Comprehensive Invasive and Noninvasive Approach to the Right Ventricle-Pulmonary Circulation Unit: State of the Art and Clinical and Research Implications
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Pulmonary Vascular Diseases

Comprehensive Invasive and Noninvasive Approach to the Right Ventricle–Pulmonary Circulation Unit
State of the Art and Clinical and Research Implications

Hunter C. Champion, MD, PhD; Evangelos D. Michelakis, MD; Paul M. Hassoun, MD

... And I ask, as the lungs are so close at hand, and in continual motion, and the vessel that supplies them is of such dimensions, what is the use or meaning of this pulse of the right ventricle? And why was nature reduced to the necessity of adding another ventricle for the sole purpose of nourishing the lungs?

—William Harvey, Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus, 1628

There is still no answer to William Harvey’s rhetorical question. He included the right ventricle (RV), its “pulse,” the large pulmonary arteries (PAs), and the lungs in the same sentence, emphasizing the concept of a “unit.” Although Harvey realized the importance of the RV and its interactions with the pulmonary circulation, 4 centuries later, the RV is largely understudied. At the same time, there has been significant progress in our understanding of the pathology of pulmonary vascular disease and, over the past few years, an explosion of clinical therapeutic trials for PA hypertension (PAH). This unbalanced approach has generated a number of problems and controversies. For example, it is now becoming apparent that even if experimental therapies improve or reverse PAH pathology, this does not necessarily lead to clinical improvement and prolonged survival unless accompanied by a parallel improvement in RV function. The degree of pulmonary hypertension (ie, PA pressure [PAP]) does not strongly correlate with symptoms or survival, whereas RV mass and size and right atrial pressure reflect functional status and are strong predictors of survival. The 6-minute walk test, used as the primary end point in most PAH clinical trials, correlates better with RV function (ie, cardiac output) than with the degree of pulmonary pressure elevation. However, this test is being heavily criticized because of multiple inherent problems and the fact that it does not provide information on specific components of RV–pulmonary vascular function. Although therapies aiming at reversing pulmonary vascular remodeling might also have a positive effect on the RV (eg, sildenafil, which has been shown to increase RV inotropy and decrease RV hypertrophy, in addition to its effects on the pulmonary circulation), others might have untoward effects on the RV. For example, imatinib, an antiproliferative/proapoptotic agent that shows preliminary promise in reversing pulmonary vascular remodeling, is potentially associated with primary negative (ie, proapoptotic) effects on the myocardium.

As our knowledge of RV physiology and biology increases, it is becoming apparent that a comprehensive approach to the RV, the pulmonary circulation, and their interactions will be beneficial in both clinical management of PAH patients and clinical research. The evolution of RV pathology from the normal to a compensated (hypertrophied) and then decompensated state parallels the evolution of pulmonary vascular pathology from a vasodilated high-capacitance state to vasoconstricted arteries and early loss of endothelial cells/capillaries to an end-stage proliferative and obliterator vascular remodeling (Figure 1). Therefore, it is important to study the RV and the PAs comprehensively and simultaneously as a unit. Here, we discuss standard clinical tests (eg, right heart catheterization and echocardiography) and evolving technologies (eg, magnetic resonance [MR] imaging [MRI] and positron emission tomography [PET]) that have the ability to study the RV–proximal PAs–PA microcirculation unit comprehensively and provide quantitative data. Such data promise to be very relevant to the clinical management of PAH patients and might prove to be ideal end points for future clinical research.

Hemodynamic Assessment of RV Function and Ventricular-Vascular Interactions

Standard Hemodynamic Approaches
Cardiac catheterization remains the gold standard for diagnosing pulmonary hypertension, assessing disease severity, and determining prognosis and response to therapy. By directly measuring pressures and indirectly measuring flow, right heart catheterization allows determination of prognostic

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markers such as right atrial pressure, cardiac output, and mean PAP. Importantly, this procedure has been shown to be safe, with no deaths reported in the National Institutes of Health registry study and a recent study showing a procedure-related mortality of 0.055%. Right heart catheterization determines the presence or absence of pulmonary hypertension, may allow definition of the underlying cause, and allows prognostication. The most critical aspect to right heart catheterization is that it should be performed appropriately and the data interpreted with accuracy and precision.

Because the end-expiratory intrathoracic pressure most closely correlates with atmospheric pressure, it is important that all RV, PA, pulmonary wedge, and left ventricular (LV) pressures be measured at end expiration. This is especially true in patients in whom there can be significant variation between inspiratory and end-expiratory vascular pressures (obese patients and patients with intrinsic lung disease). After determination of the presence of pulmonary hypertension, pulmonary venous pressures should be evaluated by the pulmonary capillary wedge pressure (PCWP). PAH is defined by a PCWP of \( \leq 15 \) mm Hg at rest or with exertion to exclude LV dysfunction, mitral valve disease, or other conditions of pulmonary venous hypertension. This value was based on the normal PCWP or LV end-diastolic pressure of \(<8\) mm Hg and the observation that 2 SDs above a normal PCWP is \( \approx 14\) mm Hg. It is important to note, however, that a PCWP of 14 or 15 mm Hg is still not normal.

For the measurement of cardiac output, both thermodilution and Fick methods are reliable in PAH patients, except those with severe tricuspid regurgitation or cardiogenic shock. Vasodilator challenges with inhaled nitric oxide or intravenous epoprostenol or adenosine are encouraged in all patients at the time of diagnosis and in follow-up studies. A favorable vasodilator response is defined by consensus as a drop in mean PAP of at least 10 mm Hg to a value ≤40 mm Hg with an unchanged or increased cardiac output. Below, we discuss a number of tests that can complement the standard procedure and provide critical data on the condition of the RV-PA unit.

**Confrontational Testing to Assess Pulmonary Circulation-RV Interactions**

Some patients with pulmonary vascular disease are not symptomatic at rest but have symptoms with exertion. This observation provides a potential for exercise or volume challenge during right heart catheterization to better diagnose early pulmonary vascular disease. In patients with risk factors for nonsystolic LV dysfunction (sleep-disordered breathing, systemic hypertension, obesity, diabetes/glucose intolerance), one should consider confrontational testing (to uncover potential increases in PCWP) by administering a fluid bolus challenge or exercise during right heart catheterization particularly if the patient has a resting PCWP between 8 and 15 mm Hg. With regard to the threshold of a mean PAP of 30 mm Hg with exercise, the data to support this as a disease state that is similar to resting PAH are much less robust. The number of pulmonary hemodynamic studies with exercise is small, and a small number of patients were included.

Exercise pulmonary hemodynamics have been reported in 218 normal subjects (125 in 1 study of subjects ranging in age...
The purpose of exercise is not just to examine PAP in response to exertion. Rather, the benefit of confrontational testing is the observation of the change/increase in PCWP in an effort to diagnose pulmonary venous hypertension or nonsystolic heart failure (diastolic dysfunction; Figure 2). Although protocols for exercise and workload vary from study to study and few subjects have been exercised to maximal workload, the main goal of exercise is to increase heart rate to 85% maximal age-predicted heart rate as is used in cardiology stress testing. Given increased thoracic pressure changes with exercise, particularly in overweight and/or deconditioned patients, it is critical that measurements be made at end expiration to ensure uniformity in interpretation. An increase in PCWP to >15 mm Hg in response to exercise or fluid challenge suggests the presence of pulmonary venous hypertension (Figure 2), a condition with dramatically different management than PAH. Because cardiac output can increase up to 5 times baseline, pulmonary vascular resistance (PVR) normally decreases with exercise (Figure 2). Poor prognostic signs in exercise right heart catheterization are the inability of the RV to augment in response to exercise (ie, lack of a significant increase in cardiac output), failure to reduce PVR with exercise, angina, and presyncopal symptoms or frank syncope.

**Exercise Right Heart Catheterization**
- Obtain Baseline hemodynamic Profile
- Perform arm or leg exercise
- Goal is 85% age predicted maximal heart rate or elevated PCWP with symptoms
- Retake measurements during exercise including CO and PA oxygen saturation

**Fluid Challenge**
- Obtain Baseline hemodynamic Profile
- Administer 1000 cc 0.9% NaCl iv until completion over 20 minute period or until PCWP exceeds 15 mmHg with symptoms
- Obtain hemodynamic measurements with every 250 cc volume

**Figure 2.** Confrontational assessment of cardiopulmonary function by exercise and fluid challenge during right heart catheterization. Top, Johns Hopkins University protocol for exercise right heart catheterization and fluid challenge and an example of the results of an exercise challenge in a patient with nonsystolic heart failure (heart failure with preserved ejection fraction, diastolic dysfunction) in which the patient’s baseline mean PAP is borderline elevated and PCWP is elevated at 12 mm Hg. With exercise, the PCWP increased significantly to 25 mm Hg with a concomitant increase in mean PAP that resulted from the elevated PCWP. Bottom, The Johns Hopkins University protocol for fluid challenge and an example of data from a patient with pulmonary hypertension and nonsystolic heart failure. At baseline, PAP was elevated (29 mm Hg), as was PCWP (12 mm Hg; note that measures are appropriately measured at end expiration). With fluid challenge, PCWP increased to 22 mm Hg, thus confirming the diagnosis of nonsystolic heart failure. CO indicates cardiac output.

**Novel Hemodynamic Techniques**

**PA Wave Reflection as a Component of RV Load and Measurement of PA Input Impedance**
Chronic pulmonary hypertension results from an increase in PVR, which is a simple measure of the opposition to the mean component of flow. However, given the low-resistance/high-compliance nature of the pulmonary circulation, the pulsatile component of hydraulic load is also critical to consider. The fact that the mean and the pulsatile components of flow are dependent on different portions of the pulmonary circulation suggests that they could be controlled separately without much overlap. The pulmonary circulation is pulsatile with multiple bifurcations, and wave reflection is an inevitable consequence. When the forward pressure wave from the heart collides with the backward pressure wave that was reflected from the bifurcations, pressure increases and flow decreases. Because the often-used PVR takes only mean flow into account, it does not allow for changes in pulsatility of the pulmonary circuit (Figure 3). One must consider the elastic properties of the pulmonary circulation/left atrium and impedance on RV performance rather than the pure resistive properties because the heart could not function if it were not for the elastic properties of pulmonary vasculature. During systole, the pulmonic valve is open at a time when the mitral valve is closed. Thus, if it were not for the elastic properties...
of the pulmonary vasculature, the heart could not develop forward flow.\textsuperscript{21–23}

Frequency-Domain Analysis of the Pulmonary Circulation: PA Input Impedance

The concept of the RV-pulmonary circulation operating as a unit is best demonstrated by the change in hydraulic load that occurs in the setting of PA stiffening and is an early and important component of the vascular remodeling in PAH. As the RV is met with increased hydraulic wave reflection (largely from increased pulmonary stiffness, resulting in decreased pulsatility) in the diseased pulmonary vasculature, its workload is greater to maintain forward flow. Impedance is a measure of the opposition to the pulsatile components of flow. RV afterload is usually considered in terms of PVR. Yet, between one third and one half of the hydraulic power in the main PA is contained in the pulsatile components of flow. Therefore, measurement of arterial input impedance is needed to obtain a complete description of ventricular afterload. It is also likely that “early” or more severe pulmonary hypertension is missed simply because this contribution to the load on the RV is not accounted for in the mean PAP measurement at the time of right heart catheterization. Research in pulmonary vascular disease has so far focused essentially on the small PAs, which appear to be the main site of resistance. Impedance is dependent primarily on the mechanical properties and the geometry of the proximal PAs. The PA input impedance spectrum is dependent primarily on the first 5 orders of bifurcation from the main PA in decreasing levels of importance and lends credence to the idea that the “total resistance” does not lie solely at the level of arterioles that are <250 μmol/L in diameter.\textsuperscript{21–24} The changes in impedance resulting from large-artery stiffening or remodeling alone can markedly alter the load on the RV. Interestingly, this can occur in the absence of a change in PVR. Moreover, congenital cardiac disease with or without surgical correction (especially

\begin{figure}[h]
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\caption{Assessment of pulmonary circulation-RV interactions using impedance analysis and augmentation index. A, Outline of technique used to measure simultaneous PAP and flow to compute PA input impedance. B, Schematic highlighting key features of summary impedance spectra. Impedance, the opposition to blood flow by the pulmonary circulation, is frequency dependent on and modulated by heart rate, vessel dimensions, vessel stiffness, and wave reflections. Z\textsubscript{0} is total resistance that does not take into account frequency and represents total PVR. C, Sample impedance spectra from a patient with normal pulmonary circulation (dashed line) showing a baseline Z\textsubscript{0} (PVR) and frequency of first minimal impedance modulus (pulse-wave velocity [PWV]) of \textasciitilde 2 to 3 Hz. Solid line shows impedance spectra from a patient with severe pulmonary vascular disease and RV dysfunction in which Z\textsubscript{0} is elevated and there is significant delay in Z\textsubscript{1}, indicating poor RV-pulmonary circulation coupling. In addition, the patient with pulmonary vascular disease displays a significant shift in the frequency of first minimal harmonic and in elevated characteristic impedance, suggesting increased large-vessel stiffness. D, Measurement of augmentation index using PA tracing (time-domain analysis). An increase in augmentation index suggests increased wave reflection in the pulmonary circulation. sPAP indicates systolic pulmonary arterial pressure; PI, input pressure; PAPP, pulmonary arterial pulse pressure.}
\end{figure}
in repaired tetralogy of Fallot with transannular patch) can significantly increase the pulsatility of the PA waveform. Moreover, with the pulmonic valvular insufficiency that often accompanies congenital disease, there is an increased diastolic volume/load exerted on the RV. With diseases such as scleroderma-related PAH and idiopathic PAH (IPAH), both large-artery and small-artery remodeling occurs, which increases resistance and impedance. However, it is more likely that large-artery involvement (as seen in scleroderma-related PAH or cardiovascular aging) plays a more significant role compared with IPAH in increasing impedance. This abnormal pulsatile load may have detrimental effects on ventricular-vascular coupling by increasing the pulsatile part of ventricular power and thus unfavorably loading the still-ejecting RV.

Several studies have documented the relationship between pulsatile pressure and flow (pulmonary input impedance; Figure 3). The first assessment of pulmonary vascular impedance dates back to 1961, shortly after impedance was first described in the systemic vascular bed. However, given the previous technical challenges in obtaining impedance spectra, its use has largely been relegated to the laboratory and reported in a few relatively small clinical trials. Only recently have we been able to measure PA input impedance routinely as a result of the ability to measure PA blood flow and PAP simultaneously with high-fidelity catheters at the time of routine right heart catheterization, adding only 5 to 10 minutes to each case. These measurements of simultaneous pressure and flow are then used to calculate the
arterial input impedance spectra and have been greatly facilitated by software that can accomplish this task quickly, although the software is not currently commercially available (eg, Matlab-based custom software). This calculation of impedance allows a more accurate quantification of RV hydraulic load from a spectral analysis of pressure and flow waves. The results of this analysis are expressed as an impedance spectrum, consisting of a pressure-to-flow ratio and a phase angle, both of which are expressed as a function of frequency. As shown in Figure 4B, the impedance spectrum includes a measure of total PVR; indexes of wave reflection such as the first minimum of the ratio of pressure and flow moduli or low-frequency phase angle; characteristic impedance (Zc), which corresponds to the ratio of intrainercy to compliance; and hydraulic load, as evaluated by low-frequency impedance and the amplitude of impedance oscillations. Prior studies have shown that the pulsatile load is also increased in chronic pulmonary hypertension, as suggested by the increased characteristic impedance and enhanced wave reflection that have generally been attributed to decreased PA compliance and complex changes in reflection sites. Moreover, pulmonary vascular impedance has been studied in the pediatric population, in which it was found to predict outcomes better than PVR.\textsuperscript{30} Impedance, in combination with compliance and resistance, has been studied with MR technology, which has shown that these techniques may differentiate between types of pulmonary hypertension.\textsuperscript{31} Finally, echocardiographic measurements of pulmonary vascular impedance have recently been shown to be feasible.\textsuperscript{20} It is hoped that the study of pulmonary vascular impedance will yield important information about the RV response to stress in pulmonary hypertension and may prove to be a more predictive measure of prognosis and response to treatment than current standards.

**Time-Domain Analysis of PA Pressure Waveforms**

Although we believe that the measurement of pulmonary vascular impedance may, in the future, become a routine test in patients with PAH, the technology and necessary equipment may currently limit its widespread use outside tertiary care academic centers.\textsuperscript{32} Time-domain analysis of pulse pressure and pressure waveform may provide valuable information on pulsatile arterial load and may be a surrogate to the full assessment of RV input impedance (Figure 3).\textsuperscript{32} Pulse pressure indicates the amplitude of pulsatile stress. Pulse pressure is determined mainly by both the characteristics of ventricular ejection and arterial compliance; the lower the compliance is, the higher the pulse pressure is. Moreover, pressure waveform analysis performed in the time domain makes it possible to calculate the timing and extent of wave reflection in systemic and pulmonary circulation with measures such as augmentation index (as shown in Figure 3D), which roughly represents reflected wave summation (AP) in the pulmonary circuit and normalizes for the PA pulse pressure.\textsuperscript{32–40} These values can be obtained easily at the time of right heart catheterization, and future studies will compare both analyses as potential prognostic indicators in patients with pulmonary hypertension and correlate with the previously described concept of capacitance.\textsuperscript{41}

**RV Pressure-Volume Loop Relations**

The use of pressure-volume (PV) loop analysis as a means of measuring load-independent contractility has largely been restricted to the study of LV hemodynamics and the interaction between the LV and the systemic vasculature.\textsuperscript{27,38–42,52} This has been due primarily to geometric differences between the 2 ventricles, the optimal conductance properties required for proper volume measurements, and the belief that it is difficult to obtain consistent data with conductance measurements in the crescent-shaped RV. Indeed, under conditions of normal PAP and RV function, RV PV loop analysis is somewhat complicated given the crescent shape of the normal RV (Figure 1) and the ellipsoid shape of the PV loop obtained under these conditions. However, under conditions of even only modestly increased load, the RV shape changes to one resembling the more spherical LV, allowing measurement of end-systolic elastance and effective arterial elastance, as well as the more accurate measurements of indexes of RV systolic and diastolic function and RV/PA coupling (Figure 4). As shown in Figure 4, the performance of such studies is relatively easy and can be made in the same acquisition time as measurements of impedance spectra with Food and Drug Administration–approved equipment. Because essentially all of the currently used PAH therapies (particularly prostaglandin analogs,\textsuperscript{53} phosphodiesterase inhibitors,\textsuperscript{54–57} and endothelin receptor antagonists\textsuperscript{58–60}) and many of the emerging experimental therapies (eg, imatinib) have primary effects on the myocardium (whether positive or negative), a study of the intrinsic contractility of the RV is perhaps the only reliable way to separate the effects of these therapies on the PAs from those on the RV myocardium. In that sense, studies of RV contractility are not only relevant to the clinical management of PAH patients but also critical for the interpretation of the clinical trial data. Moreover, many of the measurements taken with conductance catheterization can be reproduced using measures of RV pressures and cardiac output/stroke volume by right heart catheterization and ventricular volumes as measured by echocardiography, CT, or MRI using standard equations.

**Echocardiography**

**Standard Echocardiographic Approaches**

**Estimating Pulmonary Pressures and Resistance**

Doppler echocardiography is the most commonly used screening modality for the assessment of RV structure and function, and it allows exclusion of valvular, primary myocardial, and congenital causes of increased right heart pressures. The tricuspid regurgitant jet is generally used to estimate RV systolic pressure via the Bernoulli equation (4v², where v is the maximum velocity of the tricuspid valve regurgitant jet; Figure 5). An estimated right atrial pressure (based on collapsibility of the inferior vena cava best visualized in the subcostal window\textsuperscript{61}) is added to the peak systolic pressure gradient of the tricuspid regurgitant flow to obtain RV systolic pressure (which approximates PA systolic pressure in the absence of pulmonary valve stenosis and RV outflow tract obstruction). Although mean PAP can be estimated by measuring the early diastolic velocity of the
pulmonary insufficiency jet, the correlation with invasive measures is weak because of difficulty in accurately visualizing the velocity regurgitant profile at the pulmonary valve. More recently, formulas for estimating mean PAP from the RV systolic pressure have been developed. In addition, Doppler echocardiography allows noninvasive estimation of PVR, measured as the ratio of the tricuspid regurgitant velocity to the velocity-time interval of the RV outflow tract. The ratio of tricuspid regurgitant velocity to the velocity-time interval of the RV outflow tract has recently been shown to predict mortality and adverse cardiovascular events in patients with stable coronary artery disease, but its usefulness in patients with pulmonary vascular disease remains to be determined.

Initial studies by Berger et al and Currie et al demonstrated good correlation between echocardiographic estimates and directly measured pressures. However, there are conflicting data as to the strength of this correlation between RV systolic pressure estimated by Doppler echocardiography and mean PAP measured via right heart catheterization. When RV and PAPs are estimated via echocardiography, they more often are higher than the pressures measured directly by catheterization, and although it is clear that Doppler echocardiography cannot be recommended at this time for use as the gold standard for diagnosis of pulmonary hypertension, it remains an excellent screening modality. Aside from a significant increase in RV systolic pressure, patients with more severe pulmonary hypertension classically present with right atrial dilatation, RV hypertrophy and dilatation, evidence of RV remodeling (thickening of the “moderator band”), and systolic flattening of the interventricular septum with D-shape deformity suggesting pressure overload (Figure 5). The presence of pericardial effusion has been correlated with poor survival in IPAH and in patients with scleroderma-related PAH.

Figure 5. Use of echocardiography in assessing pulmonary hypertension. Top, Representative images of echocardiographic 2-dimensional imaging and Doppler assessments in PAH. Note the septum shift toward the LV from RV pressure overload, resulting in a decrease in LV volume and perhaps a secondary increase in LV filling pressures. Middle, The standard tricuspid regurgitation velocity method currently used to estimate systolic PAP (see text) using continuous-wave Doppler. Bottom, Pulsed-wave Doppler interrogation of the main PA to measure PAAT (the time from the start of the envelope to its peak) in patients with severe PAH (left) and no PAH (right). In pulmonary hypertension, the peak velocity of the Doppler envelope decreases and the time to peak velocity (measured from the onset of flow) or PAAT shortens. In severe pulmonary hypertension, there may be “notching” or early systolic deceleration, which, like the premature partial closure of the pulmonic valve on M mode, reflects reflection of velocity waves and cancellation by reverse flow. EDV indicates end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; TAPSE, tricuspid annular plane systolic excursion; RA, right atrium; and RVD, RV dimension.

Exercise echocardiography has been suggested as a reliable means to detect pathological increases in PAPs. One example has been its use in patients at risk for pulmonary hypertension. However, this test has not been standardized, and interpretation of changes with exercise has to be considered with caution, particularly because age- and gender-related variations have not been fully elucidated. It is noteworthy that significant elevations of PAP can occur in well-trained athletes at peak workloads or in patients with impaired LV filling. The use of exercise echocardiography is not specifically recommended at this time to assess patients with PAH.
Novel Uses of Echocardiography

Estimating RV Function
RV dysfunction and hypertrophy may be difficult to quantify on echocardiography because of the complex geometry and poor RV endocardial definition, the characteristic mode of myocardial contraction related to muscle fiber orientation (compared with the LV), and operator and acoustic window differences that determine image quality. However, when present, these findings can provide important information about cardiac effects of chronic pressure overload. Three-dimensional (3D) echocardiography can give accurate estimates of RV ejection fraction, structure, and function; however, this technique is not currently widely available (Figure 6). Great attention has been paid to alternative measures of RV function. The Tei index yields a computed value that combines Doppler-derived RV systolic and diastolic function to assess RV function quantitatively. Indexed right atrial area, the degree of septal shift in diastole, and a high Doppler RV performance index have been associated with poor outcomes. These measurements, although not routinely obtained in the standard echocardiogram, can be made in clinical practice. More recent studies have focused on the value of echocardiography in assessing RV function by various techniques, including 2-dimensional strain, tissue Doppler echocardiography, tridimensional echocardiography, or the speckle tracking method. Systolic and diastolic tissue Doppler imaging–derived velocity profiles of the RV free wall and the lateral tricuspid annulus may also help detect early RV dysfunction. For instance, quantification of RV function can be estimated by ultrasonic strain-rate imaging. The local rate of the wall deformation (strain rate) and the amount of deformation (strain) can be measured by processing regional myocardial velocity data. Strong correlations have been reported between apical strain and invasively measured mean PA and PVR. Similarly, derivation of regional RV isovolumetric relaxation time (defined as the interval between pulmonary valve closure and tricuspid valve opening) from tissue velocity recordings of RV myocardial

Figure 6. Top, Example of 3D echocardiography in which multiple views of the RV are reconstructed to provide a 3D volumetric image for assessment of RV volumes and function (Courtesy Kirk Spencer, MD, and Lissa Sugeng, MD, MPH, University of Chicago). Bottom, Representative M-mode recording through the lateral tricuspid valve annulus for the purpose of measuring the tricuspid annular plane systolic excursion. Excursion is measured from end diastole to end systole as shown on right. Ao indicates aorta.
wall motion (at the tricuspid annulus along the long axis) correlates strongly with invasively measured PA systolic pressure when corrected for heart rate. However, there is loss of correlation between PA systolic pressure and corrected isovolumetric relaxation time in the presence of significant RV dysfunction. Therefore, corrected isovolumetric relaxation time can be considered a simple and reproducible measurement of PA systolic pressure (and an alternative to tricuspid regurgitation–derived PA systolic pressure when tricuspid regurgitation cannot be recorded for technical reasons); however, results should be interpreted with caution when RV function is depressed.

More recently, measurement of the tricuspid annular plane systolic excursion as a marker of RV ejection fraction has been shown to be an important prognostic marker in PAH. This measurement is based on the observation that the stroke volume of the RV is largely related to shortening of the longitudinal axis (thus drawing the tricuspid annular plane toward the cardiac apex) rather than reduction in the cavity diameter, as is the case for the LV. This measurement can be made on standard M-mode or 2-dimensional echocardiography and is therefore widely available (Figure 5). Aside from predicting survival (which was poor for a tricuspid annular plane systolic excursion value <1.8 cm), this simple measurement accurately reflects RV remodeling, RV-LV disproportionate (RV/LV diastolic area), and load (PVR). Thus, given the wide availability of M-mode and dimensional echocardiography, tricuspid annular plane systolic excursion may prove to be the most useful marker of RV function and structure (eg, remodeling) that is available to the broadest population of practitioners. Finally, 3D echocardiography might provide better insight into RV and LV dimension and function by obviating geometric assumptions (Figure 6).

In the future, greater attention may be paid to RV diastolic function. This can be assessed in much the same way as the LV with E/A and E'/A' analysis. Moreover, diastolic forward flow in the RV outflow tract may serve as a marker of RV diastolic function. More recently, the improvement of PAH therapy on RV diastolic function has been noted.

**Pulsed Doppler**

Pulsed Doppler measurement of PA flow velocity in the main PA is an extremely useful qualitative and quantitative technique for measuring PAP and, unlike estimates based on tricuspid regurgitation velocity, is available in virtually all patients. In pulmonary hypertension, the peak velocity of the Doppler envelope decreases, and the time to peak velocity (measured from the onset of flow) or PA acceleration time (PAAT) shortens. In severe pulmonary hypertension, there may be “notching” or early systolic deceleration, which, like the premature partial closure of the pulmonic valve on M-mode echocardiography, represents reflection of velocity waves and cancellation by reverse flow. This is due to the noncompliant nature of the distal vascular bed in pulmonary vascular disease. The normal PA flow velocity is 81±17 cm/s and occurs with a PAAT of 121±27 seconds. A typical Doppler signal in patients with pulmonary hypertension is often triangular rather than the normal broad shield shape seen in normotensive patients, and the PAAT is shortened (Figure 5). Although there is a fair correlation between acceleration time and PA systolic pressure, Dabestani et al found a better correlation between PAAT and mean PAP, a more physiological measurement. They used a regression equation to develop the following formula predictive of mean PAP: mean PAP=79 to 0.45×PAAT. This relationship has been confirmed, albeit with modified regression formulas.

This technique is somewhat dependent on heart rate but correlates well with mean PAP in patients with heart rates between 60 and 100 bpm.

In summary, echocardiography can provide anatomic and functional assessments of both the RV and the pulmonary circulation. Therefore, it is a powerful tool in the assessment of the RV-PA unit, particularly in that novel applications like 3D echocardiography, tricuspid annular plane systolic excursion, and PAAT are used more frequently and are validated in large cohorts and clinical trials.

**Cardiac MR**

MRI and MR angiography (MRA) are techniques that can, noninvasively and in a single setting, study the RV-PA unit and provide multiple data ranging from structure (RV volume, mass, pulmonary angiography) to function (RV function, pulmonary blood flow [PBF]/perfusion) to molecular imaging. All of the described studies can be performed in standard clinical 1.5-T magnets and can be completed without or with a small amount of gadolinium contrast injected through a peripheral vein. More important, they can be completed within a short period of time (ie, <1 hour), providing a comprehensive assessment in a “single-stop shop” manner.

**Standard MRI Approaches**

**RV Mass and Volume**

There have been major advances in MRI techniques in the last several years with ECG gating and respiratory suppression, diminishing imaging artifacts and allowing computations of RV volumes. The complex 3D structure of the RV can be directly studied with MRI to measure RV volume and mass without the need for computational assumptions; values for RV mass and volume in normal cohorts also have been reported. Conventional (gradient-recalled echocardiography) or newer (steady-state free precession pulse) sequences can be used to create cine images of a complete cardiac cycle. In stacks of contiguous 5- to 10-mm slices, endocardial and epicardial contours can be drawn in end systole and end diastole (Figure 7). The sum of the individual slice volumes will give the end-systolic (RVESD) and end-diastolic (RVEDV) volumes, from which RV ejection fraction (RVEF) can be calculated: RVEF=((RVEDV−RVESV))/RVEDV. RV mass can be calculated by multiplying RV volume by the myocardium specific gravity (1.05 g/cm³). The anatomy of the RV is more complex than the LV, and moderator bands can vary in presence and size; some might include them in the tracing of the RV endocardial contour, whereas others might not. This results in somewhat lower interstudy reproducibility in the RV compared with the LV.
but this is overall very high and definitely better than echocardiography, making MRI the gold standard for the study of RV size and function. The published data for interstudy reproducibility in MRI-studied RV size can be useful in calculations of sample sizes in clinical trials. Although the RV ejection fraction and calculation of stroke volumes can be complicated by the presence of significant tricuspid regurgitation (similar to mitral regurgitation and the LV), the calculation of RV volumes is direct and not affected by other factors.

RV hypertrophy is mostly an adaptive or compensated state in response to the increased RV afterload (Figure 1). During that stage, RV mass correlates well with PAP. Beyond that stage, RV enlargement is associated with a decrease in RV contractility, further decreases in cardiac output, worsening right heart failure, and death. Therefore, it is not surprising that in a prospective study of 64 PAH patients followed up for 32 months, RV volume at diagnosis was a strong predictor of mortality, stronger than RV mass. Further RV dilatation at follow-up was an even stronger predictor of survival.

Studies are now reporting RV mass changes in response to PAH therapies, showing feasibility in including RV mass/volume as end points in clinical trials. For example, in a small study, RV mass decreased in response to sildenafil therapy. In another blinded randomized study, RV mass decreased in response to sildenafil but not in response to bosentan therapy, despite similar decreases in the PAPs. The inclusion of RV mass in this last study suggested the potential for direct effects of sildenafil on the RV, a possibility that

Figure 7. MRI and the RV-PA unit. Top left, Standard MRI techniques can be used to trace the endocardium and epicardium of the RV and to calculate RV volumes in systole and diastole, as well as RV mass, as discussed in text. Top right, Iron tagging of cells used in cell-based therapies can be used to track the homing of these cells in both the pulmonary circulation and the RV. In this example from Hill et al, the homing of mesenchymal cells in an infarct area of the LV is shown. Used with permission. Copyright © 2003 Lippincott Williams & Wilkins). Bottom left, Gadolinium injection in a peripheral vein shows a much worse obliterative remodeling, resulting in less opacified vessels, in a patient with a severe compared with moderate PAH, correlating with invasively measured mean PAPs (mPAP). Bottom right, On the left, Ohno and colleagues show mean PBF measured, after a small gadolinium infusion, in a healthy subject vs a patient with severe IPAH, showing the quantitative nature of this technique (see text). Used with permission. Copyright © 2007 American Roentgen Ray Society. On the right, a similar technique developed at the University of Alberta (see text) showed that the decrease in PBF in a patient with IPAH after 50 mg sildenafil PO was similar to the ~35% decrease in PVR measured during catheterization. These data suggest that such techniques can be used to generate quantitative end points in clinical trials in the future.
could not have been predicted by hemodynamic values alone. This possibility was later confirmed by studies showing a significant increase in phosphodiesterase type 5 expression (the target enzyme of sildenafil) in the hypertrophied (but not the normal) RV myocardium.4

In summary, RV mass and volumes can be easily acquired, do not require sophisticated software or specific operator skills, and can provide valuable quantitative data. Captured in large databases, such data could easily be validated in larger cohorts and finally included as primary end points in large multicenter clinical trials.

Pulmonary Angiography

The loss of perfusion in the distal PAs, resulting from proximal oblitative remodeling and microvessel loss, is recognized both in animal studies and in human PAH, as reflected by the classic sign of pulmonary vascular “pruning” in pulmonary angiography. Loss of peripheral vascularity and branching pattern in the pulmonary vascular tree provides a direct visual assessment of the degree of vascular remodeling, and its regression may reflect response to experimental therapies. Through MRA, a detailed 3D pulmonary angiogram can be obtained with injection of gadolinium in a peripheral vein (Figure 7). Although the quantification of remodeling by angiography has to be developed and validated in the assessment of PAH, MRA can offer additional and clinically relevant information. For example, it can easily detect filling defects that would suggest pulmonary thrombi. Because exclusion of thrombi is an essential part of the workup in PAH and usually requires a CT scan with contrast and a V/Q scan, MRA performed as part of a comprehensive study in a single setting might be an efficient and potentially cheaper alternative.

Novel Uses of MRI in Pulmonary Hypertension

Pulmonary Vascular Perfusion

Early studies using the phase-contrast technique and velocity-encoded MRI showed the feasibility of estimating right-side hemodynamics,100-101 but the ease of Doppler echocardiography has limited the enthusiasm of proceeding with large-scale validation studies. Furthermore, these parameters are dependent on many factors beyond the pulmonary microcirculation; eg, pulmonary flow increases in anemia or in liver failure, resulting in increased systolic PAPs without a true increase in PVR. In addition, because RV function deteriorates and is dependent on many factors beyond the pulmonary microcirculation; eg, pulmonary flow increases in anemia or in liver failure, resulting in increased systolic PAPs without a true increase in PVR. In addition, because RV function deteriorates and is unable to support forward flow, the PAP might drop, giving a false sense of improvement. Thus, the measurement of PAP is not necessarily a sensitive index of the condition of the pulmonary vasculature. The high capacitance of the pulmonary circulation results in a rise in PAP only after a very large percentage of the pulmonary vasculature has been compromised. It is surprising that despite the progress in the imaging of tissue perfusion in organs like the heart and brain, there are currently no widely used clinical tests for pulmonary tissue perfusion. This is unfortunate because whether there is microvessel loss early in the disease or proliferative oblitative remodeling in more proximal vessels later on in the development of PAH,102,103 there is loss of blood flow and tissue perfusion. The aim of all current and future therapies for PAH is to increase tissue perfusion, whether by regenerative approaches early or by antiremodeling strategies later.1,102 There is indeed a great need for methods that can assess the pulmonary circulation directly and quantitatively.

Recent advances in MRA have made it possible to calculate regional quantitative perfusion parameters in the lung on the basis of 3D contrast-enhanced dynamic MR perfusion and principles of the indicator dilution theory.104-108 After validation in animal models, these techniques have now been applied in humans108,109 (Figure 7). Using standard 1.5-T machines, pulses, and a single gadolinium injection as low as 2 to 5 cm3,93 we can directly measure PBF in different regions of the lung. In a recent study measuring PBF with this technique in normal volunteers and patients with IPAH who underwent both MRA and cardiac catheterization, the PBF in the 2 groups differed significantly (129.6±14.6 versus 70.9±10 mL · 100 mL·min⁻¹, respectively; n=14 per group; P<0.0001).110 Moreover, PBF had a strong negative correlation with PVR and moderate negative correlation with mean PAP, as would be expected.93

In Figure 7, regional quantitative pulmonary perfusion is shown in a healthy man. The mean PBF in the slice shown was 126 mL · 100 mL·min⁻¹. In contrast, in a patient with IPAH, there is a significant decrease in the mean PBF to 44 mL · 100 mL·min⁻¹ (Figure 7). In another example shown in Figure 7, a patient with IPAH was studied at the University of Alberta with a similar technique, and the increase in PBF after a single dose of 50 mg sildenafil given orally is shown. Although the contrast agent arterial input function measured in the RV is similar before and after, reflecting consistent venous injections between studies, the contrast delivery in a specific region of the lung increased significantly after sildenafil, reflecting increased tissue perfusion. Such an increase also can be expressed as the area under the curve, as shown, and can be used to track the progress of this patient with time. The same patient showed a similar increase in PVR with sildenafil during catheterization. In the example shown, the images were obtained without a breath hold using respiratory variation suppression protocols, which is a significant advantage because patients with severe PAH often have difficulties with breath holding (Figure 7; courtesy of Drs I. Patterson and R. Thompson, University of Alberta). It is obvious that such a direct and quantitative measurement would be very desirable in the clinical assessment of PAH patients in response to therapies and would be a valuable end point in clinical trials with regenerative and antiremodeling therapies.

Such techniques have potential limitations because many assumptions are made in the equations and modeling of the indicator dilution theory. For example, the blood volume is not equal to the distribution volume of gadolinium because the latter extravasates into the interstitium and lung permeability may vary. It is important to emphasize that the value of measuring PBF with MRA does not lie in measuring the true PBF but rather assessing the “change” in the signal that occurs with disease progression or in response to therapy.

RV-PA Interactions

The more complex hemodynamic studies discussed earlier on RV contractility and RV-PA coupling can also be performed...
with MRI, as early evidence indicates. RV contractility can be studied using several parameters, including MRI-derived PV loops. Large PA stiffness can also be studied with MRI, as can RV diastolic dysfunction, a potentially early finding in PAH.

**Molecular Imaging**

Systemically delivered proapoptotic or regenerative cell-based therapies can obviously affect the RV and the pulmonary circulation. Tracking the molecular response in both the PAs and the RV will be important for the assessment of such experimental therapies. Apoptosis imaging is used in oncology to assess the early and late effects of proapoptotic chemotherapies in tumors. A large number of emerging therapies in PAH are proapoptotic, but induction of apoptosis in the myocardium can be detrimental. For example, the antcancer agent imatinib, which has shown promise as an antiremodeling agent in PAH, might cause apoptosis in the heart, perhaps explaining its documented myocardial toxicity. In vivo induction of apoptosis can be tracked, localized, and quantified with annexin V imaging. Annexin V is expressed on the cellular surface of cells undergoing early apoptosis, and binding of annexin to superparamagnetic iron particles allows MRI-based detection of apoptosis in vivo. Therefore, a single study can assess the effects on both the PA and the RV. Furthermore, iron-tagged cells can be tracked and their homing and retention quantified, as illustrated by the presence of mesenchymal stem cells in an ischemic LV.

**PET Imaging**

Among the many functions that can be imaged with PET imaging is glucose uptake. Increased glucose uptake is usually associated with a glycolytic phenotype. A switch from the mitochondria-based glucose oxidation to the cytoplasm-based glycolysis, even in the absence of hypoxia, is recognized in many disease states characterized by increased proliferation and suppressed apoptosis. This is well described in cancer and has been suggested more recently in PAH vascular remodeling. In addition, a switch to glycolysis (from fatty acid oxidation) characterizes cardiac hypertrophy; the hypertrophied RV myocardial cells have hyperpolarized mitochondria (compared with the normal RV cardiomyocytes), similar to the hyperpolarized mitochondria of cancer cells. Similarly, PA smooth muscle cells have hyperpolarized mitochondria compared with normal PA smooth muscle cells. In that sense, glycolysis (and thus increased glucose uptake) characterizes both the pulmonary circulation (proliferating PA smooth muscle cells and PA endothelial cells) and RV hypertrophy in PAH (for further discussion, see Reference 1, another article in this series). It is thus possible that the degree of glucose uptake (measured by the standardized uptake value of 18F-fluorodeoxy-glucose [FDG] with PET) might correlate

![Figure 8. PET and the RV-PA unit. Standard FDG-PET imaging can be used to measure RV and pulmonary microcirculation metabolism. (Top left) Increased RV FDG glucose uptake (y axis) correlates with mean PAP in a cohort of patients with IPAH (see text). More important, Oikawa and colleagues have shown that effective therapy with Flolan results in a decrease in RV FDG uptake, compatible with a decrease in RV glycolysis, indicating an improvement in RV performance (top right). Reprinted with permission. (© 2005 Elsevier. Because RV ejection fraction measurement can be limited by a number of parameters, including tricuspid regurgitation, RV metabolism might prove to be a more sensitive way to follow RV function in PAH patients. Bottom, At the same time as RV imaging, FDG uptake can be followed in the pulmonary microcirculation, where an increase in FDG uptake (resulting from an increase in glycolysis) is associated with a proliferative and antiapoptotic state (see text). In this small cohort of PAH patients and normal control subjects, Xu et al show that FDG uptake in the lung parenchyma is much higher in the PAH patients vs normal subjects. Reprinted with permission. Copyright © 2007 National Academy of Sciences USA.)](circ.ahajournals.org)
with both the degree of vascular remodeling and RV function in PAH and in response to therapy in a manner similar to cancer.\textsuperscript{124} Preliminary data in animals and more recently in humans support this possibility. In 24 patients with PAH, FDG-PET showed increased glucose uptake in the RV free wall corrected for the increase in myocardial volume; the standardized uptake value correlated to mean PAP, PVR, and right atrial pressure (Figure 8).\textsuperscript{125} More important, after 3 months of therapy with epoprostenol, the standardized uptake value decreased significantly in the responders but not in nonresponders (Figure 8, top right).\textsuperscript{125} In another cohort of 4 PAH patients versus 3 healthy control subjects, FDG-PET showed an increase in the glucose uptake in the lung tissue (a highly vascular tissue reflecting metabolism in the pulmonary microvessels) normalized for lung tissue density\textsuperscript{119} (Figure 8, bottom).

Thus, imaging of both the RV and the lungs in the same noninvasive setting and in a quantitative manner such as with MRI and echocardiography might be useful in the study of the RV-PA unit, particularly in response to therapy. If validated in larger cohorts, FDG-PET–measured glucose uptake might be considered an end point in PAH clinical trials. Furthermore, similar to MRI, the new hybrid PET–64-slice CT systems might allow simultaneous acquisition of functional (PET) and high-fidelity anatomic (CT) data in both the RV and pulmonary vessels.

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**Disclosures**

None.

**References**

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