

Right ventricular plasticity and functional imaging

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ABSTRACT

Right ventricular (RV) function is a strong independent predictor of outcome in a number of distinct cardiopulmonary diseases. The RV has a remarkable ability to sustain damage and recover function which may be related to unique anatomic, physiologic, and genetic factors that differentiate it from the left ventricle. This capacity has been described in patients with RV myocardial infarction, pulmonary arterial hypertension, and chronic thromboembolic disease as well as post-lung transplant and post-left ventricular assist device implantation. Various echocardiographic and magnetic resonance imaging parameters of RV function contribute to the clinical assessment and predict outcomes in these patients; however, limitations remain with these techniques. Early diagnosis of RV function and better insight into the mechanisms of RV recovery could improve patient outcomes. Further refinement of established and emerging imaging techniques is necessary to aid subclinical diagnosis and inform treatment decisions.

Key Words: right ventricular function, right ventricular failure, pulmonary arterial hypertension, echocardiography, cardiac magnetic resonance imaging

The importance of the right ventricle (RV) in global cardiopulmonary function remains imperfectly understood and historically underappreciated despite increasingly detailed investigations of RV function as it applies to long-term outcomes and clinical trial endpoints.^[1,2] This is highlighted by a recognized disconnect between therapeutic improvement in pulmonary pressures and long-term outcomes. In patients with pulmonary arterial hypertension (PAH), for example, long-term outcomes more closely follow RV function and reverse remodeling than reversal of pulmonary hypertension and vascular pathology.^[1] In light of these findings, some have called for clinical trial endpoints to be more focused on measures of global RV function. Therefore, urgency exists for the development of clinically useful and universal definitions of RV function derived from both invasive and noninvasive means.

The RV is understudied in relation to its hemodynamic and prognostic importance in a number of distinct cardiac and pulmonary diseases. As we learn more about RV function, it is clear that it exhibits remarkable plasticity in its ability to recover after injury (for example, after RV myocardial infarction (RVMI), left ventricular assist

device (LVAD) placement, and lung transplantation). This may reflect a combination of the unique physiology of the RV and genetic and neurohormonal modifiers of RV function. With the expansion of LVAD implantation and lung transplantation, there is an exigent need to reliably measure the functional reserve of the RV to help determine a patient's suitability for these procedures. A more reliable measure of the recovery capacity, or plasticity, of a dysfunctional RV would help clinicians predict which patients will have improved function after being "unloaded." Although noninvasive imaging and invasive hemodynamic assessment are helpful, they are limited by the complexity of RV anatomy and the often dramatic load dependence of many indices of RV function as well as lack of widespread availability. Here we review the prognostic significance of RV function, its plasticity in the face of injury, and the unique physiology which contributes to those features. We also discuss the current noninvasive assessment of RV function, the limitations therein, and future directions for research.

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DEVELOPMENT, GENETICS, AND ANATOMY

Unlike the other three chambers of the heart (derived from the primary heart field), the RV and both outflow tracts are derived from the anterior heart field with its own unique genetic pathways and chamber-specific transcription factors.^[3,4]

The macroscopic anatomy of the RV includes three parts: the inlet, which includes the tricuspid valve and papillary attachments; the trabeculated apex; and the infundibulum. This arrangement results in a crescentic shape which contracts with a peristaltic “bellows” action. This contraction pattern is the result of muscle fibers arranged mostly longitudinally with lesser contributions from circumferential fibers and LV attachments to the RV free wall.^[5,6] The complex shape of the RV has led to historical difficulty in creating models to determine RV volume, a necessary component of measuring function. Using contrast angiography and different derivations of the area-length method, the RV has been modeled as a parallelepiped, ellipsoid of revolution, triangular prism, and pyramid, all of which are less accurate than modern methods using cardiac magnetic resonance imaging (CMR) or three-dimensional echocardiography (3DE).^[7,8]

During fetal development, the wall thickness and force generated by the RV and LV are equal. In the first year after birth, RV thickness regresses, increasing compliance. These changes, in concert with a low impedance pulmonary bed, allow the RV to produce the same cardiac output as the LV with one-fourth the stroke work and one-sixth the muscle mass.^[1,9] This regression is not observed in patients with congenital heart disease associated with pulmonary hypertension, which may contribute to their relatively good outcome compared to patients with PAH.^[10-12] Some have postulated, improved outcomes which may also be due to persistence of the fetal gene program (for example, a decrease in α -myosin heavy chain and an increase in fetal β -myosin heavy chain gene expression).^[13]

The RV is subject to unique neurohormonal signaling as indicated by increased RV gene expression of endothelin-1 and endothelin receptors in RV tissue in a rat model of PAH.^[14] This observation may explain in part why endothelin receptors lead to improved exercise capacity and reverse RV remodeling in PAH patients but no such improvements in patients with left heart failure.^[15,16] In addition, patients with RVH of disparate etiologies show upregulation of phosphodiesterase type 5 mRNA and protein in the RV myocardium which is not present in the normal RV.^[17]

The unique embryological, genetic, and neurohormonal processes that occur in the RV serve as the basis for the

development of RV-specific therapies. It has also led to the hypothesis that there exists a “permissive genotype” that leads to early failure of some RVs while others tolerate the same hemodynamic conditions with impunity. One piece of supporting evidence for this hypothesis lies in the angiotensin-converting enzyme DD polymorphism. Among patients with PAH and equal PA pressures, those with DD polymorphism had normal RAP pressure and cardiac output whereas non-DD patients had elevated RAP and decreased cardiac output;^[18] however, these findings have not been replicated to date.

RV PHYSIOLOGY AND PLASTICITY

Global RV function is determined by a dynamic combination of preload, afterload, and contractility. Preload is determined by volume status, tricuspid valve (TV) gradient, and return from the vena cava. RV afterload is a combination of resistance at the level of the pulmonary valve (usually negligible), pulsatile flow reflected from the main pulmonary arteries (PAs) and early bifurcations, impedance of the proximal PAs, and arterioles (pulmonary vascular resistance, PVR). Using PVR as a surrogate for total RV afterload, therefore, may be inaccurate, especially in patients with non-compliant pulmonary vasculature (as in PAH) or proximal disease involvement such as with chronic thromboembolic pulmonary hypertension (CTEPH). In clinical practice, contractility of the RV, theoretically independent of loading conditions, reflects dynamic changes in preload and afterload, calcium loading, heart rate, adrenergic state, pharmacologic milieu, and ventricular interdependence.

It is important to make a distinction between RV dysfunction and RV failure. RV dysfunction may occur in the absence of clinical signs or symptoms. RV failure implies clinical sequelae as a result of RV dysfunction. This distinction is critical because one of the goals of RV imaging is to detect RV dysfunction before irreparable damage develops.

Under resting conditions, metabolic demand is low compared to supply. Compared to the LV, the RV has a lower mass as well as lower preload and afterload, resulting in lower overall oxygen demand.^[9] These circumstances allow the RV to produce the same cardiac output as the LV with one-fourth the stroke work and one-sixth the muscle mass.^[9] As a result, at times of stress, the RV is better prepared for increasing oxygen extraction.^[19,20] RV physiology creates a favorable situation to maintain RV perfusion. As much as one-third of the RV free wall is partially perfused by left coronary artery branches creating a dual blood supply.^[21] The thin RV wall results in lower intramyocardial and intracavitary pressures allowing coronary flow throughout the cardiac cycle. Further, a transcavitary gradient from

left to right favors the formation of acute collateral vessels during RV ischemia.^[22] This may explain why patients with isolated RV infarcts often do not experience angina.^[23]

Like the LV, the RV tolerates volume overload better than pressure overload. Isolated volume-overload states such as tricuspid regurgitation or an atrial septal defect can be sustained for years without a measureable decrement in RV function, though emerging evidence suggests an increase in morbidity and mortality with untreated tricuspid regurgitation.^[24] The RV exhibits greater sensitivity to increases in afterload. While acute pressure overload (as in massive pulmonary embolism) results in failure of RV compensation and cardiovascular collapse, chronic pressure overload leads to RV dilation, a decrease in cardiomyocyte density, and an increase in connective tissue.^[25,26] In the setting of normal pulmonary resistance, RV failure rarely occurs. In the unconditioned RV, small increases in pulmonary pressure result in dramatic decreases in systemic pressure and cardiac output.^[27] Modest increases in right atrial pressure can generate an adequate transpulmonary gradient to maintain cardiac output.^[28] In the unconditioned RV, small increases in pulmonary pressure result in dramatic decreases in system pressure and cardiac output.

Ventricular interdependence (VI) has critical hemodynamic implications in patients with right heart failure, particularly due to pressure overload or RV infarction. The septum is shared by both ventricles and normally bows toward the RV. When the RV dilates, the septum moves toward the LV and can dramatically affect LV filling compromising cardiac output (Fig. 1). Up to one-third of RV stroke work is performed by septal contraction, and when RV dysfunction is severe LV septal contraction into the RV can compensate by providing pulmonary perfusion.^[29] RV contractility improves with increased systemic mean arterial pressure (and thus peak-developed LV pressure), likely due to increased coronary perfusion pressure. Inactivation of septal contraction decreases peak-developed RV pressure by one-half, indicating the important contribution of LV septal contraction to RV function.^[30] RV enlargement decreases pericardial compliance, placing constraint on diastolic filling of both ventricles. Decreasing RV afterload or improving RV systolic function can result in the movement of the septum back toward the RV and resolution of deranged hemodynamics.

NONINVASIVE ASSESSMENT OF RV FUNCTION AND HEMODYNAMICS

Invasive and noninvasive assessment of RV function and pulmonary hemodynamics provides a wealth of information but is limited by inherent characteristics of the RV

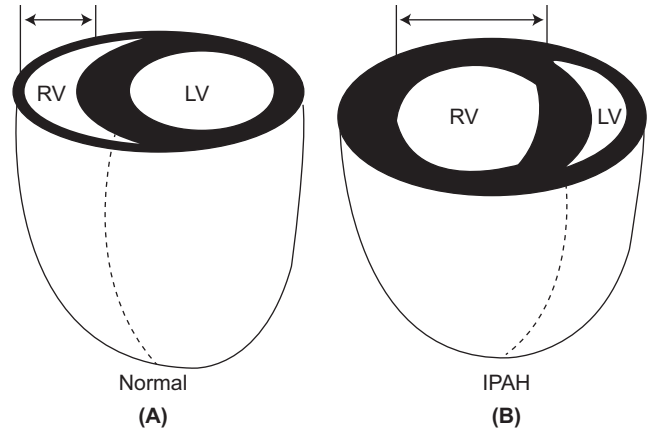


Figure 1: Reproduced with permission from Voelkel et al.^[1] RV dilation changes LV geometry decreasing LV preload and worsening diastolic function. If acute, RV dilation may contribute to pericardial constraint, limiting filling of both ventricles. IPAH = idiopathic pulmonary arterial hypertension; LV = left ventricle; RV = right ventricle.

including retrosternal position, complex geometry, and load dependence of many measurements. Invasive measurements are more accurate by virtue of direct measurement but come with the attendant risks of catheter-based procedures. Due to morphological considerations discussed above, multiple tomographic views are necessary to obtain a complete appraisal of RV structure and function. Unlike the LV in which the biplane Simpson's method is generally accepted as a global assessment of systolic function, no single parameter is considered a sufficient global measure of RV function. Cardiac MRI is emerging as a valuable tool in the assessment of RV and pulmonary vascular function and is considered the gold standard for measurement of RV volume.^[31] A proposed algorithm for the assessment of RV function is found in Table 1.

Echocardiography

Echocardiography is favored as a screening test for RV dysfunction and pulmonary hypertension due to ease of acquisition and reproducibility. Technical aspects of the RV echocardiographic assessment, including normal values, acquisition tips, and limitations are found in Table 2. Examples of important parameters of RV function are found in Figure 2. Representative echocardiographic findings in RV dysfunction are found in Figure 3.

The accuracy of echo-derived PASP is variable when referenced to right-heart catheterization.^[32] This variability precludes the use of echo as a sole diagnostic modality, and, as such, all patients with suspected PH should undergo invasive testing if such a diagnosis will change the patient's management.

In patients without intrinsic lung disease, Doppler estimation of PASP has a fair correlation with invasive measurements.^[33,34] In patients with intrinsic lung

Table 1: Proposed algorithm for the assessment of RV function**Echocardiography**

- Recommended screening test for known/suspected RV dysfunction
- Useful for serial assessment, response to therapy
- Parameters assessed
 - Dimensions
 - RV size
 - Right atrial size
 - ASE recommended for assessment of RV function (at least one)^[41]:
 - Fractional area change
 - TAPSE
 - S' (PW TDI)
 - RV index of myocardial performance
 - Consider in patients with RV dysfunction
 - dP/dT
 - Isovolumic acceleration
 - Diastolic function (E/A, E/E')
 - RV/pulmonary hemodynamics
 - PASP
 - Right atrial pressure estimate (from IVC dimensions)
 - Consider
 - PADP
 - Pulmonary vascular resistance
 - Additional parameters: RV free wall and septal strain, pulmonary acceleration time

MRI

- Consider if
 - Echo is technically difficult or discrepancy exists among echo parameters
 - Discrepancy between echo results and clinical impression
 - MRI is indicated for assessment of biventricular failure, RV-specific etiology (ARVD), pericardial disease, unexplained syncope
- Parameters assessed
 - Dimensions
 - RV size, volume
 - RV mass
 - Right atrial size
 - RV ejection fraction
 - Volume and severity of tricuspid regurgitation, pulmonary regurgitation
 - Late gadolinium enhancement
 - Pulmonary vascular assessment
 - Pulmonary transit time
 - Pulmonary blood volume
 - Capacitance
 - Additional parameters: Myocardial strain

Radionuclide ventriculography

- Consider if echo inconclusive and MRI contraindicated
- Parameters assessed
 - RVEF
 - Pulmonary transit time
 - Diastolic function

dP/dT: change in pressure/change in time; **E/A:** ratio of early to late tricuspid inflow velocity; **E/E':** early tricuspid inflow velocity/early lateral tricuspid annular velocity; **IVC:** inferior vena cava; **PADP:** pulmonary artery diastolic pressure; **PASP:** pulmonary artery systolic pressure; **RV:** right ventricle; **S':** systolic tissue velocity; **TAPSE:** tricuspid annular plane systolic excursion; **TDI:** tissue Doppler imaging

65 patients with various forms of PH, Fisher et al. found that DE estimated PASP accurately in only 48% of patients, over- and under-estimating PASP in the remaining patients equally.^[37] The mean pulmonary artery systolic pressure can be estimated by Doppler as well and used to corroborate the Doppler estimate of PASP. The time to peak velocity of PW Doppler in the RV outflow tract (RVOT; pulmonary acceleration time, PAC) of <70 ms indicates a high likelihood of mPAP > 40 mmHg whereas PAC > 100 ms indicated that PH is unlikely.^[38] The presence or absence of PH should not be diagnosed based on sub-optimal TR signals, and PASP should not be used in isolation to make a diagnosis of pulmonary hypertension (PH) or guide management decisions.

The interaction between RV function and pulmonary hemodynamics and the concept of RV-PA coupling is becoming increasingly important to our understanding of RV dysfunction. As discussed above, PVR is an imperfect surrogate for total RV afterload but the gold standard, pulmonary input impedance, cannot currently be assessed noninvasively. PVR can be qualitatively estimated by the formula $[(\text{TR velocity}/\text{RV outflow tract velocity} - \text{time integral}) \times 10 + 0.16]$ which accurately stratifies patients with high- and low-PVR. A cutoff value of 0.175 predicts PVR > 2WU with a sensitivity and specificity of 77% and 81%, respectively,^[39] but is less accurate at PVR > 8WU.^[40]

While echocardiographic measurement of RV ejection fraction is unreliable and not recommended by the American Society of Echocardiography, there are a number of other ways to assess RV systolic function.^[41] The most basic is the fractional area change (FAC) in which endocardial borders are traced at end-systole and end-diastole and a per cent area change is calculated. FAC correlates with RV ejection fraction (EF) measured by MRI and predicts heart failure and stroke in patients with pulmonary embolism and MI.^[42-44]

The RV index of myocardial performance (RIMP) or Tei index is a Doppler or tissue Doppler-derived measure of global function defined as the sum of isovolumic relaxation and contraction times divided by the ejection time. A normal RV has essentially no isovolumic contraction time (IVCT). Equations for pulse Doppler and tissue Doppler-derived RIMP are in Table 2. RIMP is thought to be preload independent and accurate across most physiologic heart rates but may be falsely low when RA pressure is elevated due to shortening of the isovolumic contraction time.^[45] RIMP is prognostically valuable in patients with PH, RVMI, and congenital heart disease.^[46-48]

One of the most widely studied indices of RV function is the tricuspid annular plane systolic excursion (TAPSE), an M-mode measurement that takes advantage of the fact

disease, however, the accuracy of DE estimation was found to correlate poorly.^[35,36] This discrepancy may be explained by sub-optimal visualization of the TR jet in patients with lung disease whose chests are hyperinflated and whose hearts are rotated rightward. In a study of

Table 2: Right ventricular morphology and function: Echo parameters^[41,169]

Parameter	View	Acquisition tips	Normal value	Limitations
RV thickness	<ul style="list-style-type: none"> Parasternal long or subcostal m-Mode or 2D 	<ul style="list-style-type: none"> Move focus and decrease depth Zoom to measure Measure at end-diastole 	<ul style="list-style-type: none"> <5 mm 	<ul style="list-style-type: none"> Lack of prognostic information
RV dimensions	<ul style="list-style-type: none"> Apical four-chamber 	<ul style="list-style-type: none"> "RV-focused view": maximize RV width while keeping LV long-axis in view If RV enlargement, measure basal RV width 	<ul style="list-style-type: none"> Base: <42 mm Mid: <35 mm Longitudinal: <86 mm 	<ul style="list-style-type: none"> Dimensions highly dependent on probe rotation
RV fractional area change	<ul style="list-style-type: none"> Apical four-chamber 	<ul style="list-style-type: none"> Trace cavity at end-diastole and end-systole Trace beneath trabeculations and papillary muscles 	<ul style="list-style-type: none"> >35% 	<ul style="list-style-type: none"> Requires clear endocardial borders
Tricuspid annular plane systolic excursion (TAPSE)	<ul style="list-style-type: none"> Apical four-chamber m-mode of lateral tricuspid annulus 	<ul style="list-style-type: none"> Align annular motion with m-mode cursor Measure difference of max and min excursion 	<ul style="list-style-type: none"> <16 mm 	<ul style="list-style-type: none"> Influenced by regional dysfunction Load dependent
dP/dT	<ul style="list-style-type: none"> TR jet in apical four-chamber 	<ul style="list-style-type: none"> Maximize jet borders Increase sweep to 100 mm/s Measure interval from 1 m/s to 2 m/s 	<ul style="list-style-type: none"> <400 mmHg/s 	<ul style="list-style-type: none"> Limited normative data Load dependent Inaccurate with severe TR
RIMP/Tei Index	<ul style="list-style-type: none"> Pulse Doppler of TR jet (apical four-chamber) and RVOT (PSAX) Tissue Doppler of lateral TV annulus (apical four-chamber) 	<ul style="list-style-type: none"> If pulse Doppler method, use same R-R interval If TDI, increase sweep speed to improve resolution 	<ul style="list-style-type: none"> Doppler: <0.4 TDI: <0.55 	<ul style="list-style-type: none"> Load dependent Influenced by regional dysfunction Inaccurate in atrial fibrillation, acute MI
TDI (S')	<ul style="list-style-type: none"> Apical four-chamber TDI of lateral TV annulus or basal RV free wall 	<ul style="list-style-type: none"> Measure max systolic velocity (S') 	<ul style="list-style-type: none"> >10 cm/s 	<ul style="list-style-type: none"> Limited normative data Influenced by regional dysfunction
Isovolumic acceleration (IVA)	<ul style="list-style-type: none"> Apical four-chamber Lateral TV annulus 	<ul style="list-style-type: none"> Align TV excursion with cursor 	<ul style="list-style-type: none"> 1.4-3.0 m/s² 	<ul style="list-style-type: none"> Angle dependent Limited normative data Angle- and heart rate-dependent
RV diastolic function	<ul style="list-style-type: none"> Apical four-chamber PW of TV inflow TDI of lateral TV annulus Subcostal PW of hepatic veins Single-plane Simpsons for RAVI (apical four-chamber) 	<ul style="list-style-type: none"> Record with breath held at end-expiration Measure ≥ 3 times if R-R intervals vary 	<ul style="list-style-type: none"> E/E' > 4 predicts RAP >10 mmHg E/A < 0.8: impaired relaxation E/A 0.8-2.1 and diastolic predominance in hepatic veins: Pseudonormal filling E/A > 2.1 and DT <120: Restrictive filling RAVI ≥ 19 ml/m² predicts adverse outcome 	<ul style="list-style-type: none"> Sensitive to changes in respiration, heart rate Further studies needed to validate sensitivity and specificity

A: late diastolic mitral inflow velocity; **dP/dT:** change in pressure/change in time; **E:** early diastolic mitral inflow velocity; **E':** early diastolic mitral annular velocity; **IVA:** isovolumic acceleration; **LV:** left ventricle; **PSAX:** parasternal short axis; **PW:** pulsed wave; **RIMP:** right ventricular index of myocardial performance; **RV:** right ventricle; **RVOT:** right ventricular outflow tract; **TR:** tricuspid regurgitation; **TDI:** tissue Doppler imaging; **TV:** tricuspid valve

that most of the RV output is produced by longitudinal (base to apex) contraction. Thus, low TAPSE indicates low contractile motion within the RV. It is easily and reproducibly measured on M mode and is prognostic in a number of cardiac and pulmonary diseases in 46 different studies.^[41,49] Limitations include angle dependence and the assumption that basal RV function reflects global function.

Tissue Doppler imaging (TDI) of the RV measures regional myocardial velocity. Pulsed TDI can be used to measure the velocity of myocardial excursion (S') at the tricuspid

annulus or lateral RV basal segment. It has been validated in a population-based study with a wide age range and discriminates normal and abnormal EFs well when compared to radionuclide angiography.^[41,50] Like TAPSE, TDI is angle-dependent and extrapolates basal RV function to assume global function.

Myocardial acceleration during isovolumic contraction (IVA) is considered the least load-dependent index of RV contractility by echocardiography. It is derived by dividing the peak isovolumic velocity by the time to reach peak

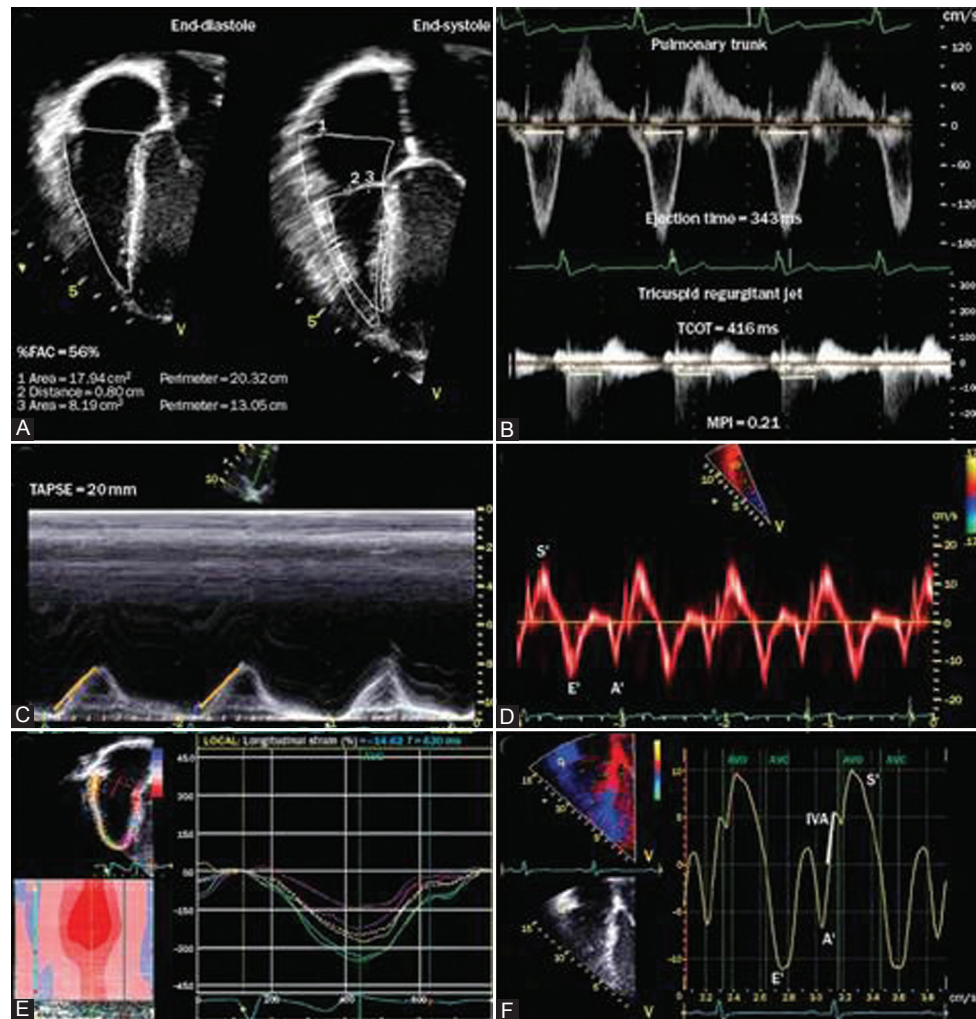


Figure 2: Reproduced with permission from Mertens and Friedberg.^[180] (A) %FAC, calculated from measures of the apical four-chamber view. The importance of longitudinal shortening can be appreciated in this image. (B) MPI, calculated by measuring the ejection time on the pulmonary artery tracing and the time between closure and opening of the tricuspid valve on the tricuspid inflow tracing. MPI = (TCOT - ET)/ET. In this patient, the MPI was normal after tetralogy of Fallot repair. (C) TAPSE. An M-mode echocardiogram through the tricuspid annulus is obtained and the excursion of the tricuspid annulus is measured as illustrated. This index enables assessment of longitudinal RV function. (D) Tissue Doppler velocities of the tricuspid annulus. Pulse tissue Doppler measurements can be used to calculate tissue velocities. Systolic velocities can be used as a parameter for systolic longitudinal RV function. (E) Longitudinal strain measurements of the right ventricle, made using speckle tracking technology. By convention, systolic longitudinal shortening is represented as a negative value and can be measured in six different segments. The mean values of these segments are used to trace a mean longitudinal strain curve (white dotted line). The value at end-systole is then measured. (F) Color tissue Doppler echocardiogram at the lateral tricuspid valve annulus and measurement of IVA. Aortic valve opening and closure are depicted by green lines for event timing. The timing of these events may be taken as that of pulmonary valve opening and closure. The slope of IVA is shown. Note that IVA occurs within the QRS complex and peaks before pulmonary valve opening in the isovolumic period. A' = late-diastolic tissue velocity; AVC = aortic valve closure; AVO = aortic valve opening; E' = early-diastolic tissue velocity; ET = ejection time; %FAC = percentage fraction area change; IVA = isovolumic acceleration; MPI = myocardial performance index; S' = systolic tissue velocity; TAPSE = tricuspid annular systolic plane excursion; TCOT = tricuspid valve closure-opening time.^[179]

velocity as measured by TDI at the lateral tricuspid annulus. IVA is a prognostic marker in patients with OSA, mitral stenosis, and congenital heart disease.^[51-53] The normal value for IVA varies with age and is unaffected by wide changes in preload and afterload.^[54]

Strain and strain rate are emerging echocardiographic technologies which quantify myocardial deformation. These techniques are relatively load independent and can provide both regional and global assessment of RV

function.^[55] The utility of strain analysis to detect subclinical RV dysfunction and predict outcomes in patients with PH has recently been demonstrated.^[56,57] Current limitations include lack of normal values and the requirement of offline software for analysis; however, when further refined, these techniques hold promise for the routine detection of early and subclinical RV systolic dysfunction.

Three-dimensional echocardiography to measure RV volumes and function correlates well with MRI

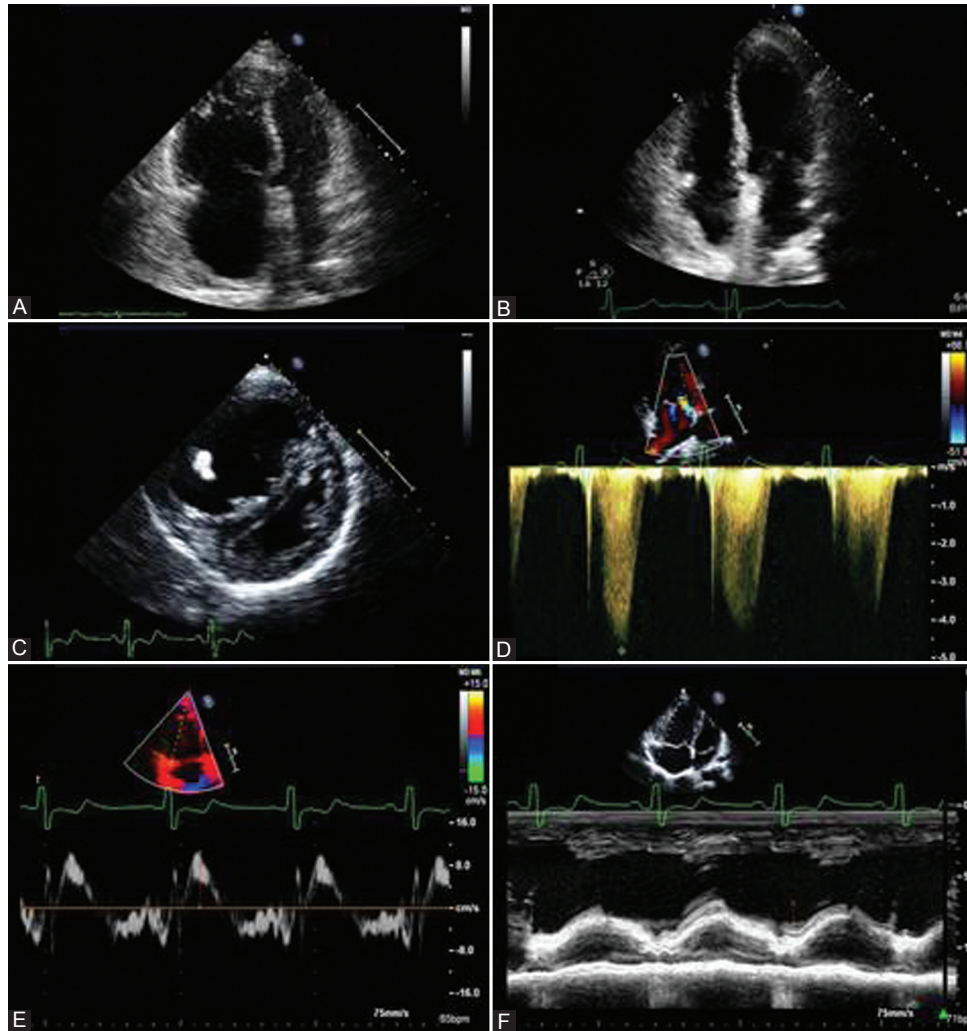


Figure 3: (A) RV enlargement and hypertrophy in patient with CTEPH. (B) Normal RV size 6 months after PTE in the same patient as in A. (C) Parasternal short-axis view demonstrating RV dilation and hypertrophy and displacement of septum. (D) Tricuspid regurgitation jet demonstrating severe PH in patient with PAH. (E) Peak systolic velocity of tricuspid annulus borderline depressed at 10 cm/s. (F) TAPSE in patient with PAH measured at 14 mm consistent with RV hypokinesis.

measurements in a number of studies, particularly those using semi-automated border detection,^[58-62] but recent studies found systemic under-estimation of RV volumes and EF on 3DE.^[63,64] ASE recommendations currently limit the use of 3DE to serial measurements, but as normative data accumulate and analysis software improves 3DE will become a practical tool for assessment of RV size and function.^[41]

RV diastolic function is increasingly recognized as having a significant hemodynamic influence in a number of cardiopulmonary diseases.^[41] It is easily assessed using pulsed Doppler of TV inflow, TDI of the lateral tricuspid annulus, and Simpson's method of RA volume. Measurements should be taken at end-expiration and may be inaccurate in patient with atrial fibrillation. Given the load dependence of RV function, diastolic parameters may be affected by heart rate, respiration, and loading conditions.^[65-67] In a multivariate model, RA volume index

strongly predicted a composite of death, transplant, or heart failure admission.^[68] RV E/E' predicts elevated RA pressure with high sensitivity and is a prognostic marker in patients with secondary pulmonary hypertension.^[69,70] Notably, RV diastolic function has repeatedly been shown to predate clinical RV systolic dysfunction. With further refinement of RV diastolic parameters, this may represent a screening tool in patients at risk of developing RV dysfunction.

Cardiac MRI

With advances in image acquisition protocols, cardiac MRI (CMR) is emerging as the technique of choice in the assessment of RV structure and function (Table 3). Representative CMR findings in RV dysfunction are found in Figure 4. Volumes are usually obtained and images oriented in short-axis stacks from which endomyocardial contours are traced at end-diastole and end-systole. Because up to 30% of the RV volume is contained in the infundibulum,

Table 3: RV morphology and functional MRI parameters

Parameter	Acquisition sequence	Normal value	Clinical comment
RVEF (%)	Conventional breathhold cine MRI	61±7 ^[170]	>40-45 used in clinical practice
RV mass (g/m ²)	Conventional breathhold cine MRI	26±5 ^[170]	
RVEDV (ml/m ²)	Conventional breathhold cine MRI	75±13 ^[170]	
TR/PR volume/severity	Velocity-encoded cine MRI	None or physiological	Mild: <20 cc Moderate: 20-50 cc Severe: >50 cc
Shunt fraction	Velocity-encoded cine MRI	Absent	$Q_p/Q_s < 1.5$ hemodynamically insignificant
Myocardial delayed enhancement	Contrast-enhanced inversion recovery gradient echo	Absent	<ul style="list-style-type: none"> Predicts arrhythmia and exercise tolerance in TOF patients^[170] Correlates with RV WMA in patients with RVMI^[79]
Pulmonary transit time (s)	Dynamic first-pass contrast-enhanced saturation-recovery gradient echo	6±1.4 ^[171] 7.2±1.2 ^[172]	<ul style="list-style-type: none"> Limited normative data Prolongation correlates with degree of LVEF, PH^[173]

CHD: congenital heart disease; **LVEF:** left ventricular ejection fraction; **MRI:** magnetic resonance imaging; **PH:** pulmonary hypertension; **Q_p/Q_s :** pulmonary flow/systemic flow; **TOF:** tetralogy of Fallot; **RV:** right ventricle; **RVMI:** right ventricular myocardial infarction; **WMA:** wall motion abnormality

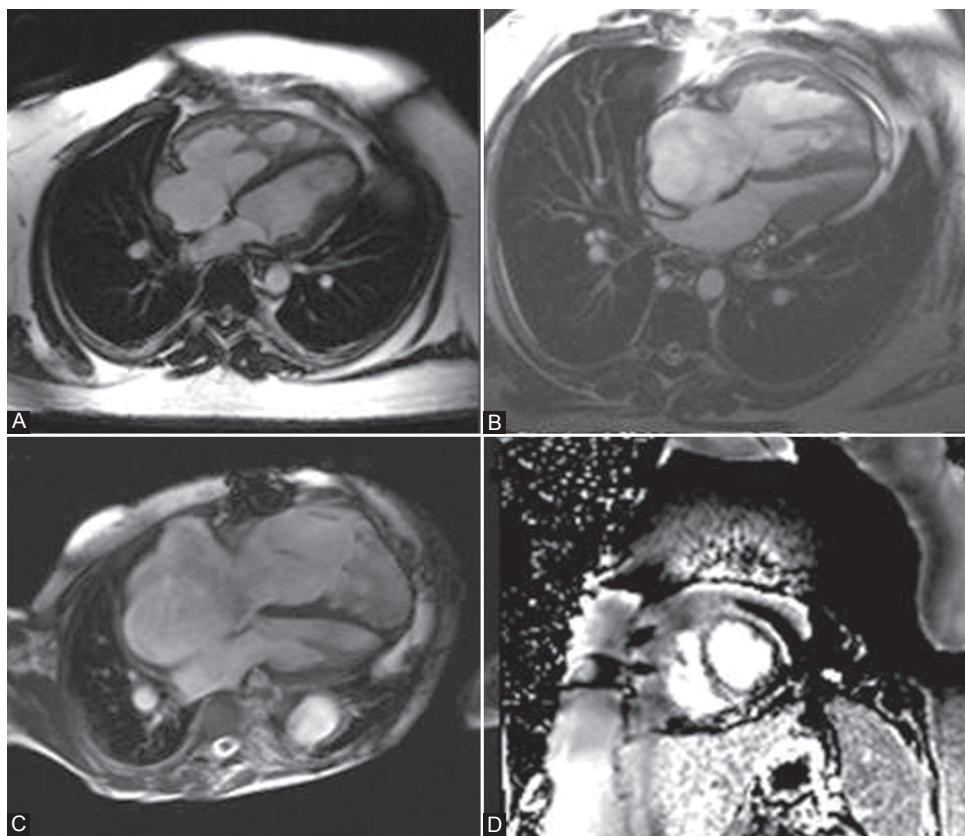


Figure 4: (A) Mild RV and RA dilation with RV hypertrophy and prominent hypertrophy of moderator band. (B) Severe RV and RA dilation with RVH and compression of left-sided chambers by septal deviation. (C) End-stage RV failure with marked RV and RA dilation and thinned out RV free wall. (D) Late gadolinium-enhanced short-axis image demonstrating fibrosis at the RV septal insertion point.

this structure should be included in volume measurements. Myocardial mass is calculated from tracing epicardial and endocardial borders and multiplying by myocardial density. Because of its good spatial and temporal resolution, CMR-derived volumes and EF are increasingly considered the gold standard against which other imaging modalities are compared.^[71] The MESA-RV study recently demonstrated significant differences among age, race, and sex in values of RV mass, RV volume, and RVEF; the clinical implications of these differences is unknown.^[72] Intra-observer and

inter-observer variability in RV measurements ranges from 3% to 6% and 4% to 9%, respectively.^[73,74] Valvular regurgitant volumes and shunt severity can be calculated with precision using velocity-encoded cine images.^[75]

Tissue characterization is another advantage of CMR over echocardiography. In arrhythmogenic RV cardiomyopathy (AVRC), MRI can detect dysplastic areas of myocardial thinning, wall motion abnormalities, and fibrofatty replacement; however, fatty infiltration is seen in normal adults and can

be obscured by epicardial fat, limiting the utility of MRI in this aspect of diagnosis.^[76] Gadolinium enhancement of myocardial fibrosis may be more sensitive than Task Force Criteria for the detection of AVRC carrier-gene status, but is not currently a diagnostic criterion.^[77,78] The identification of RV fibrosis on MRI is also of value in patients after Tetralogy of Fallot repair in whom the degree of fibrosis correlates with global RV function and risk of ventricular arrhythmias.^[79] The extent of myocardial fibrosis also correlates with RVEF in PAH and survival after RVMI.^[80,81] Cardiac MRI is particularly valuable in assessing diseases which involve the RV including arrhythmogenic RV dysplasia, response to therapy in PAH, congenital heart disease with shunt lesions, differentiating constrictive and restrictive physiology, and diagnosing RVMI by late gadolinium enhancement.^[78,81-83] Evolving clinical applications include strain analysis using myocardial tagging and diastology assessment using phase-contrast CMR to measure deceleration time and IVRT.^[84,85]

Metabolic imaging

Just as tomographic imaging techniques have improved our understanding of RV function, so has molecular imaging advanced the concepts of a metabolic phenotype and metabolic remodeling. PET imaging allows measurement of the relative use of glucose (FDG) and fatty acids (C-11 palmitate as surrogate) as myocardial energy substrates. In the RV in PAH, there is a well-described switch from predominant fatty-acid oxidation to glycolysis as a source of fuel,^[86] which, although less efficient, may produce a cellular survival advantage similar to cancer cells.^[87] In patients with PAH, FDG accumulation in the RV free wall correlates with PVR and mean PAP.^[88,89] After three months of epoprostenol, FDG uptake decreased significantly in responders in proportion to reduction in PVR.^[88] Increased RV FDG uptake correlates with RV dysfunction in patients with left heart failure,^[90] though the response to treatment is unknown. PET may thus allow assessment of RV-specific metabolic therapies.

Magnetic resonance spectroscopy is an emerging tool which can quantify intracellular triglyceride content. Myocardial lipid accumulation has been observed in diabetics and patients with dilated cardiomyopathy.^[91,92] In diabetics, the degree of triglyceride content strongly correlates with RV systolic and diastolic dysfunction as assessed by strain and strain rate.^[92]

ASSESSMENT AND PROGNOSTIC IMPLICATIONS OF RV FUNCTION IN SPECIFIC DISEASE STATES

In many cardiopulmonary diseases, RV function is an independent prognostic predictor (Table 4). Right heart

dysfunction is associated with poor outcomes in patients with valve disease, congenital heart disease, ischemic and dilated cardiomyopathy, pulmonary embolism, post-cardiac transplantation, post-LVAD implantation, and post-valve surgery.^[93-102] In patients with PAH, outcomes parallel RV function more so than PA pressure, in part because PA pressure falls as RV dysfunction becomes severe (Fig. 5).^[103,104] Conversely, preserved RV function even in the setting of elevated PA pressure is associated with improved survival, decreased hospitalization, and improved exercise capacity in patients with chronic heart failure.^[94,105]

EVIDENCE FOR RV PLASTICITY AND IMAGING

In a number of diseases, the RV can sustain damage and recover to a remarkable degree. This plasticity should serve as the impetus to better understand RV physiology and pathology and to develop clinical techniques to help predict whether or not an individual RV will recover from insult. With this knowledge, for example, clinicians could exercise more parsimony in referral for LVAD or lung transplantation and better prognosticate after RVMI. In the absence of a tool to predict RV recovery, early diagnosis of RV dysfunction and appropriate therapy remain paramount.

Table 5 describes useful functional and morphologic parameters assessed by echocardiography or CMR in each of the diseases discussed below.

Right ventricular MI

RV myocardium is involved in up to 50% of inferior myocardial infarctions (MI) and ischemic RV dysfunction is associated with increased morbidity and mortality.^[106-109] Despite this high prevalence, long-term damage to RV function after RVMI is exceedingly rare.^[106] Acute hemodynamic

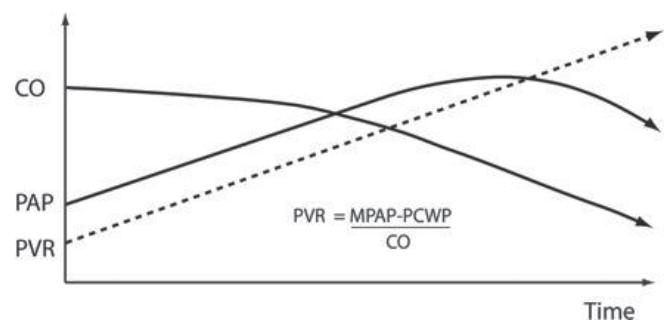


Figure 5: Reproduced with permission from Haddad et al.^[181] A decrease in pulmonary arterial pressure in patients with PH may indicate low cardiac output and severe right ventricular failure. CO = cardiac output; MPAP = mean pulmonary artery pressure; PAP = pulmonary artery pressure; PCWP = pulmonary artery capillary wedge pressure; PVR = pulmonary vascular resistance.^[180]

Table 4: Prognostic importance of right ventricular function in various cardiopulmonary diseases

Disease state	Study	Population	N	Definition of RVD	Findings
Ischemic and non-ischemic cardiomyopathy	Polak et al., ^[174]	CAD, NYHA II-IV	34	RVEF < 35%	23% survival vs. 71% survival at 2 years
	de Groot et al., ^[95]	CAD, IDC, NYHA II-III	205	RVEF < 35%	59% survival (RVEF < 35%) vs. 93% survival (RVEF > 35%) at 2 years
	Ghio et al., ^[94]	CAD, IDC, NYHA III-IV	377	RVEF < 35%	Combination of RVD and PAP predicting survival
	Meluzin et al., ^[175]	CAD, IDC, NYHA II-IV	140	RIMP > 1.20, IVA < 2.52 cm/s, TAPSE < 10.8 cm/s	RIMP and TDI indexes were predictive of mortality or event-free survival
	Meyer et al., ^[93]	CAD, IDC, NYHA III-IV	2708	RVEF < 20%	Associated with mortality and heart failure hospitalization
Acute pulmonary embolism	Goldhaber et al., ^[98]	Acute pulmonary embolism	1135	Visual hypokinesis	RV hypokinesis conferred HR of 2.0 at 3 months
Valve disease	Hochreiter et al., 1986 ^[102]	Mitral regurgitation (unoperated)	53	RVEF < 30%	> 50% mortality at 2 years
	Messika-Zeitoun et al., 2004 ^[24]	TR with flail leaflets	60	Severe RV enlargement	86% (present) vs. 39% (absent) event rate (HF, new atrial fibrillation, cardiac surgery, or death)
	Haddad et al., 2007 ^[176]	Mitral or aortic surgery	50	RIMP > 0.49	OR 25.2 (CI 5.24-121.15) for perioperative mortality and heart failure
	Dang et al., 2006 ^[100]	Post-LVAD implantation	108	Need for RVAD, ≥ 14 days of inotrope/pulmonary vasodilator	30-day post-LVAD mortality right heart failure vs. non-right heart failure 19% vs. 6.2%; bridge-to-transplantation 65% vs. 89.9%
PAH	van Wolferen et al., 2007 ^[166]	PAH	64	RVEDVI ≥ 84 ml/m ²	Predicted mortality at 1 year (HR 4.2, CI 1.31-8.3)
PAH	Forfia et al., 2006 ^[49]	PAH and non-PAH pulmonary hypertension	63	TAPSE	2-year survival with TAPSE > 1.8 cm vs. < 1.8 cm, 88% vs. 50%
	Yeo et al., 1998 ^[162]	PAH	53	RIMP	5-year survival free of cardiac death or lung transplant with RIMP < 0.83 vs. ≥ 0.83, 74% vs. 4%
Congenital heart disease	Rutledge et al., 2002 ^[182]	ccTGA	121	Visual dysfunction (moderate or severe)	Moderate or severe RV dysfunction predicted mortality (RR 5.9; CI 4.8-7.0)

CAD: coronary artery disease; **ccTGA:** congenitally corrected transposition of the great arteries; **CI:** confidence interval; **HR:** hazard ratio; **IDC:** idiopathic dilated cardiomyopathy; **IVA:** isovolumic acceleration; **LVAD:** left ventricular assist device; **NYHA:** New York Heart Association; **OR:** odds ratio; **PAP:** pulmonary artery pressure; **RIMP:** right ventricular index of myocardial performance; **RV:** right ventricle; **RVAD:** right ventricular assist device; **RVEDVI:** right ventricular end-diastolic volume index; **RVEF:** right ventricular ejection fraction; **TDI:** tissue Doppler imaging; **TR:** tricuspid regurgitation.

compromise may result during RV ischemia due to cavity dilation, diastolic and systolic dysfunction, ventricular interactions, and arrhythmia.^[22,27,29,110] Even if revascularization is not performed, hemodynamic improvement usually manifests within 3-10 days and RV function returns to normal within several weeks.^[111-114] If culprit artery revascularization is achieved expeditiously, short-term dysfunction is infrequent and the detrimental effects of RV dilation on left ventricular diastolic filling can be mitigated.^[22,115] Laster and colleagues showed in a canine model that preservation of RV function after RCA occlusion is in part due to favorable development of collateral circulation to the RCA territory.^[22] In some patients with chronic RCA occlusion, RV function may be preserved at rest but exhibit significant dysfunction on stress echocardiography.^[116] Long-term outcomes in patients with RVMI likely depend primarily on the degree of concomitant LV dysfunction.^[117]

While echocardiography in acute MI is most informative for assessing LV function, evidence of RV dysfunction adds prognostic value and can inform treatment decisions. Visual assessment of RV free wall motion by experienced readers is a sensitive qualitative measure of RV function

and can serve to confirm or provoke clinical suspicion of RV involvement.^[112] RV dilation and septal bowing can be seen on echocardiography and the inter-atrial septum may bow leftward due to increased right atrial pressure transmitted from the RV. As outlined in Table 5, a number of quantitative measures of RV function have been shown to be diagnostic or predictive of adverse outcomes. More quantitative measures of RV function such as decreased TAPSE and lateral tricuspid annular velocity on TDI indicate RV involvement in acute MI.^[118,119] Antoni et al. studied 621 patients within 48 hours of acute MI and found that RV FAC (≤32%), TAPSE (≤15 mm), and RV strain (≤-22.1%) independently predicted mortality, reinfarction, and hospitalization at 2 years follow-up.^[120] RIMP was found to have a sensitivity and specificity of 94% and 80%, respectively, for the diagnosis of RVMI.^[121]

Advanced techniques such as strain imaging and 3D echocardiography may eventually prove more accurate than current 2D methods at detecting RV dysfunction. CMR has evolved as the gold standard for assessing RVEF and morphology; however, in the setting of acute MI it is currently limited to post-reperfusion assessment of systolic function and scar burden.

Table 5: Imaging in specific disease states

Disease	Study	Parameter Assessed	Population	Outcome
MI	Engstrom, et al ^[118]	TAPSE, S'	STEMI patients with cardiogenic shock	TAPSE ≤ 14 had HR of 2.1 for death S'= 7.8 vs. 10 in IMI with and without RV involved
	Antoni, et al ^[120]	TAPSE, RVFAC, RV Strain	Inferior MI	TAPSE ≤ 1.5 , RVFAC $< 32\%$, and RV Strain $< -22.1\%$ predicted death/MI/HF readmission
	Ozdemir, et. al ^[121]	RIMP	Acute MI	RIMP > 0.70 has sensitivity and specificity of 94% and 80% for RVMI
	Kumar et al ^[81]	RV-LGE on CMR	STEMI	RV-LGE outperformed exam, ECG, and echocardiogram for detection of RVMI
PAH	Forfia et al ^[49]	TAPSE	All forms of PH	One year survival with TAPSE $> 1.8\text{cm}$ of 94% versus 60% for TAPSE $< 1.8\text{cm}$
	Yeo et al ^[162]	RIMP	IPAH	5 year survival free of cardiac death or lung transplant with RIMP < 0.83 vs. ≥ 0.83 , 74% vs. 4%
	Sachdev et al ^[56]	RV Strain	WHO Group 1 PAH	RV free wall strain worse than -12.5% predicted 1-4 year mortality
	McGann et al and Shehata et al ^[80,164]	RV LGE on MRI	All forms of PH	Extent of RV LGE correlated directly with RV mass index and inversely with RVEF
	van Wolferen et al ^[166,177]	RVEDVI, SVI on CMR	IPAH	<ul style="list-style-type: none"> RVEDVI $\geq 84\text{mL/m}^2$ and SVI $\leq 25\text{mL/m}^2$ predict mortality SV increase of 10ml after treatment considered clinically relevant
	van Wolferen ^[155,166] et al and Wilkins et al	RV mass after therapy	WHO Group 1 PAH	Significant decrease in RV mass, increase in CI on sildenafil/ bosentan combination but not bosentan alone
CTEPH and post-lung transplant	Menzel et al ^[137]	RV volume and EF by 3DE	CTEPH	RVEDV decreased from 121ml to 80 and RVEF increased from 25% to 36% post-PTE
	Menzel et al ^[138]	RIMP	CTEPH	RIMP decreased from 0.55 to 0.37 post-PTE
	Reesink et al ^[139]	RV volume and mass by CMR	CTEPH	RV volume normalized and RV mass decreased significantly post- PTE
	Katz et al ^[125]	RV volume and FAC	Post-lung transplant	RV volume decreased significantly but FAC did not improve immediately post-transplant
	Kramer et al ^[128]	RVEF by radionuclide angiography	Post-lung transplant	RVEF increased from 23% to 48% at 3-6 months
	Frist et al ^[131]	RVEF and RV mass by CMR	Post-lung transplant	RVEF near-normal at 3 months, RV mass normalized by 1 year
	Topilsky et al ^[147]	FAC	Pre-LVAD Implant	FAC $< 20\%$ predicts post-operative RV failure
LVAD	Puwanant et al ^[153]	TAPSE	Pre-LVAD Implant	TAPSE $< 7.5\text{mm}$ predicts RV failure (sensitivity 91%, specificity 46%)
	Topilsky et al ^[178]	Corrected TR Duration (TRDc)	Pre-LVAD Implant	TRDc $\leq 461\text{ms}$ is associated with decreased 1 and 2 year survival
	Kukucka et al ^[151]	RV-to-LV end-diastolic diameter ratio	Pre-LVAD or BiVAD implant	R/L > 0.72 predicted RV failure (OR 11.4)
	Topilsky et al ^[152]	S' and septal deviation	30 days post-LVAD implant	Decreased S' (OR 0.70) and septal deviation to left (OR 3.0) associated with 90 day mortality, HF readmission, or NYHA ≥ 3

3DE: tridimensional echocardiography; **BiVAD:** biventricular assist device; **CI:** cardiac index; **CMR:** cardiac magnetic resonance imaging; **CTEPH:** chronic thromboembolic pulmonary hypertension; **ECG:** electrocardiogram; **HF:** heart failure; **HR:** hazard ratio; **IDC:** idiopathic dilated cardiomyopathy; **IPAH:** idiopathic pulmonary arterial hypertension; **IVA:** isovolumic acceleration; **LGE:** late gadolinium enhancement; **LVAD:** left ventricular assist device; **MI:** myocardial infarction; **NYHA:** New York Heart Association; **OR:** odds ratio; **PASP:** pulmonary artery systolic pressure; **PH:** pulmonary hypertension; **PTE:** pulmonary thromboendarterectomy; **RIMP:** right ventricular index of myocardial performance; **RV:** right ventricle; **RVAD:** right ventricular assist device; **RVEDVI:** right ventricular end-diastolic volume index; **RVEF:** right ventricular ejection fraction; **RVFAC:** right ventricular fractional area change; **S':** myocardial velocity at the lateral tricuspid annulus; **STEMI:** ST-segment myocardial infarction; **SVI:** stroke volume index; **TAPSE:** tricuspid annular plane systolic excursion; **TDI:** tissue Doppler imaging; **TR:** tricuspid regurgitation; **TRDc:** tricuspid regurgitation duration (corrected for heart rate); **WHO:** World Health Organization

Post-lung transplantation and post-thromboendarterectomy

There are two interesting experiments of nature that demonstrate the plasticity of the RV in response to correction of pulmonary vascular disease: lung transplantation and pulmonary thromboendarterectomy (PTE) for chronic thromboembolic pulmonary hypertension (CTEPH). In both cases, the cause of elevated PVR is removed and thus load stress is essentially eliminated.

In patients with end-stage pulmonary hypertension, heart-lung transplantation was initially felt to be the only viable surgical option due to profound RV dilation and dysfunction.^[122] Based on observations of significant RV functional recovery in patients with chronic thromboembolic disease who underwent thromboendarterectomy, lung transplantation alone has been pursued with success.^[123,124]

In the immediate post-operative period, RV function may not improve,^[125] but RVEF and PA systolic pressure (PASP) normalize within two to three months post-lung transplant; however, LV recovery may take up to a year.^[126,127] Toyooka et al. showed similar results in 33 patients in whom RV function normalized within two months but LV functional recovery was delayed for 6-12 months after living-donor lobar lung transplantation.^[127] Echocardiography in post-lung transplant patients frequently demonstrates evidence of marked RV reverse remodeling: RV and right atrial (RA) size decrease, the tricuspid valve annulus shrinks with a decrease in TR, and the interventricular septum resumes its normal position.^[25,128-130] Residual elevation in pulmonary vascular resistance with a single lung transplant is frequent and may be accompanied by some degree of post-operative RV dysfunction.^[25,128,130] Magnetic resonance imaging (MRI) in post-lung transplant patients indicates that while RV performance is improved in the short term, reduction in RV mass can take up to one year, demonstrating the utility of MRI as a complementary tool for assessing RV remodeling.^[131]

CTEPH causes increased RV afterload, RV hypertrophy, and dilation as well as a shift of the IVS toward the left decreasing LV filling and cardiac output.^[132,133] Preoperative findings on CMR or echocardiography are virtually indistinguishable from other forms of elevated pulmonary vascular disease.^[132,134] Successful PTE results in dramatic improvements in mean pulmonary pressure, PVR, and cardiac output.^[135] Reverse remodeling can be seen on echocardiography and MRI as evidenced by reduction in RV chamber size and mass, improvement of RV systolic and diastolic function to near normal, and a decrease in tricuspid regurgitation (Fig. 3).^[136-140]

Post- LVAD implantation

RV dysfunction is both an obstacle to LVAD placement and

an independent prognostic indicator. Right heart failure occurs in 15-20% of patients after LVAD implantation and confers a worse outcome.^[141,142] In the largest randomized trial to date, post-operative RV failure was less frequent with a continuous-flow device (Heart Mate II) compared to a pulsatile device (Heart Mate I).^[143]

LV unloading may favorably alter RV function through decreased RV afterload and normalization of the neurohormonal milieu characteristic of heart failure.^[144-146] LV unloading can adversely affect RV function as well. A leftward shift of the interventricular septum distorts RV geometry and leads to depressed RV contractile efficiency as well as increased tricuspid regurgitation. RV preload also increases following LVAD implantation, which may further exacerbate RV failure.^[147]

Despite significant unloading, the degree of RV remodeling post-LVAD implant is unclear. Explanted hearts of patients with pulsatile LVAD support showed no evidence of RV remodeling as measured by volume reduction, myocyte diameter, force-frequency relationship, and SERCA2a content.^[148] However, improvement in RV mass, myocyte size, and RV end-diastolic pressure-volume relationship was observed with biventricular devices compared to no or left ventricle only support.^[149] In a series of continuous-flow LVADs, pre-existing RV dysfunction remained stable over 4.5 months despite a decrease in right-sided pressures and chamber size.^[150] These findings suggest that reduction in RV afterload must be coupled with preload reduction for RV reverse remodeling to occur.

Accurate assessment of RV function with echocardiographic and hemodynamic assessment prior to LVAD implantation is crucial. Qualitative assessment of RV contractility in the apical four-chamber and RV inflow views provides a general sense of RV function. Quantitatively, preimplant FAC, RV-to-LV end-diastolic diameter ratio (R/L), and TAPSE predict post-implant RV failure.^[151] The duration of TR corrected for heart rate ($TDRc = TR \text{ flow time} / \sqrt{RR\text{-interval}}$) predicts RV failure and mortality in patients with a Heart Mate II LVAD. In a study of 83 patients from the Mayo Clinic implanted with the Heart Mate II LVAD demonstrated that the TDRc predicted right heart failure and mortality. Patients with a $TDRc \leq 461$ ms had a significantly lower 1- and 2-year survival compared with patients with $TDRc \geq 461$ ms.^[147] Recently, S' and leftward deviation of the septum at 30-day post-implant were associated with adverse outcomes.^[152] RVFAC < 20% has been shown to predict right heart failure following LVAD implant.^[147] Puwanant et al. reported that tricuspid annular motion < 7.5 mm predicts RV failure following LVAD with a sensitivity of 91% and specificity of 46%.^[153] Finally, it is important to assess the severity of tricuspid regurgitation as valves with more than moderate regurgitation require

operative repair or replacement at the time of LVAD implant.

The same protocol and parameters to determine RV function pre-implant should be utilized and assessed post-implant. Right atrial and inferior vena cava size can be used to estimate right atrial pressure, and the estimated RVSP can be monitored in patients with pre-implant pulmonary hypertension. Ramped speed studies are useful to optimize LVAD rotor speed by determining the speed with optimal LV unloading while maintaining a midline interventricular septum.^[147]

Pulmonary arterial hypertension

Evidence of RV plasticity in the surgical management of PAH is discussed in the post-lung transplantation. In regard to medical therapy, the addition of sildenafil to bosentan therapy in PAH resulted in a significant decrease in RV mass and increase in cardiac index compared to bosentan alone.^[154,155] Other studies have confirmed that RV hypertrophy can regress and RV function can improve acutely on sildenafil.^[156,157]

Although echocardiography is the most commonly used modality for assessment of the RV in PAH, superior quantitative abilities of CMR with respect to the RV have driven interest in this technique both for the diagnosis of PAH and for the determination of response to therapy. Nevertheless, because of widespread availability and challenges with pumps associated with prostacyclin delivery and cost, echocardiography remains most widely used. Familiarity with both techniques is essential in the assessment of PAH.

The primary role of imaging in suspected pulmonary hypertension is determination of the severity of RV compromise, not subcategorization of pulmonary hypertension (e.g., PAH vs. pulmonary venous hypertension [PVH] vs. CTEPH).^[158,159] Conformational changes in the RV include RV and RA dilation,^[2] RV wall and moderator band hypertrophy, reduced RV fractional area change,^[160] and septal bowing to the left ventricle.^[161] As functional assessments, TAPSE and RIMP are broadly useful in all forms of PH and have been shown in PAH specifically to correlate with survival.^[49,162] RV strain imaging has recently been shown to correlate with survival and RVEF measured by CMR in PAH patients and will likely become more clinically useful as normative data emerge.^[56,57]

The shape of the RV outflow tract Doppler envelope has been demonstrated to discriminate patients with high pulmonary vascular resistance from those without,^[163] with mid-systolic notching indicating high PVR and uncoupling between the RV and PA. As described earlier, PVR can be estimated as greater or less than 2WU based on the ratio of

the peak TR velocity to velocity-time integral of the RVOT.^[39]

CMR allows accurate assessment of RV mass, volume, and EF which have been shown to correlate with disease severity and death in various types of PAH.^[82] CMR has also allowed more specific determination of regional abnormalities in PH including patterns of myocardial delayed enhancement. The degree of late gadolinium enhancement (LGE) at the RV septal insertions, thought to be due to local fibrosis,^[80,164] has been observed in patients with scleroderma-associated PAH and IPAH to correlate inversely with RVEF.^[165] RV mass strongly predicts the presence or absence of PAH in patients with scleroderma, while increased RV volume and decreased LV volume predicts death in IPAH.^[165,166] Recent evidence using adenosine stress CMR demonstrated that reduced biventricular myocardial perfusion reserve correlates with RVEF in PAH, suggesting role of ischemia in RV dysfunction in these patients.^[167] In both conditions, RV mass has been studied as a predictor of death. While in idiopathic PAH RV mass was not found to predict death, it is a strong predictor of death in scleroderma-associated PAH. In idiopathic PAH, the primary CMR predictors of death are large RV volume, low stroke volume, and reduced LV volume. In echocardiographic analysis, TAPSE remains an important marker of poor prognosis in both idiopathic and scleroderma-associated PAH.

Unfortunately, there are few imaging techniques for diagnosis of PH subtype, particularly discerning PAH from PVH. Recently, the shape of the RV Doppler envelope has been demonstrated to discriminate patients with high pulmonary vascular resistance from those without.^[163] The flow velocity envelope of the RV outflow tract is altered in response to pathologic wave reflection in the setting of increased pulmonary arterial impedance; mid-systolic wave reflection is present in elevated pulmonary vascular resistance while normal notching pattern or late systolic notching is present in lower PVR patients.^[39] The primary limitation of both echocardiography and CMR is their inability to accurately measure pulmonary arterial pressures, cardiac output, or pulmonary artery occlusion pressure, essential features in the diagnosis and assessment of pulmonary vascular disease.^[32,37,134] Until better diagnostic modalities or techniques are available, current recommendations are to obtain right heart catheterization in order to confirm etiology of pulmonary hypertension as this cannot be reliably discerned through echocardiography, CMR, or other noninvasive imaging techniques.^[134,168]

Once PAH is confirmed, little is known about differences in RV imaging between the various subtypes, including heritable, idiopathic, connective-tissue disease-associated, or associated with congenital left-to-right shunt. There is a clear indication for CMR in the diagnosis of congenital heart disease-associated PAH, but the utility of echocardiography or CMR for the other subtypes is under investigation. Since

idiopathic and scleroderma-associated PAH make up the bulk of patients, these are the primary subgroups studied, though rarely compared.

CONCLUSION AND FUTURE DIRECTIONS

RV dysfunction is a strong contributor to poor outcomes across a broad range of cardiopulmonary diseases, and clinical appreciation of this fact is widening. The RV displays remarkable resiliency in the face of insult, at least in part due to its unique physiology. The development of noninvasive imaging techniques to assess RV function is growing apace with investigation into genetic and neurohormonal modifiers. A biomarker profile diagnostic or predictive of RV failure would also be valuable as a routine part of clinical assessment. Given the dynamic beat-to-beat changes in RV loading conditions, imaging techniques that are load independent should be the focus of future advances. Development of exercise imaging protocols may also shed light on RV functional reserve and help predict response to therapy.

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