Pulmonary hypertension: echocardiographic assessment

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Pulmonary arterial hypertension (PAH) is a clinical condition characterized by elevated vascular resistance, associated with a poor prognosis and usually diagnosed in late stage. Echocardiographic assessment of PAH includes early disease detection and functional heart evaluation, in order to introduce a more accurate surveillance at an early stage of the disease and to contribute to prognostic stratification of advanced disease. Detection involves pulmonary artery systolic pressure (PASP) estimation. There is no clear consensus on defining normal distribution, but a PASP of 36 mmHg has been widely assumed as a cut-off value for mild PAH, requiring a more aggressive surveillance to detect further progression. Functional heart evaluation requires an accurate characterization of morphologic and hemodynamic changes, secondary to PAH development, which involves description of dimensional parameters, ventricular interdependency, intracardiac flow patterns, and right ventricular systolic performance. A valid assessment of these issues results in a useful evaluation of cardiac function, supporting clinical context in defining heart failure condition.

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Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure (PAP) of > 25 mmHg at rest, or > 30 mmHg during exercise. However, the diagnosis of PAH does not imply necessarily right ventricular (RV) dysfunction, neither a clinically relevant condition. Echocardiographic assessment of PAH includes two different issues: detection of elevated PAP values and functional evaluation of the right ventricle.

Detection of pulmonary hypertension

Correlation between Doppler and catheter measurement of pulmonary artery systolic pressure. Noninvasive pulmonary artery systolic pressure (PASP) is determined by measuring the peak systolic pressure gradient of the right ventricle to the right atrium, according to the simplified Bernoulli equation. Adding the mean right atrial pressure (RAP) to the transtricuspid pressure gradient one can predict the RV systolic pressure, which approximates the PASP.

The prevalence of tricuspid regurgitation increases as PAP increases. Berger et al.[1] observed tricuspid regurgitation in 80% of patients with PASP > 35 mmHg and in roughly 96% of those > 50 mmHg. Unfortunately, not all patients with detectable tricuspid regurgitation will have velocity profiles suitable for measurement, ranging from 44[2] to 96%[3], as a consequence of factors that limit accurate visualization of velocity profile, such as disease severity, obesity and hyperinflated lungs.

It has been reported a variable correlation between transthoracic Doppler echocardiography (TTE) and right heart catheterization measurements of PASP, depending on the underlying disease, lung conditions, and time from TTE examination to catheter measurement, ranging from 0.96-0.98 in patients with cardiac disease[1,4], to 0.69 in patients with advanced lung disease[2]. Furthermore, in the latter population, despite a significant correlation, a discordance > 10 mmHg between estimated and measured PASP was present in 52% of patients, resulting in a poor positive predictive value for the diagnosis of PAH, with confirmation of PAH by right heart catheterization in only one half of those patients in whom TTE suggested its presence. Finally, despite a good correlation between transthoracic echocardiography and right heart catheterization measurement of PASP, widely reported in several studies, the diagnostic performance characteristics of TTE should be considered, with sensitivity and specificity values strongly depending on the threshold value used as a cut-off point, PAH severity, and conditions limiting the capability of detecting and measuring the velocity profile. Moreover, the positive and negative predictive values of Doppler-estimated PASP depend not only on sensitivity and specificity, but mainly on differences in the prevalence of PAH in the patient population. Overall, the attention should be focused on the accuracy of Doppler-estimated PASP (possibly within 10 mmHg of right heart catheterization measurement), particularly in those patients with borderline values for PAH diagnosis.

Normal values and clinical implications. Right heart catheterization is currently used as the gold standard for firmly establish the hemodynamic status, although there is no clear consensus as to what value of PAP is needed for PAH diagnosis. Various threshold values have been proposed for PAH diagnosis, based on mean PAP or PASP, ranging from 18 mmHg[5,6] of mean PAP at rest to 20 mmHg[7-9] and 25 mmHg[7,10], or a resting PASP > 30 mmHg[6,7]. A mean PAP > 25 mmHg is the most often cut-off value used in recent PAH clinical trials. The Third World Symposium on PAH held in Venice in 2003 defined mild PAH as a resting Doppler estimated PASP between 36 and 50 mmHg, assuming a fixed 5 mmHg RAP[11], but a value > 36 mmHg is not rarely reported in otherwise normal subjects. In a recent large scale TTE study of 15 596 healthy subjects, McQuillan et al.[12] reported a mean RV to right atrial gradient of 18.3 ± 4.9 mmHg (range 5 to 47 mmHg), equivalent to a mean PASP of 28.3 ± 4.9 mmHg, assuming a fixed 10 mmHg RAP. An increase in PASP was associated with age, body mass index and male sex, supporting the use of age- and body mass index-corrected values in establishing the normal pressure range, since a PASP > 40 mmHg was found in 6% of healthy subjects > 50 years of age and in 5% of healthy subjects with a body mass index > 30 kg/m^2.

Possible explanations for mildly elevated PASP detected by TTE include the following physiological and technical considerations: an increase in pulmonary vascular resistance (PVR) and decreased left ventricular (LV) compliance with aging; an increase in cardiac output, and therefore in pulmonary pressure, associated with a higher body mass index, unless there is an accompanying decrease in PVR; presence of a stable mild PAH, associated with underlying conditions such as pulmonary obstructive disease; discovery of an early progressive PAH; overestimation of the Doppler-estimated PASP in a patient with true normal pulmonary pressure.

Overall, in diagnosing PAH attention should be focused on the clinical relevance of the patient's conditions, which represents the final objective of a diagnostic test. Thus, the clinical suspicion of PAH should be further investigated in a hierarchical diagnostic framework, comprehensive of RV function evaluation, and not limited to a PASP Doppler determination.

Functional evaluation of the right ventricle

Morphologic evaluation. Morphologic description comprises right side chamber dimension evaluation and pericardial effusion description. To assess RV dimensions, important preliminary considerations are needed. The right ventricle is a structurally complex cavity that changes greatly in geometry, orientation and spatial relationship with the left ventricle, when pressure and/or volume overload conditions occur. Thus, RV dimension evaluation is both technically and conceptually difficult to study in a quantitative manner. The most difficult approach to evaluate RV dimensions is represented by volume determination, so there is poor correlation with RV volume as measured by angiography[13,14] or nuclear angiography[15].

An alternative approach to assess RV size consists on simple linear dimension measurements. Unfortunately, several limitations affect this kind of evaluation, greatly related to particular RV shape, thereby affecting the recorded diameters. As a result, these measurements should be useful to alert to the possibility of RV dilation and hence that the right ventricle needs to be evaluated in a different manner. A robust dimensional measurement is mandatory in this context. It is recognized that hemodynamic conditions or clinical outcome are the best endpoints available for defining severity of morphologic changes, so attention should be focused on pathophysiologic considerations regarding ventricular interdependency and hemodynamic impairment, reason whereby comparison of relative RV and LV size may be more useful. Thus, under PAH conditions the pattern of abnormal septum motion, more closely reflecting RV hemodynamics, affects LV geometry and can be well expressed by an eccentricity index. In a cohort of patients with pressure or volume overload, Ryan et al.[16] evaluated LV geometry defining the LV eccentricity index (in parasternal short axis, LV index = D2/D1, where D1 is the diameter perpendicular to and bisecting the septum, and D2 is the diameter perpendicular to D1 and parallel to the septum) at end-diastole (LVd index) and end-systole (LVs index). This index has been subsequently evaluated in clinical trials (Table I)[17-20]. In a multicenter, randomized, unblinded study assessing the effect of epoprostenol infusion in idiopathic PAH patients, as compared with conventional therapy alone, Hinderliter et al.[17] found a baseline LVd index significantly related to baseline mean PAP, mean RAP, cardiac index ($p < 0.001$), and exercise capacity ($p < 0.01$). At the end of the 12-week treatment period, epoprostenol therapy was associated with an improvement of both LVd and LVs indexes. Raymond et al.[18] examined the associations between TTE findings and the clinical outcomes at the end of 1-year open-label period of the same cohort of patients evaluated by Hinderliter et al. The LVd index was identified by univariate analysis as the only dimensional parameter significant-

Table I. Echocardiographic parameters and prognostic value in idiopathic pulmonary arterial hypertension (IPAH).

Parameters	Patients	Study characteristics	Follow-up	Hemodynamic correlations	Prognostic value
LVs index	IPAH[17]	MR open-label[17]	Short-term	MPAP, MRAP, CI, NS	
	IPAH[18]	M open-label[18]	Long-term		No
LVd index	IPAH[17]	MR open-label[17]	Short-term	MPAP, MRAP, CI, $p < 0.001$	
	IPAH[18]	M open-label[18]	Long-term		Yes (univariate)
RA area index (cm^2/m)	IPAH[18]	M open-label[18]	Long-term	MRAP, $p < 0.001$	Yes (multivariate)
Pericardial effusion (Yes/No)	IPAH[19]	M open-label[19]	Long-term	MRAP, CI, $p < 0.001$	Yes
	IPAH[18]	M open-label[18]	Long-term		Yes (multivariate)
Doppler RV index	IPAH[20]	Retrospective[20]	Long-term		Yes (multivariate)

CI = cardiac index; Doppler RV index = Doppler index of right ventricular performance (Tei index); LVd index = left ventricular diastolic eccentricity index; LVs index = left ventricular systolic eccentricity index; M open-label = multicenter, prospective, open-label study; MPAP = mean pulmonary artery pressure; MRAP = mean right atrial pressure; MR open-label = multicenter, randomized, open-label study; Multivariate = multivariate analysis; RA = right atrial; Univariate = univariate analysis.

ly associated with the composite endpoint of death or transplantation ($p = 0.004$). Galiè et al.[21], further, examined a subgroup of PAH patients enrolled in the BREATHE-1 study[22], a multicenter, randomized, placebo-controlled trial. The objective of the study was to evaluate the effect of 16-week bosentan therapy on TTE parameters. Bosentan therapy improved LV eccentricity index in both diastole and systole, although no statistical significance was reached.

Another dimensional TTE parameter, easy to obtain and no time-consuming, is represented by the right atrial area index. Right atrial enlargement denotes high RAP, as a consequence of elevated RV diastolic pressure and functional tricuspid regurgitation. The right atrial area index has been identified as a strong predictor of adverse clinical outcome (Table I)[17-20]. In the study of Raymond et al.[18] the right atrial area index correlated closely with RAP ($r = 0.72$, $p < 0.001$) and was identified by multivariate analysis as an independent predictor of the composite endpoint of death or transplantation ($p = 0.106$).

Finally, pericardial effusion has been identified as the strongest TTE predictor of exercise capacity and clinical outcome (Table I)[17-20]. In patients with severe PAH, pericardial effusion is a manifestation of right heart failure and is likely related to impaired venous and lymphatic drainage due to elevated RAP. In the study of Hinderliter et al.[19] mean RAP was the hemodynamic parameter most closely related to effusion size ($r = 0.50$, $p < 0.001$), thereby supporting its pathophysiologic origin. Effusion size was also inversely related to the cardiac index ($r = -0.40$, $p < 0.001$), but no significant correlation was observed with mean PAP. Furthermore, larger effusion was significantly associated with more severely impaired exercise capacity ($r = -0.50$, $p < 0.001$), greater right atrial dilation, as determined by the right atrial area index ($r = 0.54$, $p < 0.001$), and greater diastolic displacement of the ventricular septum, as determined by the LVd index ($r = 0.34$, $p < 0.01$). Overall, in the study of Raymond et al.[18], the presence of pericardial effusion resulted from the multivariate analysis, incorporating echocardiographic, clinical and hemodynamic variables, as the strongest independent predictor of mortality ($p = 0.011$).

Right and left ventricular interdependency

The right ventricle represents an extremely important structure with significant hemodynamic effects, resulting in appropriate cardiac performance. There is a high degree of interdependence between the right and left ventricles due to three different conditions: 1) the presence of a common structure that is the interventricular septum; 2) the restrictions imposed by the inextensible pericardium; and 3) the "in-series" condition of the cardiovascular system.

The close association between the cardiac cavities can be well evaluated by TTE. Ryan et al.[16] were the first to describe different LV geometric changes to separate RV volume from pressure overload, finding a LVs index > 1 as a characteristic of the latter group. Soon afterwards, Lavine et al.[23] described the distribution of LV diastolic filling secondary to RV dilation with or without pressure overload, observing a LVs index markedly abnormal in the RV dilation and pressure overload group compared with the RV dilation group ($p < 0.05$). These findings were associated with a redistribution of LV diastolic filling to late diastole in the former group compared to the latter, as confirmed by the changes in the peak atrial filling velocity ($p < 0.01$) and the atrial filling period ($p < 0.05$). In another study, Louie et al.[24] evaluated the LV diastolic filling pattern in patients with idiopathic PAH and found an abnormal motion of the interventricular septum at end-systole, persisting throughout early diastole and resulting in a relative redistribution of LV filling from early to late diastole.

These and other studies[25-28] support the hypothesis that an abnormal LV shape at end-systole and during early diastole alters LV relaxation and compliance, influencing the rate of LV pressure decline and chamber stiffness and resulting in impaired LV diastolic filling. Thus, LV relaxation and compliance together with the "in-series" effect of RV output on pulmonary venous return are the major determinants of LV stroke volume in PAH patients. The close correlation between these pathophysiologic conditions and clinical outcomes is well documented by clinical trials. In the echocardiographic substudy[21] of the BREATHE-1 trial, treatment with bosentan was associated with an improvement of early diastolic LV filling parameters. After 16 weeks of treatment the peak E velocity, the E/A ratio, and the time-velocity integral of the transmitral flow profile, all increased compared to the placebo group ($p < 0.003$, $p < 0.004$, and $p < 0.001$, respectively). Multiple stepwise regression analysis showed that changes in the primary endpoint, exercise capacity, were significantly correlated with changes in peak E transmitral flow velocity ($r = 0.65$, $p = 0.001$). Furthermore, clinical and hemodynamic improvement observed after successful thromboendarterectomy in patients with chronic thromboembolic PAH are coupled with an increase in the diastolic mitral flow indices and a decrease in LV eccentricity index, explained by an improvement of RV output and normalization of septal motion[29,30].

Right ventricular systolic performance

Although commonly RV systolic function could appear to be covered by ejection fraction, this point of view leads to the misunderstanding of the RV failure concept. A physiological definition of "function" may be expressed as "the mode of action by which an organ fulfils its purpose". In the face of tissue metabolic demand heart function will be maintained until LV stroke volume can be guaranteed. Thus, the right ventricle behaves toward the left ventricle as a volume pump, accounting for left side venous return through an adequate RV output. When PAH develops the thin-walled highly compliant right ventricle dilates, with increases in both end-diastolic and end-systolic volumes, reason whereby stroke volume is usually maintained in face of a progressive decrease in ventricular ejection fraction. Indeed, RV ejection fraction (RVEF) is much more sensitive to changes in afterload than LV ejection fraction. Nevertheless, a decrease in RVEF does not mean that there is true ventricular dysfunction, but mainly reflects an increased afterload.

Assessment of the RVEF by cross-sectional echocardiography is difficult owing to the complex structure, asymmetrical shape and contraction pattern of the ventricle. Thus, there is poor overall agreement between radionuclide angiography and TTE regarding RVEF measurement, especially when pronounced cavity remodeling is present[31].

The longitudinal function of myocardial RV fibers and its contribution to pump effectiveness in systole has been suggested as an alternative approach to global RV systolic performance evaluation. Animal experiments have demonstrated that the right ventricle ejects blood primary by shortening of the longitudinal axis, while LV ejection is accomplished mainly by a reduction in cavity diameter with a limited extent of longitudinal axis shortening[32-34]. On the basis of these pathophysiologic considerations, Kaul et al.[35] proposed to measure the tricuspid annular plane systolic excursion (TAPSE) as a reliable index of RV systolic performance, finding a strong correlation between TAPSE and RVEF obtained by radionuclide angiography ($r = 0.92$). In a recent study mainly composed of PAH patients, Ueti et al.[36] observed a significant correlation between TAPSE and both RVEF determined by radionuclide angiography ($r = 0.79$, $p < 0.001$) and TTE-derived mean PAP ($r = -0.61$, $p < 0.004$), supporting the well known dependence of RVEF on afterload. Similar results have been obtained by Ghio et al.[37] in patients with idiopathic and chronic thromboembolic PAH. They found a significant correlation between TAPSE and thermodilution-derived RVEF ($r = 0.51$, $p < 0.001$), whereas an inverse correlation was found between mean PAP, measured by right heart catheterization, and both TAPSE ($r = -0.31$, $p < 0.001$) and thermodilution-derived RVEF ($r = -0.47$, $p < 0.001$). In another study the same authors[38] demonstrated the prognostic usefulness of TAPSE in predicting outcome in patients with congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy, with a TAPSE value ≤ 14 mm as a predictor of death or emergency cardiac transplantation ($p = 0.001$).

Further studies investigated the efficacy of pulsed tissue Doppler velocity of tricuspid annular systolic motion in predicting RV systolic performance and clinical outcome in patients with heart failure. Meluzin et al.[39] evaluated patients with heart failure, due to idiopathic or ischemic cardiomyopathy, and found a cut-off value of the peak systolic lateral annular velocity (Sa) < 11.5 cm/s as predictor of RVEF < 45%, determined by radionuclide angiography. The same authors[40] have subsequently examined the prognostic importance of pulsed tissue Doppler, finding an Sa value < 10.8 cm/s as an independent predictor of survival ($p < 0.048$) and event-free survival ($p < 0.001$) in symptomatic heart failure patients. Up to date no data are available on the prognostic importance of TAPSE and Sa in PAH patients.

Recently, considerable interest has been proposed in the clinical application of the Doppler index of RV performance, defined as the sum of RV isovolumic contraction and relaxation times divided by the ejection time and initially described by Tei[41]. The use of Doppler offers the possibility of high feasibility even in those patients with poor image quality or evident remodeling of chamber geometry. When PAH develops, as global RV dysfunction progresses, the value of the index increases, due to both an increase in isovolumic contraction time and a decrease in RV ejection time. Yeo et al.[20] retrospectively evaluated a cohort of patients with idiopathic PAH followed up over a mean of 2.9 years (Table I)[17-20]. On multivariate analysis the Doppler RV index was identified as the strongest predictor of an adverse outcome, defined as death or transplantation ($p < 0.004$). Furthermore, comparing the survival by Kaplan-Meier curves, the median value of the Doppler RV index (0.83) dichotomized the patients into two distinct subgroups with markedly different outcome ($p = 0.00001$). Thus, the global RV performance Doppler index seems to provide additional information to functional and prognostic evaluation of PAH patients.

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