Recent Advances in Pulmonary Hypertension

Noninvasive Imaging in the Assessment of the Cardiopulmonary Vascular Unit

Anton Vonk Noordegraaf, MD, PhD; Francois Haddad, MD; Harm J. Bogaard, MD, PhD; Paul M. Hassoun, MD

Noninvasive imaging plays a key role in both the diagnosis and management of patients with pulmonary hypertension (PH). In recent years, there have been 2 major changes in perspective of imaging in PH. The first was the realization that imaging should focus on the evaluation of not only the pulmonary pressures but also the cardiopulmonary unit (Figure 1). The second was the emergence of multimodality imaging with a complementary role for echocardiography, magnetic resonance (MRI), computed tomography, and positron emission tomography (PET). These techniques not only help in the diagnosis of PH but also help identify factors that determine risk and prognosis and gauge therapeutic effects on right ventricular (RV) function in patients with pulmonary arterial hypertension (PAH). Although echocardiography is the mainstay in the assessment of hemodynamic and ventricular function in PH, MRI has emerged as the gold standard for quantifying volumes, function, and flow in the right side of the heart. PET is also offering novel insights into perfusion and blood flow, metabolism, neurohormonal activation, and other molecular processes in the right side of the heart but is used mainly for research at this time. Catheterization of the right side of the heart remains the gold standard for defining PH and assessing hemodynamics both at rest and with exercise. Invasive assessment of cardiac output (CO) may, however, have limited accuracy when assumed instead of measured oxygen consumption is used to derive CO (eg, using the Fick method) or when thermodilution is used in the setting of a low-CO state.

This review covers RV imaging studies performed in the field of PH and discusses recent advances in echocardiography and cardiac MRI and PET imaging for detailed assessment of RV function. The review starts with a discussion of important physiological considerations and unmet needs in imaging research of the right side of the heart in PH. Computed tomography angiography, which plays an important role in evaluating chronic thromboembolic PH, is not discussed extensively in this review.

Physiological Considerations

Although PH is a syndrome affecting the pulmonary vasculature, survival of patients with PH is closely related to RV function. The RV initially adapts to the increased afterload by increasing its wall thickness and contractility. These mechanisms are, however, often insufficient, and RV dysfunction eventually occurs. After the recent Fifth World Symposium on Pulmonary Hypertension, a definition of failure of the right side of the heart secondary to PH was adopted: “Right heart failure in the setting of PH can be defined as a complex clinical syndrome due to a suboptimal delivery of blood or elevated systemic venous pressure at rest or exercise as a consequence of elevated RV afterload.” The proposed definition takes into account both the systolic and diastolic characteristics of function of the right side of the heart, as well as physiological demands such as exercise.

In understanding RV adaptation to PH, one important metric that takes into account both contractility and afterload is ventriculo-arterial coupling. When in PH the increased pulmonary vascular afterload is matched by an adaptive increase in RV contractility, the RV is said to be coupled to the pulmonary arterial circulation. Altered ventriculo-arterial coupling occurs with increasing afterload, with some patients showing a better compensation or adaptability than others. Most of the metrics of RV function used in clinical practice today are a reflection of ventriculo-arterial coupling rather than contractility (load-independent measure). In fact, although contractility is increased in patients with PH, RV ejection fraction (RVEF), RV strain, or tricuspid plane annular excursion is often decreased. In addition, a recent study has also highlighted the importance of serial assessment of function of the right side of the heart in PAH, with patients with stable ventricular function showing good long-term outcomes. In comparisons of RV and left ventricular (LV) adaptation to pressure overload, one important distinction is the fact that the right side of the heart dilates early and that eccentric hypertrophy is, by far, the most common RV geometry. In the left side of the heart, both concentric hypertrophy and eccentric hypertrophy occur in response to systemic hypertension, and myocardial fibrosis is more common. Finally, although the focus is often placed on the RV, ongoing studies will determine whether right atrial function adds independent prognostic information in PH or failure of the right side of the heart.
Unmet Needs in Noninvasive Imaging of the Cardiopulmonary Unit in PH

Although imaging of the cardiopulmonary unit is a routine part of clinical evaluation, several unmet needs in the field remain (summarized in Table 1), which span from defining normal scaled reference values, to refining the definition of exercise-induced PH (EIPH), to developing integrative diagnostic and prognostic scores, to determining the best surrogate end point for research, and to developing novel physiological management strategies in PH. We anticipate that several of these questions will be answered within the next 5 to 10 years.

Echocardiography

Overview of Echocardiographic Evaluation

Transthoracic echocardiography is the mainstay in the assessment patients with PH. Basic assessment of the cardiopulmonary unit by echocardiography involves assessment of cardiac chamber size; metrics of RV function such as tricuspid annular plane systolic excursion, fractional area change, and myocardial performance indexes; valvular regurgitation or function; pulmonary hemodynamics; and septal curvature, which can integrate metrics on ventricular interdependence. Table 2 summarizes normative values for the measures of function of the right side of the heart, and Figure 2 illustrates some of these measures. As discussed in the following paragraphs, myocardial deformation imaging is also emerging as a useful modality for imaging the right side of the heart.

Several pearls are important in evaluating the cardiopulmonary unit by echocardiography. The most important pearl in evaluating patients with PH is that the focus of the study should not be limited to evaluation of RV systolic pressures (RVSPs) but rather should include evaluation of both systolic and diastolic function. Three-dimensional imaging, including a 3-dimensional print model, may also guide patient-tailored interventional therapy.

Table 1. Selected Unmet Needs in the Assessment of the Right Side of the Heart

<table>
<thead>
<tr>
<th>Field</th>
<th>Unmet Research Need in Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference values</td>
<td>To establish normal scaled values for chambers of the right side of the heart in echocardiography (adjusted for age, sex, level of activity)</td>
</tr>
<tr>
<td>Physiological indexes</td>
<td>To establish the best index of contractility, to determine physiological bases of deformation indexes, to determine and standardize methods to assess myocardial deformation, to develop better indexes to assess the septal contribution of the function of the right side of the heart, and to better determine the role of atrial function in patients with right heart disease.</td>
</tr>
<tr>
<td>Screening</td>
<td>To develop novel imaging scores for screening patients at risk of PH that may incorporate strain imaging parameters, to develop and validate scores to identify patients with increased PVR in disease of the left side of the heart, and to standardize exercise or stress testing for screening of PH screening purposes</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>To determine the best imaging correlate(s) for fibrosis of the right side of the heart and to refine molecular imaging of the right heart. This would be useful to predict recovery and arrhythmia potential in disease of the right side of the heart. Multimodality imaging will help in the search of genetic and epigenic factors modulating RV adaptation in PH by identifying better-defined phenotypes.</td>
</tr>
<tr>
<td>Prognosis</td>
<td>To validate simple and reproducible imaging-based prediction scores in PAH. This will provide a better perspective of the complementary value of novel circulating biomarkers and will be useful for randomization or propensity matching.</td>
</tr>
<tr>
<td>Physiological based therapeutic management</td>
<td>To determine how a physiology-based approach that incorporates metabolism, fibrosis, and ventriculo-arterial coupling can help tailor the management of acute and chronic failure of the right side of the heart. Specifically for surgical planning for end-stage PAH, determine whether strain imaging or markers of fibrosis can help identify which patients would benefit from heart-lung or double-lung transplantation. Three-dimensional imaging, including a 3-dimensional print model, may also guide patient-tailored interventional therapy.</td>
</tr>
<tr>
<td>Surrogate end points</td>
<td>To determine whether function of the right side of the heart would be a better surrogate end point for phase 2 clinical trials than hemodynamic measures</td>
</tr>
</tbody>
</table>

PAH indicates pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; and RV, right ventricular.
and diastolic parameters of the right side of the heart. This is especially important because prognosis in PH is strongly related to function of the right side of the heart; moreover, pulmonary pressures may decrease when function of the right side of the heart deteriorates and can thus be deceiving in the estimation of severity. A second pearl is that not all cases of increased right-sided systolic pressures are caused by PH; for example, pulmonary stenosis or a double-chambered RV can cause elevation of RVSP in the absence of PH. A third and associated pearl is that the cause of an increased RVSP does not necessarily lie within the pulmonary circulation per se. Rather, in many patients, the increase in RVSP relates to increased pulmonary venous pressure. Findings such as LV hypertrophy and increased left atrial size represent common and practical clues that strongly sway the diagnosis of PH toward pulmonary venous hypertension. A forth pearl in the assessment of PH is that, in the presence of severe hypertension or severe PA enlargement, a congenital cause of PH should be excluded and strong consideration for MRI should be given. Finally, in the presence of hypoxemia, evaluation of a right-to-left shunt through a patent foramen ovale should always be considered in the differential.

The following sections highlight recent controversies with regard to the noninvasive evaluation of pulmonary hemodynamics, the renewed interest in the use of exercise stress testing in the evaluation of PH, the use of scores to differentiate patients with PH and increased pulmonary vascular resistance (PVR) from patients with normal PVR, and the growing interest in the field of myocardial deformation imaging.

Controversies in Screening Patients for PH

There has been controversy recently about whether echocardiography is a useful screening method or is accurate for the evaluation of PH. Although earlier studies demonstrated an excellent correlation between echocardiographic estimates and pulmonary pressures measured invasively, the strength of this correlation has been challenged in recent studies. For example, in the landmark clinical study by Yock and Popp, there was an excellent association between Doppler values and pulmonary pressures measured invasively, the strength of this correlation has been challenged in recent studies.20,32–37

Table 2. Selected Useful Functional Metrics for the Right Ventricular–Pulmonary Arterial Unit Obtained By Echocardiography

<table>
<thead>
<tr>
<th>Metric</th>
<th>References</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic phase indexes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVEF &gt;50%</td>
<td></td>
<td>&lt;35% often considered as moderate RV systolic dysfunction</td>
</tr>
<tr>
<td>RVFAC &gt;35%</td>
<td></td>
<td>Less than 25% denotes moderate RV systolic dysfunction</td>
</tr>
<tr>
<td>TAPSE &gt;18 mm</td>
<td></td>
<td>Abnormal value suggested in ASE guideline &lt;16 mm</td>
</tr>
<tr>
<td>RVMPI–pulsed tissue &lt;0.55</td>
<td></td>
<td>Nongeometric index of global systolic and diastolic function. Pseudonormalized values have been reported in patients with severe RV dysfunction</td>
</tr>
<tr>
<td>Deformation indexes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global long. strain &lt;−25%</td>
<td></td>
<td>Severe often if &gt;−15% by speckle tracking. RV values need to be better defined for clinical practice; average normal value around −2/s (longitudinal)</td>
</tr>
<tr>
<td>Peak systolic SR ...</td>
<td></td>
<td>III defined</td>
</tr>
<tr>
<td>Peak diastolic SR ...</td>
<td></td>
<td>III defined</td>
</tr>
<tr>
<td>Velocity metrics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>...</td>
<td>Depends on methodology; usually &gt;2 m/s² (considered less load dependent)</td>
</tr>
<tr>
<td>S velocity &gt;12 cm/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic metrics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVRT (TDI) corrected &lt;65 ms</td>
<td></td>
<td>IVRT divided by square root of RR interval</td>
</tr>
<tr>
<td>HV systolic VTI &gt;55%</td>
<td></td>
<td>sHV VT/(sHV VT+dHV VT) &lt;55% predicts RAP&gt;8 mm Hg</td>
</tr>
<tr>
<td>Pulmonary flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary AT &gt;93 ms</td>
<td></td>
<td>Has been shown useful to screen for PH</td>
</tr>
</tbody>
</table>

Adapted from several references.22,24–26 ASE indicates American Society of Echocardiography; AT, acceleration time; d, diastolic; HV, hepatic vein; HVF, hepatic vein flow; IVA, myocardial acceleration during isovolumic contraction; IVRT, isovolumic relaxation time; long, longitudinal; PH, pulmonary hypertension; RAP, right atrial pressure; RV, right ventricular; RVEF, right ventricular ejection fraction; RVFAC, right ventricular fractional area change; RVMPI, right ventricular myocardial performance index; s, systolic; S velocity, tissue Doppler systolic velocity; SR, strain rate; TAPSE, tricuspid annular systolic excursion; TDI, tissue Doppler imaging; and VTI velocity-time integral.
strain or strain-rate index (Table 3).\textsuperscript{21,38–41} Moreover, in future studies, screening algorithms should be tested in patients with very mild pulmonary vascular disease to identify the most reliable early markers of pulmonary vascular disease and dysfunction of the right side of the heart.

Differentiating Patients With Increased PVR

Another important interest in the evaluation of PH has been differentiating patients with normal from those with increased PVR. Two different approaches have been described in the literature. The first uses multiple approximation formulas that estimate pulmonary capillary wedge pressure and CO, and the other uses a score that focuses on key differentiating features.\textsuperscript{18,19} The first approach has the advantage of being simpler but is limited by the cumulative effects of several measuring errors. The second approach has the advantage of taking into account remodeling, hemodynamics, and epidemiological features but does not lead to quantification of PVR. In a recent study, Opotowsky et al\textsuperscript{44} developed a simple score based on left atrial size, the ratio of E to e’, and acceleration time or the presence of a pulmonary notch to discriminate patients with increased PVR. Of note, patients with left-sided heart failure without increased PVR are often much older with more comorbidities, as was shown by Thenappan et al.\textsuperscript{45} Validation of these scores by several research groups is currently underway.

EIPH and Dynamic Testing in PH

In recent years, there have been several key studies on exercise testing in patients with PH. The renewed interest in exercise in PH is based on the premise that, although patients may have normal pulmonary pressures at rest, any increase in these pressures with exercise would be significantly higher than in healthy control subjects. Previously, EIPH was defined as a mean pulmonary arterial pressure (mPAP) >30 mm Hg with exercise; however, this definition was abandoned because it does not take into account changes in CO. On the basis of both invasive and noninvasive data, several investigators have now shown that the mPAP-CO relationship can be approximated by a linear relationship.\textsuperscript{46–49} This is unlike the systemic circulation in which several slopes are needed to describe the systemic pressure–CO relationship. In control subjects, the slope of the mPAP-CO relationship is usually <1.5 to
2.5 mmHg-minL⁻¹, with older healthy individuals having higher average slope values. Although no consensus has yet been reached on the definition of EIPH, an mPAP-CO slope >3 mmHg-minL⁻¹ or an mPAP >30 mmHg at a CO of 10 L/min (approximation because the slope does not perfectly intersect the zero origin) could be considered a potential criterion. Patients with higher-than-normal mPAP deserve a clinical evaluation to exclude the 2 major causes of EIPH: conditions of the left side of the heart (eg, dynamic mitral insufficiency) or increased PVR (eg, PAH or late closure of an atrial septal defect).

There are several noteworthy studies in the literature; here, we chose to highlight three recent studies. Grünig et al²⁶ showed in a large multicenter study that relatives of patients with PAH had a significantly higher pulmonary hypertensive response with exercise compared with control subjects and that this was higher in patients with BMPR2 mutations. In their study, PH was defined by a tricuspid regurgitation velocity jet >3.08 cm/s based on a 90% value of control subjects. This study was followed by the study by D’Alto et al,⁵² which showed that patients with New York Heart Association class I or II scleroderma without evidence of PH at rest had a greater incidence of EIPH, defined as the upper limits of control subjects (13%). Furthermore, they demonstrated that the slope of change in the relationship between PASP and cardiac index was significantly greater than normal. In the field of degenerative mitral regurgitation, Magne et al²³ also recently showed that EIPH, defined as an RVSP >60 mm Hg with exercise, better discriminates patients who progress to symptomatic disease compared with rest RVSP. Although these results are very promising, some challenges remain as we move forward such as proving the feasibility and reproducibility of these tests in clinical practice and standardizing the pulmonary pressure–CO or pulmonary pressure–cardiac index slope criteria. In addition, demonstrating a potential value when added to a multiparameter screening approach would be an important step at this time.

Further insight into RV function during (endurance) exercise was provided by a recent study by La Gerche et al.⁵⁴ Whether it was due to EIPH or prolonged volume loading, the authors showed that, immediately after an endurance race, RV volumes increase and functional measures (ie, tricuspid plane annular excursion and RVEF) decrease, whereas LV volumes decrease and LV function remains unaltered. Reflective of a degree of cardiac injury during endurance exercise, B-type natriuretic peptide and tropinin levels increased after a race and correlated with reductions in RVEF. Although RV function mostly recovered by 1 week after the race, evidence of localized fibrosis was demonstrated in the interventricular septum of 5 of 39 athletes who had greater cumulative exercise exposure and lower RVEF than those with normal cardiovascular magnetic resonance. The long-term clinical significance of these findings requires further study but may include the generation of arrhythmias.

### Myocardial Deformation Imaging of the RV: Holy Grail or Flavor du Jour

In a recent editorial, Reichek⁵⁵ noted that there have been several hundred publications on RV myocardial imaging over the past few years. Considering this impressive body of literature, an obvious question is, How does myocardial deformation imaging affect screening or prediction of outcome in patients with PH? As shown in Figure 3A, there are 4 essential components of myocardial imaging: velocities, displacement, strain (normalized deformation), and strain rate.⁴²,⁵⁷ Either spatial or temporal integration or derivation links the different concepts together. Methodologically, imaging can be accomplished with either tissue Doppler imaging or speckle tracking. Tissue Doppler imaging appears to be ideal for determining velocity profiles (Figure 3B), whereas speckle tracking imaging may be superior for strain and strain-rate imaging. In addition, global strain of the ventricle can be assessed by manually measuring 2-dimensional changes in entire wall segments. The measures that have captured more attention include global RV strain, peak systolic strain rate, and early diastolic strain rate (Figure 3C and 3D). Analysis of right strain or strain rate involves a comparison of peak values, timing of deformation, or comparative left values. Although very interesting conceptually, the technology used to derive these measures makes several assumptions; thus, quality control cannot be overemphasized in the interpretation of the results.⁵⁸,⁵⁹ Ongoing studies will determine the best methodology to use for strain measurements.

For screening purposes, Kittipovanonth et al⁴⁰ have shown that, in patients with early PH (n=30), both RV peak strain and strain rate were significantly lower than in control subjects (n=40), whereas there were no significant differences in RV dimension, tricuspid plane annular excursion, RV fractional area change, or RV myocardial performance indexes. In an earlier study by Rajdev et al,⁴¹ RV free wall strain was significantly lower than in control subjects, whereas there were no difference in strain rate measures.

### Table 3. Useful Parameters and Formulas for PH Screening by Echocardiography

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Indexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of pulmonary pressures by Doppler echocardiography (gradients)</td>
<td>RVSP=4×TRV²+RAP</td>
</tr>
<tr>
<td></td>
<td>MPAP=4×peak PRV⁴</td>
</tr>
<tr>
<td></td>
<td>DPAP=4×PRVED+RAP</td>
</tr>
<tr>
<td></td>
<td>MPAP=2 mm Hg+0.59 RVSP</td>
</tr>
<tr>
<td>Estimation using pulmonary flow</td>
<td>MPAP=79–0.45(AT)</td>
</tr>
<tr>
<td>Septal curvature</td>
<td>Systolic septal flattening reflects anatomic, hemodynamic, electric ventricular interdependence</td>
</tr>
<tr>
<td>Supporting evidence</td>
<td>RV enlargement; ↑ RV IVRT; ↑ RAP</td>
</tr>
<tr>
<td>Exercise-induced PH</td>
<td>Emerging field but signal acquisition may be difficult</td>
</tr>
<tr>
<td>Investigational</td>
<td>Ongoing studies on RV strain and strain-rate imaging</td>
</tr>
</tbody>
</table>

AT indicates acceleration time; DPAP, diastolic pulmonary artery pressure; IVRT, isovolumic relaxation time; MPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; PRV, pulmonary regurgitation velocity; PRVED, pulmonary regurgitation end-diastolic velocity; RAP, right atrial pressure; RV, right ventricular. RVSP, right ventricular systolic pressure; and TRV, tricuspid regurgitation velocity. Adapted from several references.⁴³,⁴⁶,⁵⁰,⁵¹,⁵²
Future studies are needed to determine the sequence of change in deformation imaging in patients with early pulmonary vascular disease.

Fine et al. recently published the largest study investigating the value of strain imaging in PH (n=406 patients with PH) for outcome prediction. They demonstrated that peak longitudinal free wall strain was independently associated with outcome, along with log N-terminal brain natriuretic peptide levels and World Health Organization functional class. Several key messages emerge from their study. First, outcome prediction in PAH can probably be simplified by the use of quantitative indexes of RV function. Second, strain measurement could offer a simpler metric in the echocardiographic evaluation of the RV. One of the merits of their study is the inclusion of all the usual 2-dimensional and time indexes of RV function. An important implication of this study is that this could help improve randomization between studies and potentially help tailor therapy in intermediate-risk groups. Table 4 places the study of Fine et al in context with recent outcome studies in PAH.

Physiologically, however, it is important to emphasize that strain or strain-rate measures are not load-independent metrics of function of the right side of the heart and that further experimental validation is needed. In the future, the study of strain-based contractility indexes may also help improve prediction. Several laboratories are currently investigating the added value of strain/afterload ratios.

Three-Dimensional Echocardiographic Imaging of the Right Side of the Heart
Reliable 3-dimensional RV echocardiographic imaging has also been an active area of research but has not yet reached routine clinical practice. To prove the incremental value of 3-dimensional imaging for predicting outcome in PH, a very large sample size will be required. Multiplane imaging of the RV may, however, be extremely helpful in securing proper 4-chamber view alignment.

In summary, echocardiography can provide structural and functional assessment of both the RV and the proximal pulmonary circulation and is therefore a useful and powerful tool in the assessment of the RV–pulmonary vascular unit, particularly when novel applications like strain imaging, 3-dimensional echocardiography, and simple scores are used.

Cardiac MRI
Volumetric Measurements
MRI has become the gold standard to noninvasively measure RV mass, volumes, and function in a reproducible, accurate manner. The volumetric measurements by cardiac MRI

Figure 3. Myocardial deformation and velocity imaging of the right side of the heart. A, The relationship between different concepts of myocardial deformation and velocities. The concepts are related to each other through spatial and temporal integration or derivation. Adapted from Gjesdal and Edvardsen. © 2011, Gjesdal and Edvardsen. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. B, A representative tissue Doppler velocity profile of the basal right ventricular (RV) wall with the different maximal velocities, ie, systolic (s), early diastolic (e), and late diastolic (a), as well as acceleration during the isovolumic contraction period (IVC) and time measures useful to measure the tissue Doppler-derived RV myocardial performance index (RVMPI). C, Superposed speckle tracking tracing on the right ventricle with numbers representing segmental peak strain. D, The strain-time curve of the different signals. Strain rate is not represented. Tissue Doppler appears to be superior for generation of velocity profiles, whereas speckle tracking appears to provide more reliable strain and strain-rate data (still a matter of debate, however). ApL indicates apex lateral; ApS, apex septum; BIS, basal interventricular septum; BL, basal lateral; GLS, global longitudinal strain; IVA, isovolumic acceleration; IVC, isovolumic contraction; IVR, isovolumic relaxation time; MIS, mid interventricular septum; and ML, mid lateral.
Table 4. SelectedOutcome Studies Using Quantitative Echocardiographic Measures in Patients With PAH

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n*</th>
<th>Comment on the Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeo et al</td>
<td>1998</td>
<td>53</td>
<td>First study to demonstrate the prognostic value of RVMI</td>
</tr>
<tr>
<td>Raymond et al</td>
<td>2002</td>
<td>81</td>
<td>First study to suggest the potential incremental value of right atrial size in PAH</td>
</tr>
<tr>
<td>Forfia et al</td>
<td>2006</td>
<td>47</td>
<td>First study to suggest the incremental value of TAPSE in prognostic assessment of PAH</td>
</tr>
<tr>
<td>Kane et al</td>
<td>2011</td>
<td>484</td>
<td>Places into perspective the incremental value of echocardiography compared with other scores</td>
</tr>
<tr>
<td>Ernande et al</td>
<td>2012</td>
<td>142</td>
<td>Suggests the prognostic importance of isovolumic contraction velocities in patients with PAH and CTEPH</td>
</tr>
<tr>
<td>Fine et al</td>
<td>2013</td>
<td>300</td>
<td>First study to demonstrate the independent predictive value of RV strain when taking into account the different functional indexes of the right side of the heart</td>
</tr>
</tbody>
</table>

CTEPH indicates chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; RV, right ventricular; RVMI, right ventricular myocardial performance index; and TAPSE, tricuspid annular plane systolic excursion.

The number of patients in the different studies.

are particularly important for monitoring PAH patients on medical treatment. The presence of a decreased stroke volume, increased RV volumes, and a decreased LV end-diastolic volume measured at baseline is associated with a poor prognosis. A subsequent further increase in RV volumes and a decrease in stroke volume during treatment are clear signs of progressive RV failure and can be observed before failure becomes clinically manifest. This is illustrated in Figure 4, which shows a patient with progressive RV dilatation over the years together with a decrease in stroke volume, preceding clinical failure. Close monitoring of RV volumes and function offers the possibility for early therapeutic interventions, but the impact of such a strategy on patient outcomes has yet to be studied. Sex differences and age need to be considered during the interpretation of RV volumes and function, and appropriate corrections for these factors may become important in future studies.

RV Mass

According to the Laplace law (ie, wall stress equals intraluminal pressure times chamber internal radius divided by wall thickness), RV hypertrophy in response to pressure-overloaded conditions is a way to reduce RV wall stress and thus should be considered as part of the adaptive remodeling process. The RV free wall, the trabeculae, and the papillary muscles are all involved in the hypertrophic process. The prognostic value of changes in RV mass in PAH is small and seems limited to patients with scleroderma PAH. The limited clinical value of the assessment of RV mass compared with RV volumes is perhaps explained by the fact that RV hypertrophy both reflects the severity of pulmonary vascular remodeling (negative impact) and is part of the normal adaptive process to an increased load (positive response). For example, despite a similar elevation in PAP, patients with Eisenmenger syndrome have a greater amount of RV hypertrophy compared with patients with idiopathic PAH, which is associated with better RV function and survival. For this reason, the assessment of RV mass as a single parameter is not informative. Recent advances in MRI, however, allow a more in-depth study of the RV myocardium, including contractile properties, perfusion, and even molecular imaging.

RV Function and Myocardium

Global RV systolic function is preferably measured by RVEF. RVEF is accurately measured by MRI and provides important prognostic information in treatment-naïve patients and during follow-up. However, this measurement is not a parameter of intrinsic RV contractility but is affected by preload, afterload, contractility, ventricular synchrony, valvular regurgitation, and shunt fraction, all at the same time.

A method to assess the shortening of the RV myocardium in the transversal and longitudinal planes has been described by Kind et al. Changes in transversal plane movements are sensitive enough to detect early signs of progressive RV failure, but this parameter is determined by movements of the RV free wall and the septum and is highly load dependent. MRI tagging techniques are considered the reference techniques to measure the relative amount of myocardial wall deformation (segmental strain), the velocity of deformation (strain rate), and synchrony (ie, timing of mechanical activation and relaxation between wall segments). All these parameters can be determined in circumferential, longitudinal, and radial axes. In healthy subjects, there is a predominantly longitudinal rather than circumferential wall deformation, resulting in a bellows-like or peristaltic action of the RV. Normal wall deformation is generally larger at the basal and apical segments than at the midsegment. Patients with PH show an altered pattern with a globally reduced longitudinal and circumferential wall deformation. Furthermore, it has been found that regional longitudinal wall deformation can already be disturbed at the time that global RV function is still intact, implying that changes in regional measures could be sensitive parameters to detect early RV dysfunction in PAH.

Insight into the global structure of the RV myocardium by MRI can be obtained by delayed contrast enhancement imaging with gadolinium or by T1 image mapping. With the use of gadolinium contrast, it was found that delayed contrast enhancement appeared at the interventricular insertion points and might be a reflection of focal fibrosis. The extent of delayed contrast enhancement was strongly correlated with increased RV mass, volumes, and pulmonary pressures (ie, RV wall stress). However, despite being very sensitive to small areas of regional fibrosis, delayed contrast enhancement techniques are not able to depict diffuse fibrosis because the technique depends on the comparison with normal reference areas of myocardium. T1 mapping may overcome this problem by directly quantifying T1 values for each voxel in the myocardium, enabling the visualization of diffuse disease. It has been shown that T1
fusion has also been demonstrated in PAH.97 The significance of the RV septum configuration in PH remain to be determined in larger cohorts.

Assessing Myocardial Perfusion by Cardiac MRI
Myocardial perfusion reserve can be assessed by cardiac MRI after peripheral intravenous injection of an agent such as adenosine. In a study of 25 patients referred for PAH evaluation, myocardial perfusion reserve indexes (for both the RV and LV) in the PAH group were significantly lower than those in control individuals. Furthermore, RV and LV myocardial perfusion reserve indexes were inversely associated with mPAP and RV stroke work index, as well as with other measures of RV workload, systolic function, and remodeling, suggesting that reduced myocardial perfusion may contribute to poor RV performance in patients with PAH.96 Decreased coronary perfusion has also been demonstrated in PAH.97 The significance and usefulness of these findings in the assessment of RV function in PH remain to be determined in larger cohorts.

Figure 4. Cardiac magnetic resonance imaging 4-chamber (A1 and B1) and short-axis (A2 and B2) cine images obtained in a patient with pulmonary arterial hypertension over time. The course from right ventricular (RV) structural compensation to end-stage RV failure is demonstrated. This patient was diagnosed with an elevated mean pulmonary artery pressure (PAP) of 45 mm Hg and a cardiac output (CO) of 4.1 L/min. At baseline, the RV showed a concentric RV remodeling pattern with increased RV mass, a crescent RV shape, small amounts of dilatation, modest RV function (RV ejection fraction [RVEF], 39%), and preserved left ventricular (LV) function (LV ejection fraction [LVEF], 62%; A1 and A2). During 7 years of follow-up, PAP was unchanged and CO remained relatively stable. However, the RV remodeling pattern has changed (B1 and B2). RV end-diastolic volume (RVEDV) showed a progressive increase from 140 to 449 mL after 7 years of follow-up. Smaller increases in RV mass were observed. Furthermore, the RV developed a spherical shape and showed apical ballooning, whereas LV underfilling, an enlarged right atrium, tricuspid insufficiency, and pericardial effusion (white arrows) developed. In addition, RVEF and LVEF showed a progressive decline to 8% and 29%, respectively.

Molecular and Perfusion Imaging
Magnetic Resonance Spectroscopy
Magnetic resonance spectroscopy is an older technique that provides indirect information on cardiac metabolism without the need to administer a tracer. There is limited experience98 with the technique in PAH, however.109 Phosphorous magnetic resonance spectroscopy studies performed in patients with advanced LV failure have repeatedly demonstrated decreased myocardial levels of creatine and ATP and correlations between these levels and survival.99

RV Metabolic Remodeling
Different pathological states of the LV myocardium are characterized by a decreased uptake of fatty acids.100,101 A decreased uptake of fatty acids was also shown to occur in the pressure-overloaded human RV through the use of single-photon emission computed tomography, a finding that was associated with impaired RV function and a poor prognosis.102 Fatty acid uptake can also be estimated by the use of PET with 11C-palmitate tracers103; however, such studies have not yet been performed in PAH. When fatty acid uptake is reduced, glucose becomes the alternative source of energy. In RV failure (at least experimentally), ATPs are increasingly generated through glycolysis rather than through glucose oxidation.104 RV myocardial glucose uptake can be quantified by PET with 18F-2-deoxy-2-fluoro-d-glucose (18F-FDG) tracers,105 and some studies have demonstrated an increase in the ratio of RV to LV glucose uptake in PAH. However, it remains unclear whether this increased ratio is explained by an increased RV glucose uptake106–108 or a decreased LV uptake.109 Inconsistent results have been reported when it comes to the correlation between quantitative changes in glucose metabolism and changes in RV load and function.105,108–112 The differences between study results
are perhaps due to differences in patient populations, scanning protocols, and data analysis. Preclinical studies have suggested that the metabolic shift toward glycolysis may not be sustained during the progression of RV failure,113 which not only complicates the comparison of different study populations but also brings into question the usefulness of RV 18F-FDG uptake as a biomarker in PAH. Importantly, it currently remains unclear whether changes in metabolism in the RV of PAH patients can be regarded as adaptive or as indicative of pathological remodeling.

RV Oxygen Consumption and Blood Flow

With a combination of 15O-labeled tracers (15O-H2O, 15O-CO, and 15O-O2) or, more practically, with 11C-acetate tracers, PET imaging allows the estimation of RV myocardial oxygen consumption (MVO2).114,115 Resting MVO2 is significantly elevated in patients with PAH,112,116 whereas New York Heart Association class III patients show a higher MVO2 than New York Heart Association class II patients (see Figure 5). The fact that RV power output is similar in class II and III PAH patients shows that, during the course of PAH, RV efficiency is progressively reduced.112

RV Angiogenesis

Whether related to a decreased overall coronary perfusion, failure of the right side of the heart in animal models of PH is clearly associated with impairment in angiogenesis relative to the degree of hypertrophy.113,117 Major angiogenic pathways converge on signaling via vascular endothelial growth factor and integrins, and novel PET imaging strategies were developed to directly measure angiogenesis with 124CU-labeled vascular endothelial growth factor118 and 19F arginine-glycine-aspartic acid peptide (with affinity for the αβ3 integrin) tracers. Imaging of angiogenesis after myocardial infarction was feasible in rats119–121 and was applied in a patient 2 weeks after myocardial infarction.122 These techniques have yet to be used in patients with PAH.

Figure 5. Impaired right ventricular (RV) mechanical efficiency in patients with pulmonary arterial hypertension is determined primarily by increased myocardial oxygen consumption (MVO2). Light gray bars indicate New York Heart Association (NYHA) functional class II patients; and dark bars, NYHA functional class III patients. Despite differences in cardiac output (CO) and mean pulmonary artery pressure (mPAP), NYHA II and III patients show a comparable RV power output, which is the product of CO and mPAP (A). However, RV MVO2 per g myocardial tissue, as determined by positron emission tomography using H15O and 15O-O2 tracers, is significantly higher in NYHA III compared with NYHA II patients (B). As a result, RV mechanical efficiency is reduced by ≈50% in NYHA III compared with NYHA II patients (C).112

RV Neurohormonal System

Preclinical studies have provided evidence for a role of dysfunctional neurohormonal signaling in the development of RV failure in PAH.118 Several PET tracers are available to study components of the sympathetic nervous system. Presynaptic (re)uptake of norepinephrine, assessed with the use of the norepinephrine analog 11C-meta-hydroxyephedrine (HED), was shown to be impaired in patients with LV cardiomyopathies, and the impairment was associated with poor outcome. Figure 6 shows an example of 11C-HED retention in a patient with PAH before and after β-blocker treatment. Likewise, a reduced density of β-adrenoceptors, as reflected by a decreased uptake of the tracers 11C-CGP-12177 and 11C-CGP-12388, was associated with worse survival of patients with LV failure.123–125 The increased renin-angiotensin-aldosterone system activity in PAH reflects disease severity.126 PET imaging with 11C-KR31173 tracers could allow the quantification of cardiac angiotensin receptor density and may provide important pathophysiological data in patients with PAH.
RV Apoptosis
Apoptosis has been attributed with a critical role in the development of heart failure. During the process of apoptosis, the phospholipid phosphatidylserine is expressed on the outer cell membrane and serves as a signal for cell removal by macrophages. Annexin is a protein that binds to phosphatidylserine, and single-photon emission computed tomography imaging showed increased ⁹⁹Tc-labeled annexin V uptake in the failing LV and in rejected cardiac transplants. Similar results were obtained in PH animal models, but these data have not yet been confirmed in patients with PAH.

Hybrid PET-MRI
Hybrid PET-MRI allows simultaneous molecular and anatomic imaging, and its application may improve the understanding of RV failure. A major limitation of hybrid systems with MRI is that information required for attenuation correction of nuclear images is not provided. Recently, the first hybrid PET-MRI results of patients with myocardial infarction have been published and have demonstrated high image quality.

Summary and Conclusions
We predict that cardiac MRI and PET will significantly contribute to a better understanding of the pathophysiological processes that lead to the development of chronic RV failure in PAH. Imaging studies have demonstrated that, in the setting of chronic pressure overload, the RV compensates enduringly to sustain CO by an increase in wall mass, dilatation, and contractility and marked changes in the RV shape. With the passage of time, these compensatory mechanisms fail, resulting in increased wall stress and impaired global RV function. Other factors that might contribute to disturbed RV function are a reduced wall deformation and an inefficient RV contraction pattern. The resulting interventricular asynchrony is associated with leftward septum bowing, impaired LV filling, and decreased stroke volume. Furthermore, the RV becomes mechanically insufficient: More oxygen is required for a comparable power output. At the same time, RV oxygen delivery is impaired and tissue oxygenation is reduced. Alterations in myocardial metabolism have been observed in PAH, but their overall relevance and whether they represent cause or consequence of RV failure remain unclear.

With the current evidence, it can confidently be stated that RV imaging parameters measured at baseline correlate with exercise capacity and functional class and predict survival. Moreover, RV imaging parameters have been shown to respond to treatment, and changes in these parameters after treatment reflect altered exercise capacity and predict subsequent survival. What is lacking at this point, however, is the demonstration of reliable monitoring and improved overall clinical outcome when a treatment strategy based on specific imaging parameters is used.

In the near future, it can be expected that the importance of changes in cellular functions and signaling pathways will become clearer and the changes will be “imageable.” This might allow a regional and quantifiable analysis of processes such as angiogenesis, apoptosis, and neurohormonal factors. Table 5 provides an overview of currently available clinical imaging tracers that could be relevant for the assessment of molecular processes of RV diseases in patients. In addition, recent developments in (hybrid) PET and MRI might allow an integrated RV assessment in vivo. They will likely provide an important basis for simultaneous measurements of multiple myocardial disease processes.

Table 5. Overview of Applicable Tracers for Molecular Imaging in Patients With Heart Failure

<table>
<thead>
<tr>
<th>Function</th>
<th>Tracer MRI</th>
<th>Tracer PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiogenesis</td>
<td>¹⁸F-arginine-glycine-aspartic acid peptide αβ3 integrins*²⁷†</td>
<td>¹¹C-CGP-12177125,143*</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Iron-labeled annexin V¹⁰⁸</td>
<td>¹⁸F-annexin V¹⁴⁷*</td>
</tr>
<tr>
<td>Metabolism</td>
<td>ATP, phosphocreatinine⁹⁸*¹⁴²†</td>
<td>¹¹C-palmitate¹⁰³*</td>
</tr>
<tr>
<td>Oxygen consumption</td>
<td>¹³C-acetate¹⁷⁵</td>
<td>¹⁸O-H₂O, ¹⁸O-CO, ¹⁸O-O ¹¹²,¹¹⁴</td>
</tr>
<tr>
<td>Neuroreceptors:</td>
<td>¹¹C- hydroxyephedrine¹²⁴,¹²⁵*</td>
<td>¹¹C-CGP-12177¹²⁵,¹⁴²*</td>
</tr>
<tr>
<td>Parasympathetic signaling</td>
<td>¹¹C-MQNB¹⁴⁵*</td>
<td>¹¹C-CGP-12388¹⁴⁴*</td>
</tr>
<tr>
<td>Renin-angiotensin-aldosterone system</td>
<td>¹¹C-KR31173¹²⁷*</td>
<td>¹¹C-KR31173¹²⁷*</td>
</tr>
</tbody>
</table>

MRI indicates magnetic resonance imaging; and PET, positron emission tomography.

*Previously performed in patients with left ventricular failure but not yet applied in patients with right ventricular failure.
†Using ³¹phosphorus magnetic resonance spectroscopy.
References


Borderline pulmonary arterial pressure is associated with decreased hemodynamics in pulmonary hypertension. Circ Heart Fail. 2011;4:797–802. doi: 10.1161/CIRCHEARTFAILURE.110.959437.


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