diastole.

systolic function with an ejection fraction of 69%. Thereafter, torsemide and antisterone were discontinued.

Discussion

TTS, first described in Japan in 1990 (1), is also known as stress cardiomyopathy, broken heart syndrome, and apical ballooning syndrome. It is a significant form of transient and reversible regional left ventricular systolic (and diastolic) dysfunction (2, 3). The typical pattern of abnormal regional left ventricular motion is apical hypokinesia/akinesia (apical ballooning) with basal hyperkinesis, resembling octopus traps used in Japan (9). This patient displayed the classic apical ballooning shape on echocardiography and left ventricular angiography. Generally, the pathogenesis of TTS is related to emotional or physical stress, and it is more common among postmenopausal women (10–12). Typical symptoms include chest pain, shortness of breath, dizziness, and occasional syncope. It can also display ST-segment elevation on ECG that

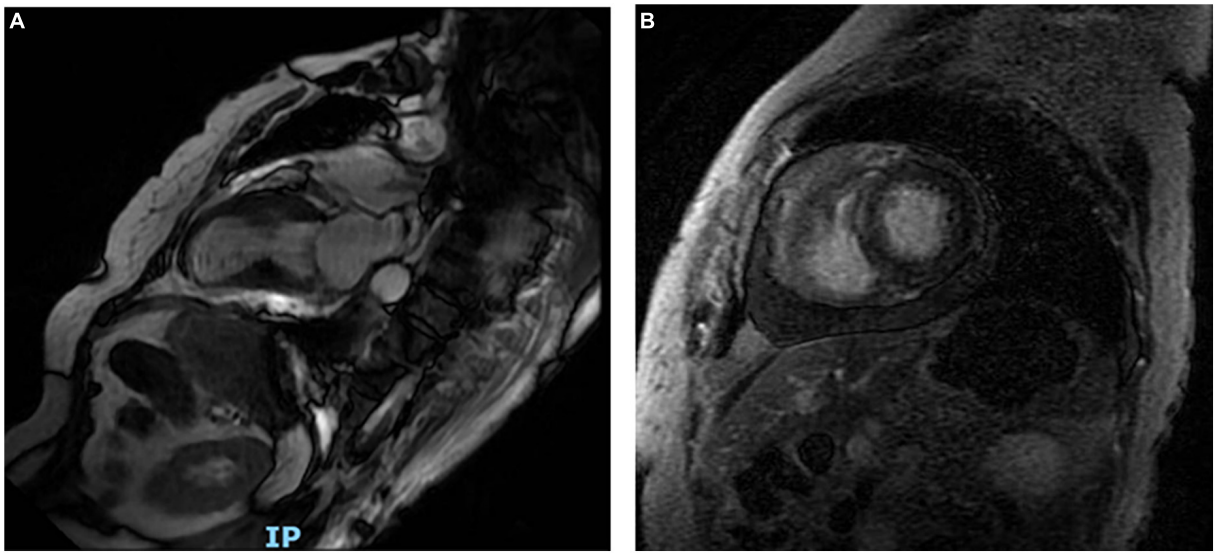

FIGURE 4
Long-axis cardiac magnetic resonance shows the heart apex bulging toward the diaphragm **(A)**. Late gadolinium enhancement reveals a weakly enhanced interventricular septum **(B)**.

mimics ACS, but with no acute plaque rupture or obstructive coronary artery stenosis on coronary angiography (9). The Heart Failure Association of the European Society of Cardiology (ESC), Mayo Clinic Criteria, and InterTAK Diagnostic Criteria provide TTS diagnostic criteria that are widely used (9).

Hypoglycemia is a medical emergency that can cause serious morbidity and mortality. It can raise the circulating levels of catecholamines, leading to excessive sympathetic nerve stimulation, which is considered a stressor that can incite TTS (6). Previous case reports have documented hypoglycemia triggering TTS (6–8), but such instances are rare, such as this case. Katoh et al. (6) reported the occurrence of inverted TTS with hypoglycemia in which the basal but not apical parts of the heart became dyskinetic. Regional differences in adrenergic sensitivity or nerve distribution may explain the ventricular wall motion abnormalities seen in patients with this condition.

Although TTS is a self-limiting syndrome with no significant coronary artery disease, several complications can occur, such as acute heart failure, left ventricular outflow tract obstruction, and mitral regurgitation, with an in-hospital mortality rate as high as 5% (9–11, 13, 14). In our case, the patient developed heart failure and presented with cardiogenic pulmonary edema and pleural effusion. This may have been related to acute left ventricular dysfunction caused by stress (8). After the administration of optimal heart failure treatment and the correction of hypoglycemia, heart function gradually improved within a few weeks, and the patient was discharged uneventfully.

The patient was eventually diagnosed with TTS induced by hypoglycemia. However, we should still take acute myocarditis into consideration. This would have been plausible given the patient's presentation with nausea and vomiting, which might have triggered hypoglycemia. The diagnostic criteria for clinically suspected myocarditis were based on the 2013 ESC consensus statement on the diagnosis and treatment of myocarditis (15). The patient had acute chest discomfort, ECG changes, elevated cardiac troponin T levels, and functional abnormalities on UCG but no obvious edema or late gadolinium enhancement of the classical myocarditis pattern (15). Therefore, the clinical diagnosis of acute myocarditis was not sufficient. Myocardial biopsy could have confirmed the diagnosis of myocarditis, but the patient declined the procedure.

Data availability statement

The original contributions presented in this 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 the Medical Ethics Committee of Shanghai Jing'an District Central Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

PX involved with the management of the patient and the write-up of the manuscript. YS made significant contributions to writing, proofreading, and submitting the manuscript. JW made significant contributions to writing and proofreading the manuscript. YZ involved in treating the patient, as well as mentoring, and making suggestions in the preparation of the manuscript. 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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Supplementary material

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EDITED BY
Matteo Cameli,
University of Siena, Italy

REVIEWED BY
Teruhiko Imamura,
University of Toyama, Japan
Michael Dandel,
German Center for Cardiovascular Research (DZHK), Germany

*CORRESPONDENCE
Nianguo Dong
✉ dongnianguo@hotmail.com

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Case report: Successful percutaneous extracorporeal magnetic levitation ventricular assist device support in a patient with left heart failure due to dilated cardiomyopathy

Ping Li[1], Xiaoying Zhang[2], Shu Chen[1], Po-lin Hsu[2], Tingting Wu[2], Shirui Qian[1], Wei Su[1], Guohua Wang[1] and Nianguo Dong[1]*

[1]Department of Cardiovascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, [2]magAssist, Inc., Suzhou, Jiangsu, China

Introduction: Mechanical circulatory support (MCS) can help to maintain hemodynamic stability, improve cardiac function, reduce cardiac load, and is an important method for the treatment of advanced heart failure. However, traditional MCS systems [IABP, Impella, TandemHerat, veno-arterial extracorporeal membrane oxygenation (VA-ECMO)] are associated with limitations including trauma, a high rate of complications (hemolysis, bleeding) and require complex care from nurses.

Case summary: We report a case of left heart failure resulting from dilated cardiomyopathy in a 24 years-old man. A catheter was placed through the right jugular vein and a drainage tube was positioned under ultrasound guidance through the superior vena cava, right atrium, atrial septum, to the left atrium, and returned to the axillary artery using an extracorporeal magnetic levitation ventricular assist device (VAD). The patient was successfully supported for 10 days and bridged to heart transplant.

Discussion: To the best of our knowledge, this is the first report of the use of an extracorporeal magnetic levitation VAD for MCS *via* a percutaneous approach. Our findings support the wider use of this strategy for patients awaiting myocardial recovery or who require heart bridging or transplantation.

KEYWORDS

extracorporeal ventricular assist device, maglev, percutaneous mechanical circulatory support, minimally invasive, heart failure

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Introduction

In China, common treatments for temporary mechanical circulatory support (MCS) in patients with cardiogenic shock (CS) include intra-aortic balloon pump (IABP) and veno-arterial extracorporeal membrane oxygenation (VA-ECMO). Although the IABP is simple to operate, the results of the SHOCK-II clinical trial showed that IABP had no clear effect on improving survival in patients with CS (1); Similarly, although VA-ECMO increases systemic flow and pressure and reduces venous congestion in pulmonary circulation without unloading the left side of the heart (2), it can lead to major complications including pump thrombosis, bleeding, ischemic limbs, and harlequin syndrome (3). Therefore, more options for MCS and more suitable implantation strategies are needed to improve prognosis in patients with CS.

The extracorporeal magnetic levitation ventricular assist device (VAD) uses a magnetic levitation rotor that can rotate without friction or wear, with less blood stagnation, turbulence or hemolysis, compared with ECMO and almost no mechanical failure (4). In our previous report, we treated a patient who developed CS following coronary artery bypass surgery for 9 days until discharge using magnetic levitation extra-VAD (5). However, this device needs to be inserted by median sternotomy, which is highly invasive and inconvenient for patients. We modified our approach and performed percutaneous left VAD placement through the right internal jugular vein, with cannulation of the axillary artery for 10 days to successfully bridge the patient to heart transplantation. This method was well-tolerated and associated with less trauma and simplified operation compared with CentriMag, which maximizes patient benefits.

Case report

A 24 years-old man (height: 185 cm; weight: 78 kg) with a history of dilated cardiomyopathy, pulmonary hypertension, severe mitral insufficiency, and moderate tricuspid insufficiency was admitted with a New York Heart Association (NYHA) cardiac function rating of IV and a left ventricular ejection fraction of 20%. He received extensive medical treatment to increase myocardial contractility, reduce pulmonary hypertension and control heart rate. Unfortunately, the patient developed persistent systemic hypoperfusion with CS. He was given temporary left ventricular assist using a magnetic levitation extra-VAD device. Before implantation, ultrasound examination showed left ventricular dilatation (left ventricular end-diastolic diameter 9.5 cm), systolic dysfunction [left ventricular ejection fraction 13%; arterial blood pressure 80/60 mmHg; N-terminal pro-B-type natriuretic peptide (NT-proBNP) 2,910 pg/ml], and pulmonary artery systolic blood pressure of 57 mmHg.

To circumvent the difficulties of atrial septal puncture through the jugular vein, puncture through the femoral vein was performed. A guide wire was inserted through the right femoral vein puncture to achieve right heart catheterization under the guidance of ultrasound and digital subtraction angiography (DSA) (**Figure 1A**, and a snare was placed in the right atrium along the femoral vein guide wire (**Figure 1B**). The catheter was delivered through the right jugular vein, captured by a snare, and placed into the left atrium along the femoral vein guide wire (**Figure 1C**). A drainage tube was placed using the guide wire approach to establish a drainage path through the jugular vein, superior vena cava, right atrium, and atrial septum to the left atrium (**Figure 1D**). Finally, the axillary artery was exposed and blocked under the right clavicle, an 8 mm artificial blood vessel was anastomosed end-to-side, and the outflow tube was inserted to establish left atrium-extra-VAD-axillary artery circulation assistance. The pump flow was set at approximately 3 L/min and the speed was 2,500 rpm.

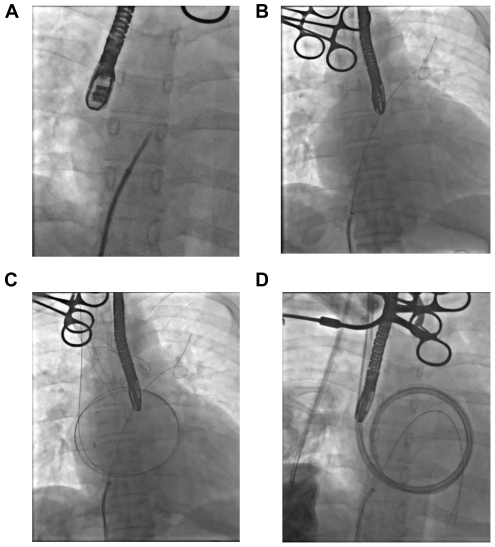

FIGURE 1
Percutaneous intubation procedure. **(A)** Atrial septal puncture. **(B)** Insertion of the snare. **(C)** Jugular guide wire creates a passage in the left atrium. **(D)** Drainage tube placement.

Hemodynamic and hematological parameters were monitored throughout extra-VAD implantation, and indicated good recovery. No hemolysis-related complications occurred (**Figure 2A**), and liver and kidney function were unaffected (**Table 1**). Heparin was used for anticoagulation therapy to maintain the target activated coagulation time (ACT) between 180 and 220 s and maintain the target activated partial thromboplastin time (APTT) between 40 and 55 s (**Figure 2B**). High-sensitivity troponin I reached 2,985.1 ng/L postoperatively and rapidly decreased to 647.7 ng/L on the second postoperative day. Similarly, lactic acid levels decreased to 0.6 mmol/L the day after surgery and remained between 0.4 and 1.0 mmol/L thereafter. These results indicated a rapid improvement in cardiac function. The extra-VAD device was removed 10 days later, and ultrasound results showed a left ventricular end-diastolic diameter of 7.6 cm. The patient subsequently underwent a successful heart transplant.

Discussion

Cardiogenic shock is a recognized cause of death in patients with heart failure due to low cardiac output resulting in severe hypoperfusion of vital organs, with a short-term mortality rate of more than 50% (6). MCS can quickly stabilize hemodynamic parameters, ensure effective perfusion of organs, and improve cardiac

Abbreviations: MCS, mechanical circulatory support; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VAD, ventricular assist device; IABP, intra-aortic balloon pump; CS, cardiogenic shock.

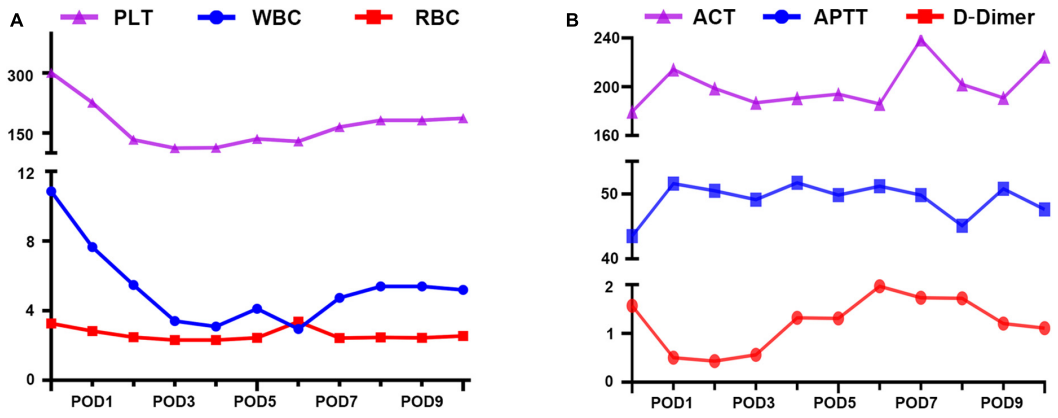

FIGURE 2
Lab rest results during extra- ventricular assist device (VAD) support. **(A)** Blood compatibility. PLT, platelet; RBC, red blood cell; WBC, white blood cell. **(B)** Anticoagulation management. ACT, active clotting time (s); APTT, activated partial thromboplastin time (s); D-Dimer (mg/L).

TABLE 1 Lab rest results during extra- ventricular assist device (VAD) support.

	POD1	POD2	POD3	POD4	POD5	POD6	POD7	POD8	POD9	POD10
Cr	149.3	103.2	83.1	81.2	79.8	86.6	91.4	104.1	107.4	110.7
BUN	7.28	5.07	2.94	2.5	2.26	3.22	3.36	3.92	4.18	4.5
Bilirubin	13.4	15.3	14.1	12	12.8	10.7	8.9	8.9	10.6	10.6
LAC	2.38	0.6	0.47	0.5	0.45	0.65	0.7	0.75	0.97	0.5
CK	337	666	460	249	–	67	42	–	–	–
LDH	323	354	294	277	296	305	323	331	389	417

BUN, blood urea nitrogen (mmol/L); CK, creatine kinase (U/L); Cr, creatinine (μmol/L); LAC, lactic acid (mmol/L); LDH, lactate dehydrogenase (U/L).

function. In recent years, clinicians have increasingly used short-term MCS to improve adverse outcomes in patients with CS (7).

Traditional short-term MCS units such as Impella, TandemHerat, and VA-ECMO use mechanical bearing axial flow pumps. In contrast, the magnetic levitation centrifugal pump increases blood compatibility and reduces the incidence of pump thrombosis, hemolysis, and gastrointestinal bleeding, thereby minimizing blood loss, the need for blood transfusion, and postoperative inflammation (8, 9). In addition, reduced thrombosis minimizes the amount of anticoagulation required to prevent thrombosis; therefore, postoperative anticoagulation management is simpler compared with VA-ECMO.

In addition, only CentriMag can offer full circulatory support; the rest of the device such as Impella CP with up to 4.3 L/min, Impella 5.5 with 5.5 L/min (Axial pump may overestimate the flow rate due to the number are not directly reading from ultrasonic flow sensor) and TandemHeart with 4 L/min can only provide partial support. In life threatening end stage heart failure patient, the support average flow range is from approximately 3.5–6.0 L/min (10). In these cases, impella or TandemHeart may not provide sufficient flow for the patients. Therefore, ECMO and Impella (ECPELLA) are combined to treat cardiogenic shock (11). However, combining two different mechanical circulatory support systems will potentially increase complications.

No bleeding or thrombotic complications and no hemolysis were observed during the entire course of circulatory support, which is consistent with our previous report (5). While our method of extra-VAD is designed for short-term use (≤30 days), we have found it to be well-tolerated over longer periods of time.

In addition, we modified the conventional method of median sternotomy and re-cannulation to a percutaneous approach. To our knowledge, this is the first time this surgical method has been reported in the literature and suggests that minimally invasive, short-term and mid-term external magnetic levitation artificial heart implantation should be considered for widespread use.

Percutaneous left VAD reduces left ventricular volume, wall stress, and myocardial oxygen consumption whilst increasing cardiac output and coronary perfusion to minimize myocardial ischemia and hemodynamic failure in high-risk patients with heart failure. This minimally invasive method greatly reduces patient trauma and avoids the risks associated with complicated thoracotomy (12).

Additionally, the percutaneous approach reduces blood loss and potential coagulation disorders, which simplifies postoperative care (13). With transjugular intubation, patients may walk early after surgery, which can accelerate postoperative activity and rehabilitation and reduce the occurrence of postoperative bed rest complications such as deep vein thrombosis and pulmonary infection (14). In addition to clinical benefits, this minimally invasive approach can significantly shorten the length of hospital stay, restore cardiac function more rapidly and greatly reduce medical costs compared with established approaches (15).

In conclusion, we propose a novel, minimally invasive and easy-to-care mode of extracorporeal ventricular assistance using an extracorporeal magnetic levitation VAD *via* jugular vein intubation. This model avoids unnecessary surgeries and is associated with fewer complications than existing methodologies. Further clinical

data are necessary to evaluate the advantages of this model over traditional MCS strategies.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PL: data curation, formal analysis, methodology, software, validation, visualization, and writing—original draft. XZ: methodology, investigation, validation, software, and formal analysis. SC and P-LH: methodology, validation, and writing—review and editing. TW and SQ: writing—review and editing. WS and GW: resources and supervision. ND: conceptualization, review and editing, supervision, and funding acquisition. All authors reviewed the manuscript and approved the submitted version.

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Conflict of interest

XZ, P-LH, and TW were employed by magAssist, Inc.

The remaining 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.

Publisher's note

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EDITED BY
Matteo Cameli,
University of Siena, Italy

REVIEWED BY
Daniele Linardi,
University of Verona, Italy
Francisco J. Noriega,
Hospital Clínico San Carlos, Spain

*CORRESPONDENCE
Raphaël Giraud
raphael.giraud@hcuge.ch

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ECMELLA as a bridge to heart transplantation in refractory ventricular fibrillation: A case report

Raphaël Giraud[1,2,3]*, Benjamin Assouline[1,2,3], Haran Burri[2,4], Dipen Shah[2,4], Philippe Meyer[2,4], Sophie Degrauwe[2,4], Matthias Kirsch[5] and Karim Bendjelid[1,2,3]

[1]Intensive Care Unit, Geneva University Hospitals, Geneva, Switzerland, [2]Faculty of Medicine, University of Geneva, Geneva, Switzerland, [3]Geneva Hemodynamic Research Group, Geneva, Switzerland, [4]Department of Cardiology, Geneva University Hospitals, Geneva, Switzerland, [5]Cardiac Surgery, Cardiovascular Department, University Hospital and University of Lausanne, Lausanne, Switzerland

Background: Extracorporeal membrane oxygenation (ECMO) is an effective cardiorespiratory support technique in refractory cardiac arrest (CA). In patients under veno-arterial ECMO, the use of an Impella device, a microaxial pump inserted percutaneously, is a valuable strategy through a left ventricular unloading approach. ECMELLA, a combination of ECMO with Impella, seems to be a promising method to support end-organ perfusion while unloading the left ventricle.

Case summary: The present case report describes the clinical course of a patient with ischemic and dilated cardiomyopathy who presented with refractory ventricular fibrillation (VF) leading to CA in the late postmyocardial infarction (MI) period, and who was successfully treated with ECMO and IMPELLA as a bridge to heart transplantation.

Discussion: In the case of CA on VF refractory to conventional resuscitation maneuvers, early extracorporeal cardiopulmonary resuscitation (ECPR) associated with an Impella seems to be the best strategy. It provides organ perfusion, left ventricular unloading, and ability for neurological evaluation and VF catheter ablation before allowing heart transplantation. It is the treatment of choice in cases of end-stage ischaemic cardiomyopathy and recurrent malignant arrhythmias.

KEYWORDS

VA-ECMO, Impella, ECMELLA, cardiac arrest, refractory ventricular fibrillation, heart transplantation

Introduction

Ventricular fibrillation (VF) is a life-threatening situation leading to cardiac arrest (CA) (1). Emergency treatment for VF includes cardiopulmonary resuscitation (CPR), antiarrhythmic drugs, and external electrical shocks (EES) with a defibrillator (2). Refractory ventricular fibrillation (RVF) is thought to be defined as failure to obtain return of spontaneous circulation (ROSC) within 10 min despite 3 defibrillation attempts, 3 mg of epinephrine, and 300 mg of amiodarone (3). The high mortality rates during VF [between 85 and 97% (4)] have brought

interest in the development of a combined approach of conventional resuscitation techniques by external cardiac compressions and defibrillation with extracorporeal life support through the use of extracorporeal membrane oxygenation (ECMO) (5). Thus, extracorporeal cardiopulmonary resuscitation (ECPR) has become a lifesaving approach for patients suffering a CA that is deemed refractory to conventional resuscitation (6). Most of the time, reperfusion of the myocardium by ECMO makes it possible to obtain ROSC (7). In some rarer cases, VF persists despite electric shocks and injection of antiarrhythmic agents (8). ECMO allows for continued resuscitation and organ perfusion, including to the brain. However, it does not allow for the unloading of the left heart chambers, increasing the risk of subendocardial ischemia and interfering with myocardial recovery. Further, by increasing afterload, ECMO carries the risks of potential atrioventricular thrombosis and refractory pulmonary oedema. Several more or less invasive techniques, such as intra-aortic balloon pump (IABP), have been described to unload the left ventricle (LV), including Impella-CP, a microaxial pump inserted through the aortic valve into the left ventricle *via* the femoral and percutaneous routes. According to some recent studies, this device reduces the mortality of patients in cardiogenic shock placed under VA-ECMO (9–11). In this regard, ECMELLA, a combination of ECMO with Impella, seems to be promising to support end-organ perfusion without causing further damage to the heart (12).

We describe the clinical course of a patient with end-stage ischemic and dilated cardiomyopathy and refractory VF leading to CA in the late postmyocardial infarction (MI) period with persistent severe LV dysfunction, who was successfully treated with ECMO and IMPELLA as a bridge to heart transplantation (HT).

Case description

A 52-year-old patient with a history of active smoking was hospitalized due to severe ischemic heart failure. A coronary angiogram performed September 2021 showed severe three-vessel coronary disease with no possibility of revascularization, confirmed by PET-CT and MRI showing transmural necrosis affecting more than 55% of the LV with no residual ischemia. Transthoracic echocardiography showed an LV ejection fraction of 20–25% and an apical thrombus measuring 6 mm × 7 mm. The patient presented with syncope caused by VF treated with an external electric shock delivered by a Lifevest® on October 4, 2021, followed by implantation of an ICD the same day.

On October 14, 2021 at 18:00, the patient reported having felt his defibrillator administered several shocks. Nine new shocks were delivered by the patient's ICD. At 18:40, the patient presented with CA secondary to refractory VF. CPR was started immediately. The patient received 17 internal shocks, then 8 EES at 200 joules, four doses of 1 mg of adrenaline IV, two doses of 150 mg amiodarone IV, two doses of 100 mg lidocaine IV, and 5 mg metoprolol IV. At 19:00, CPR was continued using a LUCAS 2^{TM} device, orotracheal intubation was performed, and the ECMO alarm was triggered. At 19:30, VA-ECMO was implanted at the bedside under transesophageal echocardiography guidance (no-flow 0 min and low-flow 50 min). A new coronary angiography showed an unchanged coronary status. While in the cath-lab, 4 new EESs were delivered, and the patient was administered amiodarone 300 mg IV, lidocaine 100 mg IV, metoprolol 5 mg IV, and 2 g of magnesium IV.

Ventricular fibrillation remained refractory, and an LV discharge by Impella-CP was implanted. In the ICU, the patient was sedated and placed on amiodarone IV infusion at a rate of 1200 mg/day and a lidocaine IV infusion at a rate of 8 mg/h. VF turned into a persistent ventricular flutter (VFl) (**Figure 1**) despite multiple attempts of EES. Occasionally a sinus rhythm appeared spontaneously or with the waning of EES, however this persisted for only a few minutes. On VA-ECMO at 4.5 l/min and Impella between P2 and P4 generating a blood flow between 1 and 2 l/min, the patient was hemodynamically stabilized with low doses of norepinephrine. Lactate levels, renal failure, and liver function normalized within 48 h. In view of the uncertain neurological prognosis, electrophysiologists were reluctant to invasively treat this VF. On the sixth day, the sedation was discontinued. The patient woke up without neurological deficits. Thus, radiofrequency catheter ablation was performed with a satisfactory result. However, the patient presented with some recurrences of VF. The time course of hemodynamic and neurologic parameters in the ICU while on ECMELLA are shown in **Figure 2**. In view of end-stage heart failure and persistent rhythmic instability, this patient was registered for emergency HT and transferred to the HT center. This was performed on Day 29 without complications. The postoperative follow-ups were simple, and a transfer to rehabilitation occurred 4 weeks after HT.

Comment

The present case report highlights that when the heart is no longer able to eject blood as in VF, the association between VA-ECMO and Impella allows to at the same time correctly perfuse the organs by solving the state of shock and organ dysfunction, as well as adequately unload the heart, avoiding the occurrence of pulmonary oedema and intracardiac thrombosis.

Cardiac arrest is a real health problem with a survival rate of 10–20% for patients undergoing conventional CPR (13). The contribution of ECMO in refractory CA (ECPR) has become a lifesaving approach (5). Indeed, ECPR helps to ensure organ perfusion while the primary cause of CA is treated. Moreover, in patients with sustained VF, ECPR allows the establishment of sufficient perfusion of the injured myocardium that usually leads to a higher chance of ROSC and organ recovery (7). Unfortunately, in the present case, this was not the result as VF persisted despite ECPR, the administration of multiple antiarrhythmic treatments, and finally defibrillations.

In ECPR patients whose heart has restarted, LV dysfunction occurs frequently. The increase in LV afterload induced by ECMO and the low cardiac contractility require the establishment of an LV unloading system (14). Impella has been shown to improve outcomes in ECMO-assisted refractory cardiogenic shock patients (15). Recent studies demonstrated the clinical benefits of LV unloading in cardiogenic shock in the setting of acute myocardial infarction. In the short term, LV unloading using mechanical circulatory support aims to reduce infarct size, limit ventricular remodeling, and prevent the development of the heart failure syndrome (16). In our patient, the persistence of VF led to a total absence of cardiac contraction and ejection, enhancing the risk of pulmonary oedema and LV thrombosis. Faced with a refractory arrhythmia, ECMELLA, by amending organ dysfunction without overloading the heart, allowed the patient to awaken. This is a "sine qua none" condition for both the continuation of resuscitation and discussion with the patient.

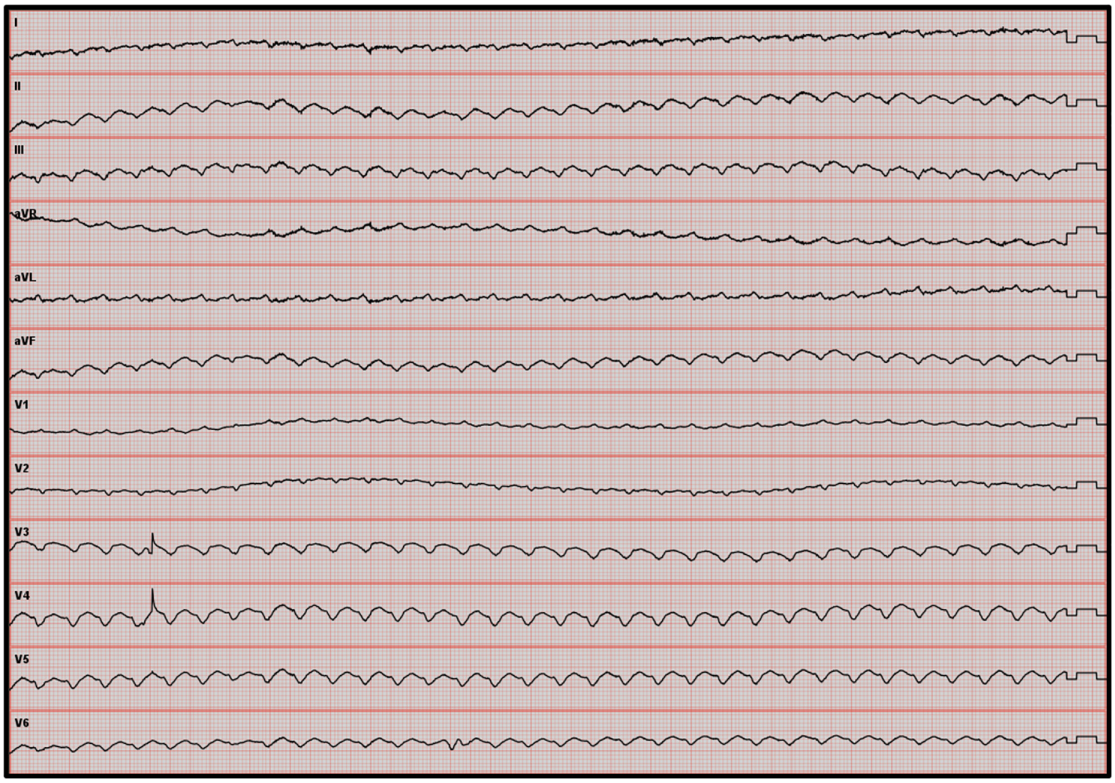

FIGURE 1
Twelve-lead ECG showing a ventricular flutter. ECG, electrocardiogram.

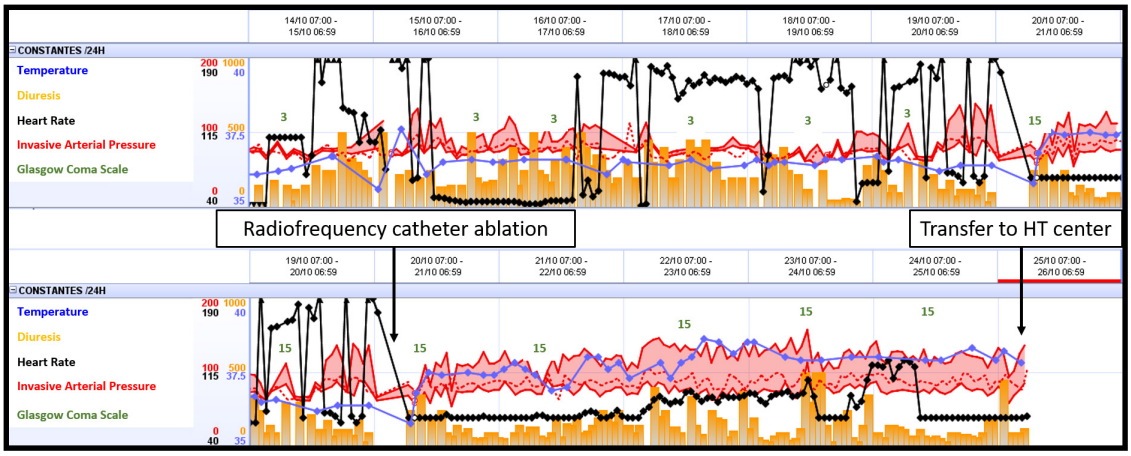

FIGURE 2
Time course of hemodynamic and neurologic parameters in the ICU while on ECMELLA. ECMELLA, combination of extracorporeal membrane oxygenation and Impella; HT, heart transplant.

Indeed, the outcome of patients with refractory CA is directly related to neurological prognosis (17), which is conditioned by the adequate selection of patients to benefit from ECPR (18). The factors contributing to a favorable prognosis are: the shortest possible no-flow with an AC in front of a witness and a CPR performed immediately by a professional; a shockable initial rhythm; and low-flow state of <60 min until establishment of ECMO (5). This patient met these criteria. Once reassured by the good neurological state, the treatment of the refractory VF was carried out according to the recommendations by a radiofrequency ablation catheter (19). Unfortunately, due to end-stage ischemic heart disease and recurrences of arrhythmias despite the treatments undertaken, only heart transplantation was a viable option in the short, medium, and long term, as HT remains the best option for end-stage heart failure patients (20), and is associated with improved outcomes and a better cost–effectiveness profile. In this regard, ECMELLA permitted the discontinuation of sedation, the treatment of the VF by radiofrequency thermoablation and the consent of the patient to be transplanted.

Conclusion

In the case of CA on VF refractory to conventional resuscitation maneuvers, early ECPR associated with an Impella seems to offer the best option to patients in terms of organ perfusion, left ventricular unloading, radiofrequency catheter ablation, and neurological evaluation. The present latter condition is a "sine qua none" condition that allows patients to be ethically consented for a heart transplant.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the patient for publication of their health data.

Author contributions

RG, BA, and KB oversaw the acquisition, analysis, interpretation of data, and drafted the manuscript. HB, DS, PM, SD, and MK revised the manuscript critically for important intellectual content. All authors provided approval for publication of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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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EDITED BY
Matteo Cameli,
University of Siena, Italy

REVIEWED BY
Nagarajan Muthialu,
Great Ormond Street Hospital for Children NHS Foundation Trust, United Kingdom
Jan Von Der Thüsen,
Erasmus Medical Center, Netherlands

*CORRESPONDENCE
Giorgia Grutter
✉ giorgia.grutter@opbg.net

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Case report: Coronary allograft vasculopathy: an accurate reflection of the histopathological findings on cardiovascular magnetic resonance imaging

Carmela Napolitano[1], Giorgia Grutter[2]*, Paola Francalanci[3], Antonio Amodeo[2] and Aurelio Secinaro[1]

[1]Advanced Cardiovascular Imaging Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [2]Heart Failure, Transplantation and Cardio-Respiratory Mechanical Assistance Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [3]Pathological Anatomy Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Heart transplant recipients undergo extensive invasive and non-invasive postoperative screening to exclude complications, such as allograft rejection and vasculopathy. Cardiac magnetic resonance imaging is a non-invasive, non-irradiating, diagnostic tool for monitoring graft health and identifying possible tissue rejection or myocardial fibrosis. We describe the case of a 29-year-old female heart transplant recipient admitted to our care center with a worsening clinical condition. The patient underwent clinical evaluation, blood tests, including troponin I and N-terminal pro brain type natriuretic peptide, transthoracic echocardiography, invasive coronary angiography, and cardiovascular magnetic resonance imaging. Cardiovascular magnetic resonance imaging showed widespread sub-epicardial hyperintensity of the myocardial segments along the course of the coronary arteries. T2 mapping sequences showed an elevated value and the myocardial native T1 values and extracellular volume percentage were significantly increased. Late gadolinium enhancement demonstrated a diffuse sub-epicardial hypersignal along the lateral, free, and left ventricular walls. All the sequences evidenced widespread hyper-enhancement of epicardial fat along the course of the thickened main coronary artery walls. One month later, the recipient underwent re-transplantation due to progressive worsening of the clinical condition and refractoriness to intravenous medication. The anatomopathological findings of the explanted heart provided impressive visualization of structural and histopathological changes. These results could guide the tailoring of preventive therapeutic strategies and non-invasive monitoring of cardiac grafts.

KEYWORDS

transplantation, heart, cardiac magnetic resonanance, chronic rejection, specimens anatomical

Introduction

Cardiac transplantation remains the most effective treatment for end-stage heart failure with excellent short- and long-term survival rates (1). Cardiac transplant recipients undergo extensive postoperative screening to exclude post-transplant complications. Chronic sequelae, such as cardiac allograft vasculopathy, play an important role in the post-heart transplantation course (2). Cardiac magnetic resonance imaging (CMRI) is a non-

invasive, non-irradiating diagnostic tool used to monitor graft health and estimate the onset of tissue rejection processes or myocardial fibrosis (3). In this study, we present a case of a young heart transplant recipient undergoing re-transplantation due to severe accelerated cardiac allograft vasculopathy (CAV). We also report the striking similarities between the CMRI results and histopathological samples obtained from the explanted heart.

Case description

A 29-year-old female heart transplant recipient presented to our care center with a generalized poor health condition. The patient was affected by congenitally corrected transposition of the great arteries with a subpulmonary interventricular defect and right ventricular hypoplasia. In 1998 at the age of twelve the patient underwent Glenn atrial switch procedure. In September 2015, heart transplantation was performed for severe heart failure refractory to therapy and episodes of paroxysmal supraventricular tachycardia that required frequent hospitalization. Due to residual claudication caused by severely impaired lower limb muscles, the patient was unable to undergo a stress test during periodical follow-up or during hospitalization. Upon admission to our care center, the patient appeared pale and complained of dizziness and fatigue. The patient's blood pressure was 123/70 mmHg with a heart rate of 105 beats/min. The 12-lead electrocardiogram (ECG) showed sinus tachycardia, first degree atrioventricular block, right bundle branch block, and diffuse non-specific abnormalities of ventricular repolarization. Transthoracic echocardiography revealed a slightly reduced left ventricular ejection fraction (46%). Laboratory findings showed a normal cardiac troponin I level (5.4 pg/ml) and an elevated terminal pro brain type natriuretic peptide level (353 pg/ml). Invasive coronary angiography showed severe stenosis at the distal portion of the circumflex coronary artery and diffuse sclerosis of the left anterior descending coronary artery. Intravascular ultrasonography showed a Stanford scale IV score (**Figure 1**). Consequently, the therapeutic strategy was revised and low-dose bisoprolol, ace inhibitors, and diuretics were added to the remaining medication, which comprised cyclosporine, everolimus, pravastatin, and aspirin. At day 7 of hospitalization echocardiography showed improvement of the left ventricular function (58%) and a reduction of the N-terminal pro brain type natriuretic peptide level (235 pg/ml). The symptoms disappeared and the patient was discharged with a scheduled CMRI 7 days later. CMRI was performed using a 1.5 Tesla scanner (Magnetom Aera 1.5 T; Siemens, Erlangen, Germany) and showed mild concentric hypertrophy of the left ventricle and moderately reduced left ventricular function. T2-weighted short-tau inversion recovery (STIR) sequence images showed widespread sub-epicardial hyperintensity of the myocardial segments (signal intensity ratio to skeletal muscle > 2) along the course of the coronary arteries (**Figure 2**). T2 mapping sequences showed an elevated value of 57 ms, and the myocardial native T1 values and extracellular volume percentage were significantly elevated (1170 ms and 41%, respectively). Late gadolinium enhancement (0.2 mmol/kg Gadoteric Acid, Dotarem®, Guerbet, France)

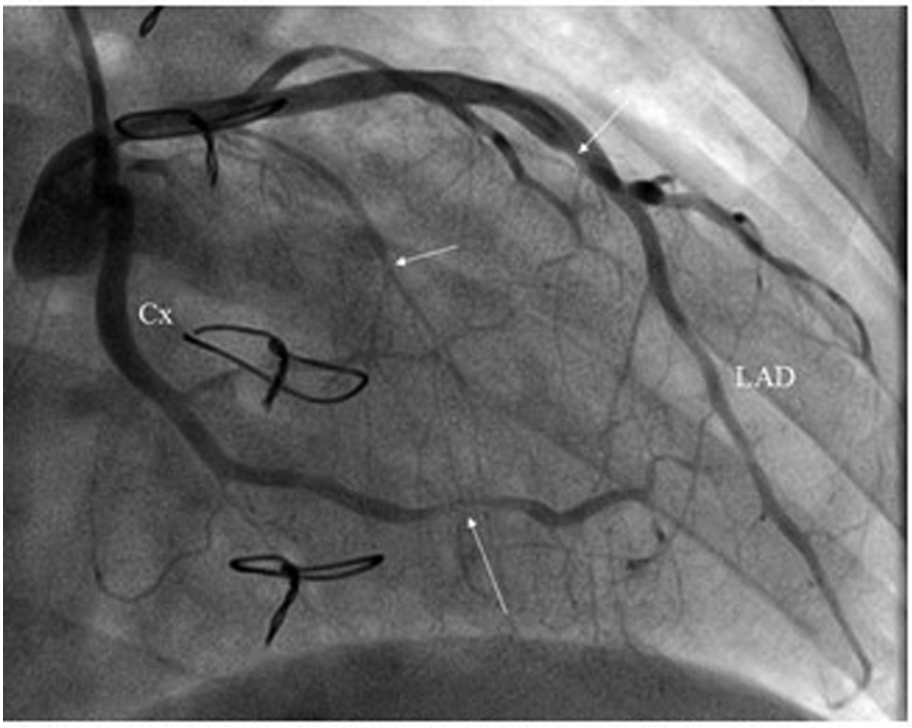

FIGURE 1
Invasive coronary angiography. CX, circumflex coronary artery; LAD, left anterior descending coronary artery.

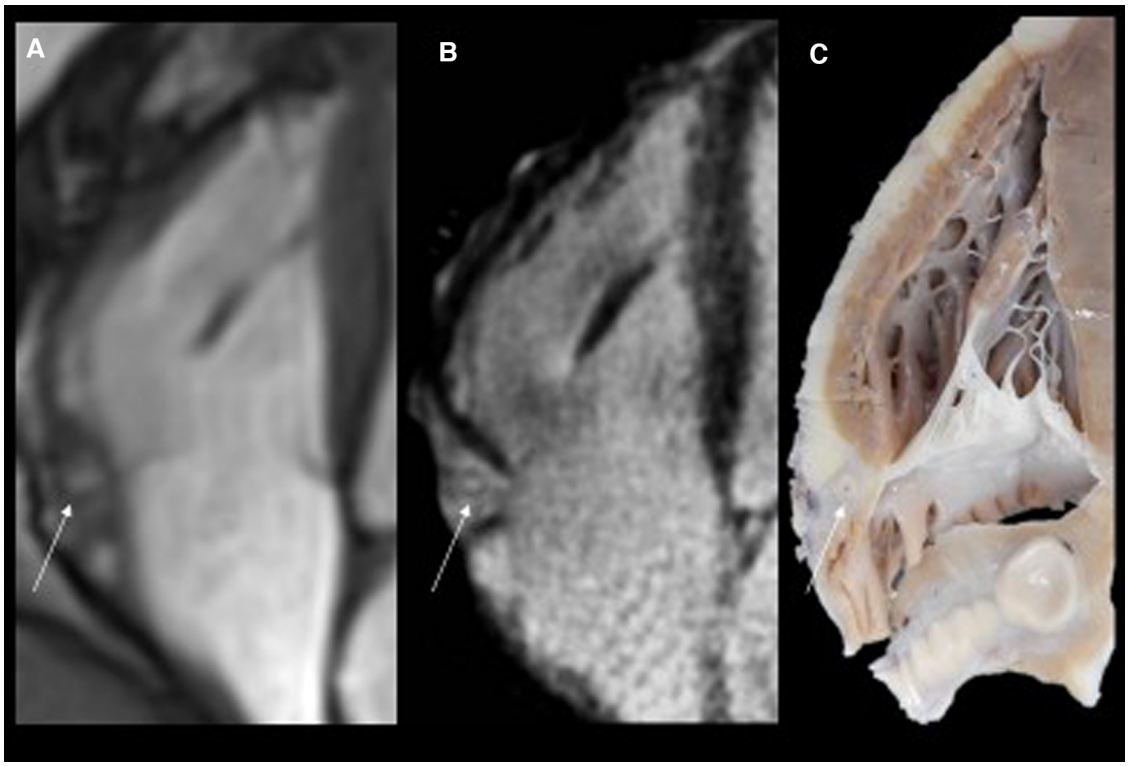

FIGURE 2
Routine magnetic resonance (MR) cine images in the four-chamber view (panel A) show thickened and hyperintense vessels (arrow) at the right atrioventricular groove. The high resolution T2-weighted and fat saturated sequence (panel B) at the same level confirms thickened walls of the right coronary artery with hyperintense epicardial fat tissue due to edema. The corresponding specimen slice confirmed significant epicardial coronary vessel wall thickening, particularly in the right coronary artery (RCA, arrow).

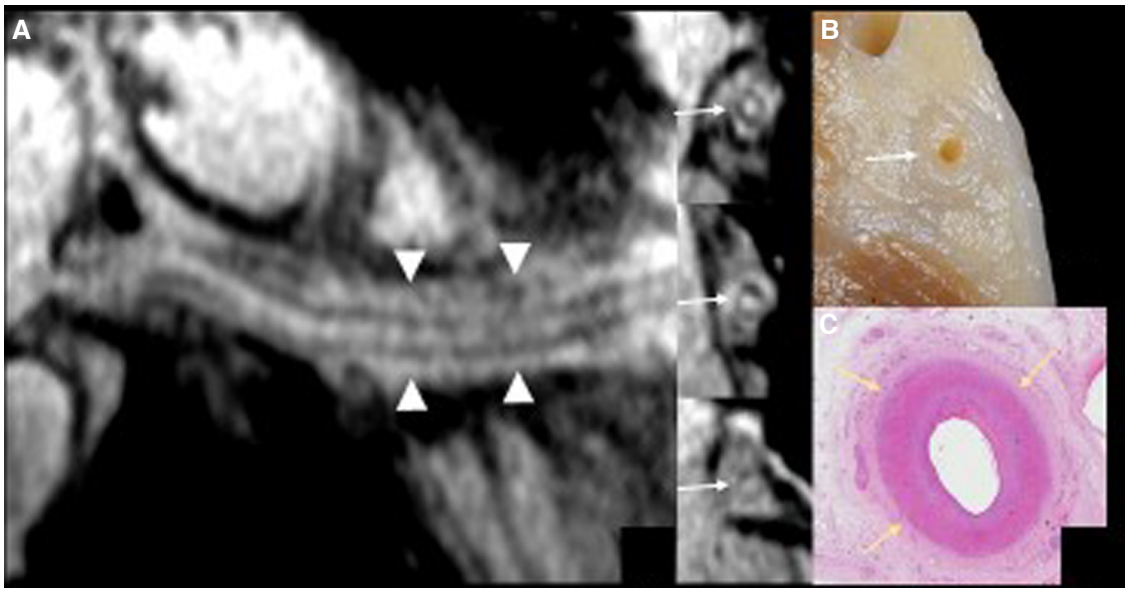

FIGURE 3
The curved multiplanar reformatting view (panel A) of the right coronary artery with the 3 short-axis vessel views using high resolution magnetic resonance (MR) coronary imaging with additional fat epicardial suppression (whole-heart imaging) confirms wall thickening along the course of the right coronary artery (arrows) and inflammatory abnormalities of the epicardial fat surrounding the vessel (arrowheads). The detailed anatomical view of the right atrioventricular groove (panel B) matches the MR coronary findings.

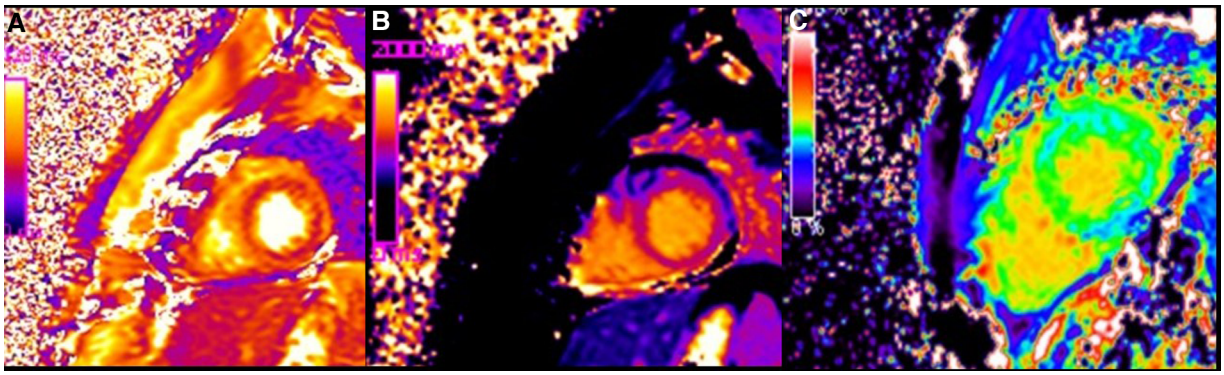

FIGURE 4
Color coded images of T2 map (**A**), native T1 map (**B**) and ECV map (**C**), demonstrating diffuse increase of T1 and T2 relaxation (on quantitative analysis native T1 was 1200 ms and T2 was 60 ms) and elevation of extracellular volume fraction (ECV: 30%) present in condition of diffuse oedema and diffuse fibrosis.

demonstrated diffuse sub-epicardial hypersignal along the lateral, free, and left ventricular walls. The "whole-heart" sequence (navigator-gated, vector ECG-triggered, fat-suppressed T2-weighted 3-dimensional gradient-echo inversion recovery) demonstrated widespread hyper-enhancement of epicardial fat along the course of the thickened main coronary artery walls (**Figure 3**) At rest, there were no sub-endocardial defects in the anteroseptal and basal infero-septal segments. Fifteen days after the CMRI was performed, the patient experienced an episode of lipothymia at home and was re-admitted through the emergency department. Due to the rapid and progressive worsening of the patient's clinical condition, which included severe hypotension and the need of inotropic drugs, the patient was placed on the transplant waiting list and underwent re-transplantation in May 2017. At the last follow-up, the patient was in a good condition and will be continuously followed at our dedicated heart transplant clinic.

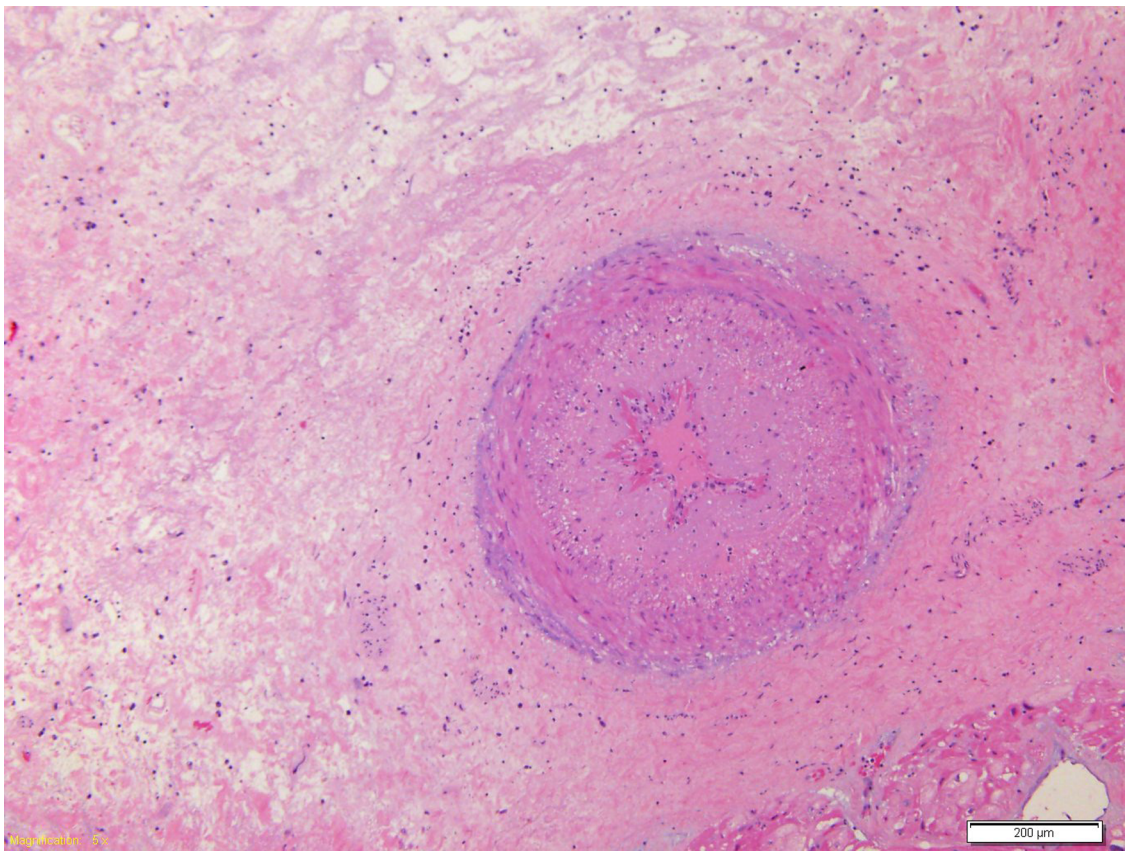

FIGURE 5
Coronary branch characterized by marked hyperplasia of the intima which causes almost complete obliteration of the lumen.

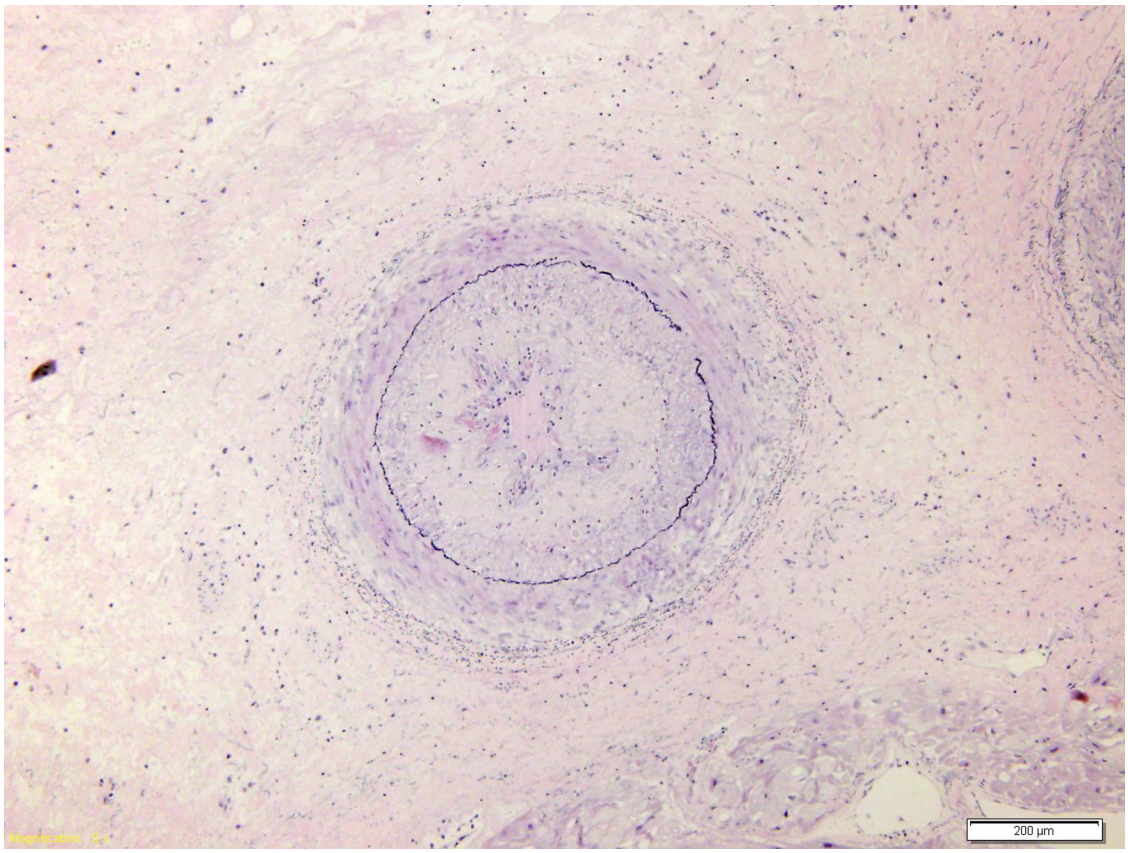

FIGURE 6
Trichrome-EVG show an intact internal elastic lamina only focally fragmented (EVG, 10x).

Discussion

CMR imaging-based myocardial tissue characterization with T1 and T2 mapping has emerged as a non-invasive and highly sensitive method of detecting cardiac allograft rejection, with numerous studies demonstrating good correlation between CMR-based mapping and histopathology-determined rejection (1). A single CMRI study can provide information on cardiac volumes, function, wall motion, tissue characterization, and ischemia at rest, pharmacological stress testing, and myocardial perfusion reserve assessment, which is an important prognostic factor in the evaluation of heart transplant recipients. CMRI can also identify edema, which is often associated with acute heart transplant rejection or myocarditis. Strategies to detect myocardial edema include semi-quantitative measures, such as T2 signal intensity ratios, or quantitative techniques, such as T2 mapping (2, 3). CMR imaging-based myocardial tissue characterization with late enhancement sequences (4) and sequences such as T1 and T2 mapping has emerged as a non-invasive and highly sensitive method of detecting cardiac allograft rejection. Numerous studies demonstrated good correlation between CMR-based mapping and histopathology-determined rejection (1). In our case, CMRI showed non-specific elevation of inflammatory indices, increased T2 mapping values (**Figure 4**), and widespread sub-epicardial hyperintensity along the course of the coronary arteries on STIR sequences (**Figure 3**). We observed an impressive correlation between CMRI, invasive coronary angiography images, and increased endocardial fibrosis of the circumflex coronary and left anterior descending arteries in the explanted heart (5). Interstitial inflammatory cellularity along the course of the coronary arteries correlated with the CMRI images; however, it was not detectable on the invasive coronary angiography images (**Figure 1**). Some authors have described the importance of the myocardial perfusion reserve (MPR) index as the only parameter able to independently predict microvascular and macrovascular CAV (3, 6). In our young girl recipient, it was not possible to estimate MPR because of her worsening clinical condition. However, first-pass perfusion imaging performed on the patient at rest did not demonstrate subendocardial defects. At late enhancement sequences, our patient did not show the typical pattern of late gadolinium enhancement, usually related to severe CAV on angiography, as some studies described (3, 7). However, we found an unusual extensive hyperenhancement of epicardial fat along the course of the main coronary arteries and diffuse subepicardial enhancement with a corresponding diffuse edema (**Figure 3**). In addition, myocardial T1 mapping showed

elevation of native T1 mapping and ECV (Figure 4), providing a quantitative measurement of extracellular volume expansion such as a more sensitive marker of adverse change within the cardiac allograft. Examination of explanted heart showed distal branches of main subepicardial coronary arteries and small peripheral vessels characterized by severe intimal proliferation, sometime till complete obliteration of the lumen (Figure 5) without necrosis, calcification and cholesterol cleft, with an intact internal elastic lamina (Figure 6) these findings are consistent to the CAV demonstrated by coronary angiography. No myocardial infarction or diffuse interstitial scarring was evident, particularly along the coronary arteries, owing to perivascular fibrous tissue being poorly vascularized and focally infiltrated by sparse mononuclear cells. These findings could be related to the development of acute perivascular inflammation, which was probably immune-mediated before intimal proliferation and, therefore, before the sequelae of myocardial scarring occurred. Existing methods for monitoring the allograft are invasive and may be insufficiently sensitive. Advanced methods, such as CMRI, may be routinely utilized to evaluate cardiac allograft vasculopathy progression and help to define the best immunosuppressive protocol strategy.

Conclusion

To our knowledge, this is the first report on the CMRI findings in allograft failure and its relation to histopathological specimens. This concept could raise the possibility of tailoring preventative therapies.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CN: revised Cardiac Magnetic resonance images GG idealized and wrote paper. PF: obtained hysthopatological findings. AA and AS: made final revision. 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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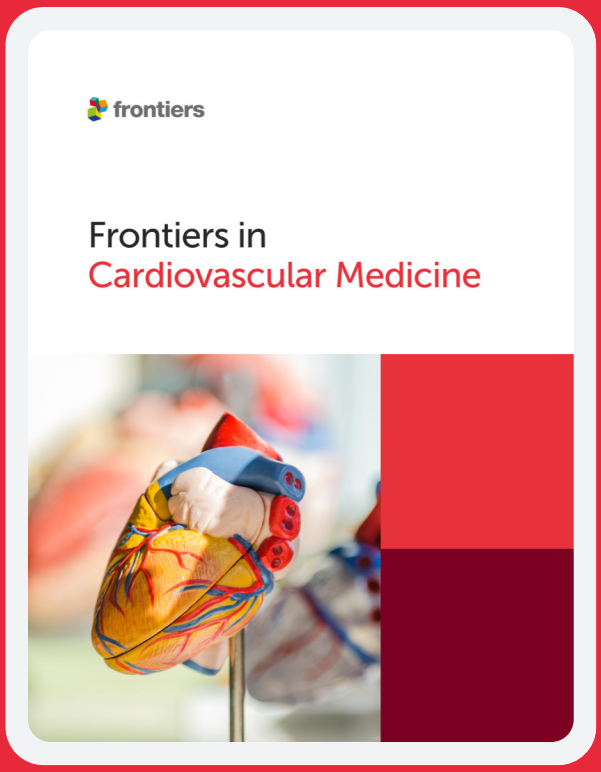

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