A novel echocardiographic method for estimation of pulmonary artery wedge pressure and pulmonary vascular resistance

Vladislav Chubuchny1, Nicola Riccardo Pugliese2, Claudia Taddei1, Elisa Poggianti1, Valentina Spini1, Andrea Barison1,3, Bruno Formichi1,4, Edoardo Airò1, Carolina Bauleo1, Renato Prediletto1,4, Luigi Emilio Pastormerlo1, Michele Coceani1, Marco Ciardetti1, Christina Petersen1, Emilio Pasanisi1, Carlo Lombardi5, Michele Emdin1,3 and Alberto Giannoni1,3*

1Cardiology and Cardiovascular Medicine Department, Fondazione Toscana G. Monasterio, Pisa, Italy; 2Cardiothoracic and Vascular Department, University Hospital of Pisa, Pisa, Italy; 3Institute of Life Sciences, Scuola Superiore Sant’Anna, Piazza Martiri della Libertà 33, Pisa, 56127, Italy; 4CNR Institute of Clinical Physiology, Pisa, Italy; 5Institute of Cardiology, ASST Spedali Civili di Brescia and Department of Medical and Surgical Specialities, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy

Abstract

Aims This study aimed to evaluate a novel echocardiographic algorithm for quantitative estimation of pulmonary artery wedge pressure (PAWP) and pulmonary vascular resistance (PVR) in patients with heart failure and pulmonary hypertension (PH) scheduled to right heart catheterization (RHC).

Methods and results In this monocentric study, 795 consecutive patients (427 men; age 68.4 ± 12.1 years) undergoing echocardiography and RHC were evaluated. Multiple regression analysis was performed to identify echocardiographic predictors of PAWP and PVR measured by RHC in the derivation group (the first 200 patients). The diagnostic accuracy of the model was then tested in the validation group (the remaining 595 patients). PH was confirmed by RHC in 507 (63.8%) patients, with 192 (24.2%) cases of precapillary PH, 248 (31.2%) of postcapillary PH, and 67 (8.4%) of combined PH. At regression analysis, tricuspid regurgitation maximal velocity, mitral E/e’ ratio, left ventricular ejection fraction, right ventricular fractional area change, inferior vena cava diameter, and left atrial volume index were included in the model (R = 0.8, P < 0.001). The model showed a high diagnostic accuracy in estimating elevated PAWP (area under the receiver operating characteristic curve = 0.97, 92% sensitivity, and 93% specificity, P < 0.001) and PVR (area under the receiver operating characteristic curve = 0.96, 89% sensitivity, and 92% specificity, P < 0.001), outperforming 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations (P < 0.001) and Abbas’ equation (P < 0.001). Bland–Altman analysis showed satisfactory limits of agreement between echocardiography and RHC for PAWP (bias 0.7, 95% confidence interval /C0 7.3 to 8.7) and PVR (bias /C0 0.1, 95% confidence interval /C0 2.2 to 1.9 Wood units), without indeterminate cases.

Conclusions A novel quantitative echocardiographic approach for the estimation of PAWP and PVR has high diagnostic accuracy in patients with heart failure and PH.

Keywords Echocardiography; Pulmonary artery wedge pressure; Pulmonary vascular resistance; Pulmonary hypertension; Right heart catheterization

Received: 13 August 2020; Revised: 26 October 2020; Accepted: 3 December 2020

*Correspondence to: Alberto Giannoni, Institute of Life Sciences, Scuola Superiore Sant’Anna, Piazza Martiri della Libertà 33, 56127 Pisa, Italy. Tel: +39-050-3152189; Fax: +39-050-3152109. Email: agiannon@ftgm.it; a.giannoni@santannapisa.it

Introduction

Right heart catheterization (RHC) is the gold standard for the evaluation of cardiopulmonary haemodynamics, because it allows to (i) diagnose pulmonary hypertension (PH) by using mean pulmonary artery pressure (PApm ≥ 25 mmHg at rest according to the European Society of Cardiology/European Respiratory Society guidelines1 or >20 mmHg according to...
the 6th World Symposium on Pulmonary Hypertension recommendations\(^3\) and (ii) distinguish by using pulmonary artery wedge pressure (PAWP) and pulmonary vascular resistance (PVR) between precapillary PH [PAWP ≤ 15 mmHg and PVR ≥ 3 Wood units (WU)], isolated postcapillary PH (PAWP > 15 mmHg and PVR < 3 WU), and combined PH (PAWP > 15 mmHg and PVR ≥ 3 WU).\(^1\) Precapillary PH is usually associated with pulmonary arterial hypertension, post-embolic PH, or PH due to lung disease or hypoxia, while isolated postcapillary and combined PH are mainly due to heart failure (HF) or valvular diseases. Therefore, misclassification of the PH subtype may cause incorrect therapy and adverse prognosis.\(^3\)

Echocardiography has emerged as a non-invasive tool to evaluate cardiopulmonary haemodynamics.\(^4–7\) Following the complex 2009 American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) recommendations for diastolic function assessment,\(^8\) in 2016, an ASE/EACVI update proposed a simplified approach to estimate PAWP,\(^9\) providing however a semiquantitative and not quantitative measurement of PAWP. As a result, PVR cannot be calculated, and the distinction between precapillary and postcapillary PH remains elusive. Abbas et al. developed an algorithm to calculate PVR in a population of patients with precapillary PH, but this method may lead to false-positive results in patients with HF and elevated PAWP.\(^5\)

Considering that PAPm is composed of PAWP plus the transpulmonary pressure gradient (TPG), we developed a mathematical model to predict the ratio between PAWP and PAPm by using standard echocardiographic variables in a derivation cohort. From this model, we obtained a quantitative echocardiographic estimate of both PAWP and PVR (PAWP\(_{\text{echo}}\) and PVR\(_{\text{echo}}\)), and we then tested the accuracy of the model against RHC in a large validation cohort.

**Methods**

In this monocentric study, patients referred for RHC from the Department of Cardiology and the Department of Pneumology of Fondazione Toscana G. Monasterio, Pisa, Italy, between 2013 and 2019 were consecutively evaluated. Exclusion criteria were the presence of uncorrected intra-cardiac or extra-cardiac shunts and poor echocardiographic image quality, including inadequate Doppler signals of tricuspid regurgitation (TR) and pulmonary regurgitation (PR).

All patients underwent a complete echocardiographic Doppler examination within 24 h from but always before RHC. Diuretics, inotropes, and vasodilators were not administered between echocardiography and RHC. Beyond echocardiography and RHC, all patients also underwent a thorough clinical evaluation and laboratory characterization including plasma N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP, ECLIA monoclonal method, Roche Diagnostics\(^6\), Basel, Switzerland) and high-sensitivity cardiac troponin T (hs-cTnT, Roche Diagnostics).

**Right heart catheterization**

Right heart catheterization with a flow-directed pulmonary artery catheter was used to measure at end-expiration right atrial pressure (RAP\(_{\text{cath}}\)), right ventricular (RV) pressure, systolic pulmonary artery pressure (PAPs\(_{\text{cath}}\)), diastolic pulmonary artery pressure (PAPd\(_{\text{cath}}\)), PAPm\(_{\text{cath}}\), and PAWP\(_{\text{cath}}\). The right position of the Swan–Ganz catheter when measuring PAWP was verified during the procedure by fluoroscopy, with deflation, retraction, repositioning, and reinfalation in a different branch of the pulmonary artery in case of suboptimal PAWP measurement.

Cardiac output (CO) was calculated by thermodilution as a mean of three or five consecutive measurements (varying <10%) in patients with sinus rhythm and atrial fibrillation (AF), respectively. TPG was calculated as PAPm\(_{\text{cath}}\) – PAWP\(_{\text{cath}}\), while PVR\(_{\text{cath}}\) as the TPG/CO ratio. We followed the 2015 European Society of Cardiology/European Respiratory Society guidelines,\(^1\) in which PAPm ≥ 25 mmHg constitutes the threshold for the definition of PH, instead of the more recent 6th World Symposium on Pulmonary Hypertension recommendations,\(^2\) because the latter does not address the patient subgroup with PAWP ≤ 15 mmHg and PVR < 3 WU.

**Transthoracic Doppler echocardiography**

Echocardiography (Philips iE33 xMATRIX echocardiography system, Andover, MA) was performed according to international recommendations.\(^10–13\) Sonographers (C. T. and E. P.) were blinded to RHC results. Every recorded image consisted of at least three or five cardiac cycles in patients in sinus rhythm and AF, respectively.

Stroke volume was calculated by multiplying the left ventricular (LV) outflow tract area by the LV outflow tract velocity–time integral measured by pulsed-wave Doppler. In patients with significant aortic regurgitation, RV outflow tract was used. CO was calculated by multiplying stroke volume by heart rate. RAP\(_{\text{echo}}\) was assessed by measuring inferior vena cava (IVC) diameter and its variations during the respiratory cycle, including a brief sniff to elicit the inspiratory response.\(^6–11\) PAPs\(_{\text{echo}}\) was calculated by adding RAP\(_{\text{echo}}\) to the maximal systolic pressure gradient from tricuspid regurgitation velocity (TRV). PAPm\(_{\text{echo}}\) was calculated by adding...
RAP\textsubscript{echo} to the PR end-diastolic gradient (PREDG). PAP\textsubscript{m,echo} was calculated as \((\text{PAP}_{\text{echo}} + 2 \cdot \text{RAP}_{\text{echo}})/3\).

Left atrial volume index (LAV\textsubscript{i}) was estimated with the disc summation algorithm (Simpson’s technique) in a biplane approach from the apical four-chamber and two-chamber view.\(^1\) The grading of mitral regurgitation (MR) was assessed by measuring the vena contracta, with proximal isovelocity surface area method when assessable, dominant E wave in the mitral inflow (>1.5 m/s), systolic flow reversal in the pulmonary veins, and jet swirling used as supportive indices of severe MR.\(^2\) LV filling pressure was evaluated according to current recommendations using a comprehensive approach, which included the estimation of TRV, LAV\textsubscript{i}, isovolumic relaxation time, and different \(E/e’\) ratio thresholds in special conditions, such as severe MR and AF.\(^9,14\)

To maximize image quality and decrease the likelihood of discarding patients for poor acoustic windows, we also employed off-axis approaches, such as the RV inflow tract for TR, subcostal view for PR, and left lateral approach for IVC dimension and variations.

**Statistical methods**

Data were analysed with SPSS version 23.0 (IBM Corp., Armonk, NY). Continuous measures were expressed as mean ± standard deviation or median and inter-quartile range and compared by using Student’s t-test or Mann–Whitney U test, as appropriate. Categorical variables were presented as numbers and percentages and compared by using the \(\chi^2\) test. The correlation coefficient \(R\) (or Spearman’s rho) was assessed when necessary. The ANOVA or Kruskal–Wallis test was used to analyse the differential distribution of data among \(>2\) groups, with subsequent post hoc corrections for multiple comparisons (i.e. Tukey–Kramer or Conover test, respectively).

**Determination of the echocardiographic model of pulmonary artery wedge pressure and pulmonary vascular resistance prediction**

Considering that PAWP should always be inferior to (being a component of) PAP\textsubscript{m}, we used the PAWP/PAP\textsubscript{m} ratio as the dependent variable of the model.

Univariate linear regression analysis was first performed to search for echocardiographic and laboratory predictors of the ratio. Variables with a significance probability value (maximized partial likelihood ratio) \(\leq 0.05\) were successively entered into a stepwise multivariable linear regression analysis showing unstandardized and standardized regression coefficients to compare the strength of the effect of each independent variable with that of the dependent variable, with variance inflation factor (VIF) used to exclude multicollinearity. The result of the multivariable linear regression analysis was used to obtain the model of prediction of PAWP/PAP\textsubscript{m} (as shown in Equation 1), which was thus completely data driven. From this model, we then calculated the echocardiographic estimate of PAWP and PVR (PAWP\textsubscript{echo} and PVR\textsubscript{echo}, as shown in Equations 2 and 3).

To test the intra-observer and inter-observer variability, three independent observers (V. C., N. R. P., and V. S.) reanalysed the parameters of the model (including CO), from 50 randomly selected patients in the ‘derivation cohort’, and reproducibility was measured with the intraclass correlation coefficient.

**Validation of the echocardiographic model of pulmonary artery wedge pressure and pulmonary vascular resistance prediction**

Pulmonary artery wedge pressure and PVR estimates from the echocardiographic model were then validated against RHC data in the validation cohort, through areas under the receiver operating characteristic (ROC) curve (AUCs) and their associated 95% confidence intervals (CIs). McNemar test was used to compare the accuracy of the model with previous algorithms. Bland–Altman plot analysis was also used to assess bias and limits of agreement (defined as 95% CI around the mean) between echocardiographic and RHC data in the whole cohort and in specific patient subgroups.

**Results**

**Patient population characteristics**

Among 968 patients screened, 15 (1.6%) were excluded because of the presence of uncorrected intra-cardiac or extra-cardiac shunt and 158 (16.3%) due to inadequate TR and/or PR Doppler signals. Finally, 795 patients were included in the analysis, as shown in Table 1.

At RHC, PH was diagnosed in 507 patients (64%, Table 1). Beyond showing higher pulmonary artery pressures (PAPs, PAPd, and PAPm), patients with PH also showed a worse CO, diastolic profile, mitral regurgitation severity, and RV function compared with patients without PH (all \(P < 0.001\)). They also showed higher hs-CtTnT and NT-proBNP plasma levels (all \(P < 0.001\)). Overall, there were 77 (10%) cases of pulmonary arterial hypertension, 345 (43%) of left heart disease, 49 (6%) of lung disease, and 36 (5%) of chronic thromboembolic PH (Figure 1A and Supporting Information, Table S1). Among patients with left heart disease, 335 (97%) had HF, due to HF with reduced ejection fraction in 166 (48%), HF with mid-range ejection fraction in 31 (9%), and HF with preserved ejection fraction (HFP EF) in 138 (40%).

At RHC, precapillary, isolated postcapillary, and combined PH were found in 192 (24.2%), 248 (31.2%), and 67 (8.4%)
Table 1  Echocardiographic, haemodynamic, and laboratory findings in the whole cohort and patients with and without PH

| Variables                             | Overall (n = 795) | Non-PH (n = 288) | PH (n = 507) | P value |
|---------------------------------------|-------------------|------------------|-------------|---------|
| Age (years)                           | 68.4 ± 12.1       | 67.0 ± 11.8      | 69.4 ± 11.6 | ns      |
| Men, n (%)                            | 427 (53.7)        | 161 (55.9)       | 266 (52.5)  | ns      |
| BMI (kg/m²)                           | 27.2 ± 9.4        | 27.4 ± 14.2      | 27.1 ± 5.1  | ns      |
| BSA (m²)                              | 1.9 ± 0.2         | 1.9 ± 0.2        | 1.9 ± 0.2   | ns      |
| Systolic blood pressure (mmHg)        | 134.2 ± 24.9      | 135.0 ± 26.2     | 133.7 ± 24.2| ns      |
| Diastolic blood pressure (mmHg)       | 72.7 ± 12.0       | 71.2 ± 11.2      | 73.5 ± 12.3 | <0.05   |
| Heart rate (b.p.m.)                   | 73.8 ± 15.2       | 69.6 ± 13.2      | 76.0 ± 15.7 | <0.001  |
| Sinus rhythm, n (%)                   | 534 (67.2)        | 222 (77.1)       | 312 (61.5)  | <0.001  |
| Atrial fibrillation, n (%)            | 205 (25.8)        | 54 (18.7)        | 151 (29.8)  | <0.001  |
| Paced rhythm, n (%)                   | 56 (7.0)          | 12 (4.2)         | 44 (8.7)    | <0.05   |
| eGFR (mL/min/1.73 m²)                 | 72.5 ± 27.2       | 76.7 ± 26.3      | 70.2 ± 27.5 | ns      |
| NT-proBNP (ng/L)                      | 1227 (373.5–3128) | 557 (191–1634)  | 1715.5 (612.3–4364.3) | <0.001 |
| hs-cTnT (ng/L)                        | 18.5 (10.5–34.3)  | 14.0 (8.7–24.6)  | 21.8 (12.6–39.0) | <0.001 |
| LV Function Data                      |                   |                  |             |         |
| LVEF (%)                              | 49.7 ± 17.7       | 49.6 ± 16.0      | 49.6 ± 18.6 | ns      |
| LVEDV index (mL/m²)                   | 76.3 ± 32.2       | 79.1 ± 29.9      | 74.7 ± 33.3 | ns      |
| LVESV index (mL/m²)                   | 42.9 ± 31.6       | 43.3 ± 28.4      | 42.6 ± 33.3 | ns      |
| LVM index (g/m²)                      | 112.1 ± 38.4      | 112.8 ± 37.2     | 111.7 ± 39.2| ns      |
| LVEDD (mm)                            | 53.2 ± 10.2       | 54.1 ± 9.4       | 52.7 ± 10.6 | ns      |
| LVESD (mm)                            | 39.9 ± 13.0       | 40.5 ± 11.9      | 39.6 ± 13.6 | ns      |
| MR Grade 1, 2, 3, n (%)               | 314 (39.5)/314 (39.5)/78 (9.8) | 136 (47.2)/96 (33.3)/16 (5.6) | 178 (35.1)/218 (43.0)/62 (12.2) | <0.001 |
| Mitral E/A ratio                      | 1.3 ± 0.9         | 1.1 ± 0.6        | 1.5 ± 1.0   | <0.001  |
| Mitral E/e ratio                      | 13.9 ± 8.3        | 11.3 ± 5.2       | 15.3 ± 9.3  | <0.001  |
| LAVi (mL/m²)                          | 41.4 ± 15.1       | 37.9 ± 13.3      | 43.4 ± 15.6 | <0.001  |
| PREDG (mmHg)                          | 9.7 ± 5.0         | 8.8 ± 4.2        | 11.5 ± 3.8  | <0.001  |
| RVFAC (%)                             | 35.4 ± 9.7        | 40.3 ± 9.6       | 33.1 ± 9.4  | <0.001  |
| TAPSE (mm)                            | 18.9 ± 5.3        | 20.4 ± 5.1       | 18.0 ± 5.2  | <0.001  |
| TR Grade 3, n (%)                     | 67 (8.4)          | 10 (3.8)         | 57 (11.2)   | <0.001  |
| TRV (cm/s)                            | 324.1 ± 65.2      | 279.6 ± 38.5     | 351.2 ± 58.1| <0.001  |
| RAP (mmHg)                            | 7.8 ± 3.6         | 6.1 ± 2.8        | 8.8 ± 3.6   | <0.001  |
| IVC diameter (mm)                     | 19.6 ± 5.5        | 17.0 ± 4.8       | 21.1 ± 5.2  | <0.001  |
| Right heart catheterization           |                   |                  |             |         |
| Cardiac output (L/min)                | 5.0 ± 1.4         | 5.4 ± 1.5        | 4.9 ± 1.4   | <0.001  |
| PAWP (mmHg)                           | 15.9 ± 7.9        | 11.3 ± 4.5       | 18.4 ± 8.2  | <0.001  |
| PVR (WU)                              | 2.8 ± 2.6         | 1.4 ± 0.8        | 3.6 ± 2.9   | <0.001  |
| Systolic PAP (mmHg)                   | 46.8 ± 16.2       | 31.3 ± 6.5       | 55.6 ± 14.1 | <0.001  |
| Mean PAP (mmHg)                       | 28.7 ± 10.1       | 18.5 ± 3.6       | 34.5 ± 7.8  | <0.001  |
| Diastolic PAP (mmHg)                  | 19.4 ± 7.7        | 12.3 ± 3.4       | 23.4 ± 6.4  | <0.001  |
| RAP (mmHg)                            | 7.8 ± 4.8         | 5.5 ± 3.4        | 9.1 ± 5.0   | <0.001  |

BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; LAVi, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVEFV, left ventricular end-systolic volume; LVM, left ventricular mass; MR, mitral regurgitation; NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PREDG, pulmonary regurgitation end-diastolic gradient; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVFAC, right ventricular fractional area change; TR, tricuspid regurgitation; TRV, tricuspid regurgitation velocity; WU, Wood units.

Data are presented as mean and standard deviation if normally distributed or median and inter-quartile range if not normally distributed or as number and %.
Figure 1 Non-invasive estimation of pulmonary artery wedge pressure (PAWP) and pulmonary vascular resistance (PVR): equations and diagnostic accuracy of the model. (A) Distribution of the general population according to the clinical (left) and haemodynamic (right) classification. (B) Equations for echo-derived estimation of PAWP and PVR. Echo-parameters used for predicting PAWP and PVR: tricuspid regurgitation velocity (TRV), left ventricular ejection fraction (LVEF), right ventricular fractional area change (RVFAC), left atrial volume index (LAVi), mitral E/e′, inferior vena cava (IVC) diameter, mean pulmonary artery pressure (PAPm) and cardiac output (CO). (C) Regression analysis showing the strong relationship of the echo-derived estimation of PAWP (on the left) and PVR (on the right) with the right heart catheterization (RHC) measures in the validation cohort. (D) Receiver operating characteristic (ROC) curve analysis of echo-derived PAWP as a predictor of PAWP > 15 mmHg at RHC (on the left) and echo-derived PVR as a predictor of PVR > 3 Wood units (WU) at RHC (on the right) in the validation cohort. AUC, area under the receiver operating characteristic curve; CTEPH, chronic thromboembolic pulmonary hypertension; LAA, left atrial area; LHD, left heart disease; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.
patients, respectively (Table 2 and Figure 1A). Patients with postcapillary and combined PH had worse LV systolic function, as well as higher LV filling pressures, compared with patients with precapillary PH (all \( P < 0.05 \), Table 2). Patients with precapillary PH had the highest TRV values, while patients with combined PH showed the worst profile in terms of RV pressure overload and RV systolic function (all \( P < 0.05 \), Table 2). Likewise, patients with combined PH had the highest values of NT-proBNP and hs-cTnT and the lowest estimated glomerular filtration rate (all \( P < 0.05 \), Table 2).

Non-invasive echo-Doppler algorithm for simultaneous pulmonary artery wedge pressure and pulmonary vascular resistance estimation in the derivation group

The echocardiographic, haemodynamic, and laboratory characteristics of the derivation cohort (\( n = 200 \)) are reported in Supporting Information, Table S2.

The univariable and multivariable regression predictors of the PAWP/PAPm ratio obtained from the derivation group

### Table 2  Echocardiographic, haemodynamic, and laboratory findings in patients with precapillary, postcapillary and combined PH

| Variables                              | Precapillary PH (\( n = 192 \)) | Postcapillary PH (\( n = 248 \)) | Combined PH (\( n = 67 \)) |
|----------------------------------------|---------------------------------|----------------------------------|----------------------------|
| Age (years)                            | 67.7 ± 13.3                     | 69.7 ± 10.6                      | 73.5 ± 8.9**†              |
| Men (\( n \)) (%)                      | 86 (46.7)                       | 148 (57.8)                      | 32 (47.8%)                 |
| BMI (kg/m\(^2\))                       | 26.5 ± 4.6                      | 27.7 ± 5.4*                     | 26.5 ± 4.8                 |
| BSA (m\(^2\))                          | 1.8 ± 0.2                       | 1.9 ± 0.2*                      | 1.8 ± 0.2†                 |
| Systolic blood pressure (mmHg)         | 132.6 ± 21.0                    | 132.2 ± 26.9                    | 135.2 ± 24.0               |
| Diastolic blood pressure (mmHg)        | 74.9 ± 11.7                     | 72.4 ± 12.8*                    | 72.2 ± 12.5*               |
| Heart rate (b.p.m.)                    | 74.4 ± 13.4                     | 76.3 ± 16.3                     | 77.8 ± 16.6                |
| Sinus rhythm, (\( n \)) (%)            | 154 (83.7)                      | 129 (50.4)                      | 27 (40.3%)                 |
| Atrial fibrillation, (\( n \)) (%)     | 30 (16.3)                       | 95 (37.1)                       | 27 (40.3%)                 |
| Paced rhythm, (n (%)                    | 0 (0)                           | 32 (12.5)                       | 13 (19.4%)                 |
| eGFR (mL/min/1.73 m\(^2\))             | 73.0 ± 28.1                     | 70.4 ± 27.8                     | 61.5 ± 21.6*               |
| NT-proBNP (ng/L)                       | 717 (210–2951.5)                | 1964 (989–4671)*                | 3884 (1384–8090)*†         |
| hs-cTnT (ng/L)                          | 16.1 (8.8–30.3)                 | 23.8 (15.1–44.3)*               | 29.3 (17.9–50.8)*†         |
| Echocardiographic data                  |                                 |                                  |                            |
| LVEF (%)                               | 63.7 ± 10.0                     | 40.8 ± 17.2*                    | 44.3 ± 18.6*               |
| LVEDV index (mL/m\(^2\))               | 52.9 ± 14.9                     | 89.5 ± 34.8*                    | 77.7 ± 32.8*               |
| LVEDV index (mL/m\(^2\))               | 19.9 ± 10.6                     | 57.4 ± 35.0*                    | 48.5 ± 33.2*               |
| LVM index (g/m\(^2\))                  | 85.4 ± 24.7                     | 129.1 ± 38.2*                   | 118.0 ± 36.3*              |
| LVESD (mm)                             | 45.4 ± 5.8                      | 57.8 ± 10.2*                    | 53.1 ± 10.8                |
| LVESD (mm)                             | 29.4 ± 6.2                      | 46.3 ± 13.0*                    | 41.6 ± 13.8*               |
| MR grade (mild/moderate/severe)         | 114 (62.0)/28 (15.2)/1 (0.5)    | 47 (18.4)/153 (59.8)/49 (19.1)  | 17 (25.4)/37 (55.2)/12 (17.9) |
| Mitral E/A ratio                       | 0.9 ± 0.5                       | 2.0 ± 1.1*                      | 2.1 ± 1.1*                 |
| Mitral E/e ratio                       | 10.2 ± 5.1                      | 18.6 ± 10.4*                    | 20.1 ± 10.8*               |
| LAVI (mL/m²)                            | 31.1 ± 8.9                      | 50.0 ± 14.9*                    | 50.0 ± 14.8*               |
| PREDG (mmHg)                           | 13.6 ± 5.6                      | 9.6 ± 3.6*                      | 13.1 ± 5.1                |
| RVFAC (%)                              | 30.1 ± 7.6                      | 37.0 ± 9.0*                     | 29.7 ± 10.1*               |
| TAPSE (mm)                             | 19.1 ± 5.6                      | 18.0 ± 4.9*                     | 15.4 ± 4.3*†               |
| TR grade, (\( n \)) (%)                | 17 (9.2)                        | 25 (9.6)                        | 15 (22.4)*†                |
| TRV (cm/m²)                            | 388.5 ± 58.2                    | 320.4 ± 38.1*                   | 363.9 ± 69.6†              |
| RAP (mmHg)                             | 6.1 ± 2.9                       | 10.1 ± 3.0*                     | 11.3 ± 2.9*                |
| IVC diameter (mm)                      | 18.6 ± 4.7                      | 22.3 ± 5.1*                     | 23.2 ± 4.2*                |
| Right heart catheterization            |                                 |                                  |                            |
| Cardiac output (L/min)                 | 5.0 ± 1.3                       | 5.0 ± 1.4                       | 4.0 ± 1.0*†                |
| Systolic PAP (mmHg)                    | 59.7 ± 16.2                     | 50.2 ± 9.3*                     | 65.2 ± 13.4†               |
| Mean PAP (mmHg)                        | 35.8 ± 9.0                      | 31.8 ± 5.0*                     | 41.3 ± 8.2*                |
| Diastolic PAP (mmHg)                   | 23.4 ± 7.1                      | 22.2 ± 4.6*                     | 28.9 ± 7.9*                |
| PAWP (mmHg)                            | 9.4 ± 2.9                       | 23.7 ± 4.8*                     | 23.4 ± 4.7*                |
| RAP (mmHg)                             | 5.9 ± 3.8                       | 10.6 ± 4.6*                     | 12.1 ± 5.2*                |
| PVR (WU)                               | 5.9 ± 3.3                       | 1.7 ± 0.7*                      | 4.6 ± 1.5*†                |

BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; IVC, inferior vena cava; LAVI, left atrial volume index; LV EDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVEF, left ventricular end-diastolic function; LVEF, left ventricular end-systolic function; LVEF, left ventricular mass; MR, mitral regurgitation; NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PREDG, pulmonary regurgitation end-diastolic gradient; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVFACC, right ventricular fractional area change; TR, tricuspid regurgitation; TRV, tricuspid regurgitation velocity; WU, Wood units.

Data are presented as number and %, mean and standard deviation if normally distributed, or median and inter-quartile range if not normally distributed.

\(^* P < 0.05\) in comparison with the group of precapillary PH.

\(^† P < 0.05\) in comparison with the group of postcapillary PH.
Mitral E/e ratio 0.83 ± 0.11
Mitral E/A ratio 12.95 ± 2.37
TRV (cm/s) 3.0 ± 0.38
C0
TAPSE (mm) 2.0 ± 0.40
LVM index (g/m²) 0.30 ± 0.04
LVESV index (mL/m²) 0.19 ± 0.03

Table 3

| Variables                      | Univariable analysis | Stepwise multivariable analysis |
|--------------------------------|----------------------|---------------------------------|
|                                | B        | P       | B unstandardized coefficient | B standardized coefficient | P       | VIF |
| LVEF (%)                       | −0.71 ± 0.09 | <0.001 | −0.44 ± 0.04 | −0.34 | <0.001 | 1.35 |
| LVEDV index (mL/m²)            | 0.18 ± 0.02 | <0.001 | — | — | — | — |
| LVESEV index (mL/m²)           | 0.19 ± 0.03 | <0.001 | — | — | — | — |
| LVM index (g/m²)               | 0.30 ± 0.04 | <0.001 | — | — | — | — |
| TRV (cm/s)                     | 13.58 ± 2.20 | <0.001 | — | — | — | — |
| Mitral E/A ratio               | 12.95 ± 2.37 | <0.001 | — | — | — | — |
| Mitral E/e' ratio              | 0.86 ± 0.18 | <0.001 | 0.54 ± 0.08 | 0.18 | <0.001 | 1.15 |
| LAVi (mL/m²)                   | 0.83 ± 0.11 | <0.001 | 0.30 ± 0.05 | 0.19 | <0.001 | 1.42 |
| PREDG (mmHg)                   | −1.99 ± 0.31 | <0.001 | — | — | — | — |
| RVFAC (%)                      | 0.97 ± 0.17 | <0.001 | 1.01 ± 0.07 | 0.41 | <0.001 | 1.27 |
| TAPSE (mm)                     | −0.03 ± 0.38 | ns | — | — | — | — |
| TRV (cm/s)                     | −0.18 ± 0.02 | <0.001 | −0.09 ± 0.01 | −0.27 | <0.001 | 1.33 |
| IVC diameter (mm)              | 1.12 ± 0.23 | <0.001 | 0.78 ± 0.12 | 0.18 | <0.001 | 1.26 |
| Inspiratory collapse of IVC > 50% | −9.94 ± 3.59 | <0.01 | — | — | — | — |
| eGFR (ml/min/1.73 m²)          | −0.01 ± 0.07 | ns | — | — | — | — |
| NT-proBNP (ng/L)               | 0.01 ± 0.01 | ns | — | — | — | — |
| hs-CtTnT (ng/L)                | 0.23 ± 0.03 | ns | — | — | — | — |

Table 4

| Model | R    | R²   | Adjusted R² | SD  | Predictors |
|-------|------|------|-------------|-----|------------|
| 1     | 0.53 | 0.27 | 0.27        | 18.8| 94 – 0.8 · EF |
| 2     | 0.63 | 0.39 | 0.40        | 17.1| 133 – 0.6 · EF – 0.2 · TRV |
| 3     | 0.70 | 0.48 | 0.47        | 16.0| 120 – 0.5 · EF – 0.2 · TRV + 0.9 · E/e' |
| 4     | 0.74 | 0.55 | 0.54        | 14.9| 83 – 0.6 · EF – 0.1 · TRV + 0.9 · E/e' + 0.75 · RVFAC |
| 5     | 0.76 | 0.58 | 0.57        | 14.4| 52 – 0.5 · EF – 0.1 · TRV + 0.8 · E/e' + 1.0 · RVFAC + 1.1 · IVC |
| 6     | 0.78 | 0.60 | 0.59        | 14.0| 43 – 0.5 · EF – 0.1 · TRV + 0.7 · E/e' + 1.0 · RVFAC + 0.9 · IVC + 0.3 · LAVi |

EF, ejection fraction; IVC, inferior vena cava; LAVi, left atrial volume index; LVEDV, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESEV, left ventricular end-systolic volume index; LVM, left ventricular mass; MR, mitral regurgitation; NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; PAPm, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; RVFAC, right ventricular fractional area change; TRV, tricuspid regurgitation velocity; VIF, variance inflation factor.
The intra-observer and inter-observer agreements for all the parameters included in the equations were satisfactory (all ICCs > 0.9 and >0.8, respectively).

**Diagnostic accuracy of the model in the validation group**

The echocardiographic model was then tested in the validation cohort (n = 595). The echocardiographic, haemodynamic, and laboratory characteristics of the validation cohort are reported in Supporting Information, Table S3.

A strong correlation was found between PAWP<sub>echo</sub> and PAWP<sub>cath</sub> (R = 0.85, P < 0.001; Table 5 and Figure 1C), which was confirmed both in patients with PH (R = 0.84, P < 0.001) and without PH (R = 0.72, P < 0.001). At ROC analysis, PAWP<sub>echo</sub> accurately predicted PAWP<sub>cath</sub> > 15 mmHg (AUC = 0.97, optimal cut-off value = 15 mmHg, 92% sensitivity, and 93% specificity, P < 0.001; Figure 1D), with the lowest accuracy being observed in patients with chronic thromboembolic PH (AUC 0.90, 100% Sensitivity, 82% Specificity; Supporting Information, Figure S5). The current model showed a higher diagnostic accuracy in identifying LV filling pressure as compared with the 2016 recommendations, both including patients with AF (92% sensitivity and 93% specificity vs. 54.5% sensitivity and 87.6% specificity, respectively; P < 0.001) and excluding patients with AF (94% sensitivity and 91% specificity vs. 61.6% sensitivity and 86.9% specificity, respectively; P < 0.001).

Using Bland–Altman analysis, reasonable limits of agreement were observed between PAWP<sub>echo</sub> and PAWP<sub>cath</sub> (Figure 2) in the overall group (bias 0.7, 95% CI −7.3 to 8.7), in patients with PH (bias 0.9, 95% CI −6.7 to 8.5), and in patients without PH (bias −1.0, 95% CI −6.8 to 4.8 mmHg). Satisfactory limits of agreement were also achieved in the different clinical PH groups, with the widest limits being observed in PH due to left heart disease (Figure 2).

A strong correlation was also found between PVR<sub>echo</sub> and PVR<sub>cath</sub> (R = 0.89, P < 0.001; Table 5 and Figure 1C), which was also confirmed in patients with PH (R = 0.88, P < 0.001) and without PH (R = 0.64, P < 0.001). At ROC analysis, PVR<sub>echo</sub> accurately predicted PVR<sub>cath</sub> > 3 WU (AUC = 0.96, cut-off value = 3 WU, 89% sensitivity, and 92% specificity, P < 0.001; Figure 1D). We observed 80% sensitivity and 95% specificity (AUC = 0.95) in the group without PH and 89% sensitivity and 91% specificity (AUC = 0.95) in the group with PH, with lowest accuracy being observed in patients with pulmonary arterial hypertension (AUC = 0.91, 84% sensitivity, and 89% specificity) (Supporting Information, Figure S2). The obtained model showed a higher diagnostic accuracy, when compared with the echocardiographic algorithm developed by Abbas’ group for PVR prediction, which in our population showed 61% sensitivity and 72% specificity (P < 0.001).

Bland–Altman analysis confirmed satisfactory limits of agreement between PVR<sub>echo</sub> and PVR<sub>cath</sub> in the overall group for PVR prediction, 5 which in our population showed 61% sensitivity and 72% specificity (P < 0.001).

### Table 5 Validation cohort (n = 595): correlation between echocardiography and RHC on the estimation of PAPm, PAWP, and PVR in patients with and without PH

| Variable                              | Echo       | RHC        | R       | P       |
|---------------------------------------|------------|------------|---------|---------|
| PAPm (mmHg)                           |            |            |         |         |
| Overall (n = 595)                     | 30.2 ± 9.1 | 29.6 ± 9.8 | 0.90    | <0.001  |
| Non-PH (n = 201)                      | 21.5 ± 4.2 | 19.0 ± 3.4 | 0.67    | <0.001  |
| Pulmonary arterial hypertension (n = 65) | 37.0 ± 11.0 | 36.4 ± 9.1 | 0.89    | <0.001  |
| PH due to left heart disease (n = 263) | 32.9 ± 6.4 | 33.4 ± 6.7 | 0.79    | <0.001  |
| PH due to lung disease and/or hypoxia (n = 41) | 39.7 ± 8.0 | 38.8 ± 7.9 | 0.80    | <0.001  |
| Chronic thromboembolic PH (n = 25)    | 40.0 ± 8.0 | 39.5 ± 9.2 | 0.81    | <0.001  |
| PAWP (mmHg)                           |            |            |         |         |
| Overall (n = 595)                     | 15.6 ± 5.9 | 16.4 ± 7.9 | 0.85    | <0.001  |
| Non-PH (n = 201)                      | 12.5 ± 3.8 | 11.6 ± 4.5 | 0.71    | <0.001  |
| Pulmonary arterial hypertension (n = 65) | 10.7 ± 3.6 | 9.5 ± 3.5  | 0.58    | <0.001  |
| PH due to left heart disease (n = 263) | 19.3 ± 5.2 | 21.8 ± 6.7 | 0.74    | <0.001  |
| PH due to lung disease and/or hypoxia (n = 41) | 12.0 ± 5.4 | 11.2 ± 6.8 | 0.88    | <0.001  |
| Chronic thromboembolic PH (n = 25)    | 11.1 ± 4.0 | 10.5 ± 6.1 | 0.71    | <0.001  |
| PVR (WU)                              |            |            |         |         |
| Overall (n = 595)                     | 3.0 ± 2.0  | 2.9 ± 2.4  | 0.89    | <0.001  |
| Non-PH (n = 201)                      | 1.8 ± 0.8  | 1.6 ± 0.9  | 0.64    | <0.001  |
| Pulmonary arterial hypertension (n = 65) | 5.3 ± 2.7  | 5.5 ± 2.6  | 0.91    | <0.001  |
| PH due to left heart disease (n = 263) | 2.9 ± 1.5  | 2.6 ± 1.8  | 0.80    | <0.001  |
| PH due to lung disease and/or hypoxia (n = 41) | 6.8 ± 2.0  | 6.7 ± 2.6  | 0.81    | 0.002   |
| Chronic thromboembolic PH (n = 25)    | 5.9 ± 2.2  | 6.2 ± 3.1  | 0.88    | <0.001  |

PAPm, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WU, Wood units.

Variables are presented as mean and standard deviation if normally distributed or median and inter-quartile range if not normally distributed.

DOI: 10.1002/ehf2.13183
population (bias −0.1, 95% CI −2.2 to 1.9), in patients without PH (bias −0.2, 95% CI −1.7 to 1.3), and in patients with PH (bias 0.0, 95% CI −2.3 to 2.3 WU), as well as in different clinical classes of PH (Figure 3).

Subgroup analysis was also performed in the challenging subgroup of patients with AF (n = 142, 23.9% of the validation group). Again, a good correlation was found between PAWP\textsubscript{echo} and PAWP\textsubscript{cath} (R = 0.72, \( P < 0.001 \)), as well as between PVR\textsubscript{echo} and PVR\textsubscript{cath} (R = 0.80, \( P < 0.001 \)). PAWP\textsubscript{echo} accurately predicted PAWP\textsubscript{cath} (AUC 0.94, 93% sensitivity, and 88% specificity), and PVR\textsubscript{echo} accurately predicted PVR\textsubscript{cath} (AUC 0.90, 91% sensitivity, and 84% specificity) also in patients with AF (Supporting Information, Figure S3). Likewise, a good diagnostic accuracy of PAWP\textsubscript{echo} and PVR\textsubscript{echo} was shown in patients with moderate-to-severe MR and paced rhythm (Supporting Information, Figures S4 and S5).

By using the PAWP\textsubscript{echo} and PVR\textsubscript{echo} obtained by the current algorithm, patients were significantly better allocated to precapillary PH, isolated postcapillary PH, and combined PH subgroups, compared with a combination of the algorithm proposed by the guidelines and the Abbas equation (all \( P < 0.001 \), Table 6).

The diagnostic accuracies relative to PAWP\textsubscript{echo} vs. PAWP\textsubscript{cath} and PVR\textsubscript{echo} vs. PVR\textsubscript{cath} according to the simplified equations are reported in Supporting Information, Figure S6.

**Discussion**

In our study, a novel echocardiographic method for the quantitative estimation of both PAWP and PVR was validated in a large population of patients with and without HF. The robustness of the model, which was completely data driven, was demonstrated against RHC across a wide range of cardiac and pulmonary diseases and regardless of the underlying cardiac rhythm. ROC analysis showed a higher diagnostic accuracy than current international recommendations.\(^5,9\) Despite a satisfactory agreement at Bland–Altman analysis, there was still some imprecision, especially for extreme values. Nonetheless, patients’ allocation to precapillary, postcapillary, and combined postcapillary was still correct in most cases and in a larger proportion (improvement in allocation ranging from 30% to 45%) as compared with current recommendations, without indeterminate cases (0% vs. 16%).\(^5,9\) Notably, all variables included in the model should be routinely acquired during a standard echocardiographic examination\(^11\) and may be easily incorporated in a reporting system.
immediately providing PAWP/PVR values for clinical use. Nonetheless, a list of simplified equations with a reasonable diagnostic performance is also provided to balance precision with quickness of execution, depending on the clinical need.

At present, echocardiography is the only non-invasive technique that allows estimation of pulmonary and LV filling pressures in HF/PH. According to PH guidelines, assessment of PVR is necessary to distinguish precapillary from isolated and combined postcapillary PH.1,2 Nevertheless, PAWP and PVR are not routinely assessed in most echocardiographic laboratories but only in cardiac catheterization laboratories. Drawbacks of echocardiography include inadequate accuracy15–19 and insufficient precision.20 Most of the previous studies have been conducted using a qualitative approach,21–29 while there are only few data on the non-invasive quantitative evaluation of PAWP mainly conducted in small, highly selected populations (e.g. HF with reduced EF, or valve disease, or post-acute myocardial infarction) and usually excluding patients with AF and moderate-to-severe valvular regurgitation.23,24,30–39

The 2016 ASE/EACVI recommendations have improved the reliability and clinical utility of LV filling pressure estimation, as compared with the previous 2009 recommendations.14 However, the number of patients classified as indeterminate is not negligible (>15% in the multicentre Euro-Filling study, similar to 16% testing the same algorithm in our study).14 Andersen et al. proposed in patients with cardiac disease a novel echocardiographic algorithm, which showed a high diagnostic accuracy for prediction of LV filling pressure (87% sensitivity and 88% specificity), reducing the number of patients in whom the evaluation was inconclusive (7%). However, a different algorithm was used for patients with severe MR and paced rhythms,40 two challenging conditions for echocardiography, similar to HfPEF or extremely reduced LVEF.41,42 We analysed a large heterogeneous population: among patients with PH (64%), the large majority had left heart disease (43%) mainly due to HF (including patients with HF with mid-range ejection fraction and HfPEF), but also

### Table 6
Improved clinical allocation of patients to PH subtypes by the current algorithm compared with the combination of guidelines and the Abbas equations in the validation group

|                      | RHC Guidelines + Abbas | Novel algorithm | \( P \) value |
|----------------------|------------------------|----------------|-------------|
| Indeterminate        | 0                      | 99 (16.6%)     | <0.001      |
| Precapillary PH      | 148 48 (32.4%)         | 115 (77.7%)    | <0.001      |
| Postcapillary PH     | 192 111 (57.8%)        | 167 (87.0%)    | <0.001      |
| Combined PH          | 54 20 (37.0%)          | 40 (74.1%)     | <0.001      |

PH, pulmonary hypertension; RHC, right heart catheterization.
patients with respiratory diseases were included (21%). Notably, the same algorithm remains highly valuable also in patients with AF and severe MR, without inconclusive cases (0%).

Some of the proposed variables in Equation 2 are already included in the latest ASE/EACVI algorithm (i.e. TRV, average E/e′, and LAVi). IVC size and dynamics are already used for RAP and consequently pulmonary artery pressure estimation. LVEF is pivotal when choosing the algorithm for grading of LV diastolic dysfunction from current recommendations, and, being load dependent, it may also add precision to the current model. RVFAC may reflect the effect of the increased LV filling pressure and/or PVR on the right ventricle, which is even more susceptible to pressure overload. Finally, PAPm mathematically encompasses PAWP and TPG, reflecting the steady component of the pulmonary circulation, differently from the pulsatile component of PAPs, which has greater respiratory and individual variability. The echocardiographic estimation of PAPm, although not routinely performed in the current practice, is actually advised by the guidelines and, in our population, does show a good correlation with PAPm measured at RHC (R = 0.85, P < 0.001). In line with our findings, Barbier et al. showed that an algorithm based on PREDG could accurately predict increased PAWP, with higher accuracy than the ASE/EACVI algorithm, in a cohort of patients with cardiac disease (183 subjects; 117 with an EF < 50%). Noteworthy, the model is mathematically independent of mitral regurgitation grade, which influences PAWP, but it is challenging to evaluate, particularly in intermediate grade. Biomarkers were also excluded by the stepwise regression analysis, similar to previous studies.

With regard to PVR estimation, Abbas et al. developed an algorithm (a ratio between TRV or TRV2 and velocity–time integral in the pulmonary artery) in a population characterized by precapillary PH (mean PAWP = 13 mmHg) and preserved LVEF (mean LVEF = 58%). However, this method may lead to false-positive results in patients with HF with reduced ejection fraction and postcapillary PH, using TRV as a surrogate of TPG. In our population, a modest performance of Abbas’ algorithm was indeed found (61% sensitivity and 72% specificity), with a ‘virtual gap’ in PVR values between 3 and 4.5 WU, due to the use of two different formulas.

The presence of multiple variables in the model might appear time consuming, but the algorithm incorporation in the electronic reporting system or the use of simplified equations may balance accuracy with clinical straightforwardness. We observed satisfactory limits of agreement between echocardiography and RHC parameters, but considering the confidence limits, a certain imprecision is still present, especially in some subgroups. However, the reclassification capability of the model in identifying PH subtypes is still striking as compared with current recommendations.

We did not use speckle tracking and strain analysis, which showed a potential role in predicting PAWP in preliminary studies. In particular, left atrial deformation during atrial systole strongly correlates with PAWP at RHC and may be used to calculate both PAWP and PVR with good diagnostic accuracy. Nevertheless, the strength of the study is the use of currently established and widely available echocardiographic techniques.

Finally, the results of this monocentric study, albeit promising, are based on internal validation only and should be replicated in larger studies with multicentric design and external validation.

Conclusions

The novel echocardiographic method for quantitative assessment of PAWP and PVR proposed in this study is feasible and provides a reliable estimation of cardiopulmonary haemodynamics in patients with HF and PH, even in the presence of AF. The model accurately identified patients with precapillary, isolated postcapillary, and combined PH, with no cases of undetermination and outperforming current echocardiographic algorithms, by using variables routinely acquired in echocardiographic laboratories. The use of an electronic reporting system with the equation embedded (simplified equation also provided) may warrant in real time, with no delay two relevant parameters as PAWP and PVR for daily clinical use, as follow-up and treatment optimization of patients with either HF or PH.

Conflict of interest

None declared.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Figure S1. Receiver-operator characteristic analysis: diagnostic accuracy of the PAWP\textsubscript{echo} in different subgroups of the validation cohort. Echo-derived pulmonary artery wedge pressure (PAWP\textsubscript{echo}) as a predictor of catheterization-derived PAWP > 15 mmHg and pulmonary vascular resistance (PVRecho) as a predictor of catheterization-derived PVR > 3 Wood Units.

Figure S2. Receiver-operator characteristic analysis: diagnostic accuracy of the PVRecho in different subgroups of the validation cohort. Echo-derived pulmonary vascular resistance (PVRecho) as a predictor of catheterization-derived PVR > 3 Wood Units in patients without pulmonary hypertension (PH) and with PH, including different subgroups of PH according to clinical classification.

Figure S3. Receiver-operator characteristic analysis: diagnostic accuracy of the PVRecho in different subgroups of the validation cohort. Echo-derived pulmonary vascular resistance (PVRecho) as a predictor of catheterization-derived PVR > 3 Wood Units in patients with atrial fibrillation. Echo-derived pulmonary artery wedge pressure (PAWP\textsubscript{echo}) as a predictor of catheterization-derived PAWP > 15 mmHg and pulmonary vascular resistance (PVRecho) as a predictor of catheterization-derived PVR > 3 Wood Units.

Figure S4. Receiver-operator characteristic analysis: diagnostic accuracy of the PAWP\textsubscript{echo} and PVRecho in patients from the validation cohort with moderate-to-severe mitral regurgitation (MR). Echo-derived pulmonary artery wedge pressure (PAWP\textsubscript{echo}) as a predictor of catheterization-derived PAWP > 15 mmHg and pulmonary vascular resistance (PVRecho) as a predictor of catheterization-derived PVR > 3 Wood Units.

Figure S5. Receiver-operator characteristic analysis: diagnostic accuracy of the PAWP\textsubscript{echo} and PVRecho in patients from the validation cohort with paced rhythm. Echo-derived pulmonary artery wedge pressure (PAWP\textsubscript{echo}) as a predictor of catheterization-derived PAWP > 15 mmHg and pulmonary vascular resistance (PVRecho) as a predictor of catheterization-derived PVR > 3 Wood Units.

Figure S6. Receiver-operator characteristic analysis: diagnostic accuracy of the PAWP\textsubscript{echo} and PVRecho in patients from the validation cohort using preliminary models of stepwise analysis. Echo-derived pulmonary artery wedge pressure (PAWP\textsubscript{echo}) as a predictor of catheterization-derived PAWP > 15 mmHg and pulmonary vascular resistance (PVRecho) as a predictor of catheterization-derived PVR > 3 Wood Units.

Table S1. Echocardiographic, hemodynamic and biohumoral findings in patients with and without PH.

Table S2. Derivation group: echocardiographic, hemodynamic and biohumoral findings in patients with and without PH.

Table S3. Validation group: echocardiographic, hemodynamic and biohumoral findings in patients with and without PH.

References

1. Galié N, Humbert M, Vachiéry J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Noordegraaf AV, Beghetti M, Ghofrani A, Sanchez MAG, Hansmann G, Klepetko W, Lancellotti P, Matsucci M, McDonagh T, Pierard LA, Trindade PT, Zompatari M, Hoeper M, ESC Scientific Document Group. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016; 37: 67–119.

2. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53: 1801913.

3. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013; 62: D34–D41.

4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members. 2016 ESC/ERS guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016; 37: 2129–2200.

5. Abbas AE, Franey LM, Marwick T, Maeder MT, Kaye DM, Vlahos AP, Serra W, al-Azizi K, Schiller NB, Lester SJ. Noninvasive assessment of pulmonary vascular resistance by Doppler echocardiography. J Am Soc Echocardiogr 2013; 26: 1170–1177.

6. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. 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.

7. Bossone E, D’Andrea A, D’Alto M, Citro R, Argiento P, Ferrara F, Cittadini A, Rubenfire M, Naeije R. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. J Am Soc Echocardiogr 2013; 26: 1–14.

8. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelias A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009; 10: 165–193.

9. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016; 29: 277–314.

10. Galderisi M, Henein MY, Dhooge J Rosa Sicari, Luigi P. Badano, José Luis Zamorano, Jos R.T.C. Roelandt, on behalf of the European Association of Echocardiography Recommendations of the European Association of Echocardiography How to use echo-Doppler in
clinical trials: different modalities for different purposes. *Eur J Echocardiogr* 2011; 12: 339–353.

11. Lang RM, Badano LP, Mor-Avi V, Afifalo J, Armstrong A, Ernande I, Flachskampff FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt J-U. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28: 1–39.e14.

12. Lancellotti P, Tribouilloy C, Hagendorff A, Bogdan A, Popescu T, Thor Edvardsen, Luc A. Pierard, Luigi Badano, Jose L. Zamorano, On behalf of the Scientific Document Committee of the European Association of Cardiovascular Imaging: Thor Edvardsen, Oliver Bruder, Bernard Cosyns, Erwan Donal, Raluca Dulgheru, Maurizio Galderisi, Patrizio Lancellotti, Denis Muraru, Koen Nieman, Rosa Sicari, Document reviewers: Erwan Donal, Kristina Hauge-Nielsen, Giovanni La Canna, Julien Magne, Edyta Plonska Recommendations for the echocardiographic assessment of native valvar regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013; 14: 611–644.

13. Mitchell C, Rahko PS, Blauwert LA, Canaday B, Fjestad JA, Foster MC, Horton K, Ogunyankin KO, Palma RA, Velazquez EJ. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2019; 32: 1–64.

14. Lancellotti P, Galderisi M, Edvardsen T, Donal E, Galiatsos G, Cardim N, Magne J-L, Cosyns, Erwan Donal, Raluca Dulgheru, Maurizio Galderisi, Patrizio Lancellotti, Denis Muraru, Koen Nieman, Rosa Sicari, Document reviewers: Erwan Donal, Kristina Hauge-Nielsen, Giovanni La Canna, Julien Magne, Edyta Plonska Recommendations for the echocardiographic assessment of native valvar regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013; 14: 611–644.

15. Denton CP, Alto M, Romeo E, Argiento P, D’Andrea A, Vanderpool R, Correra A, Bossone E, Sarubbi B, Cabařo R, Russo MG, Naeije R. Accuracy and precision of echocardiography versus right heart catheterization for the assessment of pulmonary hypertension. *Int J Cardiol* 2013; 168: 4058–4062.

16. Rosslov O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. *J Am Coll Cardiol* 1993; 21: 1687–1696.

17. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease: additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocities at atrial contraction. *J Am Coll Cardiol* 1993; 22: 1972–1982.

18. Giannuzzi P, Imparato A, Temporelli PL, Vito, Silva PL, Scappato L, Giordano A. Doppler-derived mitral deceleration time of early filling as a strong predictor of pulmonary capillary wedge pressure in postinfarction patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 1994; 23: 1630–1637.

19. Pozzoli M, Capomolla S, Pinna G, Cobelli F, Tavazzi L. Doppler echocardiography more predict pulmonary artery wedge pressure in patients with chronic heart failure with and without mitral regurgitation. *J Am Coll Cardiol* 1996; 27: 883–893.

20. Temporelli PL, Scappato F, Corrò U, Eleuteri E, Imparato A, Giannuzzi P. Doppler echocardiography in advanced systolic heart failure: a noninvasive alternative to Swan-Ganz catheter. *Circ Heart Fail* 2010; 3: 387–394.

21. Opotowsky AR, Ojeda J, Rogers F, Prassana V, Clair M, Moko L, Vaidya A, Afifalo J, Forlì PR. A simple echocardiographic prediction rule for hemodynamics in pulmonary hypertension. *Circ Cardiovasc Imaging* 2012; 5: 765–775.

22. D’Alto M, Romeo E, Argiento P, Pavelescu A, Mélot C, D’Andrea A, Correra A, Bossone E, Calabrò R, Russo MG, Naeije R. Echocardiographic prediction of post- versus postcapillary pulmonary hypertension. *J Am Soc Echocardiogr* 2015; 28: 108–115.

23. Biner S, Topisky L, Banai S, Steinivil A, Arbel Y, Siegel RJ, Beigel R, Keren G, Finkelstein A. Echo Doppler estimation of pulmonary artery wedge pressure in patients with chronic heart failure. *Am J Echocardiogr* 2011; 12: 857–864.

24. Scalii GM, Scalii IG, Kierle R, Beaumont R, Cross DB, Feenstra J, Burstow DJ, Fitzgerald BT, Platts DG. ePLAR—the echocardiographic pulmonary to left artery catheters. *Circulation* 2004; 109: 2432–2439.

25. Dokainish H, Nguyen JS, Bobek J, Goswami R, Lakkis NM. Assessment of the American Society of Echocardiography-European Association of Echocardiography guidelines for diastolic function in patients with depressed ejection fraction: an echocardiographic and invasive haemodynamic study. *Eur J Echocardiogr* 2011; 12: 857–864.

26. Rich JD, Shah SJ, Swamy RS, Kamp A, Rich S. Inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension: implications for clinical practice. *Chest* 2011; 139: 988–993.

27. D’Alto M, Romeo E, Argiento P, D’Andrea A, Vanderpool R, Correra A, Bossone E, Sarubbi B, Calabrò R, Russo MG, Naeije R. Accuracy and precision of echocardiography versus right heart catheterization for the assessment of pulmonary hypertension. *Int J Cardiol* 2013; 163: 8458–8462.

28. Rosslov O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. *J Am Coll Cardiol* 1993; 21: 1687–1696.

29. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease: additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocities at atrial contraction. *J Am Coll Cardiol* 1993; 22: 1972–1982.

30. Giannuzzi P, Imparato A, Temporelli PL, Vito, Silva PL, Scappato F, Giordano A. Doppler-derived mitral deceleration time of early filling as a strong predictor of pulmonary capillary wedge pressure in postinfarction patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 1994; 23: 1630–1637.

31. Pozzoli M, Capomolla S, Pinna G, Cobelli F, Tavazzi L. Doppler echocardiography reliably predicts pulmonary artery wedge pressure in patients with chronic heart failure even when atrial fibrillation is present. *Eur J Heart Fail* 2001; 3: 173–181.

32. Fiorentino M, Cobelli P, Zoccali C. Doppler echocardiography reliably predicts pulmonary artery wedge pressure in patients with chronic heart failure even when atrial fibrillation is present. *Eur J Heart Fail* 2001; 3: 173–181.

33. Traversi E, Cobelli F, Pozzoli M. Doppler echocardiography reliably predicts pulmonary artery wedge pressure in patients with chronic heart failure even when atrial fibrillation is present. *Eur J Heart Fail* 2001; 3: 173–181.

34. Diwan A, McCulloch M, Lawrie GM, Reardon MJ, Naeije SF. Doppler estimation of left ventricular filling pressures in patients with mitral valve disease. *Circulation* 2005; 111: 3281–3289.

35. Temporelli PL, Scappato F, Eleuteri E, Imparato A, Giannuzzi P. Doppler echocardiography in advanced systolic heart failure: a noninvasive alternative to Swan-Ganz catheter. *Circ Heart Fail* 2010; 3: 387–394.

36. D’Alto M, Romeo E, Argiento P, Pavelescu A, Mélot C, D’Andrea A, Correra A, Bossone E, Calabrò R, Russo MG, Naeije R. Echocardiographic prediction of pre- versus postcapillary pulmonary hypertension. *J Am Soc Echocardiogr* 2015; 28: 108–115.

37. Biner S, Topisky L, Banai S, Steinivil A, Arbel Y, Siegel RJ, Beigel R, Keren G, Finkelstein A. Echo Doppler estimation of pulmonary artery wedge pressure in patients with chronic heart failure. *Am J Cardiol* 2011; 108: 689–694.

38. Abudab MM, Chebrolu LH, Schutt RC, Naeije SF, Zoghbi WA. Doppler echocardiography for the evaluation of pulmonary capillary wedge pressure in patients with present or previous heart failure. *Am J Cardiol* 2012; 110: 689–694.
atrial ratio—a novel non-invasive parameter to differentiate pre-capillary and post-capillary pulmonary hypertension. *Int J Cardiol* 2016; **212**:379–386.

38. Naghè SF, Kopelen HA, Quiñones MA. Assessment of left ventricular filling pressures by Doppler in the presence of atrial fibrillation. *Circulation* 1996; **94**:2138–2145.

39. Chirillo F, Brunazzi MC, Barbiero M, Giavarina D, Pasqualini M, Franceschini-Grisolia E, Cotogni A, Cavarzerani A, Rigatelli G, Stritoni P, Longhini C. Estimating mean pulmonary wedge pressure in patients with chronic atrial fibrillation from transthoracic Doppler indexes of mitral and pulmonary venous flow velocity. *J Am Coll Cardiol* 1997; **30**:19–26.

40. Andersen OS, Smiseth OA, Dokainish H, Abudiab MM, Schutt RC, Kumar A, Sato K, Harb S, Gude E, Remme EW, Andreassen AK, Ha JW, Xu J, Klein AL, Naghè SF. Estimating left ventricular filling pressure by echocardiography. *J Am Coll Cardiol* 2017; **69**:1937–1948.

41. Hummel YM, Liu LCY, Lam CSP, Fonseca-Munoz DF, Damman K, Rienstra M, van der Meer P, Rosenkranz S, van Veldhuisen DJ, Voors AA, Hoendermis ES. Echocardiographic estimation of left ventricular and pulmonary pressures in patients with heart failure and preserved ejection fraction: a study utilizing simultaneous echocardiography and invasive measurements. *Eur J Heart Fail* 2017; **19**:1651–1660.

42. Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. *Circulation* 2009; **119**:62–70.

43. Konstam MA, Ejection Fraction AFM. Misunderstood and overrated (changing the paradigm in categorizing heart failure). *Circulation* 2017; **135**:717–719.

44. Ryan JJ, Archer SL. The right ventricle in pulmonary arterial hypertension: disorders of metabolism, angiogenesis and adrenergic signaling in right ventricular failure. *Circ Res* 2014; **115**:176–188.

45. Chemla D, Humbert M, Sitbon O, Montani D, Hervé P. Systolic and mean pulmonary artery pressures: are they interchangeable in patients with pulmonary hypertension? *Chest* 2015; **147**:943–950.

46. Barbier P, Cucco C, Guglielmo M, Simonietc A, Fabiani I, Pugliese NR, Savioli G, Dini FL. Estimation of increased pulmonary wedge pressure by an algorithm based on noninvasively measured pulmonary diastolic pressure in cardiac patients independent of left ventricular ejection fraction. *Echocardiography* 2020; **37**:215–222.

47. Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. *Circulation* 2012; **125**:2138–2150.

48. Kawasaki M, Tanaka R, Ono K, Minatoguchi S, Watanabe T, Iwama M, Hirose T, Arai M, Noda T, Watanabe S, Zile MR, Minatoguchi S. A novel ultrasound predictor of pulmonary capillary wedge pressure assessed by the combination of left atrial volume and function: a speckle tracking echocardiography study. *J Cardiol* 2015; **66**:253–262.

49. Tossavainen E, Henein MY, Grönlund C, Lindqvist P. Left atrial intrinsic strain rate correcting for pulmonary wedge pressure is accurate in estimating pulmonary vascular resistance in breathless patients. *Echoardiography* 2016; **33**:1156–1165.

50. Yoshizane T, Kawamura I, Kawasaki M, Tanaka R, Minatoguchi S, Nagaya M, Sato H, Ono K, Tomita S, Matsuo H, Noda T, Suzuki T, Minatoguchi S. Validation by cardiac catheterization of noninvasive estimation of time constant of left ventricular pressure decline as an index of relaxation by speckle tracking echocardiography. *Am J Cardiol* 2018; **121**:1645–1651.