ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 3975–3983
Published online 28 June 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13496

ORIGINAL RESEARCH ARTICLE

Role of 3D echocardiography-determined atrial volumes in distinguishing between pre-capillary and post-capillary pulmonary hypertension

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Abstract

Aims The current guidelines on pulmonary hypertension (PH) recommend the use of invasive examination for differentiating between left-sided heart disease-related (post-capillary) and pre-capillary PH. However, atrial sizes are considered markers of ventricular filling pressures. Therefore, we aimed to test the clinical applicability of atrial volumes measured by transthoracic three-dimensional echocardiography (3DE) in differentiating between pre-capillary and post-capillary PH.

Methods and results Seventy-five consecutive patients with PH were prospectively examined with transthoracic 3DE. After less than 24 h, the patients underwent right heart catheterization and 3DE and were classified as pre-capillary or post-capillary PH according to the recommendations of the ESC guidelines. The atrial volumes were measured offline with dedicated commercial software. Thirty-eight patients (13 men, age 65 ± 18 year) had pre-capillary PH, and 37 (23 men, age 62 ± year) had post-capillary PH. The mean pulmonary artery pressures were similar in patients with pre-capillary and post-capillary PH (38 [IQR 26, 54] mmHg vs. 41 [IQR 33, 48] mmHg, respectively, $P = 0.49$). The left atrial indexed maximum (LAVi max) and minimum (LAVi min) volumes were significantly larger in the post-capillary PH patient group than in the pre-capillary PH patient group (LAVi max: 64 ± 32 mL/m^2 vs. 41 ± 25 mL/m^2, $P = 0.001$; LAVi min: 50 ± 22 mL/m^2 vs. 26 ± 24 mL/m^2, $P < 0.0001$). The indexed right atrial minimum volume (RAVi min) was also higher in patients with post-capillary PH (51 ± 27 mL/m^2 vs. 38 ± 26 mL/m^2; $P = 0.02$). Both the left atrial (LA) and right atrial (RA) volumes, especially the LA minimum volume, correlated with the pulmonary artery wedge pressure (PAWP) ($r = 0.62$ ($P < 0.0001$) for LAV min vs. $r = 0.49$ ($P < 0.0001$) for LAV max; $r = 0.32$ ($P = 0.005$) for RAV min vs. $r = 0.24$ ($P = 0.04$) for RAV max). Multivariate logistic regression analysis showed that LAVi min was an independent predictor of post-capillary PH. In the receiver operating characteristic (ROC) curves of parameters predicting the post-capillary PH, the areas under the curve (AUC) for LAVi min, LAVi max, and RAVi min were 0.86 (95% CI, 0.76–0.95), 0.78 (95% CI, 0.67–0.89), and 0.66 (0.53–0.78), respectively. Concerning the performance of the atrial volume ratio for differentiating post-capillary PH, the AUC of the atrial volume ratio was significantly lower [AUC: 0.66 (95% CI, 0.53–0.78)]. The ROC analysis indicated a possible cutoff value of 27.7 mL/m^2 for LAVi min to predict post-capillary PH (AUC = 0.86; sensitivity = 86%, specificity = 76%).

Conclusions The BSA-indexed left atrial minimum volume measured by transthoracic 3DE is a useful parameter for differentiating pre-capillary from post-capillary pulmonary hypertension.

Keywords Echocardiography; 3-dimensional; Left atrial volume; Pre-capillary pulmonary hypertension; Post-capillary pulmonary hypertension; Right atrial volume

Received: 15 January 2021; Revised: 3 May 2021; Accepted: 16 June 2021
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Introduction

Multiple clinical conditions can contribute to the development of pulmonary hypertension (PH). According to recent recommendations, PH can be classified into two main subtypes: pre-capillary PH (mainly due to disease of the lung vasculature or the lung itself) and post-capillary PH (secondary due to left heart disease). The two PH subtypes require distinct therapeutic strategies. The current guidelines on PH recommend the invasive measurement of pulmonary arterial wedge pressure (PAWP) using right heart catheterization (RHC) to classify PH patients into different subtypes. Post-capillary PH is defined as a PAWP above 15 mmHg.

The atrial dimensions seem to be important in PH, because they correlate with ventricular filling pressures. It is known that left atrial (LA) size is a marker of left ventricular filling pressure, which has a close relationship with PAWP.[1] Moreover, there is a strong evidence that in acquired heart disease, PAWP correlates stronger with left atrial pressure than left ventricular end-diastolic pressure.[2] The relationship between PAWP and right atrial pressure and dimensions is not clear. Several studies have shown a connection between right atrial pressure and left ventricular filling pressure in patients with heart failure with both a preserved and a reduced ejection fraction.[3,4] The left atrial size is an established marker of left ventricular filling pressure, and the right atrial dimensions may also be used as a marker of right atrial pressure.[5] These findings suggest that the right atrial size could be useful in selecting patients with pulmonary hypertension caused by left-sided heart disease.

The main limitation of conventional 2D echocardiography is that it often underestimates the atrial size, while volumes measured by three-dimensional echocardiography (3DE) tightly correlate with cardiac magnetic resonance measurements.[6,7] The study also demonstrated that LA volume provided by the 3DE measurements were more accurate and reproducible than 2DE calculations.[5] In this study, we aimed to examine the role of 3DE-measured atrial sizes in differentiating pre-capillary from post-capillary pulmonary hypertension.

Methods

Eighty-eight consecutive patients with pulmonary hypertension followed by the Pulmonary Hypertension Outpatient Clinic of the Department of Cardiology and Cardiac Surgery, University of Debrecen, between December 2018 and January 2020 were included. The patients were scheduled for an echocardiographic examination and right heart catheterization to verify the diagnosis and to plan a treatment strategy. All of the patients read and signed the informed consent before the examination, as approved by the local ethics committee (No: 5893-2/2018/EKU). This investigation conforms with the principles outlined in the Declaration of Helsinki (Br Med J 1964; ii: 177).

Right heart catheterization

Right heart catheterization examination was performed by an independent cardiologist who was blinded to the results of the echocardiographic examination and data. The initial access site was the superior vena cava via the jugular vein, and a 7-F Swan-Ganz catheter (B. Braun Melsungen AG, Melsungen, Germany) was introduced. The methods used for the right heart catheterization and the measurement of the haemodynamic parameters were performed as previously described.[8] A triple-lumen, balloon-tipped thermodilution catheter was used for the measurement of intracardiac pressures, pulmonary artery wedge pressure (at end-expiration), and cardiac output (CO). A blood sample was drawn to evaluate the pulmonary artery oxygen saturation. CO was calculated with a minimum of three (in atrial fibrillation or frequently occurring premature contractions, a minimum of five) consecutive measurements that should not differ by $>$10%. Pulmonary vascular resistance (PVR) was calculated based on the inflow and outflow pressure values, and CO was measured by thermodilution. The variables that were collected included pulmonary artery pressure (PAP, systolic, diastolic, and mean), mean PAWP, mean right arterial pressure, PVR, CO, and CI. None of the patients had interatrial or interventricular shunts. Pressure values were expressed as mmHg, and PVR was expressed as dyne/s/cm. PH was defined as a mean pulmonary arterial pressure (PAPm) $\geq$25 mmHg at rest[9] by direct pressure measurements during right heart catheterization. Seventy-five patients fulfilled the PAPm criteria. Pre-capillary PH was defined if the PAWP was 15 mmHg or lower, and post-capillary PH was defined if the pulmonary capillary wedge pressure was higher than 15 mmHg.[9]

Echocardiography

Echocardiography examinations were performed in all 75 patients within 24 h of right heart catheterization according to the local protocol. 3DE was acquired using an Epiq 7C (Philips Medical Systems, Andover, MA) equipped with an X5-1 transducer. Patients were scanned in the left lateral decubitus position on an examination bed with a dedicated left-sided cutout, which allows optimal probe access for apical RV-focused acquisitions. Full-volume acquisitions of the RV, including the RA, were performed from the RV-focused apical view during a single breath-hold using second-harmonic imaging, and the full-volume acquisitions of the LA were performed from the LA-focused apical view.

The image acquisition method was the same as that used for recording the RV images. The gain settings were optimized before the data acquisition. The temporal resolution was maximized by optimizing the sector width and minimizing the depth. The image optimization manoeuvres were implemented as previously described.[10] Whenever possible, imaging included 6-beat 3D full-volume datasets focused on the desired chamber in one single breath hold. The average frame rate was 32 ± 9 volumes/s for RV, 32 ± 17 volumes/s for RA, and 42 ± 24 volumes/s for the LA datasets. All 3D datasets were digitally stored and analysed offline.

3D measurements

3DE datasets of the RV were analysed offline to measure the end-diastolic and end-systolic volumes and the ejection fraction of the right ventricle using a commercial software package (4D RV-Function 2.0, TomTec Imaging Systems GmbH, Unterschleissheim, Germany). The software was previously validated against cMRI.[11,12] Commercial software was used to analyse the 3DE datasets of the LA and RA, where the maximum and minimum atrial volumes were analysed (4D Cardio-view 3, Tomtec Imaging Systems GmbH, Unterschleissheim, Germany). The end-systolic and the end-diastolic frame chosen by the software were checked and adjusted manually to the timing of the AV valve movement, if necessary. All of the volumetric analyses were performed by an experienced cardiologist who was blinded to the RHC-derived data. The atrial volume ratio was calculated from the ratio of the RA volume to the LA volume.

Statistical analysis

Statistical analyses were performed with SPSS 24.0 for Windows (Statistical Product and Service Solutions, version 24, SPSS Inc., Chicago, IL, USA). Normality was assessed with a normal probability (Q-Q) plot and with a Shapiro–Wilk test. All continuous variables are reported as the mean ± standard deviation. The analyses for continuous data were performed with independent *t*-test. Non-normally distributed values are expressed as the median (interquartile range) and were compared using the Mann–Whitney *U* test. The correlations were checked using Spearman's correlations. Univariate logistic regression analysis was performed to determine factors associated with post-capillary PH. Continuous variables with significant correlations >0.70 or <-0.70 were considered to have collinearity. Clinical relevance determined which variables were to be included in the multivariate regression models. Significant associations from the univariate analysis then were analysed with a multivariate logistic regression model with forward selection depending upon likelihood ratio statistics to identify the independent predictors of post-capillary PH. Odds ratio and 95% CIs were calculated at each independent continuous variable. Mathematical calculations regarding the variables without normal distribution were performed before the logistic regression analysis. ROC analysis was used to compare the distinction performance of the independent parameters and to determine the cutoff value. Agreement between 2DE and 3DE left atrial volumes was analysed using Bland–Altman method. To assess the reproducibility in left atrial volumes, 10 randomly selected patients were remeasured by the observer who initially analysed the selected images (intraobserver variability) and by an independent observer who was blinded to the initial observer's results (interobserver variability). Intraobserver and interobserver variability was expressed in percent variability, defined as the absolute differences between pairs of repeated measurements divided by their mean. A value of $P < 0.05$ was accepted as indicative of statistical significance, and all *P* values were two-sided.

Results

Patient characteristics

Thirty-eight patients had pre-capillary PH, while 37 patients had post-capillary PH. *Table 1* summarizes the characteristics of the patients. There were more male patients in the post-capillary PH group, and their body surface area (BSA) was significantly higher. Systemic blood pressure and heart rate did not differ between the groups. According to the NICE classification,[9,13] patients with post-capillary PH predominantly belonged to group 2, while most of the patients with pre-capillary PH could be classified into group 1, 3, and 4.

Right heart catheterization parameters

Although their pulmonary artery pressure values were similar, the pulmonary vascular resistance was higher in the pre-capillary PH group than in the post-capillary PH group (571 (IQR 279, 942) dyne/s/cm vs. 370 (IQR 253, 452) dyne/s/cm; $P = 0.017$). The mean right atrial pressure was found to be significantly higher in the post-capillary group (13 ± 6 mmHg vs. 8 ± 5 mmHg; $P = 0.001$), as was the PAWP (12 (IQR 9, 13) mmHg vs. 22 (IQR 17, 26) mmHg; $P < 0.0001$) (*Table 1*).

Echocardiographic parameters

Right ventricular systolic function was impaired in both groups (the RVEF was 34 ± 12% in pre-capillary PH vs. 29 ± 8% in post-capillary PH; $P = 0.06$). The right ventricular indexed end-systolic volume was higher in the post-capillary

Table 1 Clinical characteristics of the patients with pre-capillary and post-capillary PH

	Pre-capillary PH (n = 38)	Post-capillary PH (n = 37)	P
Clinical characteristics			
Age (year) mean (mean ± SD)	65 ± 18	62 ± 8	0.33
Male, *n* (%)	13 (34)	23 (62)	0.015
BSA (kg/m^2) median (IQR)	1.73 (1.63, 1.85)	1.98 (1.82, 2.18)	<0.0001
HR (1/min) (mean ± SD)	77 ± 15	78 ± 12	0.71
ABPs (mmHg) (mean ± SD)	129 ± 25	121 ± 23	0.17
ABPd (mmHg) (mean ± SD)	72 ± 14	73 ± 11	0.68
Atrial fibrillation, *n* (%)	9 (24%)	14 (38%)	0.14
Mitral regurgitation			0.004
Mitral regurgitation, mild *n* (%)	20 (53%)	14 (38%)	
Mitral regurgitation, moderate *n* (%)	7 (18%)	20 (54%)	
Mitral regurgitation, severe *n* (%)	0 (0%)	1 (3%)	
Mitral stenosis, *n* (%)	0 (0%)	0 (0%)	
Tricuspid regurgitation			0.08
Tricuspid regurgitation, mild *n* (%)	0 (0%)	1 (3%)	
Tricuspid regurgitation, moderate *n* (%)	35 (92%)	27 (73%)	
Tricuspid regurgitation, severe *n* (%)	3 (8%)	9 (24%)	
Classification (NICE) *n* (%)			
Group 1	19 (50%)	1 (2.7%)	
Group 2	1 (2.6%)	35 (94.6%)	
Group 3	9 (23.7%)	0 (0%)	
Group 4	8 (21.1%)	1 (2.7%)	
Group 5	5 (2.6%)	0	
Right heart catheterization			
PAPm (mmHg) median (IQR)	38 (26, 54)	41 (33, 48)	0.49
PVR (dyns) median (IQR)	571 (279, 942)	370 (253, 452)	0.017
RAPm (mmHg) (mean ± SD)	8 ± 5	13 ± 6	0.001
PAWP (mmHg) median (IQR)	12 (9, 13)	23 (17, 26)	<0.0001
3D echo parameters			
Right ventricle			
RV EDVi (mL/m^2) median (IQR)	103 (78, 132)	118 (96, 142)	0.07
RV ESVi (mL/m^2) median (IQR)	69 (45, 93)	81 (65, 101)	0.03
RV EF (%) (mean ± SD)	34 ± 12	29 ± 8	0.06
Right atrium			
RAVi max (mL/m^2) (mean ± SD)	55 ± 26	63 ± 25	0.19
RAVi min (mL/m^2) (mean ± SD)	38 ± 26	51 ± 27	0.03
Left ventricle			
LVEDVi (mL/m^2) median (IQR)	40 (33, 53)	92 (49, 128)	<0.0001
LVESVi (mL/m^2) median (IQR)	18 (16, 27)	62 (36, 103)	<0.0001
LVEF (%) median (IQR)	53 (49, 57)	27 (18, 41)	<0.0001
Left atrium			
LAVi max (mL/m^2) (mean ± SD)	41 ± 25	64 ± 32	0.001
LAVi min (mL/m^2) (mean ± SD)	26 ± 24	50 ± 22	<0.0001
Atrial volume ratio (RAVi max/LAVi max)	1.66 ± 1.1	1.1 ± 0.6	0.02

ABPd, diastolic arterial blood pressure; ABPs, systolic arterial blood pressure; BSA, body surface area; HR, heart rate; IQR, interquartile range; LAVi max, BSA indexed left atrial maximum volume; LAVi min, BSA indexed left atrial minimum volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; PAPm, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAPm, mean right atrial pressure; RAVi max, maximum right atrial volume index; RAVi min, minimum right atrial volume index; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume index; SD, standard deviation.

PH group (pre-capillary PH: (69 (IQR 45, 93) mL/m^2 vs. 81 (IQR 65, 101) mL/m^2; P = 0.032). Both the maximum and minimum indexed left atrial volumes were larger in the post-capillary PH group (LAVi max: 41 ± 25 mL/m^2, LAVi min: 26 ± 24 mL/m^2 in the pre-capillary PH vs. the LAVi max: 64 ± 32 mL/m^2, LAVi min: 50 ± 22 mL/m^2 in the post-capillary PH; $P < 0.0001$), even though only the indexed minimum volume of the right atrium was significantly lower in the pre-capillary PH group (RAVI min: 38 ± 26 mL/m^2 in the pre-capillary PH vs. 51 ± 27 mL/m^2 in the post-capillary PH; P = 0.02). The atrial volume ratios were similar in the two patient groups (1.66 ± 1.1 in the pre-capillary PH vs. 1.1 ± 0.59 in the post-capillary PH; P = 0.02). The left ventricular volumes were significantly larger, while LVEF was lower in the post-capillary PH group (*Table 1*).

Regression analysis

Linear regression analysis revealed a significant correlation between the LA minimum and maximum volumes and the PAWP (r^2 = 0.38 ($P < 0.0001$) for LA minimum volume and

r^2 = 0.24 ($P < 0.0001$) for LA maximum volume) (*Figure 1*). Both RA minimum and maximum volumes correlated with the mean right atrial pressure and the PAWP; however, the relationship between the PAWP and the RA minimum volume was stronger (r^2 = 0.1 (P = 0.005) for RA minimum volume vs. PAWP; r^2 = 0.05 (P = 0.04) for RA maximum volume vs. PAWP, *Figure 2*). The RA volumes showed a stronger correlation with the mean right atrial pressure, and the RA minimum volume correlated better with the RAPm than the RA maximum volume (r^2 = 0.29 ($P < 0.0001$) vs. r^2 = 0.22 ($P < 0.0001$), respectively, *Figure 2*). According to the relevant LV parameters, the BSA indexed LV end-diastolic volume correlated with the PAWP (r^2 = 0.37; $P < 0.0001$), and it was stronger than the correlation of LVEF with the PAWP (r^2 = −0.27; $P < 0.0001$).

Logistic regression analysis was used to determine which of these parameters can be used to distinguish between pre-capillary and post-capillary PH. The univariate logistic regression analysis demonstrated that the PVR, mean right atrial pressure, RAVi min, indexed left atrial maximum and minimum volume, LVEDVi, and LVEF were correlated with post-capillary PH (*Table 2*). When association between the parameters was tested, significant correlations (Spearman rank correlation <-0.70 and >0.70) were observed between LVEF and end-diastolic volume, and LAVi maximum and minimum volume. We opted to include the highly correlated parameters in those pairs. The following parameters were chosen as inputs for multivariate logistic regression model: PVR, mean RAP, LVEDVi, right atrial and left atrial minimum volume. The model showed three significant variables: mean RAP (OR: 1.39; 95% CI, 1.13–1.72; P = 0.002), LVEDVi (OR: 1.05; 95% CI, 1.02–1.08; P = 0.001), and LAVi minimum (OR: 1.09; 95% CI, 1.02–1.16; P = 0.011), which were identified as the strongest independent predictors detecting post-capillary PH. Regarding the ROC curves of the parameters for predicting post-capillary PH, the AUCs for mean RAP, LVEDVi, and LAVi min were 0.71 (95% CI, 0.59–0.82), 0.80 (95% CI, 0.71–0.9), and 0.86 (0.76–0.95), respectively. Concerning the performance of the atrial volume ratio and the LAVI max for differentiating post-capillary PH, the AUCs were much lower [AUC of atrial volume ratio: 0.66 (95% CI, 0.53–0.78) and AUC of LAVi max: 0.78 (95% CI, 0.67–0.89)]. The ROC analysis indicated a possible cutoff value of

Figure 1 Linear regression plots of left atrial volumes, left ventricular end-diastolic volumes and ejection fraction, and pulmonary artery wedge pressure. Relationship between the left atrial minimum volume and the pulmonary artery wedge pressure (A), the left atrial maximum volume and the pulmonary artery wedge pressure (B). Correlation between left ventricular end-diastolic volume and the pulmonary artery wedge pressure (C) and between the left ventricular ejection fraction and the pulmonary artery wedge pressure (D). LAV min, left atrial minimum volume; LAV max, left atrial maximum volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; PAWP, pulmonary artery wedge pressure; r^2, Spearman correlation coefficients.

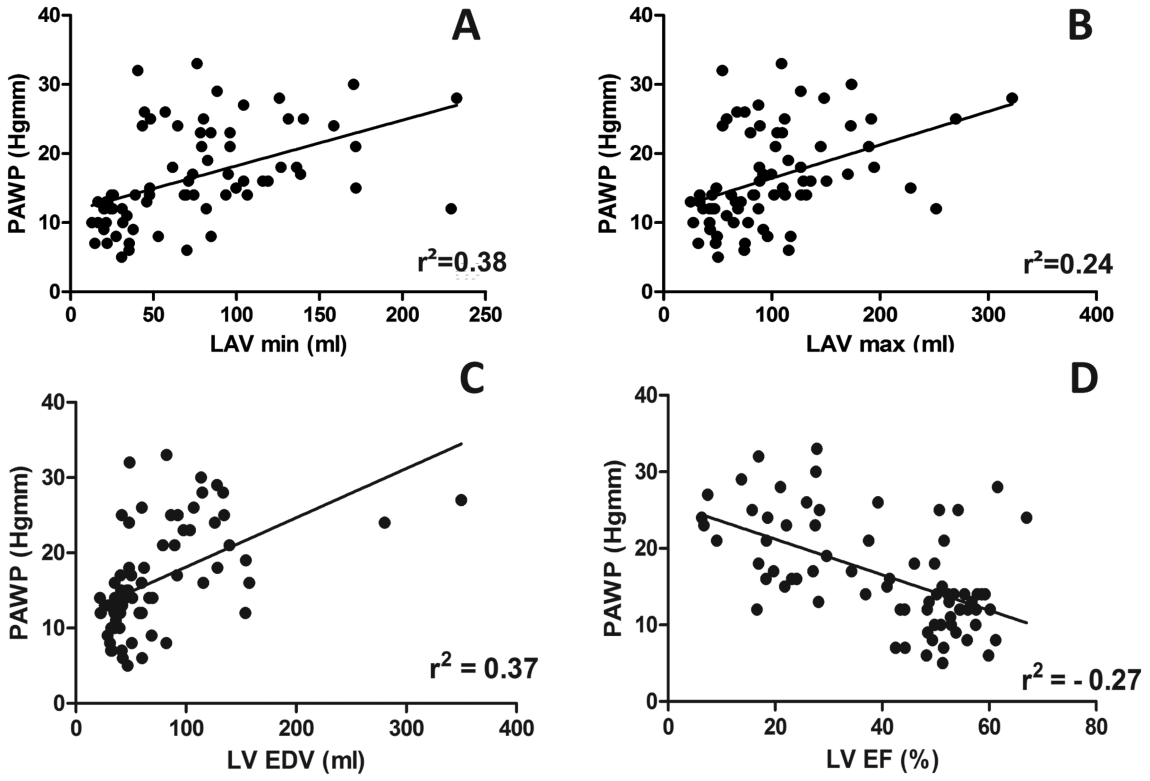


Figure 2 Linear regression plots of right atrial volumes and pulmonary artery wedge pressure and mean right atrial pressure. Relationship between the right atrial minimum volume and the pulmonary artery wedge pressure (A), the right atrial maximum volume and the pulmonary artery wedge pressure (B), the right atrial minimum volume and the mean right atrial pressure (C) and the right atrial maximum volume and mean right atrial pressure (*D*). RAV min, right atrial minimum volume; RAV max, right atrial maximum volume; PAWP, pulmonary artery wedge pressure; RAPm, mean right atrial pressure; r^2, Spearman correlation coefficients.

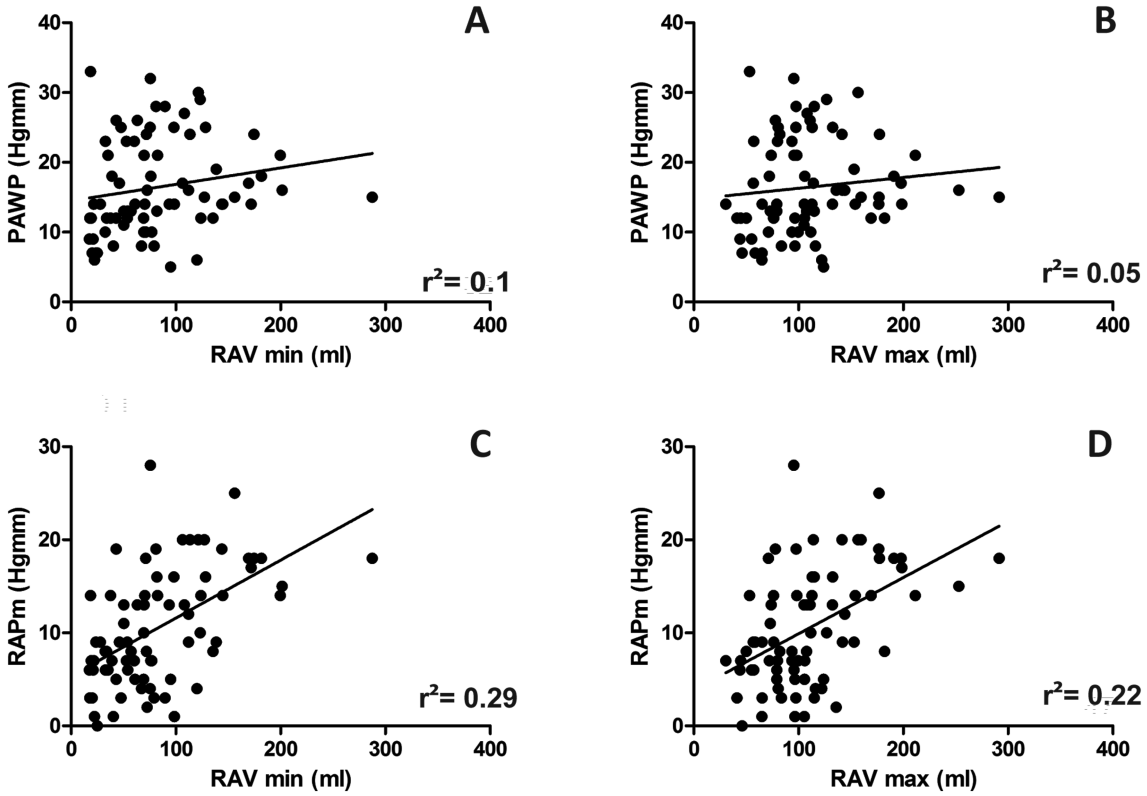


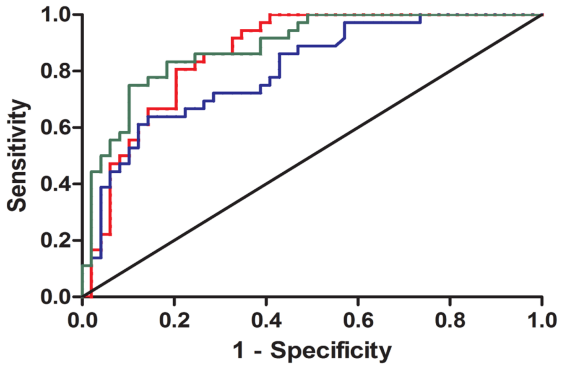
Table 2 Univariate and multivariate modelling of parameters discriminating pre-capillary from post-capillary PH

Variable	Univariate analysis: OR (95% CI)	*P* value	Multivariate analysis: OR (95% CI)	*P* value
PAPm	1.01 (0.98–1.1)	0.5		
PVR	0.998 (0.997–1)	0.015		
RAPm	1.16 (1.05–1.28)	0.002	1.39 (1.13–1.72)	0.002
RV EDVi	1.01 (0.998–1.02)	0.11		
RV ESVi	1.01 (1–1.03)	0.06		
RV EF	0.96 (0.91–1)	0.66		
RAVi max	1.01 (0.99–1.03)	0.194		
RAVi min	1.02 (1–1.04)	0.038		
LVEDVi	1.04 (1.02–1.05)	<0.0001	1.05 (1.02–1.08)	0.001
LVEF	0.88 (0.83–0.93)	<0.0001		
LAVi max 3D	1.04 (1.02–1.06)	<0.0001		
LAVi min 3D	1.09 (1.05–1.13)	<0.0001	1.09 (1.02–1.16)	0.011

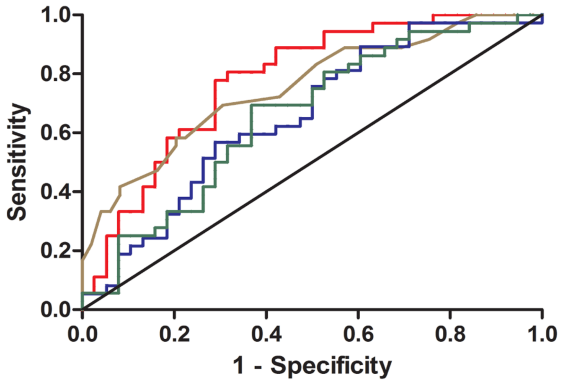
CI, confidential interval; LAVi max, BSA indexed left atrial maximum volume; LAVi min, BSA indexed left atrial minimum volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; PAPm, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RAPm, mean right atrial pressure; RAVi max, maximum right atrial volume index; RAVi min, minimum right atrial volume index; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume index.

27.7 mL/m^2 for LAVi min (AUC = 0.86; sensitivity = 86%, specificity = 76%) and 59 mL/m2 for LVEDVi (AUC = 0.80; sensitivity = 72%, specificity = 71%) to predict post-capillary PH (*Figure 3*). Combining the LVEDVi and LAVI min, the differentiation capability of the volumetric measurement could increase the performance (AUC = 0.89 (95% CI, 0.82–0.96);

Figure 3 Receiver operating characteristic curves for detecting post-capillary pulmonary hypertension. RAPm, mean right atrial pressure; LVEDVi, BSA indexed left ventricular end-diastolic volume; LAVi min, BSA indexed left atrial minimum volume; LAVi max, BSA indexed left atrial maximum volume; RAVi min, BSA indexed minimum right atrial volume; AUC, area under curve; CI, confidential interval.



	AUC	95% CI
LAVi min	0.86	0.76-0.95
LV EDVi	0.80	0.71-0.90
LAVI min + LV EDVi	0.89	0.82-0.96



	AUC	95% CI
LAVi max	0.78	0.67-0.89
RAPm	0.71	0.59-0.82
RAVi min	0.66	0.53-0.78
Atrial volume ratio	0.66	0.53-0.78

sensitivity = 83%, specificity = 82%) which underlines the additive value of LAVI minimum over the LVEDVi for predicting post-capillary PH (*Figure 3*). Because of the correlation of the mean RAP and the RAVI min, we tested the performance of RAVI min, which was low, as expected (AUC = 0.66; 95% CI, 0.53–0.78) (*Figure 3*).

Intraobserver and interobserver variability for LAVi min was good, as reflected by percent variability of 2% at 2DE and 1% at the 3DE measurements (*Table 3*). As expected, the bias between the 2DE and the 3DE measured volume was larger in post-capillary PH group (9 mL (IQR 3, 15) in pre-capillary and 20 mL (IQR 6, 31) in post-capillary, $P = 0.006$) where the atrial volumes were significantly larger causing less accuracy regarding probably the geometrical assumption (*Table 4*).

Table 3 Reproducibility of left atrial volumes by three-dimensional echocardiography

Variable	Intraobserver	Interobserver
2DE LAV max (bias% ± SD)	3.1 (9)	2.1 (3)
2DE LAV min (bias% ± SD)	2 (23)	2.2 (26.7)
3DE LAV max (bias% ± SD)	0.2 (2.1)	0.6 (2.6)
3DE LAV min (bias% ± SD)	1.1 (4.2)	1.3 (4.5)

LAV max, left atrial maximum volume; LAV min, left atrial minimum volume; SD, standard deviation.

Discussion

This study revealed that the BSA-indexed left atrial minimum volume (LAVi min) is a useful (sensitive and quite specific) parameter in differentiating between pre-capillary and post-capillary PH: the LAVi min is higher in pre-capillary PH and is able to differentiate pre-capillary and post-capillary PH better than the atrial volume ratio or the maximum LA volume. The differentiation ability could be improved if the 3DE measured atrial minimum volume data combined with the left ventricular end-diastolic volume.

Distinguishing between pre-capillary and post-capillary PH is important because of their different treatment strategies. The current guidelines recommend a classification that requires invasively measured mean PAP and PAWP. The differential diagnosis is challenging without these invasive measurements (RHC).

Recent studies have examined the role of atrial size in the differential diagnosis of the two PH phenotypes. Veld *et al*.

Table 4 Bias between 2DE and 3DE measurement

Bias between 2DE and 3DE measurement	Pre-capillary PH	Post-capillary PH	
LAV max bias (mL median, IQR)	11 (5, 20)	17 (8, 33)	$P = 0.03$
LAV min bias (mL median, IQR)	9 (3, 15)	20 (6, 31)	$P = 0.006$

IQR, interquartile range; LAV max, left atrial maximum volume; LAV min, left atrial minimum volume.

demonstrated that the ratio of LA and RA maximum area ratio assessed by CT is a potentially useful parameter.[14] Saito *et al*. also showed that the atrial volume ratio (RA maximum volume divided by LA maximum volume) is a useful parameter for differentiating pre-capillary and post-capillary PH.[15] These studies mainly focused on the LA maximum volume.

It is known that LA size is a marker of left ventricular diastolic dysfunction, as increased left ventricular filling pressure leads to LA enlargement. Most of the studies describing the prognostic value of LA size have focused on the LA maximum volume, but the most recent results support measuring the minimum volume of LA instead, because during diastole, the exposure of the LV diastolic pressure is the major factor that determines the LA minimum volume.[16] It was found that the LA minimum volume is a better marker of LV filling pressure and elevated PAWP. Moreover, it predicts major cardiovascular events better than the LA maximum volume.[17] Currently, the standard echocardiographic method used to estimate the LA volume is the 2DE biplane method, but it gives inaccurate results due to the LA shape complexity. Wu *et al*. evaluated the prognostic value of the LA volume, demonstrating that the 3DE-measured LA minimum volume is superior to the conventional 2DE-based estimation.[18]

In our patient population, PAWP correlated better with the LA minimum volume than the LA maximum volume. The LA volumes were increased in the post-capillary PH group, where the PAWP was significantly higher than that in the pre-capillary PH group. The elevated left ventricular filling pressure affected both the PAWP and the left atrial volumes, mainly the LA minimum volume. Our results confirmed that the left atrial minimum volume reflects the increased left ventricular filling pressure.[16,17] Left atrial pressure also correlates with PAWP and the LV end-diastolic pressure. The relationship between PAWP and the LVEDV was good in our population. Adding this to the left atrial minimum volume increased the atrial volume performance in differentiating post-capillary PH.

In contrast, the RA volume is affected by right ventricular pressure overload due to elevated PAP, and it was similarly increased in both the pre-capillary and post-capillary PH groups. Both the RA minimum and maximum volumes were correlated with mean right atrial pressure and the PAWP, and their relationship with the RA minimum volume was stronger for the pressure values than for the maximum volume. The RA minimum volume was significantly lower in the pre-capillary PH group, while the right atrial pressure was lower than that in the post-capillary PH group. This is a potential explanation for why the right atrial minimum volume could discriminate between the pre-capillary and post-capillary PH groups, but with less efficacy than the LA minimum volume.

A recent study assessing LA and RA maximum volumes by TTE showed that these parameters are useful in differentiating pre-capillary and post-capillary PH.[15] Their results were comparable with our findings: the LA maximum volume was larger in the post-capillary PH group, and the RA maximum volume did not differ significantly between the PH groups. In addition, we found that the LA minimum volume was a more powerful parameter for differentiating between pre-capillary and post-capillary PH.

Limitations of the study

This study was a single-centre study with a relatively small sample size. The software used for the measurement of the LA volumes was 3D-based but was not specifically dedicated to 3D left atrial volume measurements.

Conclusions

The left atrial minimum volume determined by 3D echocardiography is a useful (sensitive and quite specific) parameter differentiating pre-capillary from post-capillary PH. The 3DE LAVi minimum discriminates better between the two PH phenotypes than the LAVI maximum or the left and right atrial maximum volume ratios.

Conflict of interest

None declared.

Funding

This work was funded by the Hungarian Government Research Fund [GINOP-2.3.2-15-2016-00043, Szív- és érkutatási kiválóságközpont (IRONHEART)].

Author contributions

Cs. Jenei and Z. Csanádi did the study design. Statistical analysis was carried out by Cs. Jenei. Manuscript editing was carried out Cs. Jenei and A. Borbély. Echocardiographic image was acquired by Cs. Jenei, A. Péter, and A. Daragó. Cs. Jenei analysed the study. Right heart catheterization was performed by L. Balogh, A. Borbély, and F. Győry. R. Kádár did the data management. Cs. Jenei and R. Kádár did the literature research. Manuscript revision (and helped in approval in article) was carried out by A. Borbély and Z. Csanádi.

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