Imaging in the Evaluation of Pulmonary Artery Hemodynamics and Right Ventricular Structure and Function

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INTRODUCTION

The term pulmonary hypertension (PH) encompasses several disorders that manifest with elevated pressures in the pulmonary arterial (PA) circulation and subsequent dysfunction of the right ventricle (RV). These disorders are grouped by the World Health Organization (WHO) into 5 distinct subsets: PA hypertension (PAH), PH from left-sided heart disease, PH from lung disease or hypoxemia, PH from chronic thrombotic and/or embolic disease (CTEPH), and miscellaneous (extrinsic compression of pulmonary vessels and so forth). Along with clinical and laboratory evaluation, several imaging modalities play a crucial role in establishing the etiology, severity, prognosis, and response to therapy.

KEYWORDS

- Pulmonary hypertension
- Echocardiography
- Cardiac magnetic resonance
- Cardiac imaging

KEY POINTS

- Imaging is an important adjunct to heart catheterization for diagnosing pulmonary hypertension (PH) and discerning the etiology of elevated pulmonary artery pressures.
- Echocardiography is useful for screening patients for PH and to obtain a baseline assessment of right ventricular function.
- Doppler echocardiography provides useful hemodynamic information and assesses left ventricular diastolic dysfunction and valvular disease and can also be used to screen for intracardiac shunts.
- Cardiac magnetic resonance imaging (CMR) has gained importance in patients with PH and is the gold standard for assessing 3-dimensional right ventricular structure and function.
- CMR plays a crucial role in quantifying and locating intracardiac shunts, identifying myocardial fibrosis due to right ventricular strain, and also provides highly reproducible measurements that can be used to track response to PH therapy.
- Cardiac computed tomography (CT) is important for diagnosing thromboembolic disease and pathologies of the lung parenchyma.
- Ventilation/perfusion nuclear scans have greater sensitivity than CT for diagnosing chronic thromboembolic disease.

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therapy in the patient population with PH.\textsuperscript{1} Imaging is used to assess physical characteristics of the PA, hemodynamic parameters, and pathologic changes in the right atrium (RA) and RV. The most commonly used modalities in current clinical practice for non-invasive hemodynamic and RV assessment are echocardiography (transthoracic, transesophageal) and cardiac magnetic resonance imaging (CMR).\textsuperscript{1}

**Pathophysiology of PH and RV Dysfunction**

A full review of the pathophysiology of PH is beyond the scope of this discussion. However, an overview of the causes of PH and the effects of PH on RV function is pertinent to this review of imaging in PH. A lesion leading to elevated pulmonary pressure, currently defined as mean PA pressure (MPAP) greater than 25 mm Hg, can lie anywhere along a path from the PAs, pulmonary capillaries, pulmonary veins, up to the left heart. PH can also result from destruction or extrinsic compression of these structures by other intrathoracic abnormalities. The gamut of imaging techniques is used to evaluate all the earlier-mentioned structures.

The major focus of imaging in PH remains the evaluation of the RV because RV function is closely linked to symptoms and mortality.\textsuperscript{2} Normally, the RV is the most anterior chamber of the heart and can be subdivided using an embryologic approach (inlet, trabeculated apex, and infundibulum/outflow tract) or using anatomic localization (anterior, lateral, and inferior walls).\textsuperscript{3} The normal RV has a complex shape, appearing crescent shaped in cross section, with the septum being concave toward the left ventricle (LV).\textsuperscript{3} A simplified schematic of the RV is depicted in Fig. 1. Although the volume of the RV is greater than that of the LV in the normal adult, RV mass is significantly less than the LV mass.\textsuperscript{3} These characteristics render the RV a much more compliant structure.\textsuperscript{2} The muscular wall of the RV is composed of a network of myofibers with a circumferential orientation in the superficial layers and a longitudinal (base to apex) orientation in the deep layers.\textsuperscript{3} Thus, RV contractile function consists of both longitudinal shortening and circumferential contraction, both of which can be assessed using imaging techniques. Under normal conditions, the primary functions of the RV are to (1) maintain low filling pressures to facilitate rapid systemic venous return and (2) generate adequate systolic pressure to permit blood flow through a normally low-impedance and low-resistance pulmonary vascular circuit.\textsuperscript{3} Although the RV is well suited for these functions given the normally low afterload, it is much less tolerant of increases in afterload compared with the LV. When PA pressure increases acutely to more than 40 mm Hg, RV dilatation and dysfunction usually ensue due to greater distensibility and vulnerability to afterload.\textsuperscript{2–4} One important mechanism for reduced cardiac output (CO) is the worsening of ventricular interdependence from an enlarging RV. Because the pericardial space constrains the RV and LV within a fixed volume, expansion of the RV can impinge on the LV, impairing the filling of the latter.\textsuperscript{2} With chronically elevated PA pressures, the RV has time to hypertrophy to generate progressively greater systolic pressures. This remodeling also leads to flattening of the normally concave right side of the interventricular septum,
which in turn affects LV diastolic performance. RV dilatation and exacerbation of ventricular interdependence occur in the later stages of chronic PH. The combination of RV hypertrophy, increased RV wall stress, and reduced CO can produce RV ischemia, resulting in a cascade of progressive RV dysfunction and dilatation.

Role of Imaging in PH

In current clinical practice, echocardiography and CMR are the major modalities used to evaluate noninvasive hemodynamics and cardiac structure and function. In addition, computed tomography (CT) of the chest can be used to evaluate for pulmonary parenchymal disease, intravascular thromboembolism, and other important intrathoracic pathologies. Although first-pass radionuclide angiography had been used in the past to assess RV ejection fraction (RVEF), this application for nuclear imaging has largely been replaced by echocardiography and CMR. However, radionuclide imaging still retains an essential role for evaluating the pulmonary vasculature in patients with PH. Although CT angiography is accurate for identifying acute thromboembolism in the proximal PAs, CTEPH often involves the smaller branch vessels that are less well resolved by CT angiography. In contrast, ventilation/perfusion scintigraphy or ventilation/perfusion scanning has demonstrated superior sensitivity to CT angiography for detecting CTEPH and is therefore the test of choice to screen for this disease. Each modality offers complementary information for establishing the etiology and severity of PH. Echocardiography is often the first-line imaging technique in patients with PH, because it is easily available, is inexpensive, lacks ionizing radiation, and provides well-validated hemodynamic information along with structural and functional assessment with excellent spatial and temporal resolution. CMR, with its high-resolution 3-dimensional (3D) capabilities, ability to assess tissue characteristics, increasingly better validated hemodynamic assessments, and high degree of reproducibility, has become the mainstay for initial and follow-up imaging of patients with PH in referral centers. There is growing advocacy for using CMR-derived end points to improve clinical trial design. A summary of available imaging modalities and their uses is provided in Table 1.

### Table 1

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<th>Desired Diagnostic Information</th>
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evaluate pressures, CO, shunt physiology, and vascular resistance. Increasingly, echocardiography and CMR are used to establish the presence of PH, although RHC remains the gold standard for confirming the diagnosis and monitoring response to therapy. In addition, although noninvasive evaluations are extremely safe, RHC is associated with a very low but nonnegligible rate of morbidity and mortality.7

**Echocardiography for Noninvasive Hemodynamics**

Doppler echocardiography has grown to become a useful noninvasive tool for hemodynamic measurements. This modality is used to measure pressure gradients between chambers of the heart and also to quantify blood flow through various chambers. Yock and Popp first described the method to estimate RV systolic pressure and thus systolic PA pressure (SPAP) by measuring the velocity of tricuspid regurgitation (TR).8,9 The peak velocity of TR (TRv) depends on the pressure difference between the RV and the RA during systole. This velocity is then used to calculate the pressure difference with a simplified form of the Bernoulli equation:

$$P_{RV} - P_{RA} = 4 \times (TRv)^2$$

RA pressure is determined using a standardized approach and then added to the pressure gradient, providing an estimate of RV systolic pressure (Fig. 2). The American Society of Echocardiography (ASE) currently recommends performing this measure routinely in adults undergoing echocardiographic evaluation.8 In one general population study, each 10 mm Hg increase in SPAP by echocardiography had an adjusted hazard ratio of 1.46 for mortality.10 In another study of patients with systolic and diastolic heart failure, this measurement had a specificity of 96% in diagnosing heart failure, compared with diagnosis by history taking, LV ejection fraction, and N-terminal probrain natriuretic peptide (NT-proBNP).11 In addition, study patients in the highest quartile of SPAP (>45 mm Hg) had a markedly increased mortality compared with those in the lower 3 quartiles.11 Although this measure may be helpful toward diagnosis and prognosis, it has also been studied as a marker for monitoring response to therapy. One study of patients with idiopathic PAH (IPAH) demonstrated improvement in SPAP by echocardiography after administration of sildenafil and epoprostenol.12,13 Strengths of this measure include ease of performance and reproducibility. However, there is potential for underestimating SPAP because of variation in the angle of Doppler interrogation and or because of the presence of severe TR.8,14 In general, use of TRv to estimate SPAP often leads to underestimation compared with SPAP as determined by RHC.13,15,16 Thus, it must be emphasized that the role of the earlier-mentioned method remains in screening and that it should not be used to confirm a diagnosis. It is recommended that a patient with an SPAP of 40 mm Hg by Doppler echocardiography undergo further evaluation.1,8 There may be

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**Fig. 2.** Spectral Doppler velocity of TR, which can then be used to estimate the PA systolic pressure.
a role for serial measurements in monitoring response to therapy as described earlier, although this is not currently recommended.\textsuperscript{12,13}

In addition to SPAP, Doppler echocardiography can be used to estimate diastolic PA pressure (DPAP) and MPAP.\textsuperscript{8} Like SPAP, DPAP is also estimated using the simplified Bernoulli equation, except it is done using the velocity of pulmonic regurgitation at end diastole. This measurement is the PA-RV pressure gradient at end diastole and can be added to RA pressure to derive DPAP ($r = 0.93$, as compared with invasive measurement).\textsuperscript{17} The Doppler profile through the PA can be used to obtain acceleration time (PAAT), which correlates with MPAP and, more recently, has been shown to correlate very well with the technique described earlier for measuring SPAP.\textsuperscript{8,18} The PA Doppler profile is obtained by placing the pulsed wave (PW) Doppler cursor in the PA in the parasternal or subcostal short-axis views. Using a validated regression equation, PAAT estimates MPAP as follows:

$$MPAP = 79 - (0.45 \times PAAT)$$

The advantage of using PAAT is that adequate images to measure PAAT can be obtained in 99.6\% of patients, whereas the correlation between PAAT and SPAP by TR velocity is very strong ($r = -0.96$).\textsuperscript{18} This has an advantage over using TRv, because up to 25\% of patients may not have sufficient TR to allow for accurate measurement of velocity.\textsuperscript{18} Like SPAP measured by Doppler echocardiography, PAAT has been shown to improve within hours after the administration of sildenafil in patients with IPAH.\textsuperscript{12} In addition to pressure measurements, echocardiography can be used to calculate pulmonary vascular resistance (PVR) by using the TRv and the PA Doppler profile together. The PVR is calculated as follows:

$$PVR = \frac{V_{maxTR}}{TVI_{RVOT}} \times 10 + 0.16$$

where $PVR$ is in Woods units, $V_{maxTR}$ is the TRv jet (m/s), and $TVI_{RVOT}$ is the pulsed Doppler time-velocity integral (cm) in the RV outflow tract (RVOT).\textsuperscript{19} Measuring PVR may be important to distinguish patients with elevated PA pressures due to high flow states from those with pathologic changes in the pulmonary vasculature.\textsuperscript{8} However, because of lack of sufficient validation and imprecise estimates for values of PVR greater than 8 Woods units, this method is currently not recommended for routine clinical use.\textsuperscript{8}

In patients being evaluated for dyspnea who have normal resting measures of pulmonary hemodynamics and without any evidence of coronary disease, the ASE has established a framework to perform exercise stress echocardiography to evaluate for exercise-induced PH. The current recommendation is to perform the resting and supine bicycle exercise measurement of SPAP at a nonextreme workload.\textsuperscript{8} In this setting, abnormal SPAP has been defined as a pressure of 43 mm Hg or greater in patients without valvular heart disease.\textsuperscript{8} However, because exercise is a condition that increases flow, elevation in SPAP may simply be due to an increased flow state rather than true PH. This can be seen in subjects older than 55 years or in well-trained athletes.\textsuperscript{8,20} To differentiate pathologic exercise-induced PH from an increased flow, it may be necessary to simultaneously measure stress PVR as described earlier. Although exercise echocardiography is recommended only for investigational uses, it has recently demonstrated promise as a potential screening tool in certain patient groups.\textsuperscript{1} For example, in family members of patients with IPAH or familial PAH, 32\% of relatives were shown to have exercise-induced PH by echocardiography in comparison with only 10\% of controls, and, of these subjects, the relatives with mutations in the $BMPR2$ gene had the greatest likelihood of exercise-induced PH.\textsuperscript{21} Other studies have shown that in patients with systemic sclerosis who do not have previously diagnosed PAH, there is a high prevalence of exercise-induced PH.\textsuperscript{20}

Given that the most common cause of RV dysfunction is left-sided heart failure, echocardiography is also an important tool for determining elevated left-sided filling pressures as an etiology of PH. Such elevations can be due to LV dysfunction or valvular disease. The most reproducible parameter to estimate pulmonary capillary wedge pressure (PCWP) by echocardiography is the ratio between early diastolic mitral inflow velocity (E) and early diastolic mitral annulus velocity (E’), or $E/E'$.\textsuperscript{22} This measure has been validated in several cardiac conditions.\textsuperscript{22} In the past, this ratio was used to directly calculate an estimate of the PCWP.\textsuperscript{23}

However, subsequent studies have demonstrated that direct calculation of PCWP is not as robust as simply using the ratio to categorize patients as normal versus having elevated LV filling pressures.\textsuperscript{24} Thus, current approaches recommend using this measure in a qualitative rather than quantitative manner.\textsuperscript{22} An $E/E'$ of 8 or less reflects normal filling pressures, $E/E'$ of 15 or more reflects elevated filling pressure, and the intermediate range is indeterminate.\textsuperscript{22} A recent study of patients with normal LV ejection fraction has shown that when $E/E'$ is combined with measurement of left atrial size, an $E/E'$ between
8 and 13 with an enlarged left atrium or an E/E’ greater than 13 has a sensitivity of 87% and a specificity of 88% in comparison with LV filling pressure directly measured by heart catheterization. Thus, this is potentially a very useful marker for patients who may have PH due to diastolic heart failure.

In addition to estimating pressures, pulsed Doppler echocardiography can be used to estimate volumetric flow such as RV stroke volume (SV), CO, and pulmonary to systemic shunt ratio (Qp:Qs). The Qp:Qs is determined by obtaining the SVs of the LV and RV. The main measurements needed for this are the PW Doppler velocity profile at the LV outflow tract (LVOT) and RVOT and the diameter of each of these outflow tracts. The PW Doppler profile for the RVOT is traced to obtain the velocity time integral (VTI). The cross-sectional area of the RVOT is calculated using the measured diameter of the RVOT. The RV SV (or Qp) is determined by multiplying the VTI by the cross-sectional area. The same procedure is repeated in the LVOT for Qs component, which finally provides the Qp:Qs estimate. This measurement assumes the absence of significant valvular regurgitation. If significant aortic or pulmonic regurgitation is present, then the measurements must instead be performed at the mitral and tricuspid annuli, respectively, although this approach is much less reproducible. Although echocardiographic estimation of shunt has limitations, it can serve as a useful screening tool in patients with known intracardiac shunts. The results must be interpreted with caution and should be confirmed with other testing when appropriate because the amount of error, driven principally by estimation of the cross-sectional area, can be as much as 20%. Although Doppler echocardiography offers a variety of approaches for assessing PA hemodynamics, particularly PA pressures and resistance, the earlier discussion was mostly limited to methods with standardized approaches outlined by the ASE. There are many additional approaches that are currently investigational but that may gain importance as more validation studies are performed.

### CM for Noninvasive Hemodynamics

The principle advantage of phase contrast CMR (PC-CMR) over any other modalities of hemodynamic assessment is its ability to accurately and reproducibly quantify volumetric flow to assess SV, CO, and regurgitant fractions (RFs). With Doppler echocardiography, volumetric flow is estimated by measuring peak velocity and then multiplying this by an assumed cross-sectional area of interest. This approach has several assumptions that can lead to significant variability in the estimate of volumetric flow. First, many of the calculations for cross-sectional areas assume a circular geometry, which may not be applicable. Second, this approach does not account for changes in the cross-sectional area during the cardiac cycle. Third, it assumes laminar flow and therefore that the velocity measured at one point is exactly the same at all other points in a given cross-sectional area. Last, velocity measurements by Doppler can be underestimated with a nonparallel angle of interrogation. In contrast, with PC-CMR, the cross-sectional area of the region of interest is measured directly by planimetry at many time points throughout the cardiac cycle. Further, the velocity of blood flow is measured not just at a single point but numerous points with high resolution in a given cross-sectional area, thus accounting for differences in blood flow velocities where flow is nonlaminar. Moreover, any plane of imaging can be selected, so obtaining the correct angle of interrogation is not an issue. There are several applications of PC-CMR in the assessment of RV hemodynamics. First, RV SV can be obtained at the level of the PA by integrating the systolic portion of the flow curve. Similarly, LV SV can be obtained at the level of the aorta and Qp:Qs computed with the 2 measurements (Fig. 3). When compared with shunt quantification by RHC in patients with congenital heart disease, shunt determination by PC-CMR has been shown to correlate very well (r = 0.91). Similarly, PC-CMR can generate volumetric flow curves for a given valve during systole and diastole, which can then be used to quantitatively estimate the severity of valvular regurgitation. A framework for categorizing the RF in terms of severity has been proposed as follows: mild for an RF of 15% or less, moderate for an RF of 16% to 25%, severe for an RF of 25% to 48%, and severe for an RF greater than 48%. PC-CMR can be used visually to help localize a shunt that may be difficult to find using other modalities (Fig. 4).

Although the determination of volumetric flow by PC-CMR is relatively accurate and reproducible, the literature on PA pressure assessment by CMR is still conflicting. Direct estimation of PA pressures by CMR has proved challenging. A method described by Laffon and colleagues computes MPAP using PC-CMR to determine mean blood flow velocity across the cross-sectional area of the main PA (MPA) at peak systole and the maximal cross-sectional area of the MPA. This technique initially showed excellent
correlation \( r = 0.92 \) in control subjects with MPAP measured by RHC,\(^{32}\) but the correlation did not exist when patients with PH were selectively evaluated \( r = 0.21 \).\(^{33}\) Other approaches using acceleration time and acceleration/ejection time ratio have also yielded poor correlations.\(^{33}\) One indirect approach for estimating PA pressures is by determining the ratio of ventricular mass of the RV to that of the LV or ventricular mass index (VMI). The VMI has demonstrated reasonable correlation with MPAP while also being shown to be reasonably reproducible.\(^{33–35}\) Nevertheless, the automation of current CMR methodologies to estimate PA pressures is limited at present, resulting in an approach that can be time and labor intensive without a significant incremental yield in information.

Although direct estimation of PA pressures by CMR has proved challenging, the modality has emerged as uniquely suitable for measuring PA stiffness. Dynamic imaging with high temporal and spatial resolution in any plane makes CMR highly suitable for quantifying PA stiffness. Decreased PA elasticity seen in patients with PH may result from a combination of increased distending pressures and pathologic changes in the vascular wall.\(^{36}\) Such changes may have a role in the pathogenesis of PH progression and appear to be linked to prognosis.\(^{36}\) One of these measures, relative area change (RAC), determines the change in cross-sectional area during the cardiac cycle in a proximal portion of the PA.\(^{37}\)

This measure is computed as follows:

\[
\text{RAC} = \frac{(\text{CSA}_{\text{Max}} - \text{CSA}_{\text{Min}})}{\text{CSA}_{\text{Min}}}
\]

where CSA is cross-sectional area of a proximal segment of the PA, both maximal and minimal. The mean RAC was lower in patients with PAH than in controls \((20 \pm 10\% \text{ vs } 58 \pm 21\%, \ P<.05)\).\(^{37}\) Moreover, in patients with PAH, RAC was significantly lower in nonsurvivors than in survivors, and patients with an RAC of 16% or less had a significantly lower survival rate than those with an RAC greater than 16%. Moreover, RAC was a better marker for death than other known prognostic indicators, including 6-minute walk distance (6MWD), systemic venous oxygen saturation, invasively measured RA pressure, and invasively measured PVR. This marker of PA stiffness holds much promise and may become central to the evaluation of patients with PH if
this relationship to prognosis is reproduced in subsequent studies. Transit time for blood through the pulmonary circulation has emerged as an important CMR marker in patients with PAH. Using time-resolved magnetic resonance angiography, PA blood volume (PaBV) and PA transit time (PaTT) are directly determined. In one small study of 12 patients with WHO Group I PH and 10 controls, PaTT of 2 seconds had a sensitivity of 92% and a specificity of 90% for predicting PAH as confirmed by RHC. If validated in larger studies, certain hemodynamic markers such as PaTT and RAC of the PA could become an essential component of noninvasive hemodynamic assessment.

EVALUATION OF RA AND RV STRUCTURE AND FUNCTION

Because the RV is subject to many of the pathologic consequences of PH, reliable imaging of this structure is essential for establishing the severity of PH and prognosis. Thus, echocardiography and CMR play essential roles in the evaluation of patients with PH. These modalities provide information on the size and morphology of RA and RV, RV systolic function, and RV diastolic function.

Echocardiography in the Quantification of Size and Morphology of RA and RV

The apical 4-chamber view focused on the RV is the view of choice for measuring dimensions of the RA and RV. In this view, the size of the RA can be quantified by length (major dimension), diameter (minor dimension), and area obtained by planimetry. A length greater than 53 mm, a diameter greater than 44 mm, or an area greater than 18 cm² has been classified as RA enlargement, which is an indirect marker of RV diastolic dysfunction. In validation studies with primary PAH, an RA area greater than 27 cm² or an RA area index greater than 5 cm²/m² has been shown to be a strong echocardiographic predictor of death or transplantation. More recently, Grapsa and colleagues showed that RA sphericity index by 3D echocardiography was an extremely strong predictor of clinical deterioration (96% sensitivity, 90% specificity, and area under the curve of 0.97). In this prospective study, this 3D marker was a clinical predictor stronger than parameters assessing change in RV geometry and even change in 3D RVEF (sensitivity, 91.1%; specificity, 35.3%; and area under the curve, 0.479).

Whereas RA enlargement reflects RV diastolic dysfunction and TR severity, RV enlargement results from chronic pressure or volume overload or RV failure. Dilatation of the RV in the apical 4-chamber view by linear dimensions is defined as a basal diameter greater than 42 mm, a midlevel diameter greater than 35 mm, or a longitudinal dimension greater than 86 mm. In patients with chronic pulmonary disease, RV enlargement based on indexed linear dimension has been shown to predict survival (hazard ratio, 1.27; 95% confidence interval [CI], 1.08–1.48). An assessment of the size of RV can also be performed qualitatively. In a normal-sized RV, the midlevel RV diameter is smaller than the diameter of the LV at the same level and the apex is occupied primarily by the LV. With moderate enlargement, the RV and LV cavity areas are of similar size and the apex is shared equally by the LV and RV. With severe enlargement, RV cavity area is greater than that of the LV and the apex is formed primarily by the RV.
flattening occurs primarily in end diastole, whereas with isolated RV pressure overload, flattening occurs both at end systole and end diastole.\textsuperscript{8} In patients with primary PAH, each 0.5-unit increase in diastolic eccentricity index has been shown to correlate with a hazard ratio of 1.45 (95% CI, 1.12–1.86) for transplantation or mortality.\textsuperscript{40,44} Measurement of the eccentricity index can be confounded by the presence of concomitant conduction system disease such as a left bundle branch block.\textsuperscript{8} In addition to 2D assessment, one recent study has demonstrated variation in 3D RV remodeling based on several etiologies of PH, including PAH, CTEPH, and PH secondary to mitral regurgitation.\textsuperscript{45} Remodeling of the RV by 3D imaging was affected most adversely in patients with PAH.\textsuperscript{45} The presence of a pericardial effusion can provide important prognostic information and has been shown to be an independent predictor of mortality.\textsuperscript{40,46} In a large prospective registry of patients with PAH using a multivariable model incorporating clinical, laboratory, catheterization, and echocardiographic data, the presence of any pericardial effusion on echocardiography conferred a hazard ratio of 1.35 ($P = .014$) for mortality.\textsuperscript{46}

**CMR for Evaluating RV Size and Morphology.** Perhaps the most established use for CMR in PAH is for the evaluation of the structure and function of RV. Although many other technologies can reasonably approach the accuracy of CMR for the estimation of the size and function of RV, all are ill suited for interrogating the irregular geometry and free wall myocardium. Thus, no other imaging technique, noninvasive or invasive, approaches the inherent accuracy of CMR for the RV. It naturally follows that one of the major strengths of CMR relative to other modalities is the ability to obtain RV volumes and mass in an accurate and extremely reproducible manner.\textsuperscript{47,48} Typically, images are acquired using steady state free precession (SSFP) technique and can be obtained in either short-axis planes from base to apex or transverse axial planes from the pulmonic valve level to the diaphragmatic level. For quantifying the volume and mass of RV, the short-axis view may be preferable because using the transverse axial plane may result in inaccurate assessment of endocardial and epicardial borders at the level of the diaphragmatic (inferior) wall.\textsuperscript{49} However, the transverse axial approach has advantages for evaluating RV systolic function as described later. After image acquisition is complete, epicardial and endocardial contours are delineated using semiautomated computer algorithms and then manually edited (Fig. 7). The papillary muscles and RV trabeculations are excluded from the RV mass. After the borders are defined, the area of myocardium and the RV cavity in each slice is multiplied by the slice thickness to yield a volume of myocardium and volume of RV cavity per slice. These volumes are then summed to yield a total RV myocardial volume and RV cavity volume. The RV myocardial volume, multiplied by the density of muscle 1.055 g/cm$^3$ provides a measure of RV mass.

In one study of patients with PAH, the ratio of RV mass to LV mass or VMI showed a stronger correlation with MPAP by RHC than with echocardiographically estimated MPAP.\textsuperscript{34} The sensitivity and specificity for VMI were 84% and 71%, respectively, for predicting PAH. However, a subsequent study of 44 patients with PAH found the correlation to be less robust for VMI, with a relatively high false-negative rate of 20%.\textsuperscript{33} At present, a mass cutoff for right ventricular hypertrophy is not formally specified, but age-based normative data are available to help guide assessments.\textsuperscript{50,51} Another study by van Wolferen and colleagues\textsuperscript{52} evaluated the volumes and mass of
RV in the PAH population using CMR and compared these measures with other conventional assessments such as New York Heart Association functional class, 6MWD, and RHC hemodynamic parameters. In the multivariate analysis of all variables, only CMR-derived volumes both at baseline and during follow-up predicted mortality. Among the other variables, 6MWD predicted mortality only at baseline and invasively measured PVR-predicted mortality only during follow-up. An RV end-diastolic volume (EDV) index greater than the median (84 mL/m²) conferred a hazard ratio of 1.61 for mortality (P < .001). With further validation studies, the reproducibility, precision, and accuracy of CMR-derived volume and mass could prove to be uniquely suitable traits for monitoring response to therapy in the PAH population.

Another distinct aspect of CMR assessment of the RV is the ability to assess tissue characteristics using gadolinium contrast (Fig. 8). A growing body of literature has emerged regarding the significance of myocardial contrast enhancement in the PH population. Gadolinium chelates allow for water visualization in the extravascular tissue space. In necrotic or fibrotic myocardium, the kinetics of gadolinium uptake are altered such that there is a higher concentration of gadolinium in the diseased myocardium than in the viable myocardium at 10 minutes after contrast administration. The late gadolinium-enhanced (LGE) areas can be visualized and quantified to assess the impact of certain disease states on the myocardium. Irrespective of the etiology of PAH, patients often demonstrate myocardial LGE at the insertion point of the RV free wall into the interventricular septum. It has been hypothesized that this finding is related to chronic RV pressure overload. Although the mass of LGE tissue correlates with RVEF, RV EDV, RV mass, and invasively measured MPAP, the prognostic significance of this finding remains to be determined by future validation studies. The use of gadolinium should be avoided in patients with end-stage renal disease because of the rare risk of developing nephrogenic systemic fibrosis.

Assessing RV Function by Echocardiography

An assessment of RV systolic and diastolic function is essentially an assessment of the functional impact of PH on cardiac performance. Compared with the LV, the geometry of the RV is complex, making an assessment of its function similarly complex. Moreover, the relative anterior position of the RV in the chest wall has made echocardiographic imaging of the RV especially challenging, particularly in the

Fig. 7. Three-dimensional RVEF obtained by outlining of RV volume at several levels.
setting of significant RV enlargement or coexisting pulmonary disease. Given these difficulties, several approaches for echocardiographic assessment of RV function have been proposed and studied. It must be understood that these approaches are complementary, and a multifaceted assessment is recommended.

**M-Mode and 2-Dimensional Echocardiography**

Given the complex geometry of the RV, extrapolation of chamber volume from 2-dimensional (2D) views using geometric assumptions has proved less reliable for the RV than for the LV. Consequently, some of the research on RV function assessment has used simpler measures as surrogates for RV systolic function such as tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change (FAC). TAPSE is a linear measurement that can be performed either using M-mode through the lateral tricuspid annulus or by 2D imaging. This measure is premised on the physiologic finding that longitudinal contraction is a significant component of RV systolic function\(^3\) and that measurement of TAPSE serves as a useful approximation of global RV systolic function. TAPSE is determined by subtracting the apex to lateral tricuspid annular distance during systole from the distance during diastole (Fig. 9).\(^4\) A TAPSE value less than 16 mm has been defined as impaired RV systolic function.\(^8\) This is a reliable measure because it is simple to perform, is easily reproduced, does not require outlining of the entire endocardial border, and does not use geometric assumptions. Given these strengths, TAPSE has been well studied in many patient populations and has been shown to predict mortality in the PAH population. In a study of patients with IPAH by Ghio and colleagues,\(^44\) a TAPSE less than 16 mm conferred a hazard ratio of 2.74 (95% CI, 1.11–6.67) for mortality. In another cohort study of patients with PAH, those with reduced TAPSE had reduced cardiac index on RHC as well as a hazard ratio of 5.7 (\(P = .02\)) for mortality.\(^58\) However, TAPSE is less valid in several of the following situations: when regional RV dysfunction is present, when RV visualization is incomplete, when severe TR is present, in the patient after cardiac surgery, or when RV dysfunction is severe.\(^59–61\) RV dysfunction causes a paradoxic increase in TAPSE because of rocking motion of the heart. Despite these limitations, TAPSE is quantitative and is performed quickly, and so it is currently recommended to perform this measure as a standard component of RV assessment.\(^8\)

In addition to linear measures, area measures can also be used to assess RV function. Measurement of RV cavity area is performed using planimetry of the cavity circumscribed by the endocardial borders, which are traced in an apical 4-chamber view focused on the RV. The RV cavity area is measured at end systole and end diastole, and RV FAC is computed as follows:

\[
FAC = \frac{\text{Area}_{\text{Diastole}} - \text{Area}_{\text{Systole}}}{\text{Area}_{\text{Diastole}}} \times 100
\]

This 2D variable has correlated reasonably well with CMR-derived RVEF\(^62,63\) and has been shown to predict mortality.\(^44\) However, reproducibility of the measure has proved challenging\(^64\) because RV visualization may be incomplete with severe RV enlargement, endocardial border definition may be difficult, and the angle-imaging plane may vary from one study to the next.
Some of the test-retest variability that occurs with 2D techniques because of complex RV geometry may be overcome by using a 3D approach. Current ultrasound transducer and processing equipment permits acquisition of real-time 3D volumetric data at a sufficient temporal resolution (20 volumes per second) to estimate RV systolic function. The 3D volumetric data are obtained using a matrix array transducer placed at the apical position. Endocardial borders are then outlined in the short-axis view at several levels using automated detection algorithms, excluding trabeculations and papillary muscles. These automated borders must then be confirmed by manual editing. The EDV and end-systolic volume (ESV) are then estimated using a summation disks method (Fig. 10). RVEF is calculated as follows:

\[
RVEF = \frac{EDV - ESV}{EDV} \times 100
\]

At present, a lower reference limit for RVEF has been set at 44% based on available data, although large-scale normative data are still lacking. Although reasonable agreement between CMR and 3D echocardiography has been demonstrated in patients with PAH for EDV and ESV \((r = 0.74\) and \(r = 0.75\), respectively), the agreement for ejection fraction was shown to be less robust \((r = 0.66)\). However, 3D echocardiography is faced with some limitations. The larger size of matrix array...
transducers can occasionally limit adequate acoustic windows. As with 2D echocardiography, inclusion of the entire RV can be difficult in patients with severe RV enlargement. Nevertheless, volumetric assessment by 3D echocardiography is reproducible and may prove to be a useful method to monitor response to therapy in patients with PAH. At present, a multicenter prospective observational trial of patients with PAH is underway to assess whether this measure adds useful prognostic information and whether it has utility in assessing efficacy of therapy.

**Doppler Techniques for Assessing RV Function**

There are several important markers of RV function derived from Doppler echocardiography. These include change in RV pressures over change in time (RV $dP/dT$), myocardial performance index (MPI), tricuspid annular velocities, tricuspid inflow for diastolic function, and strain imaging.

RV $dP/dT$ was first described as an invasive measure of contractile performance that reflected the ability of a normal ventricle to rapidly generate pressure. Echocardiographically, this is measured using the velocity profile of the tricuspid regurgitant jet using continuous wave Doppler of the TR jet; $dP/dT$ is the time interval for the TR velocity to rise from 1 to 2 m/s. Although relatively easy to measure, RV $dP/dT$ can be dependent on loading conditions and may be less accurate in the setting of severe TR. Because of lack of normative data, this measure is not recommended for routine use and should only be used in patients who have suspected RV dysfunction.

Another important Doppler measure is the RV myocardial performance index or Tei index. This marker measures both global systolic and diastolic function, and it has been validated in CTEPH, PH in the setting of congenital heart disease, IPAH, and PAH from connective tissue disease. RV MPI is the ratio of nonejection work to ejection work of the RV:

$$\text{MPI}_{\text{RV}} = \frac{IVCT + IVRT}{ET}$$

where $IVCT$ = isovolumic contraction time, $IVRT$ = isovolumic relaxation time, and $ET$ = ejection time. The measurement of these time intervals can be performed by separate PW Doppler evaluation of the tricuspid inflow and RVOT. An alternative approach is to perform a single-tissue Doppler interrogation of the lateral tricuspid annulus (Fig. 11). These velocities are then used to measure the respective time intervals. RV MPI by the single-tissue Doppler method been shown to have a better correlation to RVEF and RV FAC in comparison with the method using separate PW Doppler of tricuspid inflow and RVOT. Compared with other Doppler techniques, this measurement is less dependent on the angle of interrogation because the magnitude of the velocity is not as important as the time intervals. Original data in the congenital heart disease population suggested that another strength of the MPI was its relative independence from loading conditions, although subsequent studies have

![Fig. 11. Tissue Doppler echocardiography can be used to measure the velocity of RV systolic contraction and also the Tei index.](image-url)
called this finding into question. Nevertheless, RV MPI is an important adjunct to the visual estimation of RV function that has been validated in many clinical settings and integrates evaluation of both systolic and diastolic function. The threshold for abnormal MPI by PW Doppler has been defined as greater than 0.40, whereas for tissue Doppler MPI, the threshold is greater than 0.55.

Another important marker of global RV systolic function, the tricuspid annular velocity or $S'$, is a tissue Doppler corollary of TAPSE. $S'$ can be measured online using pulsed tissue Doppler or offline by performing color-coded tissue Doppler and selecting the tricuspid annulus as the region of interest during postprocessing. The highest velocity in the systolic velocity profile is measured (see Fig. 11). In contrast to many other echocardiographic parameters, this measure has a substantial amount of normative data to support its use. Its strengths and limitations are similar to those described earlier for TAPSE. In addition, as with many Doppler measurements, accurate $S'$ depends on a parallel angle of interrogation to avoid underestimation of velocities. With these considerations in mind, it is recommended to perform this measurement when possible. The lower limit of normal is 10 cm/s by pulsed tissue Doppler and 6 cm/s by color-coded tissue Doppler. In addition to the peak velocity, the tissue Doppler profile can be used to measure isovolumic acceleration (IVA). The tissue Doppler velocity waveform usually has 2 distinct components: an isovolumic contraction phase and an ejection phase. The IVA, which is the slope of the first component, has been validated in many disorders and is less affected by preload and afterload conditions. However, this measure is not recommended for routine clinical use because normal cutoff values have not yet been established.

### CMR for Evaluating RV Systolic Function

Given its 3D capabilities and excellent spatial resolution, CMR has become the standard for evaluating the accuracy of other modalities to assess RV systolic function (see Fig. 7). Its primary role has become that of a confirmatory test to quantify RV function when dysfunction is suspected based on other modalities. Functional RV assessment, such as assessment of RV volumes, is usually performed using bright blood sequences such as SSFP that are used to generate dynamic (cine) images during a 5- to 18-second breath-hold to limit respiratory motion artifact. Axial plane rather than the short-axis plane. This is because inclusion of basal short-axis segment contributes to a significant proportion of RV volume, and variability in measuring this segment can result in substantial variation in RVEF assessment. In contrast, using the transverse axial approach, there is clear delineation of the valve planes and thus elimination of the error in RVEF assessment at the base of the RV. Conversely, there is somewhat increased variability in the measurement of the diaphragmatic portion of the RV using the transverse axial approach, although this may be counterbalanced by the reduction in error at the basal portion of the RV. Thus, although short-axis images are excellent for volume and mass measurements, it may be more reliable to use transverse axial assessments for RVEF. Compared with CMR, volumes are underestimated by 3D echocardiography and often overestimated using cardiac CT. Thus, CMR-derived RVEF seems to have the greatest accuracy among the various imaging modalities. This was demonstrated recently by the authors’ laboratory, where they showed a strong correlation ($r = 0.96$) between CMR-derived RV mass and actual RV mass measured in explanted hearts from transplant recipients.

### Echocardiographic Evaluation of RV Diastolic Function

A growing area of interest is the study of RV diastolic function. Many components of the assessment of RV diastolic function are similar to those of the LV. The major components include transtricuspid Doppler blood flow velocities, tricuspid annular tissue Doppler velocities, hepatic vein Doppler flow, inferior vena cava size and collapsibility, and RA size. The latter indicators of diastolic dysfunction, inferior vena cava distention/loss of collapsibility and RA enlargement, have been discussed earlier. Transtricuspid flow is measured using PW Doppler in a medially angulated apical 4-chamber view with the sample volume placed at the tips of the tricuspid leaflets. As with the LV, there are 2 distinct peak diastolic flow velocities, the early (E) and late diastolic (A) peak velocities, which are used to compute the ratio between the two (E/A). These velocities can be significantly affected by breathing and, for the purpose of standardization, should be performed at an end-expiratory breath-hold. Transtricuspid flow velocities are also affected by loading conditions, so it is important to obtain diastolic tissue Doppler velocities (early diastolic or $E'$, late diastolic or $A'$) of the lateral tricuspid annulus as well. These velocities are less susceptible to changes in
loading conditions and are important in differentiating normal filling from pseudonormal filling. Along with transtricuspid and tricuspid annular velocities, it is important to obtain PW Doppler flow in the hepatic veins (subcostal view) and PA (parasternal or subcostal view).

In noncardiac surgical patients, a ratio of tricuspid E/E’ greater than 4 predicts RA pressure greater than 10 mm Hg in noncardiac surgical patients with a sensitivity and specificity of 88% and 85%, respectively; whereas in cardiac transplant recipients, an E/E’ greater than 8 has a sensitivity and specificity of 78% and 85%, respectively. An E/A less than 0.8 suggests impaired relaxation, whereas an E/A of 0.8 or greater and 2.1 or lesser is pseudonormal if the E/E’ is greater than 6 or there is a diastolic flow predominance in the hepatic veins. An E/A greater than 2.1 with an E wave deceleration time less than 120 milliseconds or late diastolic forward flow in the PA indicates restrictive filling of the RV.

CMR for Evaluating RV Diastolic Function

CMR has emerged as an important tool in the evaluation of RV diastolic function. The ability of CMR to simultaneously visualize the motion of the entire pulmonic and tricuspid valves with excellent spatial and temporal resolution offers a unique window into RV diastolic function that is unavailable with other modalities. Using SSFP imaging, Gan and colleagues were able to obtain 2-chamber RV views for simultaneously visualizing pulmonic valve closure and tricuspid valve opening to determine isovolumic relaxation time (IVRT) in 25 patients with PH and 11 controls. This method seems to be promising in that IVRT strongly correlated with other clinically used markers including NT-proBNP ($r = 0.70; \ P<.001$), cardiac index on RHC ($r = −0.70; \ P<.001$), and RVEF ($r = −0.69; \ P<.001$). In addition, sildenafil therapy was shown to decrease IVRT in this patient population.

Along with IVRT, CMR can be used to generate diastolic RV filling profiles similar to echocardiography. There are 2 methods for obtaining these volume curves, either using PC-CMR through the tricuspid annulus or tracing RV volumes at each frame taken in the diastolic portion of the cardiac cycle. The latter technique was used by Gan and colleagues, who showed that patients with PH have reduced early diastolic filling rate (similar to echocardiographic E velocity), reduced E/A filling ratio, and an increased A filling rate. However, this approach of tracing multiple RV volumes is relatively more labor intensive than tracing the contour of the tricuspid valve orifice during diastole for PC-CMR. The latter approach was compared with Doppler echocardiographic evaluation of RV diastolic function and found to have excellent correlation for early (E) filling, atrial-systolic (A) filling, and E/A ratio ($r=0.89$) in normal subjects. In addition, this approach can be used to assess superior vena cava flow profiles, similar to the echocardiographic assessment of pulmonary vein flows. Although there is early evidence that RV diastolic function may have prognostic significance, validation in larger studies and therapeutic trials will be important to understand the clinical significance.

Strain Imaging

Strain echocardiography for evaluation of RV function

Strain imaging is a quantitative tool for assessing regional myocardial deformation (shortening or lengthening of the myocardium), which serves as a measure of myocardial contractility. It is expressed as a percentage of change in myocardial length between end diastole and end systole relative to the original length in end diastole or

$$\varepsilon = \frac{\Delta L}{L_0}$$

where $\varepsilon$ is strain, $\Delta L$ is change in length of a specified region of myocardium from end diastole to end systole, and $L_0$ is the original length at end diastole. This was originally performed using tissue Doppler techniques. However, this approach has now largely been replaced by the use of speckle-tracking technology on 2D B-mode echocardiography. The latter technique does not rely on Doppler techniques but rather uses echocardiographic tissue speckle signatures that are unique to the region of interest and can be tracked over time through the cardiac cycle using a software algorithm. These techniques, because they do not require Doppler, are not angle dependent, in contrast to tissue Doppler strain. Although there are multiple components of strain that can be measured when evaluating the LV, strain measurements in the RV are most reproducible in the apical 4-chamber view and are thus limited to measures of longitudinal strain. Normative data for RV strain are limited, therefore this technology is still experimental. However, patients with PH have clearly been shown to have reduced longitudinal strain in comparison with normal controls. Moreover, based on preliminary data, it seems that PAH can also adversely affect LV mechanics as assessed by strain.

Strain by CMR for evaluation of RV function

Tissue tagging can be performed during CMR to track the motion of ventricular tissue during the
cardiac cycle. Given that the RV is a thin-walled structure, use of such magnetic tags is more difficult because they are spaced far apart. An alternative approach is through the use of strain-encoded (SENC) CMR. This approach generates 2 sets of images, with bright areas designating static tissue in the first image set and contracting tissue in the second image set. The 2 sets of images are then combined to generate a strain image. RV strain measurement by CMR has some advantages over echocardiography, principally that there is no angle dependence as there is with Doppler echocardiography. Also, some of the limitations of measuring strain in a 2D imaging plane are overcome with the use of SENC. This approach has been demonstrated to accurately assess regional RV systolic function. Along with assessing systolic function, strain imaging by CMR has been used to study LV diastolic mechanics such as LV diastolic torsion recovery rate (also known as untwisting). Such measures correlate extremely well with the relaxation constant tau, with little influence from variations in loading conditions such as elevated left atrial pressure or elevated aortic pressures. Such techniques may have important applications for assessing RV diastolic function but have not yet been studied for this purpose. If validated in clinical trials, strain by CMR may become an important and highly reproducible quantitative marker of RV systolic and diastolic function.

**SUMMARY**

Evaluating hemodynamics and determining RV function are cornerstones in the assessment and management of patients with PH. For this purpose, echocardiography and CMR are indispensable tools in the patient population with PH. Echocardiography provides a well-validated, widely available, inexpensive, and reliable method to screen and follow pulmonary pressures and RV function without exposure to ionizing radiation. CMR techniques are highly accurate, are highly reproducible, have excellent 3D capabilities, and allow for complete visualization of any structure in any imaging plane. These technologies offer complementary information and, as more data become available, will be used increasingly to track the severity of PH in patients as well as the response of patients with PH to specific therapies.

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