The role of Doppler echocardiography in the evaluation of pulmonary hypertension*

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A precise evaluation of pulmonary pressure is of fundamental importance in the diagnosis and management of patients with pulmonary hypertension (PH). Doppler echocardiography is a low cost, non-invasive method that is widely used for anatomical and functional assessment of the right cardiac chambers and estimation of pulmonary pressure and the hemodynamic data obtained correlates well with that obtained through cardiac catheterization. Although the most appropriate and common technique for determining pulmonary pressure is measurement of the gradient between right ventricle and right atrium through tricuspid regurgitation, it can also be determined by analysis of pulmonary regurgitation or systolic pulmonary flow. When transthoracic echocardiography does not provide adequate viewing, transesophageal echocardiography is an excellent option, allowing for high quality imaging of cardiac structures and detection of some PAH-related disorders. In the literature, the role of echocardiography in the diagnosis of PAH, as well as in therapeutic and prognostic evaluation has been well established. In pulmonary thromboembolism patients, right ventricular dysfunction, an important indicator for thrombolytic therapy, can be detected using echocardiography. In addition, echocardiography is currently being widely used for monitoring therapeutic response in patients with primary PH, in the assessment of chronic obstructive pulmonary disease and in the follow up of lung transplant patients.

Key words: Echocardiography, Doppler/methods. Hypertension, pulmonary.

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Abbreviations used in this paper:
RA – Right atrium
PH – Pulmonary hypertension
PAP – Pulmonary arterial pressure
RV – Right ventricle
LV – Left ventricle
COPD – Chronic obstructive pulmonary disease

INTRODUCTION

Pulmonary hypertension (PH) can be defined as the hemodynamic state caused by various pathological processes that result in increased pulmonary arterial pressure (PAP). According to The National Institutes of Health, PH is defined as an at-rest systolic PAP higher than 30 mmHg or an average at-rest PAP over 20 mmHg. Understanding PAP levels is fundamental to the proper care of patients, regardless of the etiology of their condition. Historically, only cardiac catheterization allowed adequate gauging of PAP, and noninvasive methods had low diagnostic sensitivity and significant limitations. The advent of M-mode and two-dimensional echocardiography – later used in combination with Doppler echocardiography – overcame such limitations, and became the method of choice for PH diagnosis.
PHYSIOLOGY OF PULMONARY CIRCULATION

The pulmonary circulatory system is composed of three different components: pulmonary, bronchial and lymphatic. The chief function of the pulmonary component – composed of pulmonary arteries and veins – is to recondition the blood by gas exchange at the alveolar-capillary level, storing approximately two-thirds of the systolic flow of the right ventricle (RV). The bronchial is composed of arteries that are responsible for the nutrition of the muscular and elastic supporting tissues of the lung and feed into pulmonary veins which, in turn, feed into the left atrium. The lymphatic component plays an important role in the removal of particles that penetrate the alveoli and of protein exudate from capillaries. Normally, pulmonary pressures are reduced, mainly due to the great transversal section area of the pulmonary circulation, which results in low resistance and pressure. Conversely, in the bronchial system, pressure is systemic, resistance is high and blood flow is reduced. Some conditions that appear immediately after birth influence the dynamics of the relation between pulmonary pressure and resistance. Such conditions include, primarily, closure of the ductus arteriosus during gestation, increased oxygen saturation, progressive elevation in systemic vascular resistance, and changes in the ability to suppress nervous reflexes triggered by mechanical or chemical stimuli. The chemical stimuli are either produced in the lungs (bradykinin, serotonin, prostaglandin, and others) or mediated by the parasympathetic nervous system.

DEFINITION AND ETIOPATHOGENESIS

In healthy individuals, systolic PAP varies from 18 to 30 mmHg, diastolic PAP from 4 to 12 mmHg, and average PAP from 12 to 16 mmHg. The syndrome known as PH is caused by cardiovascular or pulmonary diseases and its physiopathological mechanism manifests as increased pressure on the right side of the heart and in the pulmonary vascular area. This is caused by three basic mechanisms: increased pulmonary vascular resistance, increased blood flow through the heart, and increased pulmonary capillary pressure. The PAP can be calculated as pulmonary vascular resistance plus blood flow through the heart plus pulmonary capillary pressure. The relation of those three elements to PH type is shown in Chart 1. The clinical conditions found in the different hemodynamic categories are represented in Chart 2. Chart 3 details the PH classifications (by etiology) proposed by the World Health Organization in 1989.

In primary PH, the precise pathogenic mechanism is unknown. However, an incidence of cases within the same families ranging from 6% to 12% suggests the existence of a genetic component as a causal mechanism. Experimental studies have shown changes in the regulation (inhibition or malfunction) of the potassium channels, promoting the passage of intracellular calcium into the smooth muscle cells of the pulmonary vessels, and consequently, arterial vasoconstriction and hypertrophy with cellular proliferation. The increased production of vasoconstrictors such as thromboxane A2 and endothelin 1, and the reduction in levels of vasodilators such as prostacyclin and nitric oxide have also been observed in patients with primary PH. Finally, hypercoagulability, which is characterized as increased levels of the plasminogen activator inhibitor 1 and fibrinopeptide A, and decreased levels of tissue-type plasminogen activator, has been suggested as a potential mechanism for the increased vascular resistance in the lung resulting from endothelial lesion and the formation of local intravascular thrombosis. In secondary PH, the common factor among all the possible causes of the physiopathological alterations seen appears to be the increased capillary pressure caused by the increased venous pressure, chronic hypoxemia, vascular lesions and pulmonary hyperflow.

ECHOCARDIOGRAPHIC DIAGNOSIS

For many years, echocardiography has been used to diagnose and monitor PH cases. Initially, qualitative evaluation of PH was carried out using M-mode and two-dimensional echocardiography. The signs shown in the M-mode are caused by a disproportional increase in the diastolic PAP in relation to the increased diastolic pressure in the right ventricle (RV). Thus, the most commonly found sign is the less pronounced (or absent) dip of the atrial contraction (A-wave) over the tracing of the pulmonary valve (Figure 1A). This sign, albeit classic, has little specificity and can occur in other situations, such as cardiac arrhythmia or the use of a pacemaker. Another sign, considered more specific, although with low sensitivity, is the M-mode dip in the pulmonary valve mid-systolic phase, which is found in the most severe cases of PH (Figure 1B). It is important to point out that the recording of the motion of pulmonary valve leaflets is difficult in adults because of poor alignment of the M-mode cursor and because of the interposition of the pulmonary parenchyma. In addition, usually only one leaflet can be observed.
With the addition of the two-dimensional mode, other qualitative signs resulting from the increased PAP can be observed. It is also possible to detect hypertrophy or dilatation of the RV (with or without dysfunction), alteration of the interventricular septum motion due to pressure overload within the RV, decreased left ventricle (LV) size caused by deflection of the interventricular septum and dilatation of the pulmonary artery following an increase in pressure.\(^{(1)}\) It is important to point out that none of the current echocardiographic methods allows adequate quantification of RV size or function because of its triangular shape and poor delineation of endocardial borders. Clinically, the assessment of PAP through Doppler echocardiography is one of the most important qualitative parameters in the assessment of RV systolic function.

The advent of the two-dimensional mode made noninvasive quantification of PAP levels possible. There are five basic types of Doppler assessment of PAP, depending upon concomitant conditions. General assessment is through determination of systolic pulmonary flow. In patients with tricuspid insufficiency, the gradient of pressure between the RV and the right atrium (RA) is evaluated. In those with pulmonary insufficiency, the gradient of pressure between the pulmonary artery and the RV is evaluated. In cases of interventricular communication, the gradient of pressure between the LV and RV is evaluated. In patients with patent ductus arteriosus, the gradient of pressure between the aorta and the pulmonary artery is evaluated. When flow between the RV and the pulmonary artery is unobstructed, as it is in cases of pulmonary valvar stenosis, the systolic pressure in the RV is the same as the systolic pressure in the pulmonary artery.

The most accurate and reliable noninvasive method of echocardiographic PAP assessment is based on tricuspid regurgitation. It reflects the difference between RV and RA pressure and can be calculated by the Bernoulli equation.\(^{(2)}\) When estimated RA pressure is added to that gradient, systolic RV pressure is obtained. Results from this method, which is simple and easily applied, have correlated well with those from invasive PAP measures in hemodynamics laboratory tests, with a correlation coefficient (r) between 0.89 and 0.94.\(^{(13-15)}\) Although this method is only valid in cases of tricuspid valve insufficiency, this is rarely regarded as a limitation, since approximately 90% of patients with PH present with this condition.\(^{(11,14)}\) The accurate estimation of RA pressure makes for more precise calculation of systolic pressure in the pulmonary artery, and several noninvasive approaches have been proposed for that assessment. The RA pressure can be determined by the respiratory variation in inferior vena cava diameter observed through the subcostal window.\(^{(16,17)}\) It is important to point out that, due to alterations in intrathoracic pressures, the estimation of the diameter and inspiratory collapse of the inferior vena cava is not useful in patients under ventilation with positive pressure. Other approaches to assessing RA pressure include clinical examination of the distention of the jugular (secondary to retrograde circulatory arrest) and the determination of values of 10 mmHg or 14 mmHg for the estimation of the RA pressure.\(^{(18)}\) Systolic RV pressure estimated using the techniques for calculating RA pressure also correlates well with values obtained in the hemodynamics laboratory.\(^{(14,15)}\)

Figure 2 shows a chest radiograph of a 38-year-old smoker suffering from progressive dyspnea (for three years) and rectal biopsy-confirmed schistosomiasis. The radiograph indicates significant dilatation of the pulmonary arteries. Transthoracic echocardiography allowed adequate evaluation of the dilatation of the right cardiac chambers, detection of tricuspid insufficiency, and estimation of pulmonary artery systolic pressure.

In cases of pulmonary valve dysfunction, diastolic and average PAP can be estimated. Pulmonary insufficiency is commonly detected in healthy patients and an even higher incidence is observed in PH patients.\(^{(20)}\) The mean end diastolic velocity of the pulmonary regurgitation curve in Doppler echocardiography reflects the final diastolic gradient between the pulmonary artery and the RV. By adding the estimated RA pressure, diastolic PAP is obtained. On the other hand, the peak of the Doppler pulmonary regurgitation curve is related to the initial diastolic gradient between the pulmonary artery and the RV, and it correlates well with average PAP. In hemodynamics laboratory tests, the PAPs obtained through the use of this technique correlate well with those measured through invasive methods.\(^{(11-13)}\)

Doppler determination of the pulmonary systolic flow into the pulmonary artery has also been used in the qualitative and quantitative assessment of PAP. However, this method presents considerable limitations. In healthy individuals, the pulmonary systolic flow curve displays symmetrical configuration – flow velocity increases and decreases gradually, with the maximum peak in the mid-systolic phase. In cases of PH, the flow displays an asymmetrical pattern with more precocious acceleration and peak phases. Acceleration times ≥ 120 ms are considered normal, whereas acceleration times ≤ 100 ms correlate with PH.\(^{(24)}\) Although acceleration time is a very useful indicator of PH, measuring acceleration times to estimate PAP is less reliable than the method of estimating PAP from tricuspid regurgitation.\(^{(25)}\)

In cases of congenital cardiopathy with communication between the left and right sides, such as interventricular communication and patent ductus arteriosus, the very flow through the defect can be used to calculate the systolic PAP. When pulmonary stenosis is absent in such patients, systolic PAP can be obtained by determining the difference between the systolic arterial pressure measured by sphygmonanometer and the...
systolic gradient between the LV and the RV, estimated by the continuous-wave Doppler of the flow curve through interventricular communication.\textsuperscript{26} In patients with patent ductus arteriosus, the diastolic flow between the pulmonary artery and the aorta can also be used to calculate the gradient through the defect. The diastolic PAP can then be estimated by the difference between the diastolic arterial pressure measured by sphygmomanometer and the diastolic gradient between the pulmonary artery and the aorta, obtained from the continuous Doppler of the flow curve through the ductus arteriosus.\textsuperscript{27}

**CLINICAL APPLICATIONS FOR ECHOCARDIOGRAPHY IN THE EVALUATION OF PH PATIENTS**

Echocardiography is currently an important tool for determining the diagnosis, management, and prognosis of PH patients and can even give clues as to the etiology. In many cases, the quality of the imaging obtained by transthoracic echocardiography does not allow for adequate viewing of the cardiac anatomy, making it difficult to detect the cause of the PH. In those patients, transesophageal echocardiography is a useful complementary exam, since it provides top-quality imaging of the heart and lower lobes, allowing detection of attendant pathologies such as mitral valve dysfunction, interatrial communication or pulmonary thromboembolism. In a study of cases of thromboembolism with significant hemodynamic repercussion, transesophageal echocardiography showed high sensitivity (97\%) and specificity (86\%) in the imaging of pulmonary artery emboli. Nevertheless, in this study, the prevalence of central embolus was relatively low (approximately 60\%).\textsuperscript{28} It is important to point out that, because it is a semi-invasive method, transesophageal echocardiography may be difficult to perform on patients with severe respiratory dysfunction.

In pulmonary thromboembolism, assessment of RV dysfunction by echocardiography can identify patients for whom specific treatment is indicated, with implications for the clinical management of their condition. The benefits of thrombolytic therapy, combined with anticoagulation, have been proven in patients with echocardiography-confirmed hemodynamic instability and RV dysfunction.\textsuperscript{29,30} In addition, this method can be used for prognostic evaluation of those patients. The most important echocardiographic discovery is RV hypokinesia which, if basal, is an independent predictor of mortality in the follow-up period of two weeks to three months, with an up to two-fold increase in the mortality rate.\textsuperscript{31} An increase in systolic PAP to levels above 50 mmHg has also been proven to be an independent predictor of PH persistence one year after the thromboembolism episode.\textsuperscript{32} In our institution, we evaluated the cases of 23 chronic pulmonary thromboembolism patients who had been operated on and submitted to follow-up exams. Echocardiography showed that systolic PAP was lower and the diastolic diameter of the right ventricle was smaller, when compared to the preoperative values.\textsuperscript{33}

Chronic obstructive pulmonary disease (COPD) is the most common cause of pulmonary disease resulting in RV dysfunction.\textsuperscript{34} Although the quality of the echocardiographic imaging may/might be lowered in patients with pulmonary emphysema or chronic bronchitis, the use of microbubble-based echocardiographic contrast agents can enhance the Doppler signal.\textsuperscript{35} In addition, technologically enhanced equipment may enable adequate PAP assessment in most patients, with important prognostic implications. In an echocardiographic study of 166 patients with advanced-stage COPD and treated with long-term oxygen therapy, multivariate analysis showed that the estimation of RV systolic pressure is an independent predictor of mortality.\textsuperscript{36} In addition, the prognosis for PH patients is worse when cor pulmonale with RV dysfunction is detected.\textsuperscript{37}

Another clinical application for echocardiography is in the serial follow up to monitor therapeutic response of primary PH patients to treatments such as calcium channel blockers or prostacyclin. In a study using transthoracic echocardiography, prostacyclin infusion had beneficial effects on RV size, interventricular septum movement and mean peak of tricuspid regurgitation. Lack of improvement in echocardiographic parameters can identify patients for whom lung transplant is indicated.\textsuperscript{38}

In lung transplant candidates, the role of echocardiography includes the identification of RV dysfunction signs and coronary artery disease, important factors to the preoperative evaluation.\textsuperscript{39} After the transplantation, some studies show there may be improvement to the septal movement and to pulmonary hemodynamics, with reversion of the RV dilatation and dysfunction.\textsuperscript{40} On the other hand, other studies including patients with RV dysfunction and important PH reported variable improvement in the RV function, despite PH improvement.\textsuperscript{41} Persistent RV dysfunction after lung transplantation, detected by echocardiography is related to worse prognosis.

In conclusion, echocardiography is a noninvasive procedure that plays an important role in the evaluation of PH. It can be used to accurately quantify PAPs, showing their impact on the right heart chambers and systemic veins. It is also useful as an analytical tool in the evaluation of therapeutic responses and prognoses.
REFERENCES


Chart 1
Hemodynamic patterns of the various PH types

<table>
<thead>
<tr>
<th>1. Precapillary PH</th>
<th>3. Mixed PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased systolic, diastolic, and average PAP, with normal pulmonary capillary pressure</td>
<td>• Increased systolic, diastolic, and average PAP, together with increased pulmonary capillary pressure</td>
</tr>
<tr>
<td>• End diastolic PAP considerably higher than pulmonary capillary pressure</td>
<td>• End diastolic PAP moderately higher than pulmonary capillary pressure</td>
</tr>
<tr>
<td>• High pulmonary vascular resistance</td>
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<table>
<thead>
<tr>
<th>2. Postcapillary PH</th>
<th>4. Increased pulmonary blood flow PH</th>
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<tbody>
<tr>
<td>• Increased systolic, diastolic, and average PAP, together with increased pulmonary capillary pressure</td>
<td>• Possible increase in systolic, diastolic, and average PAP</td>
</tr>
<tr>
<td>• Normal pulmonary vascular resistance</td>
<td>• Normal or slightly increased pulmonary vascular resistance</td>
</tr>
<tr>
<td>• End diastolic PAP equal to or slightly higher than pulmonary capillary pressure</td>
<td>• Normal or moderately higher pulmonary venous pressure</td>
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<td>• Pulmonary blood flow increased</td>
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PH: pulmonary hypertension; PAP: pulmonary arterial pressure.
Chart 2

Signs and symptoms seen in cases of the various types of pulmonary hypertension

<table>
<thead>
<tr>
<th>Type</th>
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<tbody>
<tr>
<td>1. Precapillary PH</td>
</tr>
<tr>
<td>Primary PH, PH combined with collagen diseases, vasculitis, altitude sickness, neuromuscular diseases, pulmonary thromboembolism, portal hypertension, acquired immuno-deficiency syndrome, drugs/toxins (anorexigens and others), persistence of fetal lung circulation pattern, Eisenmenger syndrome and others.</td>
</tr>
<tr>
<td>2. Postcapillary PH</td>
</tr>
<tr>
<td>Left ventricular systolic or diastolic dysfunction, left atrial myxoma or thrombus, mitral valve disease, aortic disease, pulmonary veno-occlusive disease (congenital or acquired) and others.</td>
</tr>
<tr>
<td>3. Mixed PH</td>
</tr>
<tr>
<td>Myocardial diseases with systolic left ventricular dysfunction, aortic stenosis and dysfunction, mitral stenosis and dysfunction.</td>
</tr>
<tr>
<td>4. Increased pulmonary blood flow PH</td>
</tr>
<tr>
<td>Interatrial communication, interventricular communication, patent ductus arteriosus, high-deficit cardiac insufficiency (e.g. thyrotoxicosis), liver disease, and chronic anemia.</td>
</tr>
</tbody>
</table>

PH: pulmonary hypertension
### Chart 3

**Etiologic PH classifications proposed by the World Health Organization**

<table>
<thead>
<tr>
<th>1. PH</th>
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<tr>
<td>Primary PH:</td>
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<tr>
<td>PH combined with some conditions such as collagen diseases, vasculitis, and congenital pulmonary-systemic shunt: a)* interatrial communication, b)** interventricular communication, and c) patent ductus arteriosus, portal hypertension, acquired immunodeficiency syndrome, drugs/toxins (anorexigens and others), persistence of the fetal pulmonary circulation pattern, and others.</td>
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<tr>
<th>2. Pulmonary venous hypertension</th>
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<tbody>
<tr>
<td>Systolic or diastolic left ventricular dysfunction, myocardial diseases, left atrial myxoma or thrombus, mitral valve disease, aortic disease, aortic coarctation, pulmonary veno-occlusive disease, extrinsic compression of pulmonary veins: a)* fibrosing mediastinitis, and b)** parahilar adenoid enlargement or tumors, and others.</td>
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<tr>
<th>3. PH combined with diseases of the respiratory system or chronic hypoxemia</th>
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<tbody>
<tr>
<td>Chronic obstructive pulmonary disease, interstitial lung disease, respiratory sleep disorder, alveolar hypoventilation, altitude sickness, neonatal lung disease, alveolar capillary dysplasia, extreme obesity (Pickwick syndrome), neuromuscular diseases, thoracic deformities, and others.</td>
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<tr>
<th>4. PH as a result of thrombolytic or embolic diseases</th>
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<tbody>
<tr>
<td>Pulmonary thromboembolism of proximal arteries, obstruction of distal pulmonary arteries: a)* pulmonary embolism (thrombus, tumor, parasites, foreign bodies), b)** sickle cell disease.</td>
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<th>5. PH as a result of inflammatory vascular diseases of the lung</th>
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<tbody>
<tr>
<td>a)* sarcoidosis, b)** pulmonary capillary hemangiomatosis, c) schistosomiasis, and others.</td>
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</table>

*sporadic **genetic

PH: pulmonary hypertension
**Figure 1** – M-mode of the pulmonary valve showing rectification of diastolic curve and lack of an atrial contraction dip in pulmonary hypertension patients (A). The mid-systolic dip (arrows), which is a specific (although low-sensitivity) sign of significant pulmonary hypertension, can be observed in the lining of the pulmonary valve during the systolic phase (B).

**Figure 2** – A) Thoracic radiogram of PH patient secondary to schistosomiasis showing pronounced dilatation of pulmonary arteries. B) Two-dimensional echocardiogram in apical cut of four chambers showing dilatation of right chambers and tricuspid insufficiency (TI) jet in the right atrium (arrow). C) Spectral curve of continuous-wave Doppler showing the flow of tricuspid regurgitation, with increased peak velocity (3.5 ms⁻¹). Using the modified Bernoulli equation, the gradient of pressure between the right ventricle and the right atrium (49 mmHg) is estimated. By adding the gradient to the average right atrium pressure value, an estimated pulmonary artery systolic pressure of 64 mmHg is obtained.

RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle.