Point/Counterpoint

Advanced Imaging Tools Rather Than Hemodynamics Should Be the Primary Approach for Diagnosing, Following, and Managing Pulmonary Arterial Hypertension

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ABSTRACT
Pulmonary hypertension (PH) is currently defined based on invasive measurements: a resting pulmonary artery pressure $\geq 25$ mm Hg. For pulmonary arterial hypertension, a pulmonary arterial wedge pressure $\leq 15$ mm Hg and pulmonary vascular resistance $> 3$ Wood units are also required. Thus, right heart catheterization is inevitable at present. However, the diagnosis, follow-up, and management of PH by noninvasive techniques is progressing. Significant advances have been achieved in the imaging of pulmonary vascular disease and the right ventricle. We review the current sensitivities and specificities of noninvasive imaging of PH and discuss its role and future potential to replace hemodynamics as the primary approach to screening, diagnosing, and following/managing PH.

Pulmonary arterial hypertension (PAH) is an orphan condition with high morbidity and mortality. Despite increased awareness of pulmonary hypertension (PH), data indicate that the majority of patients are still diagnosed in late stages of the disease. A higher World Health Organization functional class is associated with poorer median survival, illustrating the importance of early diagnosis. In this article, we were asked to defend the value of noninvasive imaging in the diagnosis and follow-up of PH. Although we agree that at this point, invasive assessment remains essential, in the long term it is hoped that noninvasive methods will eliminate the need for invasive assessment. Our original mandate was to discuss PAH; however, because this is a rare condition with relatively little information available, we have broadened our approach to include PH in general.

Limitations of Invasive Assessment

Invasive hemodynamic assessment by right heart catheterization is relatively safe but has technical limitations

At the Nice 5th World Symposium on PH, right heart catheterization (RHC) was confirmed as essential for the diagnostic workup of PH to assess the severity of the disease and to perform a vasoreactivity test. However, RHC is associated with rare, albeit serious, procedure-related complications, including death. In an analysis of 7218 RHC procedures performed in experienced PH centres, 76 serious adverse events, including 4 fatalities, were observed. The most common serious adverse events were supraventricular and ventricular tachycardia, vagal reactions, and systemic hypotension. Although RHC is relatively safe, reports of complications do appear, even in expert centres. Data acquisition during RHC requires resting supine patients. There is no standard operating procedure for
capturing hemodynamic changes that occur with an upright posture or with physical activity using RHC. In addition, hemodynamic measurements acquired by RHC are subject to intraindividual spontaneous variability and represent only a hemodynamic snapshot.1,6 Routine RHC relies on the use of fluid-filled catheters, which have an insufficient frequency response. Standard Swan-Ganz catheter manometry systems used in clinical practice have a frequency response of 12 Hz, whereas a minimum of 50 Hz would be required for the assessment of instantaneous pressure signals. Fluid-filled catheters require fast flushes to remove air bubbles in the monitoring system, which account for most of the variability compared with the true gold-standard high-fidelity micromanometer-tipped catheters.7 In contrast to high-fidelity micromanometer-tipped catheter systems, fluid-filled catheter transducers have to be positioned at a “zero reference level,” which is most accurately obtained at midthoracic level or at one third of the thoracic diameter below the anterior thorax surface.8 A deviation of 1 cm of the transducer from zero level affects pressures by 0.78 mm Hg, thus leading to significantly different results if 2 different zero reference levels are used in a single patient.8

Currently used invasive cardiac output measurements estimate but do not measure true cardiac output

The gold standard for the assessment of cardiac output (CO) is the direct Fick method in which CO equals 02 consumption divided by the difference between arterial and venous 02 content. Although 02 consumption can be measured accurately, that measurement is cumbersome, and many laboratories use standard tables for an assumed value instead of direct measurements. Such estimation may cause an error of as much as 40% in the assessment of CO.7 Most laboratories now use thermodilution based on an indicator dilution methodology to measure CO.10 When compared with the direct Fick method, thermodilution measurements show little bias, with a mean difference of 0.1 L/min and a confidence interval of 0.2 L/min, corresponding to excellent accuracy even in the presence of tricuspid regurgitation, but limits of agreement are ±1 L/min, corresponding to moderate precision.11

Need for an integrated diagnostic approach

Clinically significant information is gained from RHC that helps guide decisions. A restrictive use of RHC may delay a timely diagnosis and treatment.6 Still, the simple distinction between pre- and postcapillary PH is a task that often cannot even be achieved by invasive RHC. In particular, heart failure with preserved ejection fraction is commonly misdiagnosed as precapillary PH.12-14 Unresolved issues are the assessment of precatheterization fluid status, standardization of fluid loading,3,15,16 and mean pulmonary arterial wedge pressure measurements—end-expiratory or as pressure-time integral.16,17 The interpretation of invasive hemodynamics is meaningless outside the context of the clinical picture, in particular echocardiography.18 To manage the growing number of PH cases resulting from left heart disease (group 2 PH) and caused by lung disease/hypoxia (group 3 PH) in the general population, successful noninvasive diagnostic algorithms combining multiple parameters have been developed to avoid unnecessary RHC.1,18

Present Value of Noninvasive Techniques

Advanced imaging tools are useful for screening

Transthoracic Doppler echocardiography is the predominant screening modality in early stages of diagnosis to assess right ventricular (RV) structure and function, including the degree of ventricular remodelling as well as the derivation of RV systolic and diastolic pressures and analysis of contraction timing,9,23 thus providing a reliable method for the early detection of PH, with a particularly high sensitivity and specificity in systemic sclerosis (Table 1). Recently, software programs for 2-dimensional (2D) strain analysis by speckle tracking have been applied to evaluate the right ventricle.31 Furthermore, significant progress has been made in the use of knowledge-based reconstruction of 3D RV structure and function from 2D images.32 Studies have suggested that 3D echocardiographic imaging of the right ventricle is feasible, and its results compare well with magnetic resonance imaging (MRI).33,34

Theoretically, imaging of the pulmonary vasculature should be more sensitive to screening because this is where disease starts; yet, the available methods do not appear to have reached adequate sensitivity and specificity for that purpose.35

Advanced imaging tools are useful for diagnosis

Any patient with unexplained PH should be evaluated for chronic thromboembolic PH (CTEPH). Diagnostic algorithms

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**Table 1. Noninvasive imaging to screen for PH**

<table>
<thead>
<tr>
<th>First author</th>
<th>Technique</th>
<th>Number of patients</th>
<th>Study population/cause</th>
<th>Functional parameter/variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denton et al.</td>
<td>TTE</td>
<td>33</td>
<td>CTD (SSc)</td>
<td>sPAP</td>
<td>90</td>
<td>75</td>
</tr>
<tr>
<td>Parent et al.</td>
<td>TTE</td>
<td>385</td>
<td>Sickle cell disease</td>
<td>Tricuspid regurgitation jet velocity</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>Rajaram et al.</td>
<td>TTE</td>
<td>81</td>
<td>CTD</td>
<td>Tricuspid gradient</td>
<td>86</td>
<td>82</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>TTE</td>
<td>123</td>
<td>CHD</td>
<td>sPAP</td>
<td>89</td>
<td>84</td>
</tr>
<tr>
<td>Kuriyama et al.</td>
<td>CT</td>
<td>23</td>
<td>Suspected PH</td>
<td>MPAD</td>
<td>69</td>
<td>100</td>
</tr>
<tr>
<td>Perez-Enguix et al.</td>
<td>CT</td>
<td>71</td>
<td>Candidates for LTX</td>
<td>MPAD</td>
<td>66</td>
<td>86</td>
</tr>
<tr>
<td>Rajaram et al.</td>
<td>CT</td>
<td>81</td>
<td>CTD</td>
<td>Ventricular mass index</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>Stevens et al.</td>
<td>MRI</td>
<td>100</td>
<td>Suspected PH</td>
<td>PVR</td>
<td>92.5</td>
<td>85.2</td>
</tr>
<tr>
<td>Rajaram et al.</td>
<td>MRI</td>
<td>81</td>
<td>CTD</td>
<td>RV mass index</td>
<td>85</td>
<td>82</td>
</tr>
</tbody>
</table>

CHD, congenital heart disease; CT, computed tomography; CTD, connective tissue disease; LTX, lung transplantation; MPAD, main pulmonary artery diameter; MRI, magnetic resonance imaging; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricular; sPAP, systolic pulmonary artery pressure; SSc, systemic sclerosis/scleroderma; TTE, transthoracic echocardiography.
for PH include ventilation/perfusion (V/Q) scintigraphy,\textsuperscript{1,36-40} multidetector computed tomography (CT), and cardiac MRI (cMRI).\textsuperscript{41} Although a mosaic pattern is common in CTEPH, it occurs in up to 12% of patients with PAH.\textsuperscript{42} MRI of the pulmonary vasculature is still considered inferior to CT but may be preferred according to local practice.\textsuperscript{43} Recent advances such as dual-energy CT,\textsuperscript{44} cone-beam CT, electrocardiographic gated 320-row area detector CT, and lung perfusion MRI—are about to change paradigms in pulmonary vascular imaging. In a pilot study, dynamic contrast-enhanced CT was used to distinguish between patients with and those without PAH by contrast material bolus propagation time and speed in the pulmonary arteries.\textsuperscript{45} Time differences between bolus peaks correlated with mean pulmonary artery pressures, and discrimination could be achieved with a sensitivity of 100% and specificity of 100% in patients without PH and a sensitivity of 93% and specificity of 80% in patients with PAH, respectively (Table 2).\textsuperscript{45}

**Suspicion should be high when the patient presents with a history of previous venous thromboembolism (VTE).** Although formal screening cannot be recommended, CTEPH should be ruled out in any survivor of a pulmonary embolism with persistent dyspnea and > 15% perfusion defects 6 months after the acute VTE after at least 3 months of effective oral anticoagulation.\textsuperscript{40} V/Q planar images in at least 6 views combined with single-photon emission CT remains the preferred initial diagnostic test for CTEPH. CT pulmonary angiography (CTPA) has a sensitivity of detecting CTEPH of 51%, compared with a > 96% sensitivity of V/Q scanning.\textsuperscript{62} A normal V/Q, but not a normal CTPA, can exclude CTEPH,
although scans tend to normalize as disease progresses. CTEPH may be the single PH subset in which advanced imaging and not RHC may be the primary approach to diagnosis, follow-up, and management. In the example shown in Figure 1, the correct diagnosis of CTEPH was made after an echocardiogram and a V/Q scan had been obtained. A CTEPH diagnosis was later confirmed by RHC and pulmonary angiography.

Advanced imaging tools are useful for follow-up and management

An important more recent finding is that although PH is a pulmonary vascular disorder, structural and functional assessments of the right ventricle play a central role in both diagnosis and serial follow-up of patients with PAH. Therefore, it is reasonable that current guidelines suggest an integrated diagnostic algorithm in which noninvasive modalities are targeted to RV function and can be serially assessed to detect changes (Table 3); such an algorithm will play an ever more important role in the near future. For example, the use of 3D speckle tracking to assess area strain, radial strain, longitudinal strain, and circumferential strain correlates with clinical outcomes, with area strain and circumferential strain correlating best with RV ejection fraction. Stroke volume and RV ejection fraction measured by cMRI are the most commonly used parameters to evaluate global systolic RV function and to assess response to therapy. However, these parameters are highly dependent on preload and afterload and do not reflect RV contractility. RV end-systolic elastance (Ees) is accepted as a load-independent measure of intrinsic myocardial contractility. Ees is usually derived from pressure-volume loops by invasive conductance catheterization. Using this method, arterial elastance (Ea) as a measure of RV afterload can also be determined. RV-to-pulmonary vascular (RV-PV) coupling, the adaptation of the right ventricle to its afterload, can be calculated by Ees divided by Ea (Ees/Ea ratio). However, this method requires the assessment of pressure-volume loops during preload reduction by temporary balloon occlusion of the inferior vena cava, thus making it very invasive and potentially dangerous. As an alternative, Ees/Ea can also be determined by combining measurements from standard RHC and MRI. Studies in healthy individuals and patients with PH have shown good agreement of MRI conductance...
The ratio of stroke volume—end-systolic volume (SV/ESV) that can be derived completely non-invasively from cMRI was found to correlate well with RV-PV coupling and to be a strong predictor of prognosis.78

Conclusions
Because of the intrinsic properties of invasive diagnostics, the desire of patients, patient advocates, and physicians is that advanced imaging tools rather than hemodynamics will eventually become the primary approach to diagnosing, following, and managing PH. The values of sensitivities and specificities of available methods shown in Tables 1-3 allow for the selection of the best noninvasive tests for screening, diagnosis, and follow-up in PH, according to testing priorities. Although noninvasive assessment cannot currently replace RHC, it has become an essential part of the management paradigm for PH, and hopefully with further development will 1 day make RHC a historical curiosity.

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Disclosures
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