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# Noninvasive Assessment of Right Ventricular Function in Patients with Pulmonary Arterial Hypertension and Left Ventricular Assist Device

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**Abstract**

**Purpose of Review** Right ventricular (RV) failure in patients with pulmonary arterial hypertension (PAH) and left ventricular assist device (LVAD) is associated with increased hospitalizations, worsening functional class, and poor survival. Accurate RV function assessment is essential in diagnosing RV failure, guiding therapies, and determining prognosis. Noninvasive imaging techniques provide fast and reliable quantification of RV morphology and function.

**Recent Findings** We review echocardiography, nuclear medicine, and cardiac magnetic resonance imaging (MRI) uses for RV function assessment in patients with PAH and LVAD. We identify current knowledge gaps in utilizing noninvasive tests to assess RV function.

**Summary** Echocardiography is most widely used to quantify RV function in patients with PAH and LVAD, followed by cardiac MRI for RV morphology and function measurement in PAH patients. The first-pass radionuclide angiography with radiolabeled RBC is the gold standard for calculating RV function. Gated blood pool SPECT can be an alternative as it separates the cardiac chambers well and provides accurate assessment of the RV function with high reproducibility, which is particularly useful for monitoring treatment. More research is needed to compare and validate these modalities in evaluating RV function.

**Keywords** Right ventricular failure · Echocardiography · Nuclear medicine · Cardiac magnetic resonance · Pulmonary arterial hypertension · Left ventricular assist device

## Introduction

Once a "forgotten ventricle," the right heart has emerged as an important prognostic indicator in many disease states. Severe right heart dysfunction portends a poor prognosis in patients with chronic heart failure, congenital heart disease, acute myocardial infarction, myocarditis, pulmonary arterial hypertension (PAH), and presence of left ventricular assist device (LVAD) [1•]. Quantifying right ventricular (RV) function helps identify high-risk patients and guide appropriate treatments. As the right heart is embryologically and morphologically distinct, noninvasive imaging tests traditionally used for the left ventricle may not be ideal in measuring RV function. Radionuclide techniques, mainly first-pass radionuclide angiography (FP-RNA) and gated blood pool single-photon emission computed tomography (SPECT), have long been used for assessing the RV function [2]. Echocardiography and cardiac magnetic resonance imaging (cMRI) are also readily available and widely used in the evaluation of RV. In this review, we summarize these noninvasive imaging modalities used to

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assess RV function in PAH and presence of an LVAD—two conditions that highlight the right heart's unique role in determining the patient's overall prognosis. We identify current gaps in knowledge where more research is needed to decipher the roles of different imaging modalities in RV function assessment.

## Scope of the Problem

### How the Right Heart Is Distinct from the Left

The right ventricle (RV) is a crescent-shaped cavity that wraps around the conical left heart. During embryonic development, the RV arises from the anterior or secondary heart field, while the primary heart field gives rise to the left ventricle (LV). Adapted to a low-pressure system of the pulmonary circulation, the RV is a thin-walled structure exquisitely sensitive to increases in afterload. While the LV is less sensitive to abrupt changes in afterload, a small rise in pulmonary arterial pressure results in a steep decline in RV stroke volume [1•]. Systolic contraction of the interventricular septum provides a major contribution to RV cardiac output, hence septal alteration or dysfunction can greatly affect RV function [3].

### RV Failure in Pulmonary Arterial Hypertension

The pathophysiology of pulmonary arterial hypertension (PAH), though incompletely understood, involves many processes such as vasoconstriction, inflammation, thrombosis, and aberrant endovascular remodeling [4]. The end result is a progressive narrowing of the pulmonary arteries and increases in pulmonary arterial pressures and resistance. The right heart, in the presence of pressure overload, initially undergoes adaptive concentric hypertrophy. Over time, RV dilation becomes more pronounced leading to tricuspid regurgitation, volume, and pressure overload. Progressive RV dilation results in decreased RV contractility. Leftward septal bowing reduces LV filling with subsequent decreases in LV stroke volume and cardiac output. Low cardiac output and elevated RV intramural pressure compromise systolic RV coronary perfusion which normally occurs throughout the entire cardiac cycle (systole and diastole). The result is a vicious cycle of RV dysfunction with low cardiac output leading to progressive RV failure and eventual death [1•, 5].

### RV Failure Following LVAD Insertion

Patients suffering from end-stage heart failure with reduced ejection fraction can now live longer and achieve acceptable functional status due to advancements in the field of durable left ventricular assist devices (LVAD) [6–8]. However, one of the limitations of LVAD therapy is the specter of RV failure, in addition to potential complications such as hemocompatibility-related adverse events and device-related infection [9–12]. Patients with severe RV failure needing a temporary right ventricular assist device in addition to their LVAD have a poor long-term prognosis [13]. Identification of predictors of RV failure after LVAD remains an area of intense research, and many risk scores have been proposed [14–18]. Although not well understood, the pathophysiology of RV failure post-LVAD is thought to stem from many factors including septal distortion in response to high LVAD speed, pre-existing RV failure now "unmasked" as forward flow is restored, additional intra-operative RV injury, and increased RV sensitivity to afterload over time [19]. Diagnosing RV failure is paramount in patient management which includes LVAD speed change, adjustment of diuretics and/or inotropes, and determining patient's status for heart transplant listing.

## RV Function Measurement by Echocardiography

### Echocardiography Background

Transthoracic echocardiography (TTE) is routinely utilized for assessment of RV size and function. There are several advantages to echocardiography. TTE is widely available and can easily be performed in critically ill inpatients as well as the outpatient setting. There is no radiation exposure associated with TTE. It yields additional information for patients with RV pathology, providing data on LV function, the cardiac valves, and the pericardial space. Disadvantages to TTE include technical challenges associated with image acquisition, particularly in post-operative patients who may have indwelling catheters, or those who are morbidly obese and have chronic lung disease. Image acquisition is highly operator-dependent, and technical differences between serial studies may limit the ability to compare serial examinations over time.

Data obtained by TTE includes two-dimensional (2D) imaging, Doppler echocardiography, M-mode, and strain. Three-dimensional (3D) echo is routinely used for LV function and valve assessment but has yet to be widely applied for clinical RV imaging. Because of the right heart's complex geometry, RV ejection fraction is not routinely reported on TTE. Alternatively, taking advantage of the right heart's primarily longitudinal contraction pattern, TTE measures parameters such as the M-mode-derived tricuspid annular plan systolic excursion (TAPSE) and the tissue Doppler-deprived RV annular systolic myocardial velocity (RV S′). Each of these modalities provides complimentary information, and a comprehensive echocardiographic assessment of RV function incorporates data from each of these areas.

## Echocardiography in LVAD: Pre-operative Assessment

The incidence of RV failure following LVAD implant is estimated between 10 and 40%, but varies based upon the definition of post-operative RV failure, which has evolved over time [20]. Intra- and post-operative factors notwithstanding, a critical step to predict RV failure post-LVAD is pre-operative RV failure risk assessment. Identification of patients at high risk for RV failure following LVAD provides an opportunity for pre-operative patient optimization and may drive advanced heart failure decision-making, including planned right ventricular assist device (RVAD) placement or proceeding directly with heart transplant. Multiple risk scores for RV failure have been developed, focusing on hemodynamic, patient-specific, and laboratory parameters, but the discussion here will be limited to echocardiographic parameters.

Pre-existing RV dysfunction is a key risk factor for post-op RV failure. Historically, and in most routine TTE reports, RV size and function are assessed qualitatively, and graded as mild, moderate, and severely abnormal. While severely abnormal RV function is predictive for post-op RV failure, qualitative assessments are highly variable between readers, and often inadequate for satisfactory discrimination [15]. TAPSE is one of the simplest and original quantitative measures of RV function. Unfortunately, TAPSE has not consistently been predictive of post-op RV failure [21].

RV fractional area change (RVFAC) reflects the difference between the RV end-diastolic area and the end-systolic area. RVFAC maybe technically challenging to obtain in all patients, and while some studies have been positive, others have not shown predictive properties [22, 23]. Other 2-dimensional parameters assessing chamber size, including right atrial volumes and ratio of RV/LV basal diameters, have also not been consistently predictive [24]. On the other hand, RV strain has been shown to be highly predictive of post-op RV failure, with a peak strain cutoff of − 9.6%, predicting post-LVAD RV failure with a specificity of 76% and a sensitivity of 68% [25]. Doppler-derived parameters such as degree of tricuspid regurgitation are predictive of RV failure [24]. A recent publication provided a comprehensive summary of echocardiographic parameters utilized for prediction of RV failure [26••].

## Echocardiography in LVAD: Post-operative Assessment

In most cases, following successful LVAD placement, there is decompression of the LV, thereby reducing mitral regurgitation and pulmonary pressures, which should reduce RV afterload and improve RV function. However, in some cases, possibly related to increased venous return to the RV, or alterations in septal mechanics, there may be a development of RV failure. While RV failure was initially felt to be an early post-op complication, development of late RV failure has been more recently described [27]. TTE plays a critical role in diagnosing post-LVAD RV failure and in monitoring recovery and response to various therapeutic interventions. Additionally, in patients with suspected RV failure, TTE is valuable in determining other causes of RV failure, including pump thrombosis, aortic regurgitation, or cannula obstruction [28].

Following LVAD surgery, the RV contractile pattern changes from a longitudinal motion to a radial motion [22]. The importance of this observation is that while TAPSE may no longer be a reliable post-op marker of RV function, RVFAC should still be a reliable parameter, though the RV free wall is often not clearly imaged. This observation was supported in a group of 20 patients who underwent LVAD placement; they had a trend towards reduction in TAPSE post-op without a notable change in global RV function [29].

In the immediate post-operative setting, the RV is most vulnerable to injury, having been subject to general anesthesia, fluid shifts, and the hemodynamic effects of positive pressure ventilation. One study found that RFVAC and RV global strain were predictive of RV failure at 72 h post-op [30]. The presence of worsening tricuspid regurgitation during this time, or septal shift towards the LV, contributes to the development of RV failure. TTE is routinely performed in the post-operative to determine the optimal ventricular septal position and the ideal LVAD speed.

RV function assessment remains a powerful clinical predictor in the intermediate term. In one study, patients underwent serial echocardiography at 1 month and 6 months post-LVAD implant. Patients with impaired RV function, as determined by RVFAC, were noted to have poorer clinical status and 6-min walk distances [31].

## Echocardiography in Pulmonary Arterial Hypertension

In patients who have a history, symptoms, and signs or symptoms suggestive of PH, TTE is the next recommended diagnostic test in the diagnostic algorithm [32]. Contemporary guidelines suggest using a combination of the peak tricuspid regurgitant (TR) velocity, which is used to calculate the pulmonary arterial (PA) systolic pressure, and additional 2D and Doppler findings to determine the likelihood of PH, and then determine whether further evaluation is indicated [33]. Parameters used to further define the risk of PH include the presence of RV enlargement, interventricular septal flattening, pulmonary arterial enlargement (> 25 mm), elevated PA acceleration time (< 105 ms), and enlarged inferior vena cava or right atrium. These parameters do not directly measure the PA systolic pressure, but suggest either the presence of PH or cardiac chamber adaptation to PH. For patients with a TR velocity ≤ 2.8 m/s, without any of the above supporting findings, the likelihood of PH is low. For patients with a TR velocity ≥ 3.4 m/s, the likelihood of PH is felt to be high, even in the absence of supporting findings. For patients with velocities between 2.8–3.4 m/s, the presence or absence of supporting findings is valuable for further assessment. Importantly, these diagnostic parameters only provide clues to the presence of PH and are not necessarily valuable in distinguishing PH etiology.

An important step in the diagnostic evaluation of PH is distinguishing between group 1 PH (PAH) and group 2 PH (PH due to left heart disease). Both PH groups may have marked elevation of RV systolic pressure and RV chamber enlargement and dysfunction. In patients with LV dysfunction, or those with severe mitral valvular disease, this is usually straightforward, but in others, especially those with heart failure with preserved ejection fraction, this distinction maybe challenging. Mitral inflow Doppler is valuable in this regard, and one study comparing group 1 and group 2 PH reported an E/E′ ratio of 95% sensitive and 96% specific for diagnosing group 2 PH, and an E/A ratio of 1.7 had a specificity of 91% for diagnosing group 2 PH [34]. The presence of left atrial enlargement, or a left atrial size exceeding the right atrial size, is also more suggestive of group 2 PH [35]. Importantly, no noninvasive study can consistently and reliably differentiate between the two diagnoses, and right heart catheterization is often required.

A comprehensive assessment of RV size and function is essential in all PAH patients. Mortality in PAH is related to the extent of RV dysfunction [36••]. Measures of RV function can improve in response to vasodilator therapy, and serial TTE is a key component of risk assessment [37]. In early phases of PAH, RV hypertrophy develops to maintain contractility and stroke volume. RV wall thickness, best measured in the subcostal or parasternal long axis, is abnormal if > 5 mm [38]. As PAH progresses, and RV contractility declines, the RV must dilate in order to maintain stroke volume. Quantitative measurements of RV enlargement are more challenging, as foreshortening, and inability to visualize the RV free wall affect accuracy. A diameter > 42 mm at the base and 35 mm mid ventricle are consistent with chamber enlargement. Septal flattening, secondary to RV dilation and leftward septal shift, can be quantified by the RV eccentricity index, which measures the RV diameter to the LV diameter, and a ratio > 1.0 is abnormal (Fig. 1) [38]. Ultimately, despite this adaptive mechanism, due to relentless disease progression, RV dysfunction develops. In routine clinical practice, 3 well-validated measures are used to quantify RV function: RVFAC, TAPSE, and RVTDI. In patients with PAH, RVFAC < 35%, TAPSE < 1.6 cm, and RV TDI < 10 cm/s are considered abnormal. In one single-center study, not only was TAPSE < 1.8 cm predictive of worse mortality, but for each additional centimeter decline in TAPSE below 1.8, there was an increase in mortality [36••].

Recently, advances in echocardiographic imaging of the RV have emerged, including strain measurement, measured by speckle tracking, and three-dimensional (3D) TTE. Global RV longitudinal strain, an angle-independent marker of RV deformation and regional contractility, is increasingly recognized as a powerful predictor of survival in PAH. RV strain reflects myocardial shortening, and normal RV strain is > −25%. In a single-center study, RV strain < −12.5% was strongly predictive of symptomatic right heart failure and short-term mortality [39]. Improvements in RV strain on serial TTE are associated with improved survival [40]. Strain packages are now available on most commercial TTE platforms. Three-dimensional TTE can be utilized to evaluate RV volumes and RVEF, and preliminary studies suggest accuracy when compared with cardiac MRI [41]. A normal RVEF is > 44%. Currently, 3D calculation of RVEF requires offline processing and manual tracing of borders, and is time consuming and not routinely performed in most centers [42].

## RV Function Measurement by Nuclear Medicine

Radionuclide angiography (RNA) with radiolabeled red blood cells (RBC) has long been used for functional quantification of LV and RV function. The technique includes first-pass radionuclide angiography and ECG-gated equilibrium radionuclide angiography. The latter can be performed either by planar acquisition best known as multi-gated acquisition (MUGA), or by single-photon emission computed tomography (SPECT), called gated blood pool SPECT (GBPS).

MUGA scan is based on planar acquisition of the chest in the left anterior oblique view which separates the LV from the RV. It is mainly used for calculation of left ventricular ejection fraction (LVEF) with high reproducibility and accuracy. Its application to right ventricular ejection fraction (RVEF) is less reliable given the overlap of the right atrium to the right ventricle on the planar views. Moreover, including counts from the right atrium can lead to RVEF underestimation in patients with chronic pulmonary hypertension due to right atrium dilation. In these cases, RVEF evaluation relies on the FP-RNA and GBPS.

First-pass radionuclide angiography (FP-RNA) technique is considered the gold standard measure for RVEF. Imaging is acquired dynamically following the initial rapid transit of injected radiolabeled RBC through the right atrium, right ventricle, pulmonary artery, lungs, and left heart during a short time interval (5 to 10 cardiac cycles). As the radioactive bolus passes through the heart chambers and large vessels, FP-RNA can quantitate RVEF accurately as problems with overlapping activity from superimposed structures are avoided. However, this is a technically demanding procedure which requires a high quality of tracer bolus injection, prompt imaging acquisition, and appropriate post imaging data process and

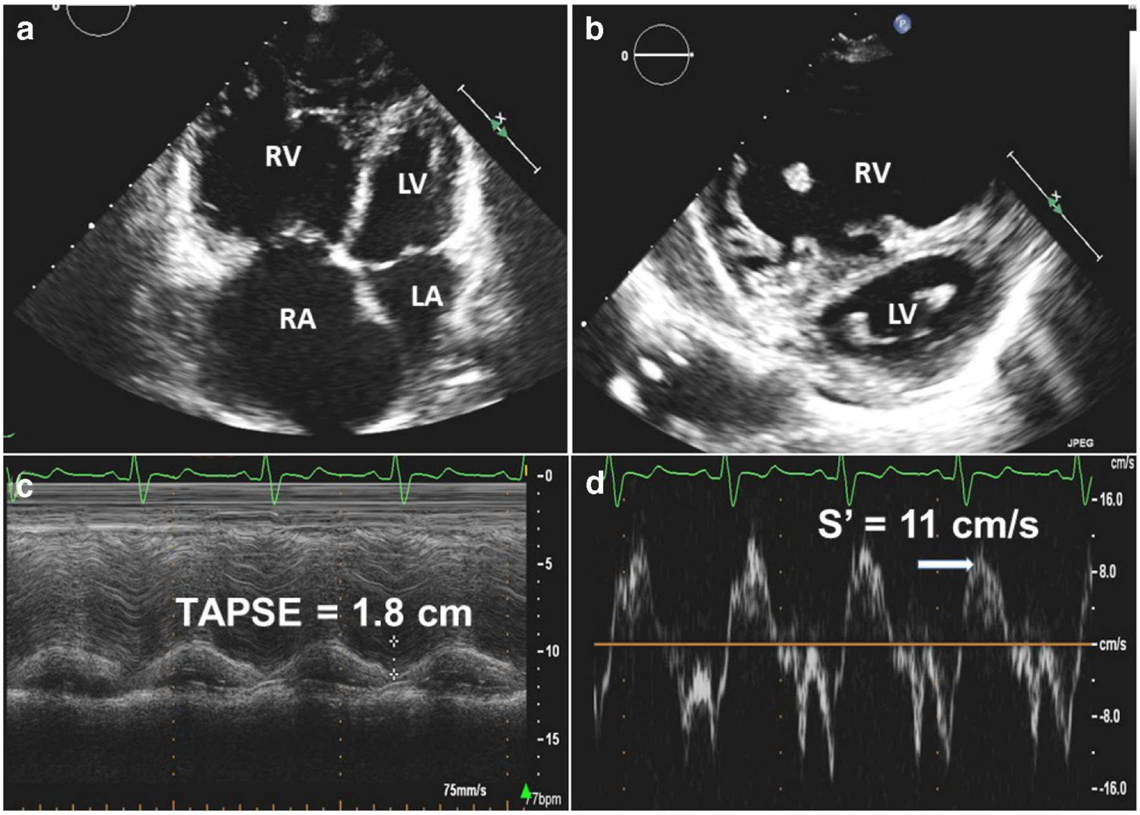


**Fig. 1** Echocardiographic findings of RV failure. **a** Right atrial and right ventricular enlargement (apical 4 chamber view). **b** Septal flattening and abnormal eccentricity index (parasternal short-axis view). **c** Tricuspid annular plan systolic excursion (TAPSE, dotted line) by M-mode echocardiography. TAPSE < 1.6 cm is considered high risk for clinical events. **d** Tissue Doppler of the tricuspid annulus (S′, white arrow). S′ < 10 cm/s is abnormal. RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium

reconstruction. The success rate of the scan and measurement accuracy are also operator-dependent. Up to 25% of FP-RNA may not be successful in clinical practice mainly due to fractionated or diffuse bolus transit [43]. In patients with pulmonary arterial hypertension, the accuracy of this technique may be further compromised because of limited tracer mixing in the dilated right ventricle. Additionally, FP-RNA does not provide other functional parameters such as RV volume because its calculation is purely count-based. Therefore, this technique is not routinely performed for clinical RVEF measurement in the majority of institutions.

An alternative to FP-RNA for RVEF calculation is the gated blood pool SPECT (GBPS). GBPS is a tomographic acquisition of the heart which can separate the RV from the right atrium and LV, thus may be uniquely suited for accurate RVEF measurement. Imaging acquisition of GBPS is easier with a higher success rate than FP-RNA. In addition, GBPS can provide other functional parameters such as RV volume in addition to RVEF (Fig. 2). Automatic or semiautomatic software programs are available from commercial vendors for analyzing GBPS data for calculation of LVEF and RVEF, either being count-based or gradient-based [44, 45]. The software programs are more valuable and validated for LVEF compared with the RVEF among different program algorithms [45].

Studies examining the utility of nuclear imaging in RVEF measurements for patients with PAH and LVAD are scarce. Direct comparison of GBPS and FP-RNA for RVEF calculations in patients with chronic thromboembolic pulmonary hypertension has shown that GBPS-calculated RVEF correlated well with FP-RNA ($r = 0.68$, $p < 0.0001$), but was also overestimated (51 + 14% calculated from GBPS vs. 37 + 12% from FP-RNA, $p < 0.01$) [43]. The overestimation is likely caused by a lower RV volume estimation by the GBPS. In patients with LVAD, the overlap of counts from the outflow cannula and the RV can lead to underestimation of RV volume and thus overestimation of the calculated RVEF. Although significant differences of RVEF exist between different processing techniques for the same GBPS images, reproducibility of measurements is high with intra-rater of 0.968 ($p < 0.01$) and inter-scan of 0.957 ($p < 0.01$) [43, 46]. Thus, GBPS may be suitable for monitoring interval change of RVEF during treatment if the same software process is used. Data are lacking regarding which commercially available program or processing technique is more accurate.

In summary, if technique is not a concern, FP-RNA should be used to measure RVEF. Otherwise, GBPS is recommended given its relatively easy imaging acquisition and higher procedure success rate. RVEF calculated from GBPS correlates

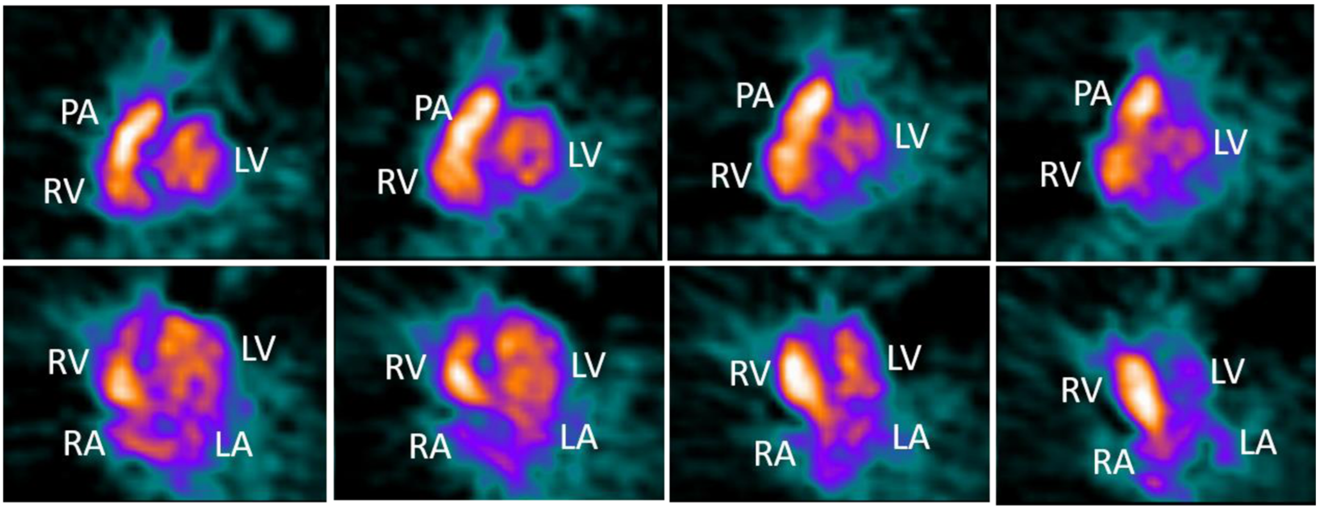


Fig. 2 Representative slides of a gated blood pool SPECT (GBPS). Top: SAX short axial view of the heart. Bottom: HLA horizontal long-axis view (4 chamber view). PA, pulmonary artery; RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium

well to the FP-RNA, but tends to be overestimated, and the results are slightly variable among different commercially available software programs. GBPS might be better used to monitor RVEF changes over time, given its high reproducibility when the same software is used.

## RV Function Measurement by Cardiac Magnetic Resonance Imaging

cMRI is considered the gold standard to assess the right heart's complex 3-dimensional structure. Endocardial and epicardial contours are used to derive highly accurate end-systolic and end-diastolic RV volumes for the calculation of EF and stroke volume [47]. Other measurements of RV function from cMRI include RV mass, regional wall motion abnormalities, patterns of late gadolinium enhancement, and pulmonary arterial flow and distensibility [47–49]. cMRI can be performed relatively quickly without the risk of ionizing radiation. It is important to note that inter-study reproducibility of RV measurements by cMRI can be lower than the left heart due to inconsistent inclusion of moderator bands in tracing of RV endocardium [49, 50].

### cMRI in PAH

During the early stages of PAH, the right heart hypertrophies to adapt an increased pressure load and can subsequently result in RV dilation. This maladaptive response portends a poor prognosis. Much research has been published on the role of cMRI to assess RV function in PAH. For example, ventricular mass index, measured as the ratio of RV to LV mass, has been shown to correlate well with systolic pulmonary artery pressure [51, 52]. On the contrary, a reduced RV mass/volume ratio has been suggested to reflect eccentric RV hypertrophy, worse RV function, and higher right atrial pressure [53]. Regional RV wall motion abnormalities can be detected by cMRI even in patients with normal global RV function [54]. Novel cMRI parameters such as RV peak longitudinal and

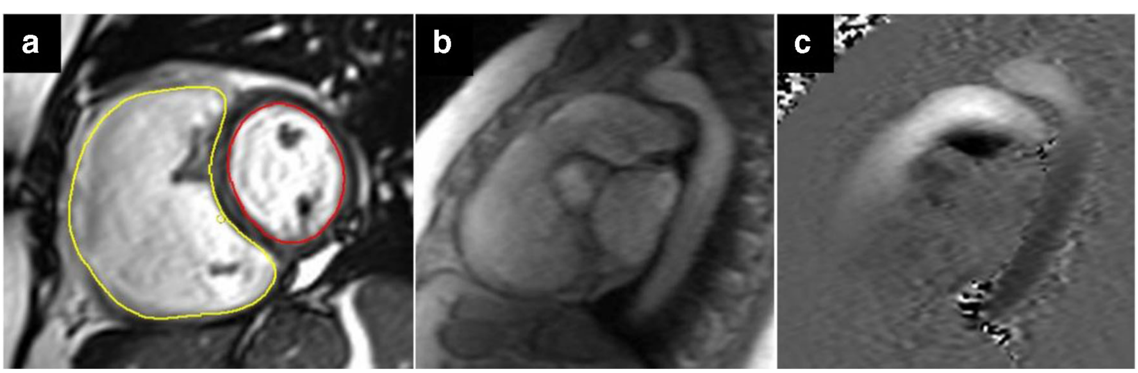


Fig. 3 Cardiac MRI of the heart in a PAH patient. Short-axis image (**a**) demonstrates marked enlargement of the right ventricle compared with the left. Segmentation of endocardial contours of the right and left ventricle (in yellow and red, respectively) is used to determine ventricular volumes and calculate ventricular function. Images of the right ventricular outflow tract of the same patient with gradient echo (**b**) and velocity-encoded (**c**) sequences allow for qualitative and quantitative evaluation of pulmonary flow

circumferential strain and strain rates have been shown to improve with PAH therapies [55]. In a cohort of PAH patients on stable pulmonary vasodilators, a decline in RVEF portends poor survival irrespective of improvement in pulmonary vascular resistance [56]. Other independent predictors of death obtained from cMRI include RV end-systolic volume index (adjusted to age and sex) and pulmonary artery area change [57]. The presence of late gadolinium enhancement at RV septal insertion site seen on cMRI correlates with RV global impairment and is suggested to reflect RV remodeling in response to increased afterload [58].

Besides RV morphological and functional assessment, cMRI is unique in its ability to delineate interactions between the right heart and the pulmonary artery (RV-PA coupling). Studies have shown that blood velocity across the pulmonary artery obtained from phase-contrast cMRI correlated linearly with invasive pulmonary pressures and resistances [59, 60]. MRI-derived pulmonary artery flow coupled with right heart catheterization data provided MRI-derived pressure-volume loops, with valuable information regarding RV afterload, myocardial contractility, and pump function [61]. Figure 3 illustrates an example of using cMRI to measure RV function and pulmonary arterial blood flow.

### cMRI Prior to LVAD Insertion

cMRI is absolutely contra-indicated in the presence of LVAD, so any use is limited to pre-op setting. As discussed previously, RV failure after LVAD insertion portends a poor prognosis [13, 18, 62]. Predicting RV failure can be difficult. Risk scores derived from one patient cohort may no longer have strong predictive power when applied to another population [63]. A thorough PubMed search yielded no study examining the predictive power of pre-op RV measures by cMRI. The reason might be due to discomfort with obtaining cMRI in the presence of defibrillators or pacemakers in patients with low EF. One could speculate that future research may focus on identifying novel pre-op parameters of RV function obtained from cMRI, such as fibrosis burden, myocardial deformation, and RV-PA coupling, which might serve as useful predictors of RV failure following LVAD implantation.

## Conclusion

RV failure is associated with a poor prognosis in patients with pulmonary arterial hypertension (PAH) and left ventricular assist device (LVAD). Accurate measurement of RV function, either by TTE, nuclear imaging or cMRI, is essential in assessing patient's prognosis, predicting post-op RV failure, and, ultimately, helps devise strategies to prevent RV failure. More research is needed to compare and validate these modalities for RV function assessment in PAH and LVAD patients.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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