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# Prediction, prevention, and management of right ventricular failure after left ventricular assist device implantation: A comprehensive review

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Left ventricular assist devices (LVADs) are increasingly common across the heart failure population. Right ventricular failure (RVF) is a feared complication that can occur in the early post-operative phase or during the outpatient follow-up. Multiple tools are available to the clinician to carefully estimate the individual risk of developing RVF after LVAD implantation. This review will provide a comprehensive overview of available tools for RVF prognostication, including patient-specific and right ventricle (RV)-specific echocardiographic and hemodynamic parameters, to provide guidance in patient selection during LVAD candidacy. We also offer a multidisciplinary approach to the management of early RVF, including indications and management of right ventricular assist devices in this setting to provide tools that help managing the failing RV.

## KEYWORDS

left ventricular assist device (LVAD), heart failure (HF), right ventricle (RV), right ventricular failure (RVF), right ventricular assist device (RVAD), hemocompatibility adverse events (HRAE)

## Introduction

Left ventricular assist devices (LVADs) are commonly used for patients with end-stage heart failure (HF) as destination therapy (DT), bridge to transplant (BTT) or to orthotopic heart transplant (OHT) candidacy (1). As the right ventricle (RV) is not supported, right ventricular failure (RVF) is a feared complication that occurs in 20–40% patients early after LVAD implantation (2). Right ventricular assist devices (RVADs) are required in approximately 5% of cases (3, 4) with an associated increase in mortality, morbidity, and cost. In patients successfully discharged from hospital, persistent

and new-onset late RVF can complicate patients' clinical course with higher rates of HF admission, mortality, and hemocompatibility-related adverse events (HRAEs). Determining the risk of developing RVF is paramount, as it may be the sole preclusion of LVAD implantation and the only way of planning ahead simultaneous RVAD support. Prediction of RVF is based on clinical variables and direct RV assessment, which integrates echocardiographic and invasive hemodynamic data. Clinical optimization before LVAD implantation, surgical technique for LVAD implantation and concomitant interventions can modify rates of both early and late RVF. Intra-operative management and decision-making about appropriateness, type, and timing of RVAD support is key. The purpose of this review is to provide a practical guideline for patient selection, RVF prognostication and RVF management by incorporating the most recent evidence, that can be used by HF specialists, cardiovascular surgeons, or anesthesiologists during LVAD candidacy assessment and post-operative period.

## Definition of right ventricular failure

The definition of RVF has been cumbersome with many working groups utilizing their own definition. Since 2014, the Interagency Registry of Mechanical Circulatory Support (INTERMACS) definition of RVF requires documentation of elevated central venous pressure (CVP) and tangible clinical or laboratory manifestations of RVF. INTERMACS grades RVF severity according to the duration of required therapy [mainly nitric oxide (iNO) and inotropes] with 0–7 days of support defined as mild RVF, 7–14 days considered moderate RVF, and >14 days or need for RVAD was defined as severe RVF (5). Subsequent studies have demonstrated that only severe, INTERMACS-defined RVF is associated with worse outcomes (6, 7). Thus, it seems reasonable to consider a clinically relevant episode of RVF as only those episodes that require RVAD or inotropic support for >14 days, acknowledging that prognosis worsens with duration (8, 9).

The INTERMACS definition, however, fails to capture late RVF, as prolonged inotropic or RVAD support are rarely needed. To account for this discrepancy, an updated definition was released by the Mechanical Circulatory Support–Academic Research Consortium (MCS-ARC) in 2020 (10). The new definition distinguishes between early acute RVF (requiring RVAD support), early RVF in the first 30 days, and late RVF after the first 30 days. For the MCS-ARC definition, RVF is diagnosed in the presence of RVF signs and symptoms in combination with increased diuretic or inotrope requirement for at least 72 h (Figure 1).

## Pre-operative prediction of right ventricular failure

Both early and late RVF most likely result from a multiple hit combination of pre-existent RV dysfunction, surgical insult, and RV loading conditions after initiation of LVAD support. Therefore, none of the published predictors has emerged as a standalone gold standard and an integrative approach is required. We advocate for a combination of patient-specific and RV-focused metrics obtained from echocardiography and pulmonary artery (PA) catheterization, summarized in Figures 2–4.

## Clinical risk factors for right ventricular failure

### Body size and cardiac size

In the MOMENTUM3 trial, the average body surface area (BSA) of patients with LVADs was 2.1 m<sup>2</sup>, a finding consistent across all large-scale, MCS registries (11). Smaller patients have historically been considered high-risk, and industry recommendations do not support the use of LVAD support in patients with a BSA <1.5 or <1.8 m<sup>2</sup>. An INTERMACS analysis of 10,813 patients, however, has shown comparable rates of survival and RVF in patients with BSA <1.5 m<sup>2</sup> and BSA >1.5 m<sup>2</sup>, a finding replicated in smaller cohorts using bigger devices such as the Heart Mate II (HM2, Abbott, TX, USA) (12–15).

In healthy patients, smaller BSA reflects smaller cardiac size, but this may not hold true in advanced HF, as BSA and left ventricular end-diastolic diameter (LVEDD) correlate poorly (14). Independently of BSA, an LVEDD <60 mm has been repeatedly associated with RVAD requirement and late RVF, worse tricuspid regurgitation (TR) severity, lower LVAD flow and more LVAD alarms in both axial and centrifugal flow pumps (14, 16, 17). This is probably explained by the interventricular septum being more prone to shifting leftwards in smaller hearts at speeds that would otherwise be considered normal for larger cavities, thus distorting RV geometry (18). In the IMACS registry, the higher mortality and RVF observed in women was partially mediated by a smaller LVEDD, but not by BSA (18).

Although surgical implant may be more challenging, smaller patients benefit equally from LVADs. BSA does not impact RVF risk unless the LVEDD is exceedingly small. Individuals with restrictive or hypertrophic cardiomyopathies and smaller LVEDDs may have poor survival and higher risk of RVF. In such patients, a left atrial (LA) configuration of the inflow cannula may be attempted if LA cavity is big enough (19).

|                          |            | Must meet criteria 1 and 2   |                                  |  |   |   |  |              |
|--------------------------|------------|--|----------------------------------|--|---|---|--|--------------|
|                          |            | Criteria 1. Elevated CVP: CVP >16 mmHg OR dilated and fixed IVC OR JVP at half neck in upright position<br>Criteria 2. Symptoms: peripheral edema ≥2+ OR ascites OR hepatomegaly OR bilirubin >2 mg/dl OR creatinine > 2 mg/dl                                       |                                  |  |   |   |  |              |
| INTERMACS (2015)         | Definition | Mild   |                                  | Moderate   |   | Severe  |  | Severe-acute |
|                          |            | Implant  | Follow-up                        | Implant  | Follow-up   | Implant   | Follow-up  | Implant      |
|                          | Severity   | Inotropes, iNO or IV vasodilators <7 days  | No readmissions AND no inotropes | Inotropes, iNO or IV vasodilators 7-14 days  | 1 readmission for IV diuretics or vasodilators AND no inotropes | Inotropes, iNO or IV vasodilators >14 days AND CVP >16 mmHg | Use of inotropes OR RVAD OR ≥2 readmissions for IV diuretics or vasodilators OR death due to RVF   |              |
| MCS-ARC INTERMACS (2021) | Definition | At least 2: peripheral edema ≥2+ OR ascites OR JVP at half neck in upright position OR CVP >16 mmHg<br>OR at least 1: bilirubin >2 mg/dl OR AST/ALT x2 ULN OR creatinine x2 baseline OR Svo2 <50% OR CI <2.2 l/min/m2 OR lactate >3 mmol/l OR drop >30% in pump flow |                                  |  |   |   |  |              |
|                          |            | Early acute  |                                  | Early  |   |   | Late   |              |
|                          | Timing     | Need for temporary or durable RVAD (or ECMO) implanted in the operating room   |                                  | 1) Need for RVAD within 30 days<br>2) Failure to wean from inotropes, vasopressors or iNO for >14 days during the initial 30 days<br>3) Death within 14 days while on inotropes or pressors in patients who have not received RVAD |   |   | 1) Need for RVAD 30 days after LVAD implant<br>2) Admission at least 30 days after LVAD implant requiring IV diuretics or inotropes for >72h |              |

**FIGURE 1**  
Definition of right ventricular failure after LVAD implantation according to INTERMACS from 2015 and from 2021. INTERMACS, interagency registry for mechanically assisted circulatory support; MCS-ARC, mechanical circulatory support–academic research consortium; CVP, central venous pressure; IVC, inferior vena cava; JVP, jugular venous pressure; iNO, nitric oxide; IV, intravenous; RVAD, right ventricular assist device; RVF, right ventricular failure; ULN, upper limit of normal; Svo2, central venous oxygen saturation; CI, cardiac index; ECMO, extracorporeal membrane oxygenator; LVAD, left ventricular assist device.

### Obesity and malnourishment

Obesity, defined as body mass index (BMI) >30 kg/m<sup>2</sup>, confers a 40% increased risk of late RVF according to a recent meta-analysis (20). Other published data report up to a 3-fold risk of RVF in obese patients (21, 22). Obesity and congestion are linked through several well-described mechanisms including increased blood volume, inflammation, microvascular dysfunction and myocardial fibrosis, as well as comorbid conditions such as sleep apnea (23). The increased risk of RVF in obese patients is not associated with increased RVAD requirement or mortality.

Conversely, undernutrition at the time of implant is more common in individuals with pre-operative RVF and gut edema, as demonstrated by a higher CVP in malnourished patients (11 vs. 7 mmHg, *p* = 0.002) (24). Poor nutritional status has demonstrated a negative impact on RVF and survival using different metrics (BMI <18.5 kg/m<sup>2</sup>, prealbumin <17 g/L, nutritional risk index <83.5 points, prognostic nutritional index <30 points) (25–27). Thus, as a modifiable risk factor, deficient nutritional status should be identified during LVAD candidacy assessment and actively addressed.

### Kidney dysfunction

Kidney dysfunction is a strong predictor for mortality and early RVE, and few centers implant LVADs in stage V chronic kidney disease (CKD) [estimated glomerular filtration rate (eGFR), <15 ml/min/1.73 m<sup>2</sup>] (28, 29). In end-stage HF, cardiorenal syndrome can cause or exacerbate CKD via chronically elevated CVP and suboptimal renal perfusion pressure, which could explain its association with RVF during the early post-operative phase (30). Support for this hypothesis

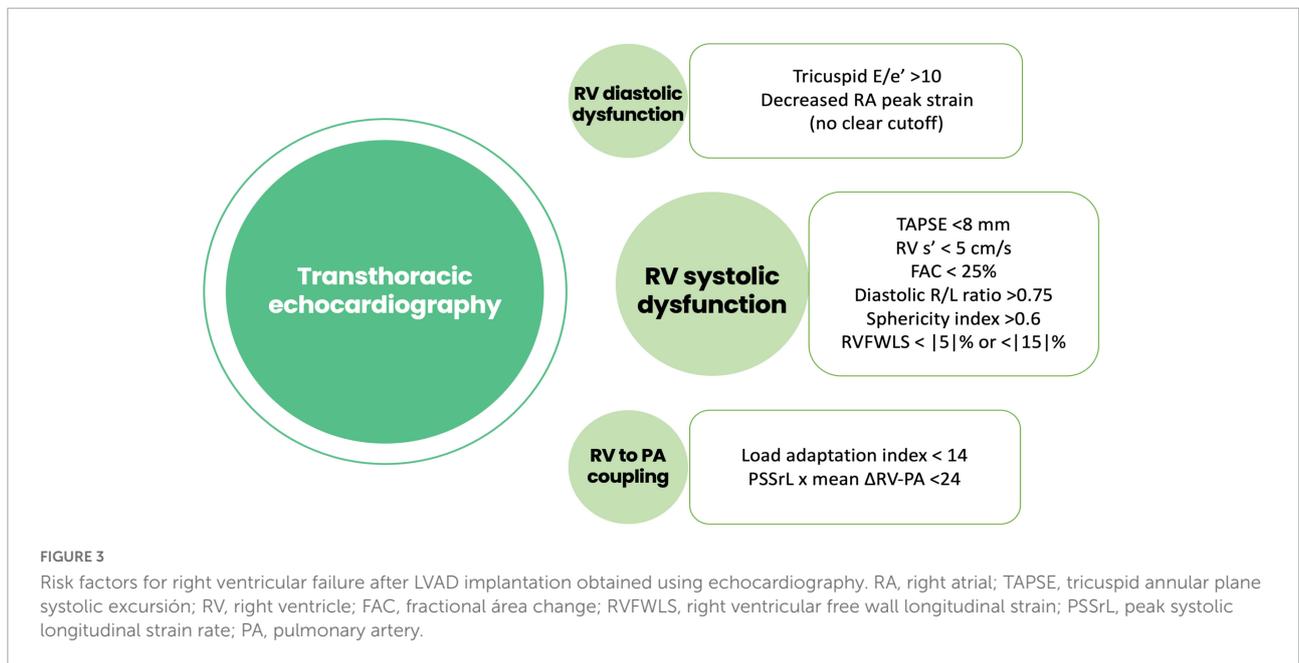
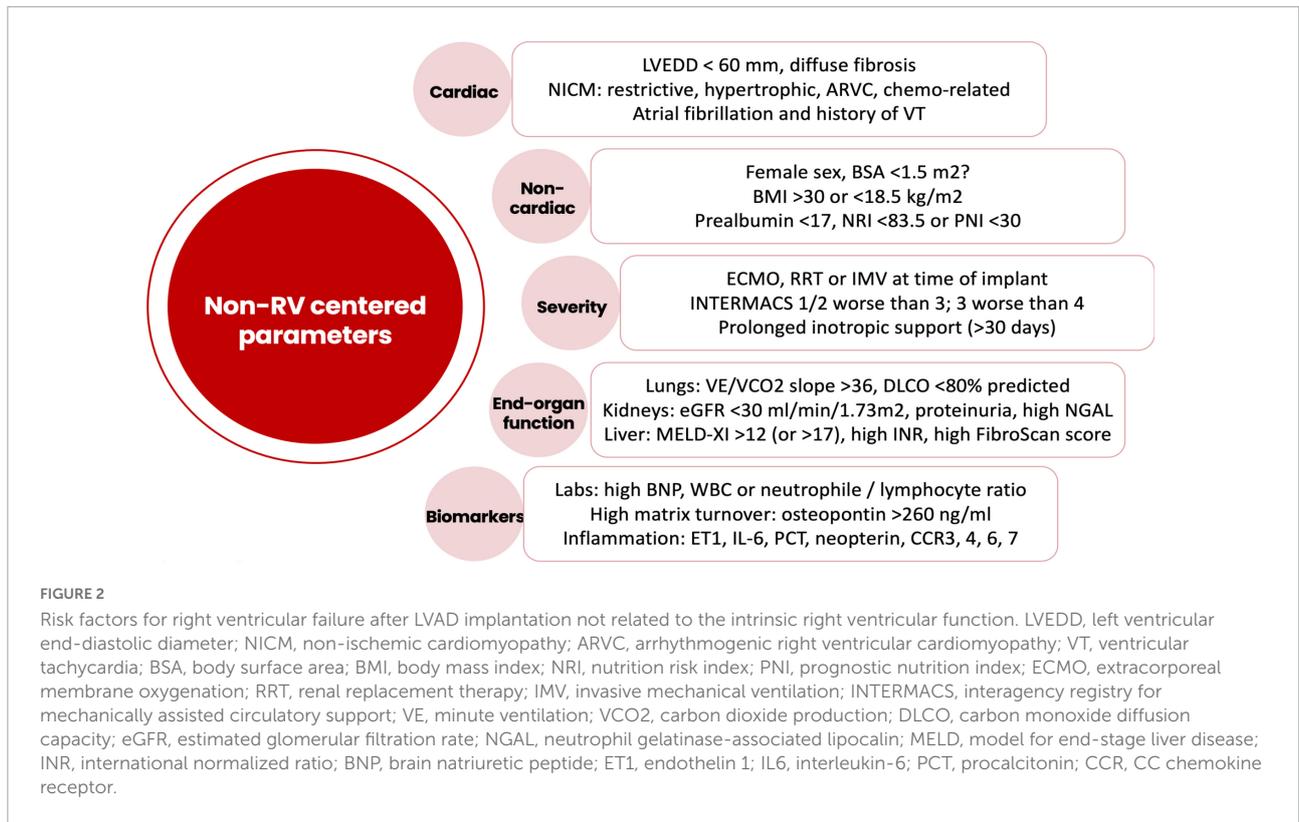
comes from the observation that kidney function improves after LVAD in a vast majority of patients, except in those who develop late RVF (28, 29, 31, 32).

In advanced HF, increased neurohormonal activation promotes the reabsorption of blood urea nitrogen (BUN) (33), with BUN levels being more strongly associated with early RVF than creatinine and eGFR (34). Muscle wasting and sarcopenia will also lower serum creatinine for a given GFR, explaining the paradoxical improvement in eGFR often seen in admitted patients. Cystatin C, a renal marker not affected by cachexia, better predicts RVF and RVAD need in the early post-operative period (35). Neutrophil gelatinase-associated lipocalin (NGAL) is an experimental marker that can differentiate intrinsic tubular damage from that attributable to hemodynamic disturbances, and can also predict an increased risk of RVF (36).

Proteinuria identifies patients with established CKD and faster disease progression and should be routinely tested during LVAD candidacy assessment. A positive dipstick or >0.55 mg protein/mg creatinine doubles the risk of renal replacement therapy (RRT), need for RVAD and mortality (37, 38).

### Liver dysfunction

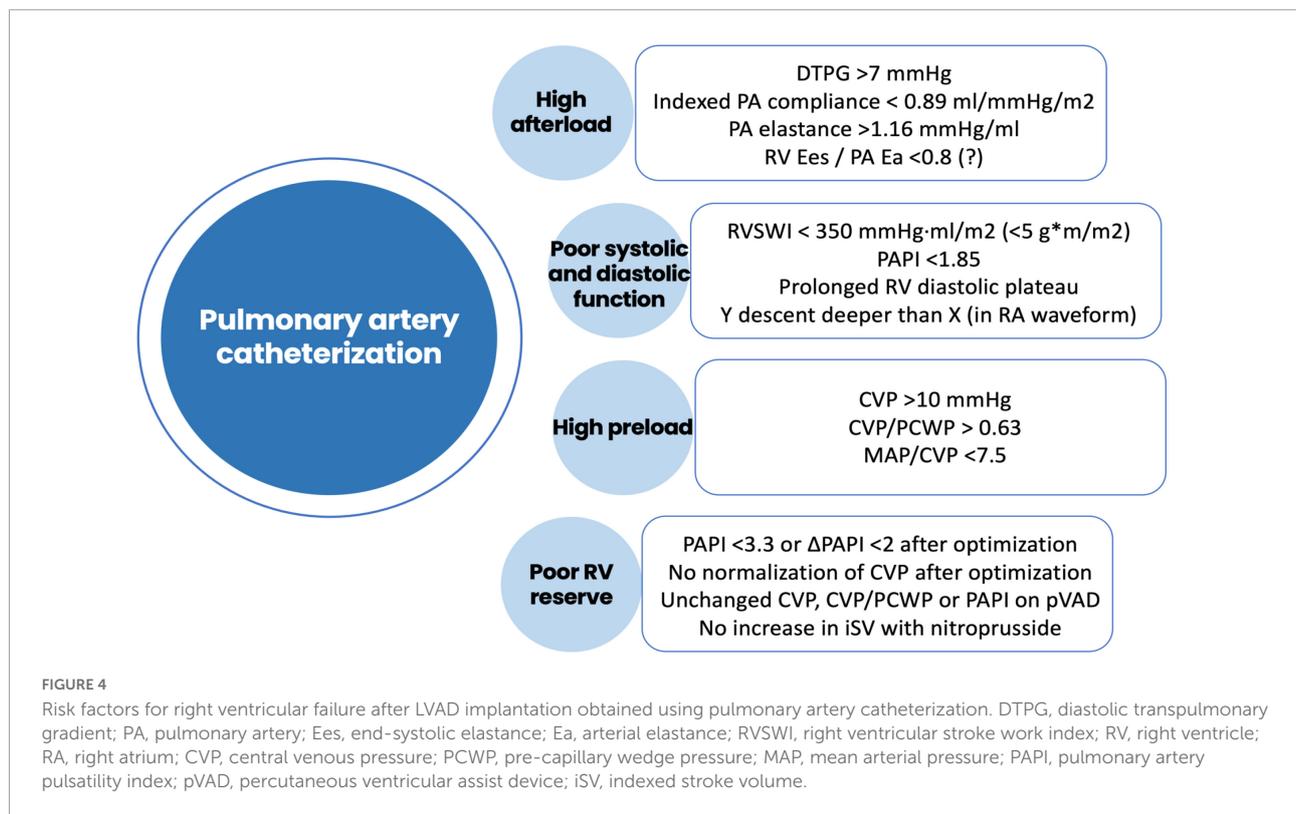
Liver dysfunction is another form of end-organ dysfunction attributable to RVF. Like eGFR, liver function tests frequently improve and remain within normal range for years after LVAD implantation, reflecting the close link with venous congestion (39, 40). The MELD score is a chronic liver disease severity scoring system that integrates both liver and kidney function, making it an excellent tool to assess RVF-related congestion before LVAD. Multiple studies have shown an association between MELD scores >12 and early RVF, RVAD support and



mortality, although no such association exists for late RVF (41–45). In the absence of warfarin treatment, the international normalized ratio (INR) is an excellent marker of synthetic liver function strongly associated with early RVF (46).

A liver biopsy may distinguish functional liver damage vs. established scarring, that may reflect a primary liver disease

or sustained right-sided congestion. In patients with periportal fibrosis (stage F1 and F2 on the biopsy), LVAD has been used successfully (47, 48). There is no data about patients with F3 or F4 fibrosis, but FibroScan elastography has identified higher rates of early RVF in patients with increased pre-operative liver stiffness, most of them within the range of severe



fibrosis (24.6 KPa vs. 9.5 KPa, >17.6 KPa being the cutoff for cirrhosis) (49).

### Pre-operative clinical profile

The number of LVAD implants in patients with INTERMACS 1 and 2 is decreasing over the years, as it is associated with greater RVF and mortality (50). When temporary MCS is used in INTERMACS 1 patients to restore hemodynamics, prognosis with regards to RVF remains equally poor, which may be related to only partial recovery of end-organ function or a more challenging assessment of RV dysfunction while on extracorporeal membrane oxygenator (ECMO) support (51). Rates of temporary RVAD utilization after ECMO is approximately 20% in multiple registries, and some authors even advocate for planned temporary RVAD support in all INTERMACS 1 patients to avoid the second surgery required for staged implantation (50, 52). In patients who cannot be weaned off ECMO, LVAD may be non-inferior to OHT, but assessment of RV function is important in deciding whether to proceed to one of these two high-risk alternatives (52). In patients who are receiving temporary MCS, assessment of RV function and reserve is more complicated due to the decrease in RV preload [in ECMO or biventricular assist device (BiVAD)] or afterload [in isolated left ventricle (LV) support], and a pulmonary artery catheter (PAC)-guided management could help in patient selection and even improve survival, as shown in a recent meta-analysis of observational data (53).

Interagency registry of mechanical circulatory support three patients, and especially those with ongoing inotropic support for >30 days, also tend to develop more RVF after the surgery than INTERMACS 4 or higher. This may be a marker of RVF pre-operatively and could identify patients with little margin for improvement solely using pharmacological adjustments if early RVF occurs (54, 55). Lastly, LVAD implantation should be considered cautiously in patients with ongoing invasive mechanical ventilation or RRT, as these have been consistently associated with early RVF (46, 56, 57).

### Biomarkers and the role of inflammation

There is a growing interest in biomarkers as predictors of RVF. Elevated BNP reflects stretch of myocardial fibers and has been correlated with higher RVF rates (58). Increased osteopontin (>260 ng/ml) is a marker for greater extracellular matrix turnover and identifies patients with an ongoing profibrotic process that may potentially involve the RV, with increased risk of RVF (59). Patients with RVF also display persistently high osteopontin levels after surgery and have less reverse remodeling (60). Direct measurement of this fibrotic process in myocardial tissue from the apical core removed at the time of LVAD implant has showed that increased collagen type 1 mRNA expression is associated with RVF and need for RVAD (61). Non-invasive measures of diffuse fibrosis such as cardiac MRI with T1 mapping have not been evaluated for this purpose.

Inflammation may be a relevant mediator of RVF in early phases. Readily available inflammatory markers such as white cell count, neutrophil to lymphocyte ratio, or C reactive protein correlate with rates of RVF (62). A more in-depth analysis showed that patients with RVF displayed a pre-operative downregulation of chemokine receptors CCR3, 4, 6, 7, and 8 that was even more profound in patients who required RVAD, which suggests a dose-response relationship that supports a causative role (63). Other inflammatory biomarkers such as procalcitonin, neopterin, or endothelin 1 have also been linked to RVF (64). As worse INTERMACS profiles have higher inflammatory biomarkers [such as interleukin-6 (IL-6)], the association between INTERMACS profile and RVF could be partially mediated by inflammation (65, 66). The therapeutic benefit of treating inflammation before LVAD implant in high-risk cohorts has not been yet explored.

### Respiratory disorders

Severe respiratory disease leads to increased pulmonary vascular resistance (PVR), a major contributor to RVF. Surprisingly, current evidence suggests that chronic obstructive pulmonary disease is not associated with overt RVF and does not impact mortality after LVAD, although quality of life and functional capacity remain compromised (67). Central sleep apnea frequently resolves with the increase in cardiac output (CO) provided by the LVAD, but obstructive or mixed episodes may persist and even cause nocturnal drops in LVAD flows (68), presumably related to transient hypoxia-mediated increases in PVR (69). A pre-operative carbon monoxide diffusion capacity <80% identified patients whose PVR will not decrease after surgery and who are at higher risk of recurrent HF admissions (70). Finally, patients with elevated ventilatory efficiency (VE)/carbon dioxide output (VCO<sub>2</sub>) slope on a cardiopulmonary exercise test (a marker of inefficient ventilation that may indicate disproportionate increase in PA pressures during effort) had a close association with RVF, higher CVP and lower pulmonary artery pulsatility index (PAPI), whereas peak oxygen consumption (VO<sub>2</sub>) had no association (71).

### Other clinical risk factors for right ventricular dysfunction

In myocardial diseases with primary involvement of the RV, such as arrhythmogenic right ventricular cardiomyopathy with severe RV dysfunction and dilatation, LVAD support will provide minimal benefit. Other cardiomyopathies impact the RV in a less apparent way, explaining the higher rates of RVF of non-ischemic cardiomyopathy (NICM) compared to their ischemic counterparts. This is most evident for NICM related to chemotherapy, which damages both ventricles, and is associated with higher rates of RVAD utilization (72, 73). Atrial fibrillation is marginally associated with RVF, presumably due to the detrimental effect of losing atrial contraction on CO

(74). Subjective assessment of lower limb hemosiderosis has been used by some as a surrogate for long-standing right-sided congestion (75).

## Right ventricular function assessment

In HF, RV dysfunction is usually related to chronically elevated left-sided filling pressures and secondary pulmonary hypertension, which constitutes a hallmark of advanced HF and is related to the remodeling of the pulmonary vasculature (76). The adaptative response of the RV is an increase in contractility to match the increased afterload, and RV hypertrophy or dilatation may occur. If RV afterload remains high, RV contractility may not be able to overcome the imposed resistance, leading to an uncoupling of RV and PA pressures. When RV-PA uncoupling occurs without correction of the RV afterload, RVF may result. As RV contractility worsens, PA pressures drop as the RV fails to generate an appropriate stroke volume. In severe RVF, even the correction of afterload will not improve RV contractility, and RVAD support may be required. This bimodal relationship between PA pressures, RV-PA uncoupling and RV contractility and dilatation explains most of the echocardiographic and hemodynamic predictors that have been studied. In all-comers with HF, higher PA pressures are usually associated with worse outcomes (77). However, in patients undergoing LVAD candidacy assessment, higher PA pressures confer a better prognosis, as low PA pressures are usually associated with a drop in RV contractility (78).

### Echocardiographic risk factors for right ventricular dysfunction

#### Right ventricular systolic function

Most echocardiographic predictors of RVF are based on RV systolic dysfunction, although all of them are afterload dependent and portend higher rates of RVF in the setting of a low afterload. Despite the existence of different cutoffs for RVF risk, all predictors should be approached as a continuum of risk rather than a dichotomous value. Tricuspid annular plane systolic excursion (TAPSE) less than 8 mm has been consistently associated with RVF risk, increasing the predictive capacity of different risk scores (79–81). The suggested cutoff to predict RVF for RV's tissue Doppler  $s'$  was <5–8 cm/s (82, 83). RV fractional area change (FAC) accounts for radial contraction in addition to longitudinal contraction, and is associated with RVF <25–30% (79, 84). RV dilatation can be assessed with the ratio between RV and LV end-diastolic diameters in a 4-chamber view, or right-to-left ratio. Another useful tool is the ratio between the end-diastolic RV mid-ventricular and longitudinal diameters, or the sphericity index. The risk of RVF increases when the right-to-left ratio is >0.72–0.75 (85, 86), or when the sphericity index is >0.6 (82, 87, 88). The contribution of septal fibers to RV contractility is severely reduced after LVAD

implant, and the assessment of RV free wall contractility with deformation techniques predicts RVF with accuracy similar to conventional RV systolic assessment. However, the cutoffs for RV free wall longitudinal strain for predicting RVF vary widely across studies, ranging from <5 to <15%, which precludes practical implementation (46, 79, 89–93). The capacity of simultaneous multiplanar echocardiography and 3-dimensional imaging to evaluate the complex RV anatomy may improve discrimination (88, 94–96).

### Right ventricular to pulmonary artery coupling

Indices of RV systolic function can be misleading, as they can be affected by excessive afterload independent of intrinsic RV dysfunction. Measures of RV-PA coupling such as TAPSE/systolic PA pressure that have been shown to be predictive of RVF in all-comers with HF do not reliably predict RVF in the LVAD population (97). This is not surprising, as a low TAPSE/systolic PA pressure identifies patients with mild RV-PA uncoupling (initial drop in systolic function related to elevated RV afterload) but cannot capture patients with more advanced stages of RV-PA uncoupling (drop in systolic PA pressure due to a decrease in RV stroke volume), who are precisely the patients at higher risk of post-operative RVF. The product of peak systolic longitudinal strain rate  $\times$  mean RV-PA gradient <24 or a load adaptation index [(mean RV-PA velocity time-integral  $\times$  longitudinal RV diameter)/RV end diastolic area] <14 identify patients with a failing RV unable to generate appropriate PA pressures, and both indexes have a very high accuracy in predicting RVF in candidates for LVAD implantation (82). Several other metrics of late-stage RV-PA uncoupling have been tested in HF population, but their usefulness remain to be proven in LVAD recipients (98).

### Right ventricular diastolic dysfunction

Diastolic RV dysfunction is frequently overlooked as a predictor of RVF following LVAD implant. A restrictive RV filling pattern and/or high filling pressures can be assessed with the tricuspid E/e' ratio, which predicts RVF when >10 in the 72 h preceding LVAD surgery (83). Chronically elevated RV end diastolic pressure is better captured by peak longitudinal right atrial (RA) strain. The only study analyzing RA strain showed striking differences between groups (average peak RA strain 11% for those with RVF vs. 33% for those without,  $p < 0.01$ ), with excellent discrimination [area under the curve (AUC) = 0.913] to predict the need for RVAD (99).

## Invasive assessment of right ventricle to predict right ventricular failure

### Right ventricular afterload

Invasive hemodynamic measurement using a PA catheter is the gold standard for assessment of RV afterload. The transpulmonary gradient (TPG) [mean PA pressure–pulmonary capillary wedge pressure (PCWP)] or the transpulmonary diastolic gradient (TPDG) (diastolic PA pressure–PCWP) are

simple measures that can identify a fixed component of RV afterload likely to persist after LVAD implant. They are of limited use because they do not account for pulmonary flow. A TPDG >7 mmHg predicted RVF after LVAD implantation in a single study (100).

Right ventricle afterload can be divided into a resistive component and a pulsatile load. The resistive component of RV afterload is captured by PVR [(mean PA pressure–PCWP)/cardiac output (CO)], but PVR has not been consistently associated with worse RV function after LVAD. Compliance, calculated as [stroke volume/(systolic PA pressure–diastolic PA pressure)], measures pulsatile RV load, and may be a better marker of RV afterload in HF patients that is highly sensitive to changes in PCWP (101). When indexed by BSA, compliance <0.89 ml/mmHg/m<sup>2</sup> predicts RVF after LVAD (7, 102). Finally, PA elastance (Ea) incorporates both pulsatile and resistive components, and may be a better measure of global RV afterload (103). PA elastance is calculated as systolic PA pressure/stroke volume, and outperforms PA compliance for predicting RVF after LVAD with a suggested cutoff of >1.16 mmHg/ml (7).

### Right ventricular systolic and diastolic function

Assessing intrinsic RV systolic performance independent of other variables remains challenging. The parameter most often used for this purpose is right ventricular stroke work index (RVSWI), a flow-dependent estimate of RV contractile function. RVSWI is calculated as [mean pulmonary artery pressure (mPAP)–CVP]  $\times$  stroke volume index (SVI)  $\times$  0.0136. An RVSWI >5 g  $\times$  m/m<sup>2</sup> (equivalent to 350 mmHg·m<sup>3</sup>/m<sup>2</sup>) is predictive of RVF after LVAD implant (46, 104). Other proposed load-independent metrics include RV dp/dt and direct estimation of end-systolic elastance (Ees) using pressure-volume loops, but there is only preliminary data using these parameters and no proposed cutoffs (105, 106).

Right ventricle diastolic dysfunction cannot be directly measured using standard monitors, which limits clinical utility. However, the RA pressure waveform provides a readily available surrogate of RV distensibility. In the absence of TR, a Y descent deeper than the X descent reflects impaired RV diastolic relaxation. Qualitative RA waveform assessment has excellent interobserver reliability, with impaired RV relaxation seen in 20% of LVAD candidates. A non-distensible RV is a strong predictor of early RVF, and in a small cohort was observed in all patients requiring RVAD support and in those with late RVF (107).

### Right ventricular preload

Systolic and diastolic dysfunction will eventually lead to inefficient volume management with a resultant increase in preload and CVP. Elevated pre-operative CVP (>10–14 mmHg depending on the study) has been consistently associated with RVF after LVAD (46, 104). Furthermore, CVP increases with

vasoplegia, often seen in combination with RVF (108). The CVP/PCWP ratio  $>0.63$  distinguishes between volume overload vs. disproportionate RVF as the cause for elevated CVP. A mean arterial pressure (MAP)/CVP ratio  $<7.5$  may also suggest high RV preload and higher risk of RVF (109).

### Integrative measures of right ventricular assessment

As with echocardiographic evaluation, an integrative approach incorporating multiple invasive hemodynamic parameters is likely to improve RVF risk prediction. Pulmonary artery pulsatility index (PAPi) (systolic PA–diastolic PA)/CVP is PAC-derived measurement that reflects both preload and afterload with excellent predictive capacity for RVF at values  $<1.85$ – $2$  (91, 104, 110, 111). PAPi  $<1.85$  is associated with higher rates of RVF, need for RVAD and mortality. Moreover, PAPi may reflect an abnormal myocardial substrate, as it has also been linked to RV sarcomere contractile dysfunction (112). Models that integrate indices of RV distensibility, PA compliance and PA elastance more accurately predict post-operative RVF from diastolic dysfunction or afterload (7, 102, 107). Likewise, patients with both RFSWI  $<5 \text{ g} \times \text{m}/\text{m}^2$  (low contractility) and elevated PVR (elevated resistance) are at significantly higher risk of RVF and RVAD (113). Other integrative measures of RV-PA coupling such as Ees/Ea ratio (normal values  $>0.8$ ) have shown excellent prognostic value in advanced HF population (114) but have not been studied to predict RVF in LVAD patients.

### Assessment of right ventricular reserve

Right ventricle function, preload and afterload are dynamic variables that may fluctuate pre- and post-LVAD implantation, and these static metrics may be unable to fully account for RV reserve. In a moderately large cohort, baseline PAPi predicted RVF, but an optimal PAPi  $<3.3$  after hemodynamic optimization or an increase in PAPi ( $\Delta\text{PAPi}$ )  $<2$  had a much stronger predictive value for RVF (115). Similarly, PAPi measurement while on inotropes better predicts RVF than when measured off inotropic support (111). The same findings were observed for CVP, as patients with normalized CVP after hemodynamic optimization had the same outcomes as those with low CVP at admission (116). The strong predictive value of pre-operative hemodynamics raises the question of whether pre-emptive percutaneous RVAD support for hemodynamic tailoring and RV unloading could improve outcomes in patients at very high-risk for RVF (117). A vasodilator challenge with sodium nitroprusside (SNP) is also helpful in predicting RVF, so that PAPi after a SNP administration was the strongest predictor of RVF in a small prospective study (118). In the same line, a multicentric collaboration also demonstrated that a blunted increase  $<22 \text{ ml}/\text{m}^2$  in indexed stroke volume after SNP challenge was consistently associated with higher rates of RVF (119).

In patients at high risk of RVF, RV reserve can be assessed using a temporary, percutaneous LVAD. Within 48–72 h of

insertion of an Impella CP (Abiomed, Danvers, MA, USA), all parameters of RV afterload improve (reduction in PCWP, PVR and Ea), as does CVP and CVP/PCWP (120). The ratios Ea/CVP and Ea/(CVP/PCWP) remain unchanged as they reflect the RV capacity to cope with a given afterload. These metrics may therefore have higher value in the static assessment of RV function (120). These results were replicated in patients bridged to LVAD with axillary Impella devices (121). Conversely, patients with little or no improvement in CVP, PAPi and CVP/PCWP ratio after Impella support developed RVF (121).

### Scores to predict right ventricular failure

Currently, there are over 20 published RVF risk scores that integrate clinical, echocardiographic, and hemodynamic variables, but few have undergone external validation. The most commonly used scores are the HM2 Risk Score, CRITT, EUROMACS, Michigan and ALMA scores (56, 57, 122–124). Most of these scores were developed using single center registries and axial flow pumps, display modest discrimination capacity (AUC 0.68–0.74), and performed poorly when externally validated (AUC 0.53–0.65) with inaccurate calibration (2). Overall, the currently available risk scores are too unreliable to aid in decision-making but remain a useful tool when comparing average risk of RVF among registries.

A meta-analysis studying predictors of RVF showed that the most robust variables were high CVP, low RFSWI, low MAP, high INR, white blood count and NT-proBNP, qualitative assessment of RV function, higher RV/LV ratio and RVFWLS, as well as pre-operative mechanical ventilation or RRT (46). A Bayesian analysis of the INTERMACS score was also developed for acute, early and late RVF and identified  $>30$  variables with different weights for each scenario, with excellent predictive value (AUC 0.83–0.9). Systolic PA pressures and inflammatory markers had more weight in predicting early RVF whereas PVR and MELD score were more relevant for late RVF (125).

## Surgical considerations to minimize risk of right ventricular failure

### Avoidance of pericardiotomy and cardiopulmonary bypass

The conventional surgical approach to LVAD implantation involves complete midline sternotomy, open pericardium, aorto-bicaval cannulation and cardiopulmonary bypass (CPB). Implantation is most often performed on CPB with a beating heart, as avoidance of cardioplegia and cardiac arrest may lessen post-CPB stunning of the RV.

After surgical LVAD placement, RV adaptation to afterload drastically diminishes, with higher CVP and CVP/PCWP ratios for a given PA elastance. This decompensation is not seen after percutaneous LVAD insertion, highlighting the deleterious effects of surgery (120, 126). CPB, cardioplegia and extensive pericardiectomy can worsen RV dysfunction and dilation and distort the RV geometry, worsening RV-PA uncoupling. In serial echocardiographic assessments during cardiac surgery, there was a 50% drop in RV contractility and increased LV compliance at the time of pericardiectomy, prior to the initiation of CPB (127, 128). RV function further deteriorated with the septal dyskinesia commonly seen upon discontinuation of CPB (129). Cytotoxin liberation during CPB may also negatively impact RV function (62, 63, 65, 66, 130).

The feasibility of a minimally invasive approach was demonstrated in the LATERAL trial, a non-randomized, single arm, prospective trial in which 144 LVAD candidates underwent on-pump HVAD placement through a lateral thoracotomy (LT) and mini-sternotomy, with only 1 patient requiring RVAD support (131). Notably, pre-existent severe RVF was an exclusion criterion for the trial. Although the HeartWare HVAD device (Medtronic, Minneapolis, MN, USA) is no longer available, the feasibility of LT approach avoiding pericardial opening has been demonstrated for Heart Mate III (HM3, Abbott, Chicago, IL, USA) (132, 133). LT was approved by the food and drug administration (FDA) for HM3 in 2020 and is endorsed by industry after the successful LT implant in 44 patients from the ELEVATE registry and in 13 patients from the LAT feasibility study. Off-pump LT implantation is also feasible, but experience is by far less common (134, 135).

The benefits of LT and pericardial preservation on RVF by preserving RV geometry and avoiding distension are still under debate. Whereas a recent INTERMACS analysis using propensity matching did not identify any benefit regarding RVF incidence (136), two contemporary meta-analyses comparing LT to median sternotomy showed a reduction of RVF, RVAD and blood product utilization by more than 50% with almost no heterogeneity in results (137, 138).

## Bleeding and coagulopathy

Intra-operative bleeding and transfusion are common during LVAD implantation and negatively affect RV performance through cytokine release, increased PVR and volume overload. It is estimated that with transfusion of each unit of blood products (red blood cells, platelets or frozen plasma), there is a 10% increase in RVF risk, so that judicious use of blood products is recommended (139, 140).

The use of rotational thromboelastometry (ROTEM) reduces blood transfusions and bleeding in patients undergoing cardiac surgery, and should be considered standard of care during LVAD surgery (141). Baseline ROTEM before surgery

can identify primary bleeding disorders or platelet dysfunction that can be addressed before coagulopathy ensues (142). Upon discontinuation of CPB, ROTEM allows for rapid, point-of-care analysis of hemostasis and coagulopathy, enabling targeted transfusion strategies that avoid the indiscriminate administration of blood products.

The main risk factors for intra-operative transfusion are previous cardiac surgery and low pre-operative hemoglobin (139). Pre-operative hemoglobin optimization strategies have been shown to reduce blood product utilization during surgery (143). In patients with unresolved coagulopathy, consideration may be given to packing the mediastinum and leaving the sternum open for delayed closure. Delayed sternal closure allows to control the coagulopathy in the intensive care unit (ICU), minimizing bleeding and avoiding tamponade and the associated excessive pressure on the RV from edematous tissues, thus potentially preventing RVF. This approach, however, has not demonstrated any benefit in the rates of RVF in observational cohorts, prevents early extubation and increases risk of infection (144–146). The peritoneum can be damaged while tunneling the LVAD driveline, allowing peritoneal fluid into the thoracic cavity. This should be avoided, as peritoneal fluid contains tissue plasminogen activator that can worsen coagulopathy (147).

## Tricuspid regurgitation

Moderate to severe TR is found in 30–40% of LVAD candidates (Figure 5) (148, 149). If left unrepaired, >70% of cases will regress to less than moderate during follow-up, likely related to the relief of RV afterload, whereas 10% of LVAD patients will develop *de novo* significant TR (150, 151). As expected, severe TR after LVAD is independently associated with RVF and mortality (150). Routine tricuspid valve (TV) repair for severe TR at the time of implantation does not improve long term outcomes, with 30% of TV repairs failing within 1 year of implant (152, 153). Instead, TV repair has been linked with increased risk of arrhythmia, stroke, bleeding, need for reoperation, higher need for RRT and longer stay on mechanical ventilation and in ICU, with no improvement in quality of life thereafter (148, 154). However, the techniques of repair vary widely and have not been standardized. Failure to demonstrate a benefit of TV repair may be associated with a failure of the repair itself or with failure of the selected strategy.

Predictors of persistent TR or *de novo* TR are tricuspid annulus dilatation >41 mm (153, 155, 156), atrial fibrillation (157–159) and normal PVR (159). Despite the risks, repair in these cases is justified to minimize the likelihood of late RVF. In patients with intracardiac devices and suspected device-related severe TR, a surgical exploration seems reasonable if the echocardiography shows a lead adherent or impinging the TV leaflets, as the chance of TR improving if left uncorrected is

|                                     | ≥ Moderate-severe TR  | Severe MR  | ≥ Mild AR  |
|-------------------------------------|---|--|--|
| <b>Prevalence</b>                   | 30-40%  | 40%  | 20%  |
| <b>Improvement</b>                  | >70% has ≤moderate  | >80% has ≤mild   | 50% has ≥moderate  |
| <b>Risk factors for progression</b> | TV annulus 41 mm<br>Atrial fibrillation<br>Normal PVR<br>Device-related | Large LVEDD<br>NICM<br>RV dysfunction<br>Severe TR<br>Female sex<br>Inflow cannula misalignment<br>Younger age | Obtuse outflow graft angle<br>Outflow graft close to aortic root<br>STJ>35 mm or >19.5 mm/m <sup>2</sup>   |
| <b>Preferred approach</b>           | Surgical repair if risk factors   | Surgical repair if risk factors?   | ≥Moderate: always surgery<br>Mild: consider surgery<br><br>Common options: 1) central coaptation stitch 2) bioprosthesis (if root dilated) 3) valve oversewing |

FIGURE 5

Prevalence, risk factors for progression and management for valvular regurgitation at the time of LVAD implant to minimize the risk of right ventricular dysfunction. TR, tricuspid regurgitation; MR, mitral regurgitation; AR, aortic regurgitation; TV, tricuspid valve; PVR, pulmonary vascular resistance; LVEDD, left ventricular end-diastolic diameter; NICM, non-ischemic cardiomyopathy; STJ, sinotubular junction.

much lower (160). However, an isolated annuloplasty band for severe TR related to a pacing lead will predictably fail.

## Mitral regurgitation

Significant mitral regurgitation (MR) is observed in 40% of patients at the time of LVAD implantation (Figure 5), but >80% experience improvement to mild or less with adequate LV unloading (161). Persistent MR after LVAD is associated with higher mortality, HF admissions, RVE, severe TR and increased PVR with elevated CVP and PA pressures, and also with worse kidney function (162–166). Patients who received a previous transcatheter edge-to-edge repair can safely undergo LVAD implantation without the need to remove the device if the mean transvalvular gradient remains below 6 mmHg. Compared with patients without transcatheter repair and severe MR at the time of LVAD implantation, previous repair was associated with greater reduction in TPG (167).

Mitral valve repair at the time of LVAD implant is not universally recommended given the high percentage of patients who improve without intervention. Review of the INTERMACS registry shows that mitral valve repair is associated with less MR during follow up, fewer HF admissions, and improved functional capacity and quality of life (161, 164, 168, 169). Risk factors for significant MR after LVAD include severe MR before LVAD, NICM with large LVEDD, RV dysfunction, significant TR, atrial fibrillation, female sex, younger patients, and HM2 support (vs. HM3) (164, 170).

Left ventricular assist device implantations are guided by transesophageal echocardiography (TEE) so that the inflow cannula is oriented toward the mitral valve to favor proper unloading. Using a conventional chest X ray, an inflow cannula

with coronal angle >65–75° for HM2 and HVAD and <28° for HM3 is associated with worse unloading, greater MR severity, lower PAPI, less decrease in PCWP per each 100 rpm LVAD speed increase and more HF admissions due to late RVE (171–174). The degree of residual MR following LV unloading can be immediately assessed during surgery, and patients with tenuous RV function and risk factors for MR persistence may benefit from simultaneous mitral valve repair. If LVAD is being used as a bridge to recovery, mitral valve repair also helps to achieve better hemodynamics.

## Aortic regurgitation

Aortic regurgitation (AR) causes a closed-loop circulation between the aorta and LV, and AR following LVAD is clearly associated with higher mortality, more HF admissions, RVE, lower PAPI and higher CVP, all of which are related to increased PCWP (175–177). Any more than mild AR needs to be surgically addressed at the time of LVAD implantation, a situation encountered in 20% of patients (Figure 5) (176, 178). More than half of patients with unrepaired mild AR progress to moderate or severe AR during their time on support (176, 179, 180). Management options include aortic valve repair, bioprosthetic aortic valve replacement, patch closure of the aortic root, complete aortic valve closure, and central aortic valve closure/Park's stitch (181). Aortic valve closure is associated with higher 2-year mortality than repair or replacement and increases the risk of sudden death in case of device malfunction. Instead of complete closure, repair with a central coaptation stitch ensures partial aortic valve opening. 20% of repairs display recurrent AR vs. 9% of replacements (182). Risk factors for progressive AR following LVAD include

a dilated aortic root or sinotubular junction ( $>19.5$  mm/m<sup>2</sup> or 35 mm), obtuse outflow graft configuration directed toward the aortic valve, and implantation closer to the aortic root (180, 183–187).

Patients who develop AR have higher BNP, reduced cardiac index, higher LVEDD and reduced PCWP decrease at higher LVAD speeds (175, 176), which subsequently increases RV afterload and leads to worse functional class, more frequent HF admissions and worse survival (176, 177, 179). Main predictors for AR are female sex, duration of support and aortic valve closure, which causes commissural fusion of the leaflets (176, 188). AR severity should be routinely monitored during follow-up of LVAD patients using the novel diagnostic criteria that use pulsed wave in the outflow graft for their better correlation with clinical endpoints (189, 190). Aortic valve intervention should be considered when *de novo* AR is at least moderate, there are congestive HF symptoms and hemodynamic ramps suggest poor unloading at increasing speeds. Although a high-risk procedure, transcatheter aortic valve implantation (TAVI) or percutaneous closure using an Amplatzer device (Abbott, Chicago, IL, USA) (191–193) can be performed (194–197), but acute resolution of AR may cause LV collapse with marked leftwards shift and acute RVF in around 15% of reported TAVI procedures (194).

## Coronary artery disease

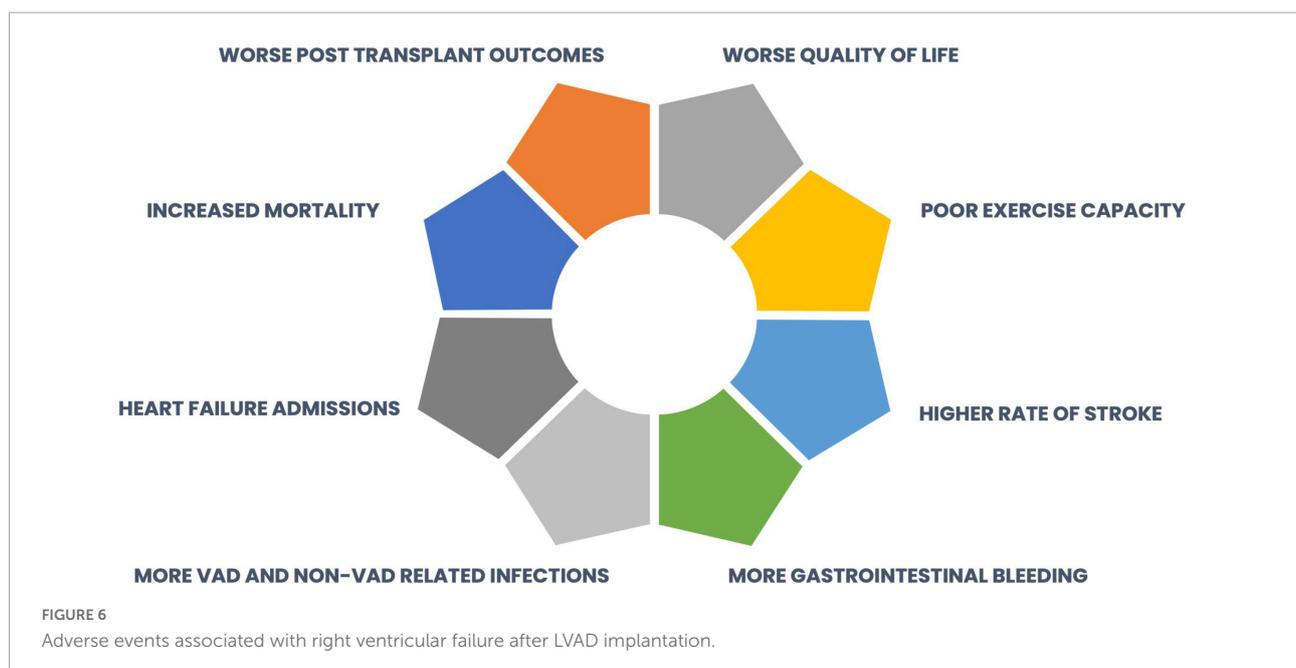
Damage or occlusion of the right coronary circulation may lead to catastrophic RVF (198, 199). In patients with ischemic cardiomyopathy, and especially in those with previous bypass,

assessment of coronary anatomy is necessary to determine RV blood supply and risk of re-entry. In patients with proximal right coronary artery (RCA) occlusion, the RV may rely on collateral branches susceptible to injury during coring for LVAD insertion or sternotomy. Likewise, septal perforators must be preserved to preserve the septal contribution to RV contraction (200, 201). Simultaneous coronary artery graft bypass, however, may be associated with more risks than benefits and there is a very low rate of coronary events in the long-term (200, 202), so that protection of RV circulation should be assessed case-by-case. Severe proximal RCA stenoses limiting coronary perfusion to the RV should likely be addressed at the time of LVAD implant.

## Early and acute right ventricular failure

### Mechanisms of early and acute right ventricular dysfunction

Acute severe RVF with RVAD requirement is the most catastrophic form of RVF and occurs in approximately 5% of LVAD implants (3, 4). Early RVF and RVAD are associated with multiple complications including prolonged ICU length of stay, acute kidney injury (AKI) and RRT, bleeding and bowel ischemia, stroke, and in-hospital mortality (Figure 6) (203–209). While on CPB, the RV is completely unloaded, and weaning from CPB should be gradual and coordinated with progressive increase in LVAD speed to avoid RV distension. RV geometry and pressure-volume relationships are altered after



pericardiectomy, and transient RV dysfunction is common post-CPB. The septal contribution to RV contraction is decreased as the septum is suctioned leftwards, and TV geometry may be distorted, causing a greater regurgitant jet with increased RV dilation, wall tension with higher VO<sub>2</sub>, and demand ischemia (210). The RV becomes afterload sensitive after LVAD (126), and high pulmonary pressures may compromise function. Early RVF is characterized by a drop in peak RV systolic pressure and RV dp/dt (211). A commonly theorized cause for RV deterioration following LVAD is an increase in RV preload with “flooding” caused by the increased CO. Very limited evidence exists to support this theory, which contradicts the principles of a closed-loop circulation, where the RV output must necessarily match LVAD output.

## Intra-operative assessment of right ventricular performance

After chest closure, invasive measurements of CVP, diastolic PAP and PAPI remain accurate for predicting RVF (212, 213). Although no specific cut-offs have been suggested for clinical use, the relevant values are likely lower than those used in pre-operative RV assessment (212, 213). Patients who develop RVF show a significant intra-operative drop in RVSWI and blunted increase in cardiac index (214). If there is residual pulsatility, pulsus alternans could also be an early sign of RVF after initiating LVAD support (215).

Transesophageal echocardiography can assist in monitoring leftwards septal shift at progressively higher speeds. Intraoperatively, the echocardiographic assessment of RV function described in the pre-operative setting has poor predictive value for acute RVF, with the exception of FAC (213, 216, 217). In the immediate post-operative period, TEE guidance can identify septal misalignment and trigger more speed adjustments than conventional monitoring with a PA catheter, with the most common indicator being a rightwards septum suggesting insufficient unloading (218).

## Decreasing afterload

### General measures

Following separation from CPB, the general principles of RV optimization apply, with reduction of RV afterload being paramount (219). Thorough de-airing is essential as air emboli have a predilection for the RCA due to its anatomic position. Maintaining adequate RV perfusion pressure can be challenging in the context of refractory vasoplegia or use of inodilators (milrinone, dobutamine). Hypercarbia, hypoxemia, acidosis, hypothermia, pain and light anesthesia can all promote pulmonary vasoconstriction and increase PVR, with a detrimental effect on LV filling and LVAD flows (220). Return

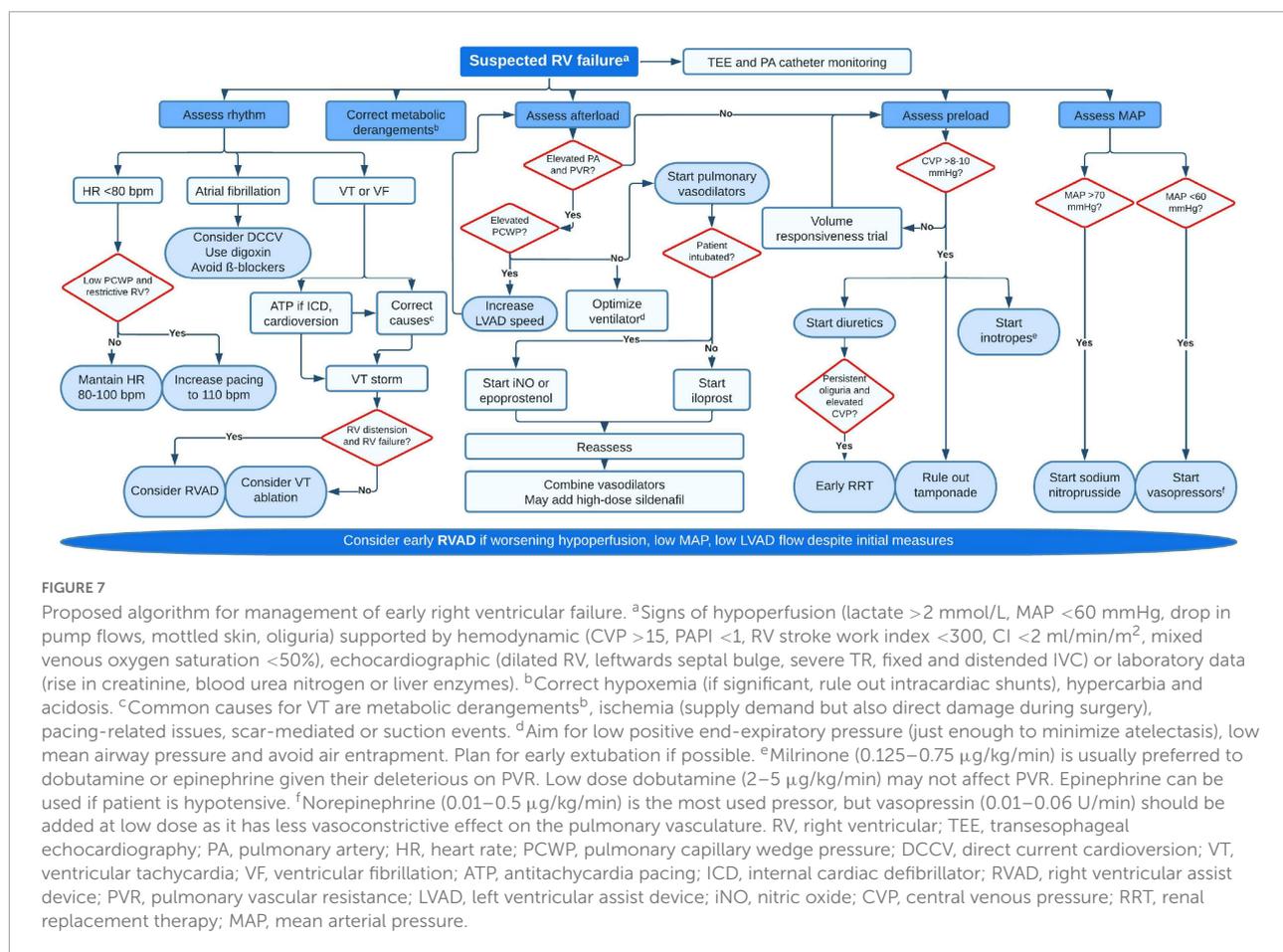
of CPB volume and subsequent transfusion should be performed slowly and with TEE guidance to prevent RV overload. Protamine reactions can cause significant increases in PVR through thromboxane release (221). For patients with tenuous RV function, intra-aortic administration of protamine bypasses the pulmonary circulation and minimizes its hemodynamic effects (222). Unexplained hypoxemia after LVAD raises the possibility of an unrecognized patent foramen ovale with right to left shunt. Low LVAD speeds may cause insufficient LV unloading and should be adjusted under echocardiographic guidance to reduce RV afterload. Notably, many factors may impact RV resistive load during surgery and general anesthesia, and diastolic PAP in the operating room may not be reflective of PCWP. **Figure 7** provides a comprehensive algorithm for management of RVF.

### Early extubation

Positive pressure ventilation increases PVR and decreases CO in an RV-dependent circulation. Positive end-expiratory pressure (PEEP) and mean airway pressure should be kept at the minimum required to avoid atelectasis (223). Ultra-fast-track anesthesia, consisting of early extubation within 4 h of the surgery, is feasible with either median sternotomy or LT (224). Early extubation with spontaneous breathing and negative intrathoracic pressure minimizes RV afterload and is associated with less RVF and pneumonia, improved RVSWI and shorter length of stay (224, 225). Unfortunately, inhaled iNO therapy often delays extubation in patients at risk of RVF, and early administration of inodilators such as milrinone may hasten iNO weaning.

### Vasoactive support

In patients undergoing LVAD surgery, the RV remains preload dependent, but with much narrower limits. At a CVP above 10–12 mmHg, volume loading further increases filling pressures without improvement in RVSWI or CO (226). Fluid responsiveness must not be mistaken for fluid tolerance, and resuscitation should be judicious (227). Inotropic support with either dobutamine, milrinone or epinephrine will improve contractility, forward flow and decrease CVP. At doses higher than 2–5 µg/kg/min, dobutamine causes a rise in PVR, and milrinone is preferred for its vasodilatory effect on the pulmonary circulation. If vasopressor support is required following milrinone initiation, low-dose vasopressin can effectively increase systemic vascular resistance (SVR) to the same extent as norepinephrine without modifying PVR (228). Intratracheal and inhaled milrinone have been successfully used to improve RVF, reduce PVR and mean PA pressures, while minimizing the effect on SVR (229, 230). Levosimendan is a calcium sensitizer that can be administered in combination with other inotropes to improve RV contractility. Reports in the LVAD population are scarce (231), but randomized trials involving levosimendan in general cardiac surgery have not



shown improved outcomes (232–234). Currently there is no evidence to support levosimendan use in LVAD patients.

## Pulmonary vasodilators

Pulmonary vasodilators may reduce RV afterload but should only be initiated once LVAD speeds are optimized. If a patient exhibits persistent pulmonary hypertension despite adequate LV offloading and a low PCWP, then pulmonary vasodilators may be of benefit. However, if the LV remains congested, pulmonary vasodilators may increase LV preload and PCWP with minimal improvement in RV afterload or performance (235).

## Inhaled nitric oxide

Inhaled iNO is a selective pulmonary vasodilator that activates guanylate cyclase to increase cyclic guanylyl monophosphate in the smooth muscle only in vessels perfusing oxygenated alveoli, reducing intrapulmonary shunting and V/Q mismatch. Unlike intravenous inodilators such as milrinone and dobutamine, iNO has minimal effects of SVR and blood pressure, making it easier to maintain RV perfusion pressure. iNO is commonly used pre-emptively in LVAD surgery due to a favorable risk-benefit profile, with cost and time-to-extubation being the primary deterrents. Methemoglobinemia is rarely

seen at clinically relevant doses of 40 ppm or less (236). Small, randomized controlled trials have demonstrated the efficacy of iNO in reducing PVR and mean PA pressure over placebo, but with a non-significant reduction in RVE, probably related to insufficient sample size and >10% crossover (237–239). The benefit of iNO seems limited to patients with elevated mean PA pressures or elevated PVR after PCWP normalization, regardless of CVP values (238–240). Abrupt discontinuation of iNO can result in rebound pulmonary hypertension and RVF. In the absence of a PAC or TEE, systemic indices of RV function such as CVP, lactate, urine output and bloodwork should be carefully monitored throughout the weaning process.

## Inhaled prostaglandins

Inhaled prostaglandins have also been used intra-operatively and in the early post-operative setting to reduce RV afterload. Epoprostenol is a synthetic analog of prostacyclin that promotes pulmonary vasodilation by increasing intracellular cyclic adenylyl monophosphate. Epoprostenol must be nebulized continuously within the breathing circuit to exert local selective vasodilation. In a non-randomized trial, Epoprostenol has shown to effectively reduce mean PA pressures after LVAD support (241). Administering epoprostenol before CPB

increases risk of bleeding, likely due to interference with platelet aggregation (241). Iloprost is another synthetic analog of prostacyclin with a more stable half-life that can be given intermittently via a nebulizer. Unlike epoprostenol or iNO, iloprost can be continued in patients after extubation. The addition of iloprost in LVAD patients receiving iNO has been shown to further reduce PVR, mean PA pressure and to increase TAPSE (242).

### Sodium nitroprusside

Sodium nitroprusside is a potent arterial vasodilator with immediate effect than can reduce PVR as effectively as iNO (243). The associated decrease in SVR may be especially useful in hypertensive patients with elevated PCWP, in which increasing LVAD speeds are unable to decompress the LV (244, 245). Unlike iNO, SNP is a non-selective intravenous medication that inhibits the physiological vasoconstrictive response to hypoxia. SNP will therefore vasodilate pulmonary vessels perfusing unventilated alveoli, causing right to left shunt and hypoxemia. Cyanide toxicity can occur with prolonged SNP infusions above 2 mcg/kg/min, and serum cyanide levels should be performed routinely for the duration of the infusion.

### Phosphodiesterase 5 inhibitors

Sildenafil is a phosphodiesterase 5 inhibitor (PDE5i) that increases cyclic guanylyl monophosphate by inhibiting its degradation, and is commonly used to wean off iNO or milrinone in patients with borderline RV function to prevent a rebound effect (246). Few studies have assessed the effect of sildenafil on clinical outcomes, but the limited data suggests a benefit for patients with persistent pulmonary hypertension after LVAD, with reduction of PVR and mPAP, and increase in RV function and CO (247). Simultaneous high-dose sildenafil, iloprost and iNO have been trialed, yielding very low rates of RVF and no need for RVAD (248). Notably, in a propensity-score-matched INTERMACS registry analysis, pre-treatment with sildenafil was associated with a paradoxical increase in RVF rates. However, this result may be due to between-group differences in baseline RV afterload, despite matching (249).

In the long-term, PDE5i could have favorable effects on RV function by decreasing RV afterload, such that it may be reasonable to try in patients with low PCWP who still display elevated PVR after LVAD. However, the major determinant of functional capacity in LVAD patients is a disproportionate rise of PCWP with activity that may limit the potential benefits of sildenafil (250). Randomized data is lacking until the results of the SOPRANO trial become available, in which macitentan will be assessed as adjunctive therapy (NCT02554903). A meta-analysis of 6 observational studies reporting data on RVF demonstrated no benefit of sildenafil to reduce RVF with very high heterogeneity between the studies included (251). These neutral results were confirmed in a propensity-matched analysis of the STS registry, and do not support the indiscriminate use of PDE5i.

## Volume status and kidney function

The differential and management for a high CVP after separation from CPB can be challenging, reflecting a combination of volume status, RV function, hemodynamic support, respiratory function, surgical manipulation and LVAD performance. The RV is directly visible during surgery and can be regularly assessed for signs of volume overload and distention. If intraoperative TEE shows inferior vena cava (IVC) plethora, a distended RV and adequate LV filling, then diuretics may help to release RV wall tension and improve contractility. AKI is commonly seen in 25–35% patients undergoing LVAD support, and RRT is initiated in 10–15%. Both AKI and RRT are associated with early RVF and RVAD use, and higher subsequent mortality (252–254). Pre-operative predictors for AKI and RRT include an eGFR <45 mL/min/1.73 m<sup>2</sup>, presence of proteinuria and CVP/PCWP >0.54 (252). This association between RRT and mortality may reflect a sicker patient population, and not deleterious effects directly related to RRT. In high-risk patients, pre-emptive initiation of RRT before systemic congestion ensues may be beneficial, especially if urine output remains inadequate after high-dose diuretics. This theory was tested in a small study of 21 patients with eGFR <30 mL/min/1.73 m<sup>2</sup> treated with aggressive pre-operative optimization including IABP placement and immediate RRT after weaning CPB, with similar rates of RVF and 1-year survival as patients with normal eGFR (255).

## Heart rhythm management considerations

### Heart rate

Temporary epicardial pacing wires are routinely implanted prior to chest closure, allowing optimization of heart rate (HR) and CO. Many patients will have permanent implanted devices, and regular interrogation can prevent competition between temporary and permanent devices. Cardiac surgery patients are routinely paced between 80 and 100 bpm in the immediate post-operative period, which maximizes output and minimizes dilatation. A higher HR may increase PCWP and thus augment RV afterload (256). If the RV has a restrictive filling pattern, CO will heavily rely on the HR, as stroke volume will plateau at low volumes. Thus, in a truly restrictive RV with adequately unloaded LV and low PCWP, higher pacing rate may result beneficial.

### Atrial arrhythmias

Atrial fibrillation is present in 30–40% of patients at the time of implant. After LVAD surgery, half of the patients convert to sinus rhythm but an additional 10% experience *de novo* post-operative atrial fibrillation (257, 258). In both INTERMACS and EUROMACS registries, atrial fibrillation is seen in 20–25% of LVAD outpatients and is associated to decreased survival, quality of life and functional capacity, likely reflecting different baseline characteristics (259, 260). Atrial contraction at the end of diastole contributes around 15–20% to CO in normal

individuals. Ventricles with restrictive filling and elevated end-diastolic pressures may be more susceptible to losing atrial contribution. In the acute setting, patients with restrictive RV filling may experience hemodynamic compromise with drop in flows due to RVF with atrial arrhythmias, and a rhythm control strategy may be advisable in these specific cases (261). An association between atrial arrhythmias and RVF and RVAD need has been reported, although the temporal sequence of events is unclear and atrial fibrillation is probably a marker of disease severity and elevated RA pressures (262).

### Ventricular arrhythmias

Sustained ventricular arrhythmias (>30 s) occur in the early post-operative period in 20–25% of patients, most often in the first 15 days after surgery (263–265). Ventricular arrhythmias can compromise RV output and LV filling, resulting in suction events. Interventricular septum position should be assessed and suction events ruled out, especially if the ventricular arrhythmias are accompanied by reduced flows and MAP (218). Ventricular arrhythmias may be triggered by metabolic derangements, R-on-T pacing, RV ischemia related to distension, or damage/occlusion of the RCA (263). Pre-operative ventricular arrhythmias are the strongest predictor for post-operative ventricular arrhythmias, highlighting the importance of scar-mediated re-entry as a leading mechanism. Initiation may be triggered by increased adrenergic tone aggravated by inotropic support. Only a minority of patients undergoing ventricular tachycardia (VT) ablation show arrhythmias related to the inflow cannula (266). RVAD at the time of LVAD insertion halved the risk of early ventricular arrhythmias after multivariate adjustment, suggesting that RVF contributes to ventricular arrhythmias in the acute setting (264).

Electrical storm is seen in 6% of patients and carries a poor prognosis with very high in-hospital mortality (264, 267, 268). Recurrent shocks can cause myocardial stunning and progressive RVF with increased support requirements including inotropes, pulmonary vasodilators, or RVAD, a functional deterioration not seen with anti-tachycardia pacing (263). Rarely, VT ablation should be considered in the acute setting for patients with RVF and recurrent intractable VT (263–265). For patients with recurrent ventricular fibrillation without preceding VT, sympatholytic therapies such as stellate ganglion blockade or ablation of the Purkinje fibers may be helpful (263, 264, 268).

### Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) is initiated in many patients with advanced HF patients who later undergo LVAD implant. There is no improvement in invasive hemodynamic measurements with biventricular pacing compared to no pacing or right ventricular pacing only (269–271). Similarly, there are no differences between pacing

modes in LV unloading during invasive ramp tests (271). Although some patients may benefit from CRT to improve RV contractility (272), frequent pack changes, reduced exercise capacity and quality of life with biventricular pacing suggests that turning off the LV-lead is advisable for most patients after LVAD (266, 273, 274).

## Right ventricular mechanical circulatory support

### Timing of right ventricular assist device implantation

Right ventricular assist device implantation is more effective as a pre-emptive strategy than a rescue device. The pre-operative LVAD assessment should identify patients at moderate to high risk of RVF. Ideally, the decision to implement RVAD support is made at the time of LVAD implantation, and not after multi-organ failure secondary to congestion and hypoperfusion are established. Several studies suggest improved survival and end-organ preservation with planned RVAD support compared to rescue (275, 276). 30-day survival for planned, combined LVAD + RVAD implant parallels survival of patients who require LVAD support alone (277). This trend is further evidenced by a STS registry analysis which showed that mortality post-operative rescue RVAD increased by almost 50% when compared to pre-emptive, planned RVAD + LVAD simultaneous implantation (278). Thus, liberal use of RVAD in patients at high-risk for RVF may be beneficial (279).

### Extracorporeal membrane oxygenation vs. right ventricular assist device

Venoarterial (VA) ECMO reduces RV preload by diverting blood from the venous system through an external pump and oxygenator, which then returns to the arterial circulation through direct aortic cannulation in the ascending aorta or through a femoral artery if peripherally cannulated. Optimizing the fine balance between the ECMO circuit and the LVAD can be challenging. If the ECMO speed is too high, there may be inadequate flow through the RV and pulmonary circulation, leading to LV underfilling and suction events. Conversely, if the LVAD speeds is too low, the increased LV afterload may lead to inadequate LV decompression with secondary pulmonary congestion. Despite these challenges, V-A ECMO has been used successfully for acute RVF following LVAD implant, but with well-recognized risks (280, 281). In an adjusted analysis using data from the STS registry, LVAD patients who required ECMO support showed higher rates of acute limb ischemia, reoperation, pneumonia, wound infection, and mortality compared to those who received an RVAD, (54.2% vs. 40.5%,  $p < 0.001$ ) (278). Notably, peripheral V-A ECMO significantly increases LV afterload and should not be used in patients receiving LVAD as bridge to recovery.

## Types of right ventricular assist device

Right ventricular assist device support can be provided through percutaneous or central cannulation. In recent years, percutaneous RVAD has gained popularity over central RVAD for its minimal invasiveness, but the preference is supported by little evidence. Disadvantages of central RVAD include the need for a second surgery if not implanted at the time of LVAD, and a third for its removal, although percutaneous removal is possible if planned at the time of insertion (277). Although large scale studies are lacking, percutaneous RVADs are associated with a shorter length of stay, shorter time on mechanical ventilation and less blood product utilization with a trend toward lower rates of RRT (27.3% vs. 52.4%;  $p = 0.09$ ) and mortality (21.1% vs. 42.9%;  $p = 0.14$ ) (282). An oxygenator allows for correction of hypoxemia and can be connected to central RVADs and some percutaneous models. A comparison between RVAD with or without oxygenator showed earlier acidosis resolution and further decrease in vasoactive medication with shorter time on support if an oxygenator was added to the system (283).

The most commonly used central RVAD device is the Levitronix CentriMag<sup>®</sup> (Abbott, IL, USA), with an inflow cannula in the RA, and an outflow cannula in the PA. The inflow cannula can be surgically implanted, or peripherally inserted through the femoral vein. CentriMag<sup>®</sup> RVAD can provide up to 10 L/min of support, and an oxygenator can be incorporated to the circuit if there is concomitant lung disease with associated hypoxemia (284).

Percutaneous RVAD systems currently available include the TandemHeart<sup>®</sup> (LivaNova, London, UK), ProtekDuo<sup>®</sup> (LivaNova, London, UK) and Impella RP<sup>®</sup> (Abiomed, Danvers, MA, USA). Tandem Heart femoro-femoral cannulation with inflow in the superior vena cava-RA junction with a percutaneously placed cannula in the PA has been largely abandoned since the commercialization of the ProtekDuo<sup>®</sup> cannula in 2014 (284). The ProtekDuo<sup>®</sup> cannula is a dual lumen cannula allowing for percutaneous, single-vessel jugular venous access. The ProtekDuo<sup>®</sup> cannula is placed under echocardiographic or fluoroscopic guidance with a proximal port in the RA and a distal port in the main PA. The cannula is connected to an extracorporeal centrifugal pump [either Lifesparc<sup>®</sup> (LivaNova, London, UK), ECMO or CentriMag<sup>®</sup> console], able to provide flow up to 4–4.5 L/min (284), and allows for the connection of an oxygenator. The ProtekDuo<sup>®</sup> has been successfully used in LVAD patients and is approved for up to 30 days of use (285–287). Its jugular insertion allows for patient ambulation and better rehabilitation, but can also cause superior vena cava syndrome given the large cannula size (288). Specific to the shape of Protek Duo is RCA compression caused by the bending of the cannula within the RV (289).

The Impella RP<sup>®</sup> is a dual-lumen 22 Fr cannula inserted under fluoroscopy through the femoral vein that incorporates a microaxial pump to propel blood from the IVC into the PA. Unlike the ProtekDuo<sup>®</sup>, the Impella RP<sup>®</sup> cannot accommodate

an oxygenator, and should not be used if hypoxemia is a concern, as an upgrade to surgical RVAD may be necessary in that scenario. It has been used successfully in RVF after LVAD and can provide up to 4–4.5 L/min of flow, but it is only approved for less than 14 days of support (287, 290), and its femoral placement precludes ambulation. Complications that can occur are device migration, clotting of the cannula or of the purge system and hemolysis, due to the high speed required by the microaxial pump (usually above 30,000 rpm to provide full support) (290).

Contraindications to use percutaneous RVAD are mechanical valves, pulmonary or supra-ventricular stenosis, severe pulmonic insufficiency, or clots in the right chambers, but a surgical RVAD with the inflow cannula in the RA or VA-ECMO could be used if the clot is limited to the RV. Impella RP should be used with caution if there are IVC filters or deep vein thrombosis. Common to both percutaneous RVADs is the risk of tricuspid or pulmonary valve damage, but incidence is low (290). Also, fracture of the cannula, bleeding at the entry site and PA perforation can occur with both percutaneous devices (290, 291). RVAD flows should be kept below LVAD flow to avoid pulmonary edema and hemorrhage, which have been associated with surgical RVAD flows >4 L/min (292).

## Right ventricular assist device weaning

There are no standardized protocols for weaning RVAD support. In preparation for decannulation, an RVAD ramp study should be performed under echocardiographic guidance with advanced hemodynamic monitoring to assess RV response to decrements in speed, although simultaneous PAC insertion may not be possible in many cases while on RVAD support. At each speed, CVP, MAP, LVAD flow and the occurrence of suction events should be assessed, along with TAPSE, tricuspid  $s'$  and the velocity-time integral in the RV outflow tract. If hemodynamics remain unchanged following a reduction in 0.5–1 L/min, further reductions are attempted as tolerated. Risk of thrombosis increases at flows below 2 L/min, and anticoagulation should be initiated, targeting an activated clotting time (ACT) >160 s, or >200 s if an oxygenator is attached to the pump to prevent clotting. In some cases, it may be preferable to maintain a low flow on the RVAD for a more prolonged time while on proper anticoagulation and assess urine output and lactate before proceeding to next steps. If CVP remains unchanged and LVAD flow is stable with no suction events, full anticoagulation is administered (ACT >300), and RVAD flows dropped to 1 L/min for 5–10 min. If all parameters remain stable and the RV is functioning adequately on TEE, the circuit can be clamped in preparation for decannulation (293).

## Exit strategies: BerlinHeart excor right ventricular assist device

If weaning cannot be achieved after multiple attempts, an exit strategy is required, as percutaneous RVADs are not

approved for long-term use. Unfortunately, in this scenario, prognosis is poor regardless of strategy. In patients who have recovered end-organ function, OHT candidacy needs to be reassessed. If the patient can be listed for OHT but long wait times are expected, more durable biventricular support can be achieved with the Excor RVAD<sup>®</sup> (BerlinHeart, Berlin, Germany). Excor is a paracorporeal pulsatile mechanical ventricle of different sizes that can be used exclusively as RVAD or combined with an LVAD. A common Excor<sup>®</sup> complications include thrombosis of the mechanical ventricle, which is risky on the right side, high rates of bleeding and wound infections (294, 295). However, approximately 50% of carefully selected patients receiving an upgrade to Excor support following a failed temporary RVAD wean could be successfully bridged to OHT, with similar survival after OHT as other recipients (294–296).

### Exit strategies: Durable right ventricular assist devices

The use of durable BIVAD remains highly experimental and should only be used as a last resort in critically ill patients as BTT candidacy. Most published cases of durable intracorporeal RVAD using bilateral continuous-flow VADs underwent upfront BIVAD and not staged implantation after RVE, which has been associated with worse outcomes (297). However, patients receiving durable BIVAD support were more acutely ill than those receiving isolated LVAD (298). When performed simultaneously, durable BIVAD is as effective as total artificial heart regarding survival until transplantation. Durable BIVAD is associated with longer time on support but higher rates of hospital discharge (299). Most durable BIVAD strategies involve off-label use of the Medtronic HVAD<sup>®</sup> pump, a smaller centrifugal, continuous-flow device that permitted intrathoracic placement (300, 301). 1-year survival with a HVAD-BIVAD configuration was 56% in a multi-center collaboration (302). Similar survival rates have been described with either right atrial or right ventricular inflow cannula configurations, with pump thrombosis occurring in 30% of cases (297–299, 302, 303). Unfortunately, the Medtronic HVAD was withdrawn from the worldwide market in 2021 amidst studies demonstrating higher rates of neurological events and mortality. As an alternative, dual HM3 support has been demonstrated, but necessitates either partial cardiectomy (304–306) or right atrial configuration (307, 308). Comprehensive studies are lacking, as reported survival rates with HM3 in an RVAD configuration widely ranges from 30% at 3 months to 92% at 18 months (298, 306–308).

## Late right ventricular failure

Late RVF is currently defined as RVF occurring at least 30 days after the implant, as recommended by the MCS-ARC (Figure 1). The prevalence of moderate-severe late RVF is 20% at 1-month, decreasing to 3–5% at 3 months and remaining

stable thereafter (309). However, if milder cases are included, the prevalence of late RVF are estimated to be as high as 40% (310). In patients with an LVAD as BTT, late RVF is associated with higher urgent HT rates (309). Although the data are conflicting (280), late RVF is a major risk factor for primary graft dysfunction, in-hospital mortality, and high 1 and 5-year mortality after HT (22, 311). RV assessment is usually more permissive and LVAD indication is more liberal in the BTT population as the time on support is expected to be shorter, but these results highlight that careful RV assessment and aggressive RVF treatment should be pursued to improve outcomes after HT.

Late RVF is associated with lower hemoglobin, higher gastrointestinal bleeding and stroke rates, VAD-related and non-VAD-related infections and persistent kidney impairment during follow-up (39, 309, 312, 313). Quality of life and functional capacity is also decreased in patients with late RVF (309, 313). The pathophysiology underlying the non-cardiovascular complications of RVF is poorly defined. LVAD patients have an abnormal von Willebrand factor metabolism and overexpression of angiotensin-2 that increases the risk of arteriovenous malformations and creates a fragile vasculature. Along with lack of pulsatility, RVF causes malnutrition due to gut edema and hepatic congestion, venous hypertension, blood stasis, coagulopathy and increased intravascular pressure within these abnormal vessels that predispose them to rupture and bleeding in the GI tract or brain (204). In addition to hemorrhagic complications, the extravasated blood and blood stasis act as an ideal substrate for infection (204).

The response of the RV to LVAD will be patient-specific depending on interventricular interdependence and RV-PA coupling. In general, higher LVAD speeds will worsen RV systolic function but improve RV compliance and relaxation (314, 315). In most cases, the RV remains sensitive to afterload (126) and higher speeds will provide better unloading, reflected in the improved RV performance and fewer RVF and HF admissions observed at higher speeds (316–319). Pressure-volume loops before and after LVAD implantation demonstrate that despite higher CVP for a similar Ea, the stroke volume/end-systolic volume as a measure of RV-PA coupling significantly improved, suggesting better RV efficiency (320). The elevated CVP may therefore reflect diastolic rather than systolic dysfunction, explaining the better long-term performance of the RV at higher speeds (321, 322). The association between recurrent HF admissions, impaired RV relaxation and restrictive RV filling is demonstrated by higher RVF rates in patients with a deep CVP Y descent or prolonged diastolic plateau (>55% of the diastole) (323, 324).

A detailed description of long-term management of RVF in LVAD patients is beyond the scope of this review, but it is worth mentioning that invasive ramp studies are feasible and reliable as

soon as 1–3 months after the implant (317) and allow case-by-case pump speed optimization. Echocardiographic surveillance is mandatory during follow-up, and can be useful in estimating filling pressures (325). With limited evidence, it seems that optimization of HF medication may improve LV function, thereby reducing RV afterload and improving its function (326). In the setting of late RVF, *de novo* AR should be ruled out, and revision of the log files looking for a progressive increase in power for a similar flow can help in suspecting an outflow graft obstruction. If the LVAD speed is optimized and there are no lesions amenable to repair, RVF should be managed as per the current HF guidelines with diuretic adjustment, or dialysis (hemodialysis or peritoneal) if RVF is refractory to medical management (327–329). Inotropes may be an option for these patients (330), as the use of oral milrinone or intermittent levosimendan infusions have been successfully reported (331, 332). RVADs for late RVF should be restricted to patients who remain on the OHT list and develop refractory RVF with cardiogenic shock.

## Conclusion

Right ventricular failure is a devastating complication occurring after LVAD implantation, but it can be predicted pre-operatively in the basis of clinical features and a combination of echocardiographic and hemodynamic RV metrics here summarized. Intra-operative assessment of RV function is paramount to decide on early RVAD support to improve patient survival. This review offers a comprehensive guidance to provide the best supportive treatment for the patient with RVF after LVAD in the early post-operative phase and considerations about RV performance later during the outpatient follow up.

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## Author contributions

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## Glossary

LVAD, left ventricular assist device; HF, heart failure; DT, destination therapy; BTT, bridge to transplant; OHT, orthotopic heart transplant; RV, right ventricle; RVF, right ventricular failure; RVAD, right ventricular assist device; HRAEs, hemocompatibility-related adverse events; INTERMACS, interagency registry of mechanical circulatory support; CVP, central venous pressure; MCS-ARC, mechanical circulatory support–academic research consortium; BSA, body surface area; HM2, Heart Mate II; HM3, Heart Mate III; LVEDD, left ventricular end-diastolic diameter; TR, tricuspid regurgitation; LA, left atrium; BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; BUN, blood urea nitrogen; NGAL, neutrophil gelatinase-associated lipocalin; RRT, renal replacement therapy; INR, international normalized ratio; ECMO, extracorporeal membrane oxygenation; CCR, chemokine receptor; IL, interleukin; PVR, pulmonary vascular resistance; VE, ventilatory efficiency; VCO<sub>2</sub>, carbon dioxide output; VO<sub>2</sub>, oxygen consumption; PAPI, pulmonary artery pulsatility index; PA, pulmonary artery; NICM, non-ischemic cardiomyopathy; TAPSE, tricuspid annular plane systolic excursion; RA, right atrium; AUC, area under the curve; TPG, transpulmonary gradient; PCWP, pulmonary capillary wedge pressure; TPDG, transpulmonary diastolic gradient; CO, cardiac output; Ea, arterial elastance; SVI, stroke volume index; RVSWI, right ventricular stroke work index; mPAP, mean pulmonary artery pressure; MAP, mean arterial pressure; PAC, pulmonary artery catheter; Ees, end-systolic elastance; CPB, cardiopulmonary bypass; FDA, food and drug administration; ROTEM, rotational thromboelastometry; ICU, intensive care unit; TV, tricuspid valve; MR, mitral regurgitation; AR, aortic regurgitation; TAVI, transcatheter aortic valve implantation; RCA, right coronary artery; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; PEEP, positive end-expiratory pressure; iNO, nitric oxide; SVR, systemic vascular resistance; SNP, sodium nitroprusside; PDE5i, phosphodiesterase 5 inhibitor; AKI, acute kidney injury; IVC, inferior vena cava; HR, heart rate; VT, ventricular tachycardia; CRT, cardiac resynchronization therapy; LV, left ventricle; VA, venoarterial; ACT, activated clotting time; BIVAD, biventricular assist device.