REVIEW

The value of tools to assess pulmonary arterial hypertension

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ABSTRACT: **Pulmonary hypertension is a common but complex clinical problem. When suspected in an appropriate clinical setting or detected incidetally, an array of investigative tools are employed with an intent to confirm the diagnosis, define aetiology, evaluate the functional and haemodynamic impairment, define treatment options, monitor the therapy, and establish long-term prognosis. However, no single tool provides comprehensive information that encompasses the aforementioned aims. Therefore, judicious use of these tools is of paramount importance, in order to maximise outcome and cost-effectiveness, while minimising risks and redundancies. Furthermore, a number of promising tools and techniques are emerging rapidly in the arena of pulmonary hypertension. These tools augment our understanding of pathophysiology and natural history of pulmonary hypertension. There is, therefore, increasing need for validating these emerging paradigms in multicentre trials. In this review, we focus on the tools commonly used to evaluate pulmonary arterial hyertension and also define some of the new approaches to pulmonary arterial hypertension.**

KEYWORDS: Cardiac magnetic resonance imaging, echocardiography, pulmonary arterial hypertension, right heart catheterisation, right ventricular strain

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Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure ($\bar{P}$pa) $\geqslant 25$ mmHg at rest on right heart catheterisation (RHC) [1]. The clinical classification of PH has evolved through a series of changes since its initial proposal in 1973 at the first international conference on primary PH, endorsed by the World Health Organization [2]. The current clinical classification groups PH into five diagnostic categories [3]: group 1: pulmonary arterial hypertension (PAH); group 2: PH with left-sided heart disease; group 3: PH associated with lung disease and/or hypoxaemia; group 4: PH due to chronic thrombotic and/or embolic disease (CTEPH); and group 5: miscellaneous group.

The clinical evaluation of suspected PH entails investigations that are intended to confirm the diagnosis, define aetiology, evaluate the functional and haemodynamic impairment, define treatment selection and monitor the therapy along with long-term prognostication. In this review, we will focus on the tools commonly used to evaluate PAH and also define some of the new approaches to PAH. Since the diagnosis of PAH involves excluding all other reasonable possibilities, the diagnostic algorithm generally starts with the identification of the more common clinical groups of PH (group 2, left heart disease and group 3, lung diseases), then distinguish group 4, CTEPH, and finally make the diagnosis and recognise the different types in group 1, PAH, and the rarer conditions in group 5. However, an abnormality of one test does not preclude that another abnormality may be contributing or predominant. Contingent tests are recommended to elucidate or confirm results taking into account appropriate clinical context.

TESTS TO CONFIRM THE DIAGNOSIS OF PAH

Right heart catheterisation

RHC is the current reference standard for the diagnosis and assessment of the severity of the haemodynamic impairment in PAH [4, 5]. The utility of RHC depends on the accuracy and completeness of the data obtained. Essential components of RHC are accurate measurements of right atrial pressure (Pra), right ventricular pressure, systolic Ppa (Ppa,syst), diastolic Ppa, $\bar{P}$pa and pulmonary capillary wedge pressure (Ppcw), along with measurements of oxygen saturation of blood sampled from the superior/inferior vena cava, pulmonary artery and systemic arterial circulation. The influence of intrathoracic pressure on

intracardiac pressure measurement is mitigated by recording the measurement at end-expiration when intrathoracic pressure is near zero [6]. Measurements at end-expiration were introduced in the 1980s. Earlier RHC studies averaged pressures over the respiratory cycle. The rationale for measurements at end-expiration is rather that it minimises the influence of lung volume on pulmonary vascular resistance (PVR) [7]. However, in the presence of increased respiratory pressure and volume swings, like in decompensated chronic obstructive pulmonary disease or at high levels of exercise, averaging pressures over the respiratory cycle is preferable. The Fick method remains the gold standard for estimating cardiac output (CO), provided it is used in strictly steady-state conditions, which is rarely the case [8]. In clinical practice, CO based on thermodilution techniques is frequently obtained. Generally, CO measured in triplicate by thermodilution suffices if the values are consistent, provided there is no significant systemic-to-pulmonary shunting, in which case the Fick method is mandatory. Contrary to the general conception, thermodilution CO is not affected by tricuspid regurgitation [9, 10].

P_{pcw}, a surrogate measurement for left atrial pressure in absence of pulmonary vein obstruction, is required for differentiating group 1 from group 2 categories of PH. To measure the P_{pcw}, the pulmonary artery catheter tip must be located in a lung segment where pulmonary vein pressure exceeds the alveolar pressure (physiologic zone 3) [11]. In a supine patient during RHC, a major portion of the lung is in zone 3 and, therefore, the catheter tip is naturally directed to this zone. Evidence of distinct A and V waves on P_{pcw} tracings indicates the catheter tip being in zone 3. Conditions such as hypovolaemia, advanced parenchymal lung disease or positive pressure ventilation will render the alveolar pressure in excess of the pulmonary vein pressure, thus creating zones 1 or 2. In these instances, P_{pcw} becomes a measure of alveolar pressure rather than left atrial pressure (P_{la}). The optimal position of the wedging catheter tip can be further ascertained by fluoroscopy and checking the pulmonary vein oxygen saturation, which should be equal to systemic arterial oxygen saturation. If the wedge pressure tracing is suboptimal, a measurement of left ventricle end-diastolic pressure should be obtained by left heart catheterisation.

PVR is obtained by dividing the transpulmonary gradient ($\bar{P}_{pa}$ - P_{pcw}) by the CO, and is considered a robust diagnostic criterion for PAH because it reflects the influence of transpulmonary gradient and CO and is only elevated if the vascular obstruction occurs within the precapillary pulmonary circulation [5]. PVR distinguishes passive PH (elevated $\bar{P}_{pa}$, normal PVR) from PH caused by pulmonary vascular disease (elevated $\bar{P}_{pa}$, elevated PVR). The conventional definition of PAH used in clinical studies includes a $\bar{P}_{pa}$ of $\geqslant 25$ mmHg at rest in the setting of a normal P_{pcw} of $\leqslant 15$ mmHg or less with a PVR >3 Wood units. However, potential exceptions to this definition will involve certain conditions with high flow rates, for instance uncorrected congenital heart disease, sickle cell disease and portopulmonary hypertension. Despite the pivotal role of RHC in evaluation of PAH, the technique has some limitations. Even at experienced centres, RHC procedures are associated with a morbidity of 1.1% and a mortality of 0.055% [12]. The haemodynamic variables obtained at RHC are susceptible to phasic fluctuation due to the respiratory cycle or artifactual fluctuations due to hyperventilation and valsalva manoeuvre. Furthermore, RHC is performed under artificial filling conditions, $e.g.$ at rest and after overnight fasting, which may not correspond to the true pulmonary haemodynamic conditions during patients' daily lives. This technique is also susceptible to common errors in zero levelling, over-damping (insufficient flushing) or under-damping (over-flushing) pressure curves and, in general, the insufficient frequency responses of fluid-filled catheters. The advent of implantable haemodynamic monitors providing continuous haemodynamic data may mitigate some of these limitations and may be useful in monitoring the therapy of PAH, although the intermediate to long-term accuracy of these estimates are not yet defined [13, 14].

Vasodilator challenge
Pulmonary vasodilatation testing is performed to evaluate the reversible component of PAH. It helps identify patients with better prognosis and patients who could potentially benefit from treatment with calcium channel blockers (CCBs) [15–17]. Acute vasodilator testing is most commonly performed using inhaled nitric oxide [18], intravenous epoprostenol [19] or intravenous adenosine [20]. A positive acute response was, until recently, defined as a reduction of both $\bar{P}_{pa}$ and PVR of at least 20% relative to baseline values [21]. However, recent consensus defines a favourable response as a fall in $\bar{P}_{pa}$ $\geqslant 10$ mmHg to a $\bar{P}_{pa}$ $\leqslant 40$ mmHg, with an unchanged or increased CO [22]. Using this criterion, only ~10% of patients with idiopathic PAH will be regarded as acute responders. About 50% of acutely responding idiopathic PAH patients respond long-term to CCBs [17]. While sensitivity of acute vasodilator test is insufficient to identify all patients who may be responsive to long-term CCB therapy, it is sufficiently specific to identify patients who have a high likelihood of benefiting from chronic CCB therapy. Caution should be exercised while performing this test as these agents could lead to an acute increase in right-to-left blood flow and, potentially, overload a poorly compliant left ventricle. Their use in patients with elevated left ventricular filling pressures can cause acute pulmonary oedema [23]. In addition, a minority of patients with PAH will have significant peripheral vasodilatation leading to hypotension (negative responders).

Echocardiography
Doppler echocardiography is the pivotal screening test for noninvasive assessment of suspected PAH and provides several variables which correlate closely with right heart haemodynamics, including P_{pa} (figs 1 and 2). The $P_{pa,syst}$ is derived from the tricuspid insufficiency peak gradient (TIPG) using the equation: $P_{pa,syst} = TIPG + $ estimated P_{ra}. P_{ra} can be estimated based on the diameter and respiratory variation of the inferior vena cava, although often a fixed value of 5 or 10 mmHg is assumed. The TIPG is derived from tricuspid jet velocity (TJV) using the simplified Bernoulli equation: $TIPG = 4 \times (TJV)^2$. In 10–25% of patients being evaluated for possible PH, the spectral Doppler profile of tricuspid insufficiency is too weak or insufficient to measure the pressure gradient across the tricuspid valve [24, 25]. The spectral tricuspid regurgitation signal can be augmented by use of contrast echocardiography ($e.g.$ agitated saline or encapsulated microbubble contrast agents), allowing proper measurement of peak TJV.
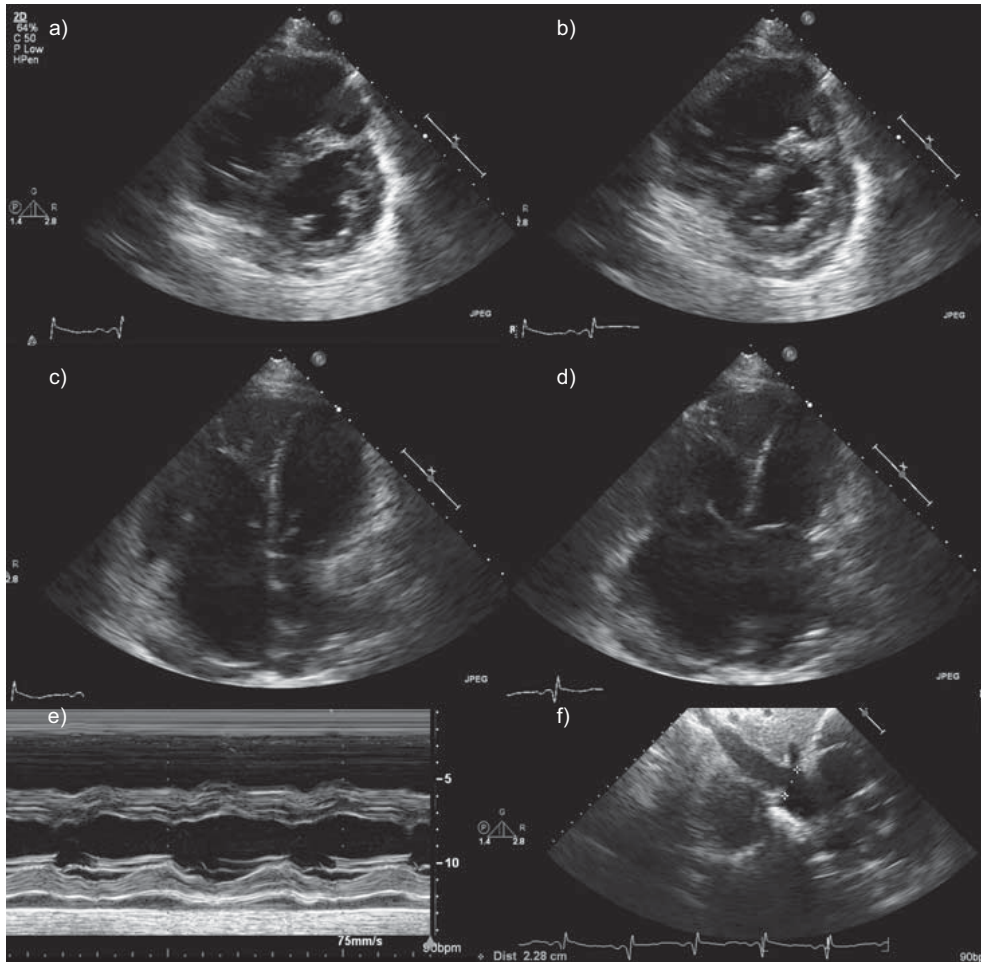
FIGURE 1. Echocardiographic evaluation of cardiac remodelling in pulmonary arterial hypertension. Short axis and four-chamber views of end diastolic (a, c) and end systolic (b, d) are shown, which demonstrate enlargement of right ventricle and flattening of interventricular septum. e) M-mode demonstrates prominent flattening of interventricular septum. f) Dilatation of inferior vena cava is also noted.

Theoretically, the $\bar{P}$pa can be derived from Ppa,syst by using the equation: $\bar{P}$pa = 0.61 × Ppa,syst + 2 mmHg [26]. However, despite strong correlation between TJV and TIPG, the Doppler-derived Ppa,syst may be inaccurate in individual patients. For example, in the ItinerAIR study that comprised of 599 patients with scleroderma, if PH is defined on the basis of Doppler-derived TJV of >3.0 m·s^{-1} or TJV of 2.5–3.0 m·s^{-1} with dyspnoea, it corresponded to a false-positive rate of 45% when compared with RHC [27].

Currently, mild PH is arbitrarily defined as TJV of 2.8–3.4 m·s^{-1}, which corresponds to TIPG 31–46 mmHg and to Ppa 36–51 mmHg, if a fixed Pra estimate of 5 mmHg is used [28]. This was endorsed by the 2009 European Society of Cardiology task force guidelines for the diagnosis and treatment of PH (table 1) [4].

A major problem of using echocardiography to evaluate the pulmonary circulation as it is practised in many centres is the exclusive reliance on the maximal velocity of tricuspid regurgitation for the calculation of pulmonary artery pressures. Since Ppa is a flow-dependent variable, it is important to couple it with a measurement of CO (Q). This can be measured from the left ventricular outflow tract (LVOT) diameter and velocity integral (VTI) multiplied by cardiac frequency (fC) [29, 30]; Q = (0.785 × (LVOT)^2 × VTI$_{LVOT}$) × fC. For the direct calculation of PVR, it is also necessary to know Pla or Ppcw. This can be calculated from the ratio of transmitral Doppler and mitral tissue Doppler E and E' waves [31]; Pla or Ppcw (mmHg) = (1.24 × E/E') + 1.9. $\bar{P}$pa can be calculated by the equation [32]: $\bar{P}$pa (mmHg) = 0.61 × Ppa,syst + 2. It is also possible to calculate pulmonary flow at the right ventricular outflow tract (RVOT) by measuring VTI$_{RVOT}$, but the calculation of volume flow produces a less stable measurement than sampled from the LVOT. VTI$_{RVOT}$ and tricuspid regurgitation flows can be combined to calculate PVR [33] as follows: PVR (in Wood units) = 0.16 + 10 × (TJV/VTI$_{RVOT}$), or using a simplified equation PVR (in Wood units) = 10 × (TJV/VTI$_{RVOT}$). If TJV/VTI$_{RVOT}$ <0.2, PVR values are likely to be normal, even in the presence of Doppler evidence of increased Ppa,syst [33]. Another useful independent method to estimate $\bar{P}$pa is based on the pulsed Doppler measurement of the acceleration time (AT) of pulmonary flow (sampled at the RVOT) [34, 35]: log$_{10}$ $\bar{P}$pa = -0.0068 (AT) + 2.1; or $\bar{P}$pa (mmHg) = 79 - (0.45 × AT). Given the importance of a reliable estimate of Ppa for the diagnosis of PH, and given the uncertainties
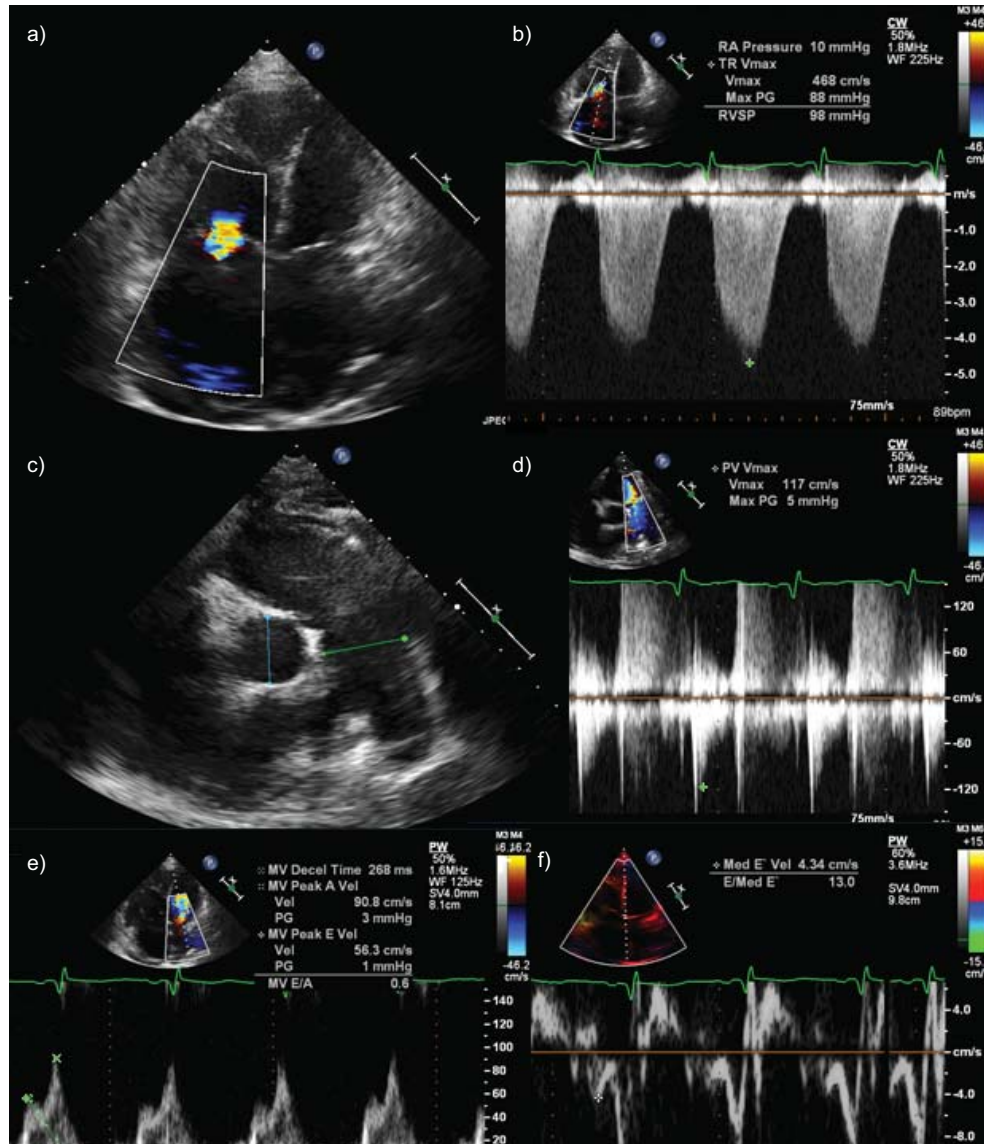
FIGURE 2. Echocardiographic evaluation of cardiac remodelling in pulmonary arterial hypertension, continued from figure 1. a) Colour Doppler across tricuspid valve reveals flow turbulence due to tricuspid regurgitation. b) Estimated pulmonary artery pressure from regurgitant velocity reveals severely elevated estimated systolic pulmonary artery pressure. c) Dilatation of main pulmonary artery is noted. d) Velocity profile across pulmonic valve is demonstrated where the systolic acceleration time is significantly shortened. e) Mitral inflow pattern revealing reduced E:A ratio. f) Tissue Doppler of interventricular septum reveals impaired tissue relaxation.

encountered with the sampling of good quality TJV or pulmonary insufficiency, it is surprising that internal controls based on AT are so uncommonly reported. However, there has been less validation of this method against invasive measurements than reported on the basis of TJV. Accurate estimates of $\bar{P}$pa are less reliable when AT exceeds 100 ms, the lower limit of normal, and the measurement may need a correction for ejection time at high heart rates [36]. However, there are data suggesting that AT may be more sensitive than tricuspid regurgitation to early or latent pulmonary vasculopathy [37], which may be due to its sensitivity to changes in pulmonary vascular impedance more than PVR. The advantage of the measurement of Ppa on the basis of the AT of pulmonary flow is in a quasi 100% recovery of good quality signals, independently on the level of Ppa. In addition to AT, the shape of the flow wave is of interest, as PH is associated with a deceleration of flow in late or in mid systole (notching).

A decreased time to notching has been reported to be of poor prognosis, and to identify proximal obstruction in patients with CTEPH [38]. Finally, as recently emphasised in the guidelines [4], estimations of Ppa or PVR have to be integrated in the context of a complete echocardiographic examination of the heart. An increased TJV in the presence of a completely normal right ventricular size and function does not require further exploration.

Cardiac magnetic resonance
Estimation of right ventricular systolic pressure
Cardiac magnetic resonance imaging (cMRI) (fig. 3) is generally considered a noninvasive reference standard for evaluating biventricular dimensions, geometry and function [40, 41]. The configuration and curvature of the septum is a function of transseptal pressure gradient [42, 43], whereas transmural pressure gradient determines the left ventricular free wall curvature [44].

TABLE 1	Definition of pulmonary hypertension (PH)
Echocardiographic diagnosis: PH unlikely	
TJV $\leqslant$2.8 m·s^{-1}, $P_{pa,syst}$ $\leqslant$36 mmHg, and no additional echocardiographic variables suggestive of PH	
Echocardiographic diagnosis: PH possible	
TJV $\leqslant$2.8 m·s^{-1}, $P_{pa,syst}$ $\leqslant$36 mmHg, but presence of additional echocardiographic variables suggestive of PH	
TJV 2.9–3.4 m·s^{-1}, $P_{pa,syst}$ 37–50 mmHg with/without additional echocardiographic variables suggestive of PH	
Echocardiographic diagnosis: PH likely	
TJV >3.4 m·s^{-1}, $P_{pa,syst}$ >50 mmHg, with/without additional echocardiographic variables suggestive of PH	

TJV: tricuspid jet velocity; $P_{pa,syst}$: pulmonary artery systolic pressure. Reproduced from [4], with permission from the publisher.

Patients with PH may have a substantially reduced trans-septal pressure gradient, which may lead to the frequently observed flattening (or bowing) of the intraventricular septum (IVS) [42]. According to the law of Laplace, wall stress is proportional to the rate of pressure rise (dP) divided by the product of wall thickness and curvature [45]. This relationship may be independently applied to derive wall stress information across the IVS and the free wall. In the absence of asymmetric hypertrophy, the wall stress in the IVS and in the free wall may be assumed to be similar; thus, any change in the dP ratio (*i.e.* trans-septal pressure gradient divided by effective distending transmural pressure) should affect the curvature ratio R_C (ratio of curvature of IVS and curvature of left ventricular free wall) proportionally. Using echocardiography, RESINER *et al.* [46] proposed an equation to obtain right ventricular systolic pressure ($P_{rv,syst}$) from systolic blood pressure (SBP): $P_{rv,syst} = SBP \times [1 - (R_C/1.03)]$. Using cMRI and RHC as reference measures this equation was validated with a good correlation (r=0.85) [47].

Sustained increase in right ventricular afterload in patients with PAH leads to alteration in right ventricle morphology; the change mirrors the severity of $\bar{P}_{pa}$. Using this concept, ventricular mass index (VMI), which is the ratio between magnetic resonance imaging (MRI)-derived right ventricle mass and left ventricle mass, were obtained in patients with suspected PAH and correlated with echocardiographic and invasive haemodynamic variables [48]. The correlation between VMI
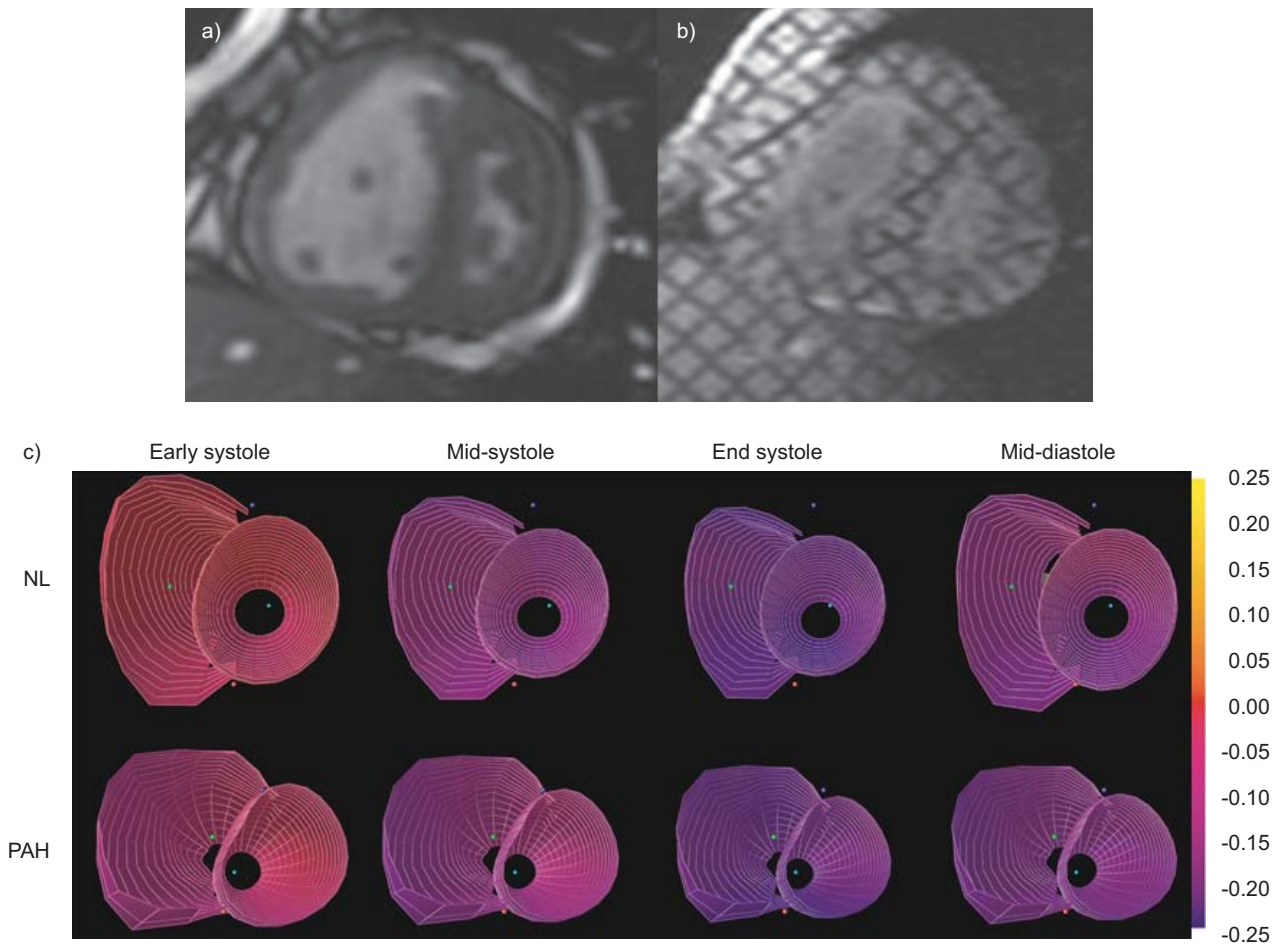

FIGURE 3. Cardiac magnetic resonance imaging (MRI) evaluation of cardiac remodelling in pulmonary arterial hypertension (PAH). a) Short axis view of cine-MRI frame at systole and b) corresponding tagged MRI images are shown. c) Three-dimensional strain maps from normal (NL) compared with PAH subjects are shown in various phases of the cardiac cycle. Adapted from [39].

and RHC-derived $\bar{P}$pa was stronger than the correlation using echocardiographically derived $\bar{P}$pa. Confidence intervals were also narrower for VMI than those for echocardiography. The sensitivity and specificity of VMI as a predictor of $\bar{P}$pa (using VMI of 0.6 as a diagnostic cut-off) were 84% and 71%, compared with 89% and 57% for echocardiography.

Phase contrast MRI-derived flow parameters
Phase contrast (PC)-MRI technique can be used to derive velocity and flow measurements in the region of interest such as pulmonary arteries. This involves use of specialised software that is routinely available from most major vendors to calculate velocity information for each pixel within the region of interest. Therefore peak and mean velocities are obtained. Integrating them over the cardiac cycle in the main pulmonary artery provides stroke volume measurements. Pulmonary artery strain, or distensibility, which is calculated as per cent change of pulmonary artery cross sectional area compared to end-diastolic area, can be obtained either from cine-MRI sequence or from PC images. Other parameters such as AT and ejection time can also be obtained from PC-MRI dataset.

When these PC-MRI parameters were compared with RHC-derived parameters, average velocity of pulmonary artery flow and minimum pulmonary artery area emerged as useful parameters for the evaluation of PAH (area under receiver operating characteristic curve 0.90 for average velocity and 0.95 for minimum pulmonary artery area) [49]. Use of velocity-encoded cine-MRI has revealed reduced peak systolic velocity and greater post-systolic retrograde flow in the pulmonary arteries of PAH patients, with retrograde flow proportional to pulmonary resistance and inversely proportional to flow volume [50]. In a study of 25 patients with PAH, mean pulmonary artery peak flow velocity, pulmonary artery blood flow and pulmonary artery distensibility were found to be significantly lower than in a matched group of volunteers (p=0.002, p=0.002 and p=0.008, respectively) [51].

LAFFON *et al.* [52] have proposed a computerised algorithm for estimating $\bar{P}$pa based on cMRI-derived indices (*e.g.* pulmonary artery cross-sectional area and blood flow velocity) that are weighted using patient-specific biophysical parameters (*e.g.* height, weight and heart rate). When this algorithm was applied to a series of 31 patients undergoing RHC, the calculated $\bar{P}$pa based on MRI-derived parameters correlated strongly with catheterisation-derived values (r=0.92). However, in a subsequent study that assessed 44 patients with established PAH, a poor correlation was found between catheterisation-derived $\bar{P}$pa and five different MRI-derived measures [53], including pulmonary vascular index, AT (defined as time from onset of pulmonary artery forward flow to maximum velocity), the ratio between AT and ejection time, and the algorithm proposed by LAFFON *et al.* [52] discussed previously. The only significant correlation between catheterisation-based $\bar{P}$pa and MRI-based measures was for ventricular mass index (r=0.56, p<0.001).

Computed tomography scan
Topographic manifestations of PAH on cardiopulmonary computed tomography (CT) are: increase in the ratio of the widest short axis diameter of the right ventricle to the left ventricle on axial CT, flattening and eventual convexity of the IVS with progressive right ventricle enlargement, and reflux of

contrast from the right atrium into the inferior vena cava [54]. It has been shown that a ratio of the mean pulmonary artery to ascending aorta size >1 is indicative of PAH [55]. In addition, the coronary sinus is dilated and correlates to pulmonary pressures determined by RHC [56]. CT scanning of the lungs can also provide morphological hints to help rule out other disorders, such as CTEPH and luminal and mural thrombi. Limitations of the use of CT in PAH diagnosis include: CT does not provide pulmonary pressure; the absence of changes in the pulmonary artery does not eliminate the possibility that a patient has PAH; pulmonary artery and ascending aorta diameters may change with body size; dilation of the main pulmonary artery can occur with other pulmonary disorders, such as pulmonary fibrosis; and size estimates of the pulmonary artery may require more than one axial dimension [54].

TESTS TO PROGNOSTICATE PAH
Right heart catheterisation
The prognostic significance of the haemodynamic variables to predict outcomes in PAH was illustrated in the pre-epoprostenol era by the National Institutes of Health registry [57]. On univariate analysis, increased $\bar{P}$pa (OR 1.16, 95% CI 1.05–1.28), increased $\bar{P}$ra (OR 1.99, 95% CI 1.47–2.69), and decreased cardiac index (CI) (OR 0.62, 95% CI 0.46–0.82) were associated with increased risk of death. Baseline Pra >20 mmHg carries a 6-month mortality rate of almost 100% without treatment. These variables were also robust predictors in multivariate analysis. Using these three variables, a regression equation was formulated to predict the probability of survival (P) in 1, 2 or 3 yrs (t) after diagnosis: $P(t)=\{H(t)\}A^{(x,y,z)}$, where $H(t)=\{0.88 - 0.14t + 0.01t^2\}$, $A^{(x,y,z)} = e^{(0.007325x + 0.0526y - 0.3275z)}$, t = years, x = $\bar{P}$pa (mmHg), y = $\bar{P}$ra (mmHg), and z = CI (L·min^{-1}·m^{-2}). This equation was subsequently validated [58] but its utility in the post-epoprostenol era has not been established. Some evidence supports that the baseline haemodynamic variables may confer less prognostic information in epoprostenol-treated patients [59]. The $\bar{P}$pa may lose its prognostic significance along the natural course of the PAH as the failing right ventricle attenuates the $\bar{P}$pa [58]. Positive response to acute vasodilator testing portends excellent prognosis with 95% survival at 5 yrs [17, 21]. However, these prognostic indices were derived from patients with idiopathic PAH and may not be directly applicable to PAH related to connective tissue disorders, congenital systemic-to-pulmonary shunts, HIV infection, or portal-pulmonary hypertension. Important information about predicting survival in PAH has been provided by a French registry and the REVEAL registry. Multivariable analysis of 354 consecutive adult patients with idiopathic, familial or anorexigen-associated PAH (56 incident and 298 prevalent cases) in the French registry showed female sex, greater 6-min walk distance and higher CO are jointly significantly associated with improved survival [60]. Analysis of 2,716 patients in the REVEAL registry, which is a multicentre, observational, US-based registry, have demonstrated additional key predictors of survival and helped generate a clinically useful prognostic equation [61].

Echocardiography
While echocardiography is pivotal in the PAH assessment paradigm as an early screening tool, the prognostic information of the echocardiographic variables in PAH is limited due to relatively small series. Those indices with the best prognostic significance identified by multivariate analysis are

pericardial effusion [61–63], indexed right atrium area [63], left ventricular eccentricity index [63] and the right ventricular Doppler index [64, 65]. Estimated $P_{pa,syst}$ derived from TJV has been shown to be non-prognostic [63]. The tricuspid annular plane systolic excursion (TAPSE), which measures the systolic displacement of the tricuspid annulus toward the right ventricle apex, has been shown to correlate closely with right ventricular ejection fraction [66]. In PH (majority PAH), TAPSE <1.5 cm is associated with clinical deterioration and worst prognosis and TAPSE >2.0 cm indicates better prognosis [67]. Similarly, TAPSE of $\geqslant$1.8 cm was associated with survival estimates of 94% and 88% at 1 and 2 yrs, respectively, and survival estimates of 60% and 50%, respectively, in subjects with a TAPSE $\leqslant$1.8 cm [67].

The myocardial performance index (Tei index or right ventricular Doppler index) is a more physiological index and is calculated as the ratio between the sum of the times of the isovolumic periods and the ejection time for the right ventricle [64]. Normal value for Tei index is 0.28 ± 0.04, and it usually increases in diseases associated with right ventricle dysfunction [64]. The Tei index appears to be predictive of an adverse outcome on univariate analysis and by multivariate regression analysis [64, 65].

Cardiovascular magnetic resonance

cMRI provides morphological and functional parameters with high accuracy, reproducibility and low inter-study variability [68]; these characteristics render it an attractive prognostication and follow-up tool. In a study of 64 patients with idiopathic PAH, baseline right ventricular stroke volume index >25 mL·m^{-2}, right ventricular end-diastolic volume <84 mL·m^{-2}, and left ventricular end-diastolic volume (LVEDV) >40 mL·m^{-2} were predictive of survival [69]. In a multivariate analysis, only 6-min walk test (6MWT) added incremental prognostic information over these three cMRI variables. In addition, a further decrease in stroke volume, progressive right ventricular dilatation, and further decrease in LVEDV at 1-yr follow-up were the strongest predictors of mortality in this study group [69]. Pulmonary artery distensiblity, as measured by relative cross-sectional area change by cMRI was predictive of survival in a cohort of 86 PAH patients. Those with a relative cross-sectional area change of <16% had a greater mortality than those with a value >16% [70].

Exercise tolerance

6MWT is a well standardised and reproducible test, which provides quantitative measures of exercise tolerance in terms of distance walked, dyspnoea on exertion (Borg scale) and finger oxygen saturation. Walking distances of <332 m [71] or <250 m [59] and oxygen desaturation >10% [72] indicate impaired prognosis in PAH. In the pivotal epoprostenol idiopathic PAH trial, performance in the unencouraged 6MWT was found to be an independent predictor of survival [73], leading to the acceptance of this test by the Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products as a primary end-point for the evaluation of treatment effects in PAH in clinical trials.

Maximal oxygen consumption determined by progressive exercise testing with cycle ergometry has also been found to be an independent predictor of survival in idiopathic PAH. Following multivariate analysis of clinical, haemodynamic and exercise parameters in 70 of the 86 patients that were able to complete the exercise protocol, peak oxygen uptake (10.4 mL·kg^{-1}·min^{-1}) and peak systolic arterial pressure during exercise (120 mmHg) independently predicted a worse prognosis in idiopathic PAH [74]. In addition, in idiopathic PAH patients treated with epoprostenol, the exercise duration has also been shown to be predictive of survival [75]. While the results of both methods do correlate in PAH, cardiopulmonary exercise test (CPET) failed to confirm improvements observed with 6MWT in randomised controlled trials [76, 77]. This discrepancy has been attributed to lack of standardisation and insufficient expertise in performing CPET [78].

Biomarkers

Both atrial natriuretic peptide and brain natriuretic peptide (BNP) are released from myocardium in response to wall stress and share similar physiological properties inducing vasodilatation and natriuresis. In a PAH study, baseline plasma BNP was an independent predictor of mortality after multivariate analysis, with supramedian level of baseline BNP of $\geqslant$150 pg·mL^{-1} associated with significantly lower survival rate than those with an inframedian level of $\leqslant$150 pg·mL^{-1}. After 3 months of target therapy, a supramedian value $\geqslant$180 pg·mL^{-1} was associated with strikingly worse survival [79]. Similarly, N-terminal pro-BNP (NT-proBNP), a high molecular precursor of BNP, is related to alteration in right ventricle morphology and dysfunction as assessed by echocardiography and RHC in PH patients with baseline serum NT-proBNP levels of $\geqslant$1,400 pg·mL^{-1} portending poor long-term prognosis [80]. Detectable cardiac troponin T also confers a poor prognosis, potentially due to the effect of right ventricle strain and ischaemia [81]. Elevated uric acid levels in PAH are also associated with severity of New York Heart Association (NYHA) functional class and impaired CO [82]. Furthermore, increased uric acid levels are independently associated with long-term mortality of patients with PAH [82].

TESTS FOR TREATMENT SELECTION AND MONITORING DISEASE

Conventionally, RHC with appropriate clinical context has been used to diagnose and determine initial treatment selection. However, there is no universally accepted consensus about the timing and frequency of subsequent RHCs. Pragmatically, most centres perform RHC when there is a change in clinical status, when change in treatment is considered, and 3–6 months after initiating new treatments, so as to ensure that the pulmonary haemodynamics are in the desired range. Currently, RHC and echocardiography are the primary tools used in the diagnosis and monitoring of PAH. However, cMRI has already superseded echocardiography as a reference standard for the noninvasive evaluation of right ventricle morphology and function that is integral to PAH management. Increasing evidence suggests that cMRI can be used effectively to guide and monitor PAH therapy [69, 83].

Figure 4 summarises various tools and parameters that are used for prognosticating and treatment selection in PAH. Interestingly, most of the predictors in PAH relate to the function of the right ventricle rather than the severity of the elevation in P_{pa}.
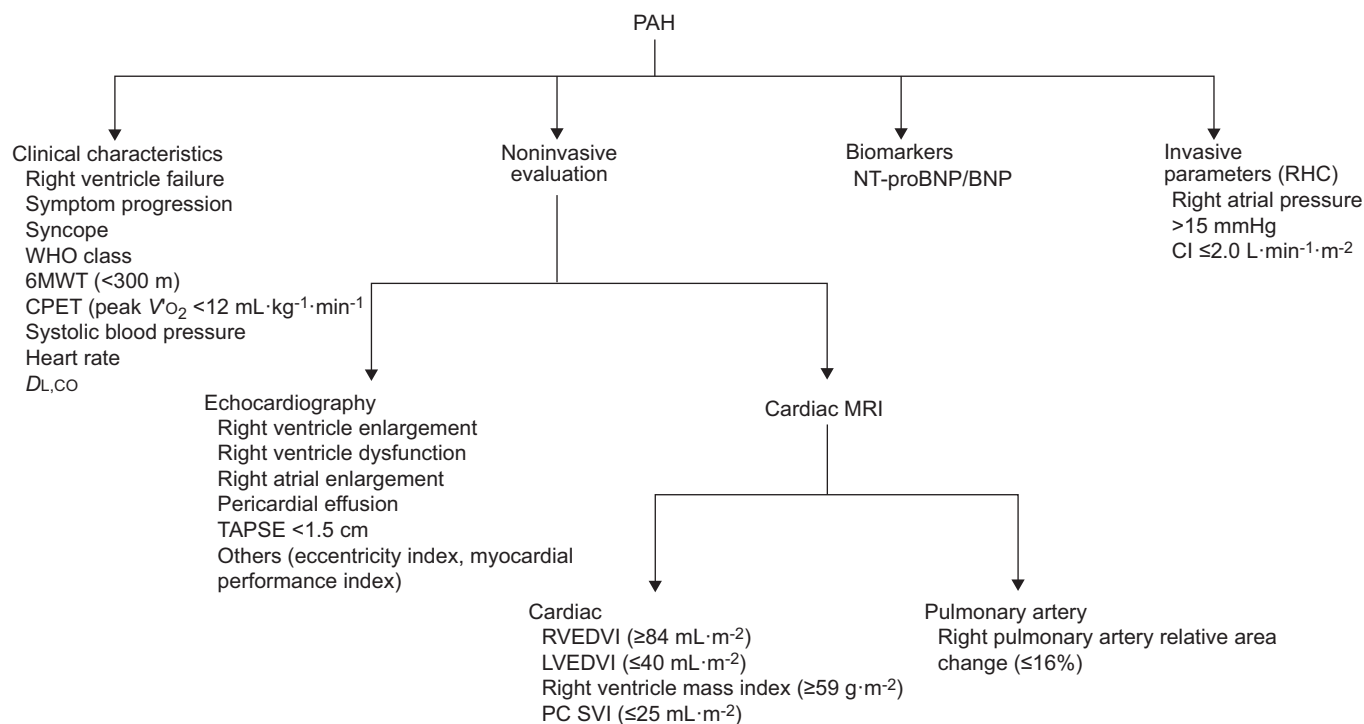
PAH

Clinical characteristics
Right ventricle failure
Symptom progression
Syncope
WHO class
6MWT (<300 m)
CPET (peak $V'O_2$ <12 mL·kg^{-1}·min^{-1}
Systolic blood pressure
Heart rate
$D_{L,CO}$

Noninvasive evaluation

Biomarkers
NT-proBNP/BNP

Invasive parameters (RHC)
Right atrial pressure >15 mmHg
CI ≤2.0 L·min^{-1}·m^{-2}

Echocardiography
Right ventricle enlargement
Right ventricle dysfunction
Right atrial enlargement
Pericardial effusion
TAPSE <1.5 cm
Others (eccentricity index, myocardial performance index)

Cardiac MRI

Cardiac
RVEDVI (≥84 mL·m^{-2})
LVEDVI (≤40 mL·m^{-2})
Right ventricle mass index (≥59 g·m^{-2})
PC SVI (≤25 mL·m^{-2})

Pulmonary artery
Right pulmonary artery relative area change (≤16%)

FIGURE 4. Tests for prognostication and treatment selection in pulmonary arterial hypertension (PAH). WHO: World Health Organization; 6MWT: 6-min walk test; CPET: cardiopulmonary exercise testing; $V'O_2$: oxygen uptake; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; NT-proBNP: N-terminal pro-brain natriuretic peptide; BNP: brain natriuretic peptide; RHC: right heart catheterisation; CI: cardiac index; TAPSE: tricuspid annular plane systolic excursion; MRI: magnetic resonance imaging; RVEDVI: right ventricular end-diastolic volume index; LVEDVI: left ventricular end-diastolic volume index; PC SVI: phase-contrast stroke volume index.

FUTURE DIRECTIONS

The right ventricle–pulmonary artery coupling

The haemodynamic variables in patients with PAH obtained from RHC are of prognostic value [57] but survival is more closely related to flow (CO) than to pressure ($\bar{P}$pa) [59, 75]. Moreover, NYHA functional class and exercise capacity correlates better to CO than $\bar{P}$pa [71, 73]. Clinical signs of right heart failure are often not clearly related to the progression of PH, as assessed by $\bar{P}$pa and PVR [84]. These observations suggest that, although RHC provides important clinical information, it neglects a number of important variables that may have important bearing on the outcomes of patients. These include considerations related to pulsatile blood flow, nonuniform patterns of histopathological changes in the pulmonary vasculature, especially in early stages of disease, and complex interaction of right ventricle with the pulmonary axis in PAH.

The prognosis/longevity in PH is highly dependent on the adaptive capacity of the right ventricle [57, 58, 85]. Nearly 25% of the total work required of the right ventricle goes into creating the pulmonary artery pulse pressure. Quantifying ventricular function in isolation without taking into consideration the pulmonary vascular function ignores the important dependency of ventricular output on arterial impedance. This ventricular–vascular coupling can be quantified by using the ventricular pressure–volume loops obtained by RHC and is expressed as ventricular end-systolic elastance (Ees) and arterial effective elastance (Ea) [86]. Ees is an index of ventricular function, Ea is a surrogate of vascular function, and their ratio measures the efficiency of ventricular–vascular haemodynamic

interactions [87, 88]. When the ventricle and the vasculature are efficiently coupled, minimal energy is wasted engendering the pulse pressure and maximal energy is transmitted in the mean pressure [89]. In this case, the ventricle operates at a maximum efficiency and submaximal stroke work such that Ees/Ea >1.5. In contrast, for a failing ventricle or high impedance vasculature, energy may be dissipated through a variety of mechanisms. In these cases, Ees/Ea <1 and ventricular–vascular uncoupling occurs [90, 91]. Pressure–volume loops at different levels of preload are required for measuring Ees, which can be difficult to achieve clinically. Single-beat methods have been developed to enable calculation of Ees and Ea from only right ventricle and Ppa waveforms [92]. The single-beat method to measure right ventricle–arterial coupling has been applied at the bedside [93, 94]. However, the application of the method needs expertise and specialised training. It is currently being refined and automated to make it easier to use in clinical practice and to base it on noninvasive measurements, *i.e.* recalculation of a right ventricle pressure curve from tricuspid regurgitation jet velocity and a relative change in right ventricle volume from pulmonary flow measurements.

To address aspects related to pulmonary impedance, the pulmonary vascular impedance spectrum (PVZ) has been proposed as a comprehensive measure of pulmonary vascular function obtained from spectral analysis of Ppa and flow waves [95]. The PVZ spectrum is expressed as a pressure/flow ratio and a phase angle, both of which are expressed as a function of frequency. Evidence suggests that it is a superior predictor of right ventricular failure in PAH compared to PVR [96]. Although

TABLE 2 Effect of pulmonary arterial hypertension (PAH) therapies on remodelling of the right heart, as assessed by noninvasive tests

Therapy	Patients	Conventional end-points	Surrogate end-points
cMRI			
Epoprostenol [83]	11 PAH	↑ 6MWD ↓ PVR	↑ RVSV ↑ CO ↔ RVEDV ↔ RV mass ↔ $\bar{P}$pa
Bosentan [116]	16 PAH	↑ 6MWD ↑ CI ↓ PVR	↔ RVEF ↔ RVEDV ↔ RVSV
Bosentan/sildenafil [117]	26 PAH (IPAH and CTD-APAH)	↑ 6MWD ↑ CI	↓ RV mass ↓ LVSEI
Bosentan and sildenafil [118]	9 IPAH 3 CTD-APAH 2 CHD-APAH 1 HIV-APAH	↑ 6MWD ↑ CI	↑ RVEF ↓ RV mass ↔ RVEDV ↔ LVEDV ↓ RVEDV/LVEDV ratio ↔ RVSV index
Ambisertan [119]	11 IPAH 1 drug-induced PAH	↑ 6MWD ↓ PVR	↑ RVEF ↔ RVEDV ↔ RV mass
Sildenafil [120]	4 IPAH 1 CHD-APAH	↑ 6MWD ↓ PVR	↓ RV mass
Echocardiography			
Epoprostenol [121]	9 IPAH 1 CTD-APAH 2 CHD-APAH 4 PPH 1 CTEPH 2 sarcoid 1 IPF	↓ NYHA FC	↓ RV dilatation ↓ TRV ↓ Ppa,syst/PVVTI ↔ RVMPI
Bosentan [122]	48 IPAH 7 CTD-APAH 1 other PAH	↑ 6MWD ↓ NYHA FC	↑ CI ↑ LVED filling velocity ↑ LVED area ↓ LVSEI ↓ RVES area ↓ RV:LV diastolic areas ↓ Pericardial effusion score
Bosentan [123]	13 CTD-APAH	↑ 6MWD	↓ RVSP ↔ $\bar{P}$pa
Sildenafil [124]	11 PAH 1 CTEPH 1 PPH	↔ NYHA FC ↔ 6MWD	↔ RVSP ↔ Tei index
Epoprostenol/treprostinil *s.c.*/inhaled iloprost plus sildenafil [125]	13 IPAH 6 toxic oil PAH 1 HIV-APAH	↓ NYHA FC ↓ Right heart failure ↑ 6MWD	↓ RVES diameter ↓ LVDEI
Epoprostenol [126]	41 IPAH	NA	↓ RVED area ↓ LVDEI ↓ LVSEI ↔ Pericardial effusion score ↓ Maximal TRV
Beraprost/inhaled iloprost/iloprost *i.v.* plus bosentan [127]	10 IPAH 6 other PAH	↑ 6MWD ↑ 6MWD	↓ Tei index

TABLE 2	Continued		
Therapy	**Patients**	**Conventional end-points**	**Surrogate end-points**
Biomarkers			
Bosentan [128]	18 CTD-APAH	↔ WHO class III ↑ 6MWD	↓ NO ↓ sCD40L ↑ P-selectin
Bosentan and sildenafil [118]	9 IPAH 3 CTD-APAH 2 CHD-APAH 1 HIV-APAH	↑ 6MWD	↓ NT-proBNP
Bosentan/sildenafil [117]	26 PAH (IPAH and CTD-APAH)	↑ 6MWD ↑ CI	↓ BNP

cMRI: cardiac magnetic resonance imaging; IPAH: idiopathic PAH/primary pulmonary hypertension; CTD-APAH: PAH associated with connective tissue disease; CHD-APAH: PAH associated with congenital heart disease; PPH: portopulmonary hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; IPF: idiopathic pulmonary fibrosis; 6MWD: 6-min walk distance; PVR: pulmonary vascular resistance; CI: cardiac index; NYHA FC: New York Heart Association functional class; NA: not applicable; WHO: World Health Organization; RV: right ventricular; RVSV: RV stroke volume; CO: cardiac output; RVEDV: RV end-diastolic volume; $\bar{P}$pa: mean pulmonary artery pressure; RVEF: RV ejection fraction; LV: left ventricular; LVSEI: LV systolic eccentricity index; LVEDV: LV end-diastolic volume; TRV: tricuspid regurgitation jet velocity; Ppa,syst: pulmonary artery systolic pressure; PVVTI: pulmonary valve velocity time integral; RVMPI: RV myocardial performance index; LVED: LV end-diastolic; RVES: RV end-systolic; RVSP: RV systolic pressure; LVDEI: LV diastolic eccentricity index; RVED: RV end-diastolic; NO: nitric oxide; sCD40L: human soluble CD40 ligand; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP.

feasibility of performing instantaneous Ppa and flow measurements during a routine RHC combined with Doppler echocardiography in patients with PAH has been shown [97], there is still a paucity of studies utilising PVZ in the PAH patient population, due to the technical difficulties of instantaneous pressure and flow measurements requiring high-fidelity, manometer-tipped catheters and flowmeters [98, 99]. Therefore, the clinical utility of PVZ in assessing responses to therapy and the prognosis of patients with severe PH is unknown.

Right ventricle strain, ventricular interaction, myocardial fibrosis and synchronicity

Strain is defined as deformation of an object compared with its initial shape and strain rate represents the deformation rate. Both MRI and echocardiography can be used to quantify these measurements (fig. 3). Echocardiographic strain and strain rate measurements have described right ventricle function in patients with PH [100] and seem to correlate to invasive haemodynamic variables [101]. Changes in right ventricle and septal systolic strain may be an indicator of early right ventricle dysfunction [102]. Attenuated right ventricle free wall longitudinal strain is associated with a greater degree of disease progression and cor pulmonale within 6 months. Patients with right ventricle free wall strain worse than -12.5% were associated with a greater degree of disease progression within 6 months, a greater requirement for loop diuretics, and/or a greater degree of lower extremity oedema, and it also predicted mortality. After adjusting for age, sex, PH cause and functional class, patients who had a 5% absolute decline in right ventricle free wall strain at 1 yr were associated with a 2.9-fold higher adjusted mortality rate per 5% absolute decline in right ventricle free wall strain at 1 yr [103].

Diastolic functions comprise ventricular relaxation and filling [64, 104, 105]. The ventricular relaxation can be quantified by isovolumic relaxation time (IVRT), the ventricular filling can be quantified by the peak filling rate and filling pattern. When diastolic function in PAH was evaluated using these indices, IVRT was found to correlate well with right ventricle mass and PVR, as well as disease severity as assessed by Pra, NT-proBNP level, CI and right ventricular ejection fraction, and IVRT was sensitive to afterload reduction with sildenafil [106].

The left ventricle is intimately connected to the right ventricle *via* the interventricular septum. Moreover, both the right and left ventricle are enclosed within a common pericardial sac occupying the same thoracic cavity. Therefore, changes in the structure and function of the right ventricle also affect the left ventricle. The MRI delayed contrast enhancement technique is used to demonstrate myocardial fibrosis with high spatial resolution. Myocardial delayed enhancement is frequently noted in right ventricular septal insertion points in PAH [107, 108]. Recent work using echocardiographic techniques in PH patients indicates that not only the right ventricle free wall and interventricular septal longitudinal shortening but also the circumferential shortening of the left ventricular lateral wall and interventricular septum and left ventricle systolic torsion are reduced [109]. With RV pressure overload, the septum flattens or even bulges to the left in early diastole. This paradoxical septal motion was classically believed to result from negative interventricular pressure gradient between left and right ventricles during diastole by studies using M-mode echocardiography and haemodynamics [110], and subsequently confirmed by cMRI [111]. Tagged MRI study indicates that this paradoxical septal motion is a result of higher pressure in the right than in the left ventricle leading to interventricular asynchrony due to a prolonged right ventricle contraction. This ventricular asynchrony impedes left ventricle diastolic filling, causing a lowered LVEDV [112, 113]. Right intraventricular dyssynchrony is also more prevalent in patients with PAH compared with controls as measured by two-dimensional strain echocardiography [114] and Doppler echocardiography [115].

CONCLUSIONS

Use of various tools has provided important insights in the natural history of PAH (table 2). No single tool provides comprehensive information regarding disease progression, stability and prognosis. There is on-going progress in better approaches for the evaluation of PAH. It is important to use existing and emerging techniques judiciously with an intent to validate some of the emerging paradigms in multicentre trials [129].

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