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The atrial workload distribution – a novel echocardiographic parameter for the differentiation of pre-capillary from post-capillary pulmonary hypertension

Aura Elena Vijiiac, Alexandru Ioan Deaconu, Silvia Iancovici, Alina Scarlatescu, Maria Dorobantu

Emergency Clinical Hospital, Bucharest, Romania

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Abstract

Introduction. Right heart catheterization remains the gold standard for the differentiation of pre-capillary from post-capillary pulmonary hypertension. We sought to assess if a new echocardiographic parameter, the atrial workload distribution, can discriminate between the two forms. This parameter is defined as the transmitral E-wave/septal mitral annular Doppler Tissue Imaging e′-wave ratio multiplied by the ratio between left atrial (LA) volume and right atrial (RA) volume: (E/e') x (LA volume/RA volume). Methods. We divided 50 patients into two groups: the pre-capillary group had 23 patients with pulmonary arterial hypertension confirmed at cardiac catheterization; the post-capillary group had 27 patients with pulmonary hypertension and significant left heart disease. We compared various echocardiographic parameters between these groups. Results. The right atrial volume was higher in the pre-capillary group: 107.83 ± 67.25 versus 78.93 ± 41.75 (p=0.082). The left atrial volume and the E/e' ratio were significantly higher in the post-capillary group: 112.26 ± 45.64 versus 43.22 ± 16.39 (p<0.0001) and 20.85 ± 8.85 versus 8.49 ± 3.09 (p<0.0001), respectively. The atrial workload distribution was significantly higher in the post-capillary group: 31.37 ± 15.04 versus 5.18 ± 3.82 in the pre-capillary group (p<0.0001). Using ROC analysis, a cut-off value of 12.71 provided excellent discrimination (AUC=0.997) between the two groups (sensitivity=100%, specificity=94%). Conclusion. The atrial workload distribution is a simple echocardiographic parameter, which seems to be a useful tool in the differential diagnosis of pulmonary hypertension. Further investigation is necessary in order to establish its potential to reduce the need for cardiac catheterization.

Keywords: pulmonary hypertension , pre-capillary , post-capillary , atrial workload distribution

Introduction

Pulmonary hypertension remains a potentially fatal and under-recognized problem, each form of pulmonary hypertension having its own treatment and prognosis. Specific pulmonary vasodilating therapies targeting particular forms of pulmonary hypertension

* Correspondence to: Aura Elena VÎJÎIAC, MD,
Emergency Clinical Hospital, 8, Calea Floreasca, 014491,
Bucharest, Romania.
Telephone: 0040215992300/418; Mobile: 0040752298189
Email: aura.apostolescu@yahoo.com

have emerged over the last decade, providing substantial clinical benefit for the patients and improving prognosis [1, 2].

Right heart catheterization is the gold standard for thorough assessment of patients with pulmonary hypertension and current guidelines [3] support the invasive measurement of pulmonary arterial pressure, pulmonary vascular resistance, pulmonary arterial wedge pressure, diastolic pressure gradient (diastolic pulmonary arterial pressure minus mean pulmonary arterial wedge pressure) and cardiac output as part of a comprehensive evaluation of patients with pulmonary hypertension. Pulmonary hypertension is currently defined as the increase in mean pulmonary arterial pressure ≥ 25 mm Hg at rest assessed by right heart catheterization.

A hemodynamic classification is routinely used, which distinguishes between two forms of pulmonary hypertension. Pre-capillary pulmonary hypertension is defined as mean pulmonary arterial pressure ≥ 25 mm Hg with normal pulmonary arterial wedge pressure (≤ 15 mm Hg); it is an obliterative pulmonary vasculopathy which affects the small arteriolar compartment and it can be idiopathic or related to parenchymal lung disease, chronic thromboembolic pulmonary hypertension, connective tissue disease or congenital heart disease. Post-capillary pulmonary hypertension is defined as mean pulmonary arterial pressure ≥ 25 mm Hg with elevated pulmonary arterial wedge pressure (> 15 mm Hg) and it is the direct result of passive backward transmission of elevated left-sided filling pressures into the pulmonary venous circulation. This venous congestion is usually encountered in left heart disease and it consequently determines elevated pulmonary artery pressures. This second group may present with isolated post-capillary pulmonary hypertension (diastolic pressure gradient < 7 mm Hg and pulmonary vascular resistance ≤ 3 Wood Units) or with combined post-capillary and pre-capillary pulmonary hypertension (diastolic pressure gradient ≥ 7 mm Hg and/or pulmonary vascular resistance > 3 Wood Units); these two entities seem to be in fact a pathophysiological continuum [4].

This hemodynamic differentiation between pre-capillary and post-capillary physiology is important because while patients with pulmonary arterial hypertension may be treated with targeted therapies, their use in post-capillary pulmonary hypertension is currently not recommended as they failed to demonstrate any benefit in clinical trials [5, 6]. Guidelines highlight that the centerpiece of post-capillary pulmonary hypertension management is the optimal treatment of the underlying disease [3].

Although right heart catheterization can accurately differentiate pre-capillary from post-capillary pulmonary hypertension, it remains an invasive method with its own risks, limited indications and far less availability when compared to transthoracic echocardiogram, which is a safe, cost-effective, and easy to perform at bedside imaging modality. Echocardiography remains the main screening tool for patients suspected of having pulmonary hypertension. Although it can accurately measure neither the pulmonary arterial pressure [7], nor the pulmonary arterial wedge pressure, it assesses both the probability of pulmonary hypertension through estimation of right ventricular systolic pressure and the hemodynamic impact on right ventricular function. Several methods [8, 9] for the echocardiographic estimation of mean pulmonary arterial pressure have been studied, with promising results. The ability of standard echocardiographic evaluation to differentiate between pre-capillary and post-capillary pulmonary hypertension has been intensely debated, but no algorithm has been validated so far.

The Atrial Workload Distribution – A New Parameter

We sought to assess if a new echocardiographic parameter, the atrial workload distribution, which is easy to obtain and interpret, can differentiate between the two forms of pulmonary hypertension. This parameter is defined as the ratio between the transmitral E-wave and the septal mitral annular Doppler Tissue Imaging e′-wave multiplied by the ratio between left atrial volume (LA vol) and right atrial volume (RA vol):

Atrial workload distribution = (E/ e') x [(LA vol)/ (RA vol)]

We hypothesized that in pre-capillary pulmonary hypertension the right atrial volume would increase disproportionately to the increase in left atrial volume, while in post-capillary pulmonary hypertension the increase in left atrial volume would be disproportionate when compared to the increase in right atrial volume,

as pulmonary hypertension in the latter case is a direct consequence of increased left atrial pressure. Consequently, the ratio between left atrial volume and right atrial volume would be a proper fraction in the post-capillary group and an improper one in the pre-capillary group. Left atrial pressure (and therefore the E/e' ratio) is increased in post-capillary pulmonary hypertension, while no significant elevations of left atrial pressure are seen in pre-capillary hypertension. We chose the name "atrial workload distribution" for the newly defined parameter as the ratio E/e' is a well-established surrogate for left atrial pressure and because work is defined in thermodynamics as the product between pressure and volume. Accordingly, our main hypothesis was that the atrial workload distribution would be higher in post-capillary than in pre-capillary pulmonary hypertension.

Material and methods

Study Population

We included 50 patients in our study, dividing them into two groups. The pre-capillary group consisted of 23 consecutive patients referred to our clinic for right heart catheterization, which confirmed the diagnosis of pulmonary arterial hypertension, according to its definition in the current guidelines [3]: mean pulmonary arterial pressure ≥ 25 mm Hg, pulmonary arterial wedge pressure ≤ 15 mm Hg, pulmonary vascular resistance > 3 Wood units. All patients were referred to our unit from a Lung Disease Center, where significant lung disease and chronic thromboembolic pulmonary hypertension had been previously excluded. Following right heart catheterization, transthoracic echocardiographic evaluation was performed for all patients within 24 hours.

The post-capillary group consisted of 27 patients from our daily clinical practice with significant left heart disease (either severe aortic stenosis, severe mitral regurgitation or severe left ventricular systolic dysfunction) and high probability [3] of pulmonary hypertension assessed by echocardiography: either peak tricuspid regurgitation velocity over 3.4 m/s, or peak tricuspid regurgitation velocity between 2.9 and 3.4 m/s combined with other echocardiographic signs of pulmonary hypertension. Patients with coexisting respiratory disease and/or history of pulmonary embolism were not considered eligible. The patients from the post-capillary group did not undergo cardiac catheterization as there was no clear indication according to current guidelines [10]. All patients underwent echocardiographic examination using conventional and special echocardiographic techniques.

Basic demographic data, past medical history and blood test results were collected from their medical records by 3 investigators. The study was approved by the human research committee of our hospital and informed consent was obtained from each patient.

Echocardiographic Assessment

Comprehensive echocardiographic examinations were performed using Vivid 7 and Vivid E9 machines with a 3.5 MHz transducer, according to current international recommendations [11]. All echocardiographic images were digitally stored and 2 well-trained echocardiographers performed offline data analysis using dedicated software (GE EchoPAC BT 12). The reference limits for all echocardiographic parameters were chosen according to the current guidelines [12].

The right atrial volume was measured in the apical 4 chamber view using the area-length method. The tricuspid regurgitant velocity was calculated using continuous- wave Doppler in multiple views and the maximum value was the one reported in the database, regardless of the view in which it was obtained. The left atrial volume was measured in the apical 4- and 2-chamber views, using the biplane area-length method. The transmitral pulsed-wave Doppler E-wave and the septal mitral annular Doppler Tissue Imaging e′-wave were obtained from the apical 4-chamber view. 3-5 beats of Doppler-derived data were averaged as required [12].

Statistical Analysis

All statistical analysis was performed using SPSS version 17.0 statistical software package. Continuous variables were summarized as mean ± standard deviation. We used T test to compare the atrial workload distribution and other echocardiographic parameters between the two groups. P-values <0.05 were considered significant. We performed receiver operating characteristic analysis to identify the optimal cut-off value for maximum sensitivity and specificity (to discriminate between pre- and post-capillary pulmonary hypertension) and to calculate the area under the curve (AUC) as a measure of discriminating power.

Table 1. Baseline characteristics of the two groups. Values are numbers of patients; percentages are given in parentheses. N= number of patients

	Pre-capillary group (N=23)	Post-capillary group (N=27)	Total (N=50)
Male	7 (30.43%)	17 (62.96%)	24 (48%)
Female	16 (69.57%)	10 (37.04%)	26 (52%)
Main underlying etiology			
• **Dilated cardiomyopathy**		15 (55.55%)	
• **Severe aortic stenosis**		10 (37%)	
• **Severe mitral regurgitation**		2 (7.45%)	

Results

Baseline Characteristics

A total of 50 patients were included, 48% of which were male, with a mean age of 63 ± 15.35 years and an age range of 26 to 90 years. The patients in the pre-capillary group were younger than the patients in the post-capillary group: 55 ± 14.19 years versus 69 ± 13.29 years, respectively (p=0.001). Right heart catheterization confirmed pulmonary arterial hypertension in all patients in the pre-capillary group, which were subsequently referred to the Lung Disease Center for specific targeted therapies. Among these patients, 21 (91.3%) had idiopathic pulmonary arterial hypertension and 2 (8.7%) had connective tissue disease.

The main underlying left heart disease in the post-capillary group was dilated cardiomyopathy with severe left ventricular systolic dysfunction (55.55% of the patients), followed by severe degenerative aortic stenosis (37%) and severe organic mitral regurgitation (7.45%). Among the patients with dilated cardiomyopathy, the majority had ischaemic heart disease as the underlying etiology, while others had idiopathic or familial forms of dilated cardiomyopathies. All these patients had optimal medical treatment according to current guidelines of heart failure [13], including cardiac resynchronization therapy when eligible.

The patients' baseline characteristics are summarized in Table 1, Fig. 1 and Fig. 2.

Echocardiographic Findings

We performed standard echocardiographic measurements for all patients and we compared various parameters between the two groups (Table 2). The right atrial volume was higher in the pre-capillary group: 107.83 ± 67.25 versus 78.93 ± 41.75 (p=0.082). The left atrial volume, on the other side, was significantly higher in the post-capillary group: 112.26 ± 45.64 versus 43.22 ± 16.39 (p<0.0001). The ratio between transmitral E-wave and septal mitral annular Tissue Doppler e′-wave (E/e' ratio) was higher in the post-capillary group: 20.85 ± 8.85 versus 8.49 ± 3.09 (p<0.0001). The atrial workload distribution, as defined above, was significantly higher in the post-capillary group: 31.37 ± 15.04 versus 5.18 ± 3.82 in the pre-capillary group (p<0.0001).

By receiver operating characteristic analysis we attempted to find a cut-off value for this parameter, which should help in discriminating between pre-capillary and post-capillary pulmonary hypertension.

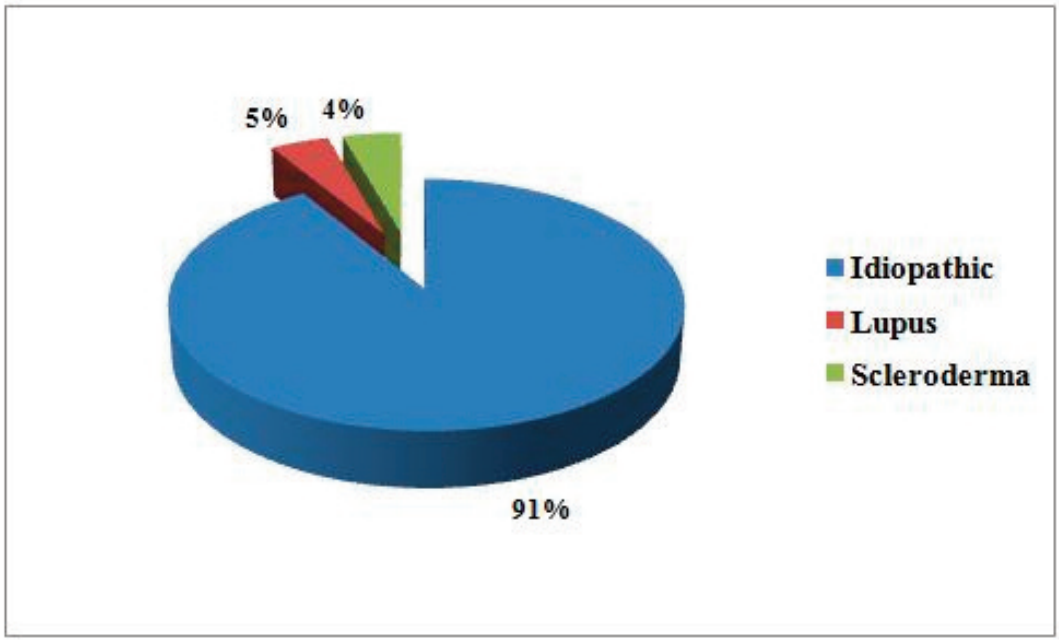

Figure 1. Etiology of pulmonary arterial hypertension in the pre-capillary group. Numbers indicate sample size in percentages for every etiology.

Using receiver operating characteristic analysis, a cut-off value of 12.71 provided excellent discrimination (area under the curve=0.997) between the two groups (sensitivity=100%, specificity=94%) (Fig. 3).

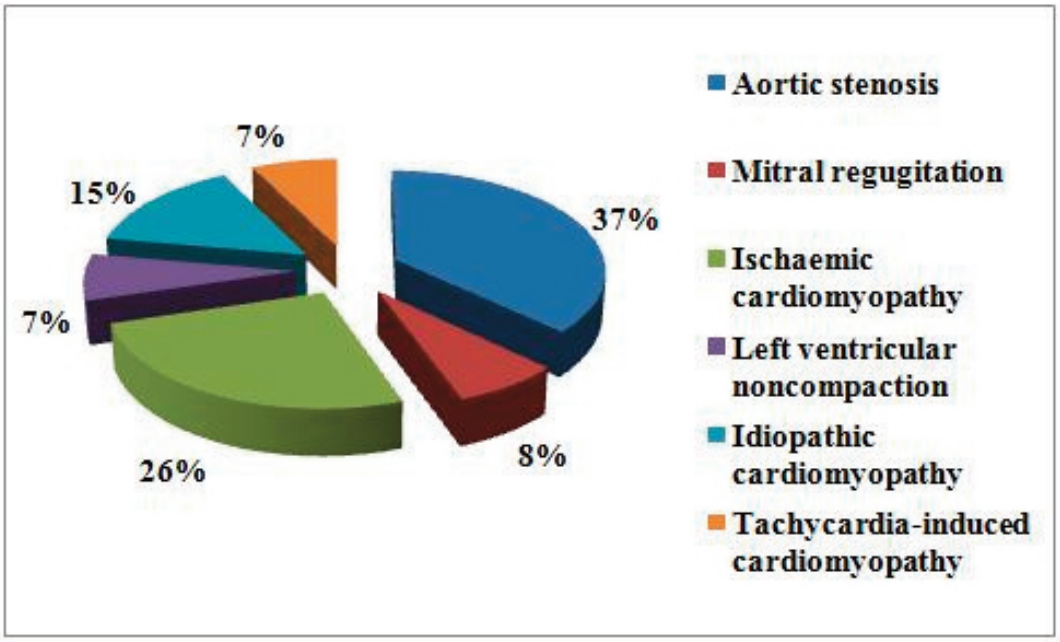

Figure 2. Underlying left heart disease in the post-capillary group. Numbers indicate sample size in percentages for every underlying condition

Table 2. Comparison of echocardiographic findings between the two groups. Values are mean ± SD. Units of measurement are given in parentheses for every parameter, except for the E/e' ratio and the atrial workload distribution, which are unitless. P<0.05 was considered statistically significant

Parameter	Pre-capillary group	Post-capillary group	
AT (ms)	59.52 ± 18.54	71.72 ± 12.77	P=0.015
Vm (m/s)	4.25 ± 1.06	3.59 ± 0.36	P=0.009
RA volume (ml)	107.83 ± 67.25	78.93 ± 41.75	P=0.082
LA volume (ml)	43.22 ± 16.39	112.26 ± 45.64	P<0.0001
E/e'	8.49 ± 3.09	20.85 ± 8.85	P<0.0001
Thickness of RVFW (mm)	8 ± 1.91	5.86 ± 1.28	P<0.0001
Atrial workload distribution	5.18 ± 3.82	31.37 ± 15.04	P<0.0001

AT=pulmonary valve acceleration time (measured in short-axis view); Vm= maximum tricuspid regurgitation velocity calculated by continuous wave Doppler; RA=right atrium; LA=left atrium; E/e'= ratio between transmitral E wave and mitral annular tissue Dopler e' wave; RVFW=right ventricular free wall (measured in subcostal view)

Both the left atrial volume and the E/e' ratio, which varied significantly between the two groups, had slightly weaker discriminating power than the atrial workload distribution. For the left atrial volume, a cut-off value of 58 ml provided excellent discrimination (area under the curve=0.930, sensitivity=88%, specificity=83%) (Fig. 4). For the E/e' ratio, a cut-off value of 11.6 provided excellent discrimination (area under the curve=0.935, sensitivity=87%, specificity=80%) (Fig. 5).

Discussion

Echocardiography is a reliable method for the non-invasive assessment of the probability of pulmonary hypertension [14]. In patients with left heart disease, pulmonary hypertension is a well-known complication and its presence is typically associated with more severe symptoms and worse prognosis [15, 16]. Routine right heart catheterization for such patients is not necessary, as the general principle for the management of pulmonary hypertension in this setting is the optimal treatment of the underlying left-sided heart disease. Nevertheless, right heart catheterization may be considered in selected patients, when the hemodynamic profile is not clear or when pulmonary hypertension is disproportionate to the clinical picture.

In patients with pulmonary arterial hypertension, a high index of suspicion is needed, particularly in the early stages of the disease, given the nonspecific and often misleading symptoms. Consequently, echocardiography is a pivotal noninvasive screening tool for patients suspected of having pulmonary hypertension

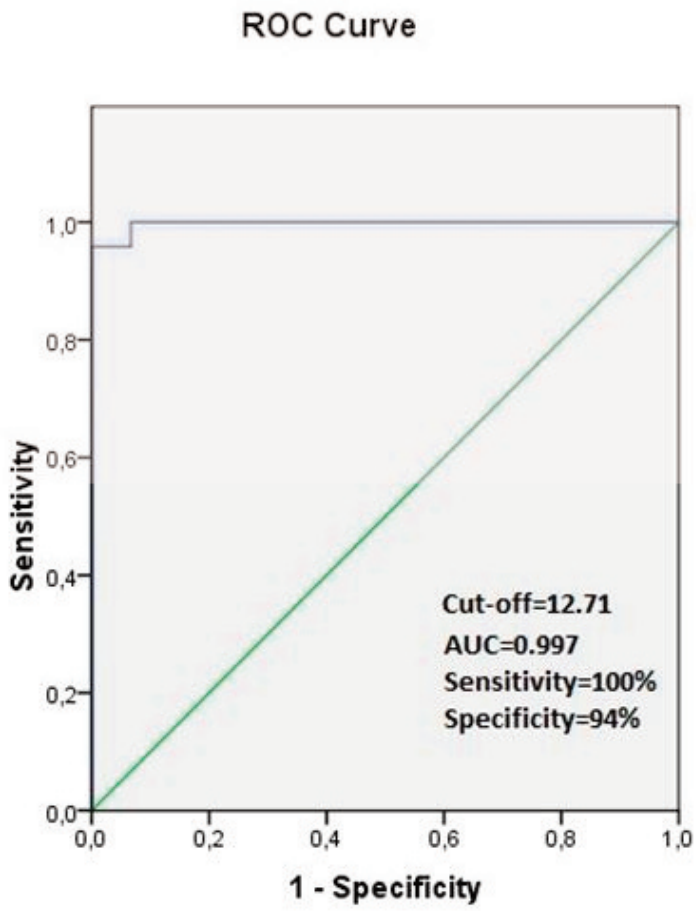

Figure 3. Receiver operating characteristic (ROC) analysis of the atrial workload distribution. A cut-off value of 12.71 had excellent discriminating power between the pre-capillary group and the post-capillary group: sensitivity=100%, specificity=94%, area under the curve (AUC)=0.997

[17], while also being used in prognostic evaluation [18]. Right heart catheterization remains the gold standard for diagnosing pre-capillary pulmonary hypertension, assessing the severity of the disease and monitoring the response to specific therapies.

Several equations for the non-invasive measurement of pulmonary vascular resistance have been studied [19-23] and echocardiographic surrogates for increased pulmonary vascular resistance (>3 Wood units) have been proposed, namely pulmonary artery acceleration time < 90 ms [24] or the presence of a midsystolic notch of the right ventricular outflow tract Doppler flow velocity envelope [25]. On the other hand, elevated pulmonary arterial wedge pressure as a direct consequence of elevated left atrial pressure can be predicted using the transmitral flow profile and Doppler tissue imaging of the mitral annulus [26, 27].

Understanding the physiology and hemodynamics of heart and pulmonary circulation is crucial for differentiating between pre-capillary and post-capillary pulmonary hypertension [28]. The atrial workload distribution is a simple, reproducible parameter, easy to obtain during a standard transthoracic examination. The rationale of this parameter lies in the assessment of left heart filling pressures, which represent the centerpiece of the hemodynamic differentiation between the two forms of pulmonary hypertension. In the post-capillary form, features of pulmonary hypertension are usually less prominent because of both left-sided and right-sided elevated filling pressures [29]. Our hypothesis was that the E/e' ratio and the left atrial volume (both markers of elevated left atrial pressure) would rise disproportionately to the right atrial volume and thus the atrial workload distribution would be high in post-

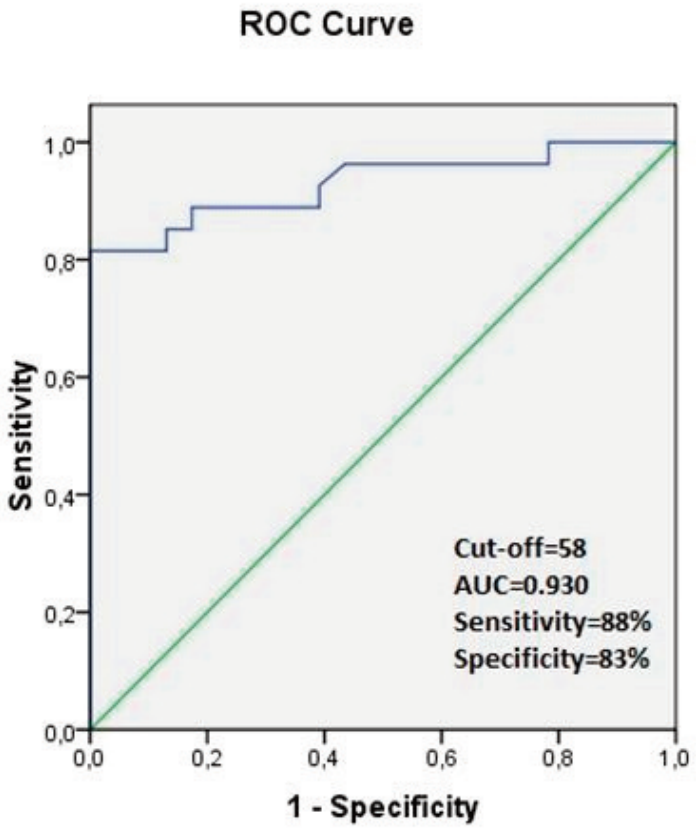

Figure 4. Receiver operating characteristic (ROC) analysis of the left atrial volume. A cut-off value of 58 had excellent discriminating power between the pre-capillary group and the post-capillary group: sensitivity=88%, specificity=83%, area under the curve (AUC)=0.930

capillary pulmonary hypertension. In the pre-capillary form, left atrial pressure will be normal or low in the absence of left heart disease, while the elevated PVR will have an impact on the right heart cavities' dimensions. Consequently, the atrial workload distribution will be low in pre-capillary pulmonary hypertension. Our study validated our hypothesis, as the atrial workload distribution was significantly higher in the post-capillary than in the pre-capillary group ($p<0.0001$), and the receiver operating characteristic analysis showed an excellent discriminating power (area under the curve = 0.997) for the cut-off value of 12.71. Furthermore, the atrial workload distribution had a greater discriminating power than its constituents; this might be explained by the divergent changes of its constituents in the two forms of pulmonary hypertension.

Over the last few years, two echocardiographic algorithms have been proposed for the differentiation between pre- and post-capillary pulmonary hypertension. The algorithm proposed by D'Alto et al.[30] takes into consideration five variables: right versus left heart chamber size, left ventricular eccentricity index, inferior vena cava diameter and collapsibility, mitral E/e' ratio, and right ventricular apical configuration. The algorithm proposed by Opotowsky et al.[31] is based on a combination of the following echocardiographic parameters: E/e' ratio, left atrial dimensions and midsystolic notching or acceleration time of the right ventricular outflow tract flow velocity. Both scores showed good discriminating power between the two forms of pulmonary hypertension. Recently, Scalia et al.[32] showed that a new echocardiographic parameter, ePLAR, defined as the maximum tricuspid regurgita-

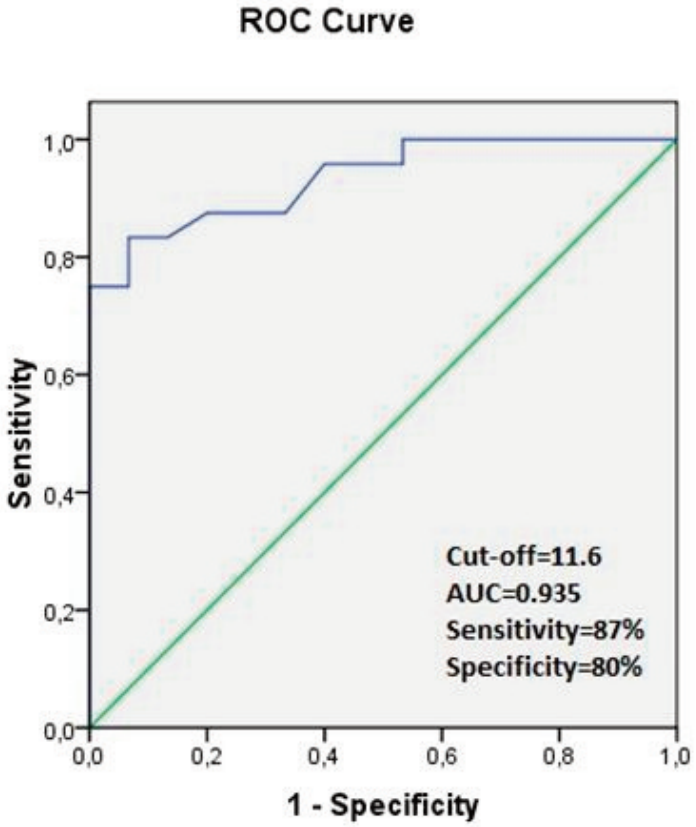

Figure 5. Receiver operating characteristic (ROC) analysis of the E/e' ratio. A cut-off value of 11.6 had excellent discriminating power between the pre-capillary and the post-capillary group: sensitivity=87%, specificity=80%, area under the curve (AUC)=0.935

tion velocity divided by the E/e' ratio, is able to accurately differentiate pre-capillary from post-capillary pulmonary hypertension.

The atrial workload distribution has greater discriminating power by receiver operating characteristics analysis (area under the curve = 0.997) than the newly defined parameter, ePLAR (area under the curve = 0.870) and the D'Alto (area under the curve = 0.756) and Opotowsky (area under the curve = 0.881) prediction rules. Moreover, the atrial workload distribution is much easier to obtain and less time-consuming than the above-mentioned scoring systems.

Study Limitations

The main limitation of the study is the absence of a normal reference value for the atrial workload distribution. Another limitation is the absence of right heart catheterization in the post-capillary group, making thus impossible further classification of the hemodynamic pattern into isolated post-capillary and combined pre-capillary and post-capillary. Even if all patients in the pre-capillary group underwent right heart catheterization, the echocardiographic data acquisition was not simultaneous with the invasive measurements, making data interpretation susceptible to variable loading conditions.

There is also a potential selection bias of the patients. On the one hand, the patients in the pre-capillary group were all referred for suspicion of pulmonary arterial hypertension, after exclusion of lung disease and chronic thromboembolic pulmonary hypertension. On the other hand, patients in the post-capillary group had either severe left systolic dysfunction or severe valvular disease; we did not include

in our study patients with diastolic dysfunction only. Further studies are needed to see if the utility of atrial workload distribution extends to other forms of pre-capillary pulmonary hypertension and to patients with heart failure with preserved ejection fraction. Last but not least, this is a single-centre experience with a small number of patients and a retrospective analysis of clinical data.

Conclusions

Comprehensive assessment of patients with pulmonary hypertension relies on the integration of clinical evaluation with imaging tools and invasive hemodynamic data; the differentiation between pre-capillary and post-capillary pulmonary hypertension is a major challenge in these patients' workup. Targeted therapies are effective only in pulmonary arterial hypertension, situation which warrants early initiation of treatment and they have no benefit in post-capillary pulmonary hypertension, making a correct diagnostic necessary in order to avoid starting an expensive, ineffective and potentially harmful treatment.

Transthoracic echocardiography is an optimal screening tool, being widely available, safe and cost-effective. Furthermore, it plays an important part in monitoring the efficacy of treatment and in prognostic assessment. Easy, reproducible echocardiographic measurements able to discriminate between the two forms of pulmonary hypertension are of the utmost importance. The atrial workload distribution is derived from simple measurements, which are routinely obtained during a standard echocardiographic study. In our study, this parameter proved to have an excellent discriminating power between the two forms of pulmonary hypertension. The simplicity and utility in clinical practice makes the atrial workload distribution a useful tool for the non-invasive differential diagnosis of pulmonary hypertension. Consequently, it has the potential to reduce the need for right heart catheterization, should it be validated in larger studies.

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Conflict of interest

The authors confirm that there are no conflicts of interest.

References

1. Galie N, Manes A, Negro L, Palazzini M, Bacchi Reggiani ML, Branzi A. A Meta-analysis of Randomized Controlled Trials in Pulmonary Arterial Hypertension. Eur Heart J 2009;30:394–403.
2. Fox BD, Shtraichman O, Langleben D, Shimony A, Kramer MR. Combination Therapy for Pulmonary Arterial Hypertension: A Systematic Review and Meta-analysis. Can J Cardiol 2016;32;12:1520–1530.
3. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I et al. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
4. Opitz CF, Hoeper MM, Gibbs SR, Kaemmerer H, Pepke-Zaba J et al. Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension: A Pathophysiological Continuum. J Am Coll Cardiol 2016;68:368-378.
5. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL et al. Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure with Preserved Ejection Fraction: A Randomized Clinical Trial. JAMA 2013;309(12):1268-1277.
6. Bonderman D, Ghio S, Felix SB Ghofrani HA, Michelakis E et al. Riociguat for Patients With Pulmonary Hypertension Caused by Systolic Left Ventricular Dysfunction: A Phase IIb Double-blind, Randomized, Placebo-controlled, Dose-ranging Hemodynamic Study. Circulation 2013;128(5):502-511.
7. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC et al. Accuracy of Doppler Echocardiography in the Hemodynamic Assessment of Pulmonary Hypertension. Am J Respir Crit Care Med 2009;179:615-621.

8. Pyxaras SA, Pinamonti B, Barbati G, Santangelo S, Valentincic M et al. Echocardiographic Evaluation of Systolic and Mean Pulmonary Artery Pressure in the Follow-up of Patients With Pulmonary Hypertension. Eur J Echocardiogr 2011;12:696-701.
9. Steckelberg RC, Tseng AS, Nishimura R, Ommen S, Sorajja P. Derivation of Mean Pulmonary Artery Pressure from Non-invasive Parameters. J Am Soc Echocardiogr 2013;26(5):464-468.
10. Patel MR, Bailey SR, Bonow RO, Chambers CE, Chan PS et al. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 Appropriate Use Criteria for Diagnostic Catheterization: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;59:1995-2027.
11. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography Endorsed by the European Association of Echocardiography, A Registered Branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23: 685-713.
12. Lang RM, Badano PL, Mor-Avi V, Afilalo J, Armstrong A et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015; 16:233-271.
13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) Developed With the Special Contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-2200.
14. Greiner S, Jud A, Aurich M, Hess A, Hilbel T et al. Reliability of Noninvasive Assessment of Systolic Pulmonary Artery Pressure by Doppler Echocardiography Compared to Right Heart Catheterization: Analysis in a Large Patient Population. J Am Heart Assoc 2014;3:e001103 doi: 10.1161/JAHA.114.001103
15. Vachiery JL, Adir Y, Barbera JA, Champion H, Coghlan JG et al. Pulmonary Hypertension Due to Left Heart Diseases. J Am Coll Cardiol 2013;62:D100-8.
16. Rezaee ME, Nichols EL, Sidhu M, Brown JR. Combined Post- and Precapillary Pulmonary Hypertension in Patients With Heart Failure. Clin Cardiol 2016;39(11):658-664.
17. Bossone E, D'Andrea A, D'Alto M, Citro R, Argiento P et al. Echocardiography in Pulmonary Arterial Hypertension: From Diagnosis to Prognosis. J Am Soc Echocardiogr 2013;26:1-14.
18. Austin C, Alassas K, Burger C, Safford R, Pagan R et al. Echocardiographic Assessment of Estimated Right Atrial Pressure and Size Predicts Mortality in Pulmonary Arterial Hypertension. Chest 2015;147(1):198-208.
19. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. A Simple Method for Noninvasive Estimation of Pulmonary Vascular Resistance. J Am Coll Cardiol 2003;41:1021-1027.
20. Abbas AE, Franey LM, Marwick T, Maeder MT, Kaye DM et al. Noninvasive Assessment of Pulmonary Vascular Resistance by Doppler Echocardiography. J Am Soc Echocardiogr 2013;26:1170-7.
21. Lindqvist P, Soderberg S, Gonzalez M, Tossavainen E, Henein MY. Echocardiography Based Estimation of Pulmonary Vascular Resistance in Patients With Pulmonary Hypertension: A Simultaneous Doppler Echocardiography and Cardiac Catheterization Study. Eur J Echocardiogr 2011;12:961-966.
22. Opotowsky AR, Clair M, Afilalo J, Landzberg MJ, Waxman AB et al. A Simple Echocardiographic Method To Estimate Pulmonary Vascular Resistance. Am J Cardiol 2013;112(6):873-882.
23. Haddad F, Zamanian R, Beraud AS, Schnittger I, Feinstein J et al. A Novel Non-Invasive Method of Estimating Pulmonary Vascular Resistance in Patients With Pulmonary Arterial Hypertension. J Am Soc Echocardiogr 2009;22:523-529.
24. Tossavainen E, Soderberg S, Gronlund C, Gonzalez M, Henein MY, Lindqvist P. Pulmonary Artery Acceleration Time in Identifying Pulmonary Hypertension Patients With Raised Pulmonary Vascular Resistance. Eur Heart J Cardiovasc Imaging 2013;14:890-897.
25. Arkles JS, Opotowsky AR, Ojeda J, Rogers F, Liu T et al. Shape of the Right Ventricular Doppler Envelope Predicts Hemodynamics and Right Heart Function in Pulmonary Hypertension. Am J Respir Crit Care Med 2011;183:268-276.
26. Ruan Q, Nagueh SF. Clinical Application of Tissue Doppler Imaging in Patients With Idiopathic Pulmonary Hypertension. Chest 2007;131:395-401.
27. Sugimoto T, Dohi K, Tanabe M, Watanabe K, Sugiura E et al. Echocardiographic Estimation of Pulmonary Capillary Wedge Pressure Using the Combination of Diastolic Annular And Mitral Inflow Velocities. J Echocardiogr 2013;11:1-8.
28. Dadfarmay S, Berkowitz R, Kim B, Manchikalapudi RB. Differentiating Pulmonary Arterial and Pulmonary Venous Hypertension and the Implications for Therapy. Congest Heart Fail 2010;16:287-291.
29. Maeder MT, Schoch OD, Kleiner R, Joerg L, Weilenmann D, on behalf of the Swiss Society for Pulmonary Hypertension. Pulmonary Hyppertension Associated With Left-Sided Heart Disease. Swiss Med Wkly. 2017;147:w14395

30. D'Alto M, Romeo E, Argiento P, Pavelescu A, Melot C et al. Echocardiographic Prediction of Pre- Versus Postcapillary Pulmonary Hypertension. J Am Soc Echocardiogr 2015;28:108-115.
31. Opotowsky AR, Ojeda J, Rogers F, Prasanna V, Clair M et al. A Simple Echocardiographic Prediction Rule for Hemodynamics in Pulmonary Hypertension. Circ Cardiovasc Imaging 2012;5(6):765-775.
32. Scalia GM, Scalia IG, Kierle R, Beaumont R, Cross DB et al. ePLAR – The Echocardiographic Pulmonary to Left Atrial Ratio – A Novel Non-Invasive Parameter to Differentiate Precapillary and Post-capillary Pulmonary Hypertension. Int J Cardiol 2016;212:379-386.