Can Pulmonary Hypertension and Increased Pulmonary Vascular Resistance Be Ruled in and Ruled Out by Echocardiography?

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Background: Several treatment options are available for pulmonary vascular disease, and more patients are considered for right heart catheterization. The aims of this study were to evaluate the diagnostic ability of echocardiography to detect pulmonary hypertension and increased pulmonary vascular resistance (PVR).

Methods: This retrospective study comprised 118 patients investigated within 48 hours of right heart catheterization. Echocardiography was used to assess pulmonary artery systolic pressure and pulmonary artery mean pressure, filling pressures, cardiac output, and PVR. To diagnose increased PVR, three echocardiographic variables related to pressure reflection in the pulmonary circulation were used. Separate cutoff values aimed at ruling in (high positive likelihood ratio [PLR]) and ruling out (low negative likelihood ratio) pulmonary hypertension (pulmonary artery mean pressure >25 mm Hg) and increased PVR (>3 Wood units) were determined from a derivation group (n = 59, receiver operating characteristic curve analysis) and evaluated in a test group (n = 59).

Results: The linear relations between hemodynamic variables assessed with simultaneous echocardiography and right heart catheterization were moderate to strong (R = 0.55 to 0.95), and there were no significant differences, but the limits of agreement were wide. With Doppler pulmonary artery systolic pressure >39 mm Hg, the PLR for pulmonary artery mean pressure >25 mm Hg was 4.7, and with Doppler pulmonary artery systolic pressure ≤29 mm Hg, the negative likelihood ratio was 0.12. The PLR for pressure reflection variables with ruling-in cutoff values ranged from 4.3 to 6.4. With all three variables positive, the PLR was 9.9. The negative likelihood ratio with ruling-out cutoff values ranged from 0.22 to 0.08.

Conclusions: Echocardiography that includes assessment of pressure reflection in the pulmonary circulation can rule in and rule out pulmonary hypertension and increased PVR. (J Am Soc Echocardiogr 2013;26:469-78.)

Keywords: Pulmonary vascular resistance, Echocardiography, Pressure reflection, Right heart catheterization, Pulmonary hypertension

The development of right ventricular failure is an ominous sign that predicts adverse outcomes and influences treatment strategies in patients with cardiopulmonary diseases.[1-3] Although right ventricular failure may be due to primary myocardial dysfunction, it is more often caused by pulmonary hypertension and increased right ventricular afterload. Compared with the left ventricle, the thin-walled right ventricle demonstrates increased sensitivity to afterload elevation.[4] Pulmonary hypertension predict all-cause mortality in patients with both preserved[5] and impaired[6] left ventricular systolic function.

Low pulmonary vascular resistance (PVR), compliant arteries, and no reflection of the pressure wave characterize the normal pulmonary circulation. In clinical practice, the level of right ventricular afterload is most often described using the pulmonary artery (PA) pressure. The PA pressure is dependent on flow and resistance. The assessment of PVR, which reflects the transpulmonary pressure gradient divided by the pulmonary blood flow, is considered to require right heart catheterization (RHC).

Several specific treatment options are available for patients with pulmonary vascular disease. The diagnosis is difficult, and diagnostic delay is a well-known problem.[7,8] In patients with pulmonary hypertension and normal left ventricular ejection fractions, is it not possible using standard echocardiography to distinguish increased pressure due to pulmonary venous hypertension from increased PVR. The treatment of pulmonary hypertension due to increased PVR in patients with left heart disease is controversial.[9] However, the diagnosis of vascular disease is increasingly important in the era of heart failure treatment with mechanical support because it affects

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Abbreviations

AcT = Acceleration time

ASE = American Society of Echocardiography

CI = Confidence interval

PA = Pulmonary artery

PAMP = Pulmonary artery mean pressure

PASP = Pulmonary artery systolic pressure

PCWP = Pulmonary capillary wedge pressure

PVR = Pulmonary vascular resistance

RHC = Right heart catheterization

RVOT = Right ventricular outflow tract

tPV-PP = time from Peak velocity in the right ventricular outflow tract to peak pressure in the right ventricle

WU = Wood units

treatment strategies. As a consequence, more patients are considered candidates for RHC.

Much attention has been given to the development of echocardiographic methods to assess PA pressures and resistance to flow. PA pressures can be estimated using different noninvasive methods with good linear relations to invasive measurements.[10-16] To estimate resistance to flow is more challenging because it combines several variables (PA pressure, pulmonary capillary wedge pressure [PCWP], and cardiac output). Surrogate variables for PVR have been proposed,[17] but their usefulness is debated, and in recent American Society of Echocardiography (ASE) guidelines for assessment of the right ventricle, it is not recommended to estimate PVR for routine use.[18] We found in previous studies that PVR could be calculated from echocardiographic data in patients with pulmonary arterial hypertension[15] and that the presence of pressure reflection in the pulmonary circulation can be used to identify patients with increased PVR.[19] In both these studies, the patient cohorts were biased toward pronounced pulmonary vascular disease with severely increased PVR. In the present study, we investigated the diagnostic ability of echocardiography to detect pulmonary hypertension and increased PVR in a population representative of those undergoing RHC at our institution.

METHODS

Study Population

This retrospective study comprised 118 patients who were referred for clinical RHC between May 2009 and November 2012. The inclusion criteria were (1) regular cardiac rhythm, (2) RHC performed within 48 hours of echocardiography, (3) pulsed Doppler recording in the PA, and (4) tricuspid regurgitation that enabled the assessment of right ventricular peak systolic pressure from Doppler echocardiography. The study was approved by the ethics committee at the University of Gothenburg (448-10).

Hemodynamic Measurements

A Swan-Ganz catheter (7 Fr; Baxter Healthcare, Edwards Critical Care Division, Deerfield, IL) was introduced through the right internal jugular vein under fluoroscopic guidance using the Seldinger technique. The following variables were measured or derived: mean right atrial pressure, PA systolic pressure (PASP), PA mean pressure (PAMP), PCWP, cardiac output, and PVR.

Cardiac output was determined using the thermodilution method as the mean of three to five consecutive measurements not varying by >10%.

Pressure Reflection

In the normal pulmonary circulation, the pressure and flow waves generated by the right ventricle are almost completely dampened and display, therefore, similar contours.[20,21] In individuals without obstruction in the right ventricular outflow tract (RVOT), the shape of the pressure waveforms in the right ventricle and PA (including the timing of peak pressure) are similar. Changes in the pulmonary precapillary properties cause a reflection of pressure and flow waves, with marked changes in wave contours. The reflected pressure wave will add on to the forward traveling wave, and there will be an increase in pressure in the right ventricle and PA while the flow is decreasing (Figure 1). The site and magnitude of pressure reflection influence the timing of peak velocity in the RVOT, the timing of peak velocity in relation to peak pressure in the right ventricle, and the magnitude of pressure increase in the right ventricle after peak velocity in the RVOT (Figure 1). In the present study, we assessed three variables in relation to PVR: (1) acceleration time (AcT): the time interval from opening of the pulmonary valve to peak velocity; (2) time from peak velocity in the right ventricular outflow tract to peak pressure in the right ventricle (tPV-PP): the time interval from peak velocity in the RVOT to peak velocity in the tricuspid regurgitant jet (peak pressure in the right ventricle); and (3) augmented pressure: the pressure increase (augmentation) in the right ventricle after peak velocity in the RVOT.

Figure 1 explains in a schematic drawing the pressure reflection phenomenon, including the three related variables, and Figure 2 describes how these variables are obtained using echocardiography.

Doppler Echocardiography

The left ventricular ejection fraction was measured using Simpson's method or estimated by eyeballing. Mitral and pulmonary vein flow was recorded using pulsed Doppler from the tip of the valve and the upper right pulmonary vein. Tissue pulsed Doppler recordings were performed in the basal part of the left ventricular septum. The volume of the left atrium was estimated using the area-length method in end-systole.[22] Right ventricular systolic function was assessed using the fractional area change method by tracing the end-diastolic and end-systolic areas (fractional area change = end-diastolic area − end-systolic area/end-diastolic area × 100) and by the tricuspid annular plane systolic excursion method by M-mode echocardiography.[18] All Doppler measurements were performed offline with a sweep speed of 100 to 200 mm/sec, and the investigator was blinded to the results of the catheter investigation.

The assessment of pressure reflection requires continuous-wave Doppler recording of the tricuspid regurgitant jet and pulsed-wave Doppler recording in the RVOT. We used multiple windows guided by color Doppler to obtain the highest velocity. Most often, the highest velocity was found in a projection that showed the right ventricle somewhere between a standard four-chamber view and a parasternal view. The flow velocity was recorded by placing a 5-mm pulsed-wave Doppler sample volume in the RVOT. The timing of the pulmonary valve opening and the peak velocity was determined as the time from a reference point on the electrocardiographic QRS complex (most often the peak of the R wave) and the onset (a-b) and peak velocity (a-d) in the RVOT registered with pulsed-wave Doppler (Figure 2). The timing of right ventricular peak systolic pressure was determined as the time from QRS to the peak velocity of the regurgitant jet (a-c) using the same QRS reference as for RVOT registration. In subjects in whom the peak velocity in the RVOT preceded the peak velocity (a-d < a-c) in the regurgitant jet, the time interval (a-d) was

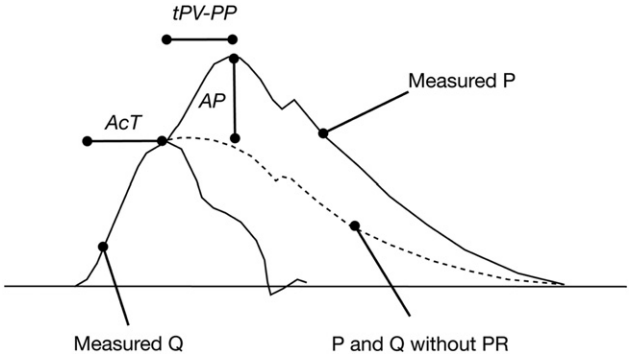

Figure 1 Schematic drawing showing the measured pressure (P) and flow (Q) in the PA in an individual with increased PVR and pressure reflection (PR). The *broken line* is the pressure and flow wave that would be measured in the absence of PR. *AP*, Augmented pressure.

superimposed onto the velocity spectrum of the tricuspid regurgitant jet to calculate the pressure gradient corresponding to the peak velocity in the RVOT. The velocity across the tricuspid valve at this time interval was measured, and the pressure gradients between the right ventricle and the right atrium were calculated (pressure gradient = 4 × velocity^2). The mean right atrial pressure was estimated using the inferior vena cava dimension and collapsibility with inspiration.[23] The tPV-PP was calculated as [(a-c)−(a-d)]. The time from the onset of flow in the RVOT to peak velocity (AcT) was calculated as [(a-d)−(a-b)]. The augmented pressure was calculated as the difference between peak pressure in the right ventricle and the pressure corresponding to peak velocity in the RVOT. In previously performed variability studies, the interobserver group variability (described by the coefficients of variation, expressed as the mean value of differences divided by the mean value of the two measurements) for measurements made on the same recording were 6%, 8%, and 9% for AcT, tPV-PP, and augmented pressure, respectively. The corresponding interobserver individual variability (the standard deviation of differences divided by the mean value of two measurements) was 7%, 9%, and 13%.[19]

Grading of Left Ventricular Filling Pressure

The grading of left ventricular filling pressure was performed according to the recommendations of the ASE.[24] In patients with depressed ejection fractions (<50%) and E/A ratios ≥2, the estimated Doppler PCWP used in the comparison with RHC and calculation of PVR was 20 mm Hg. If the PCWP was considered normal, we used 9 mm Hg in the comparison, and if the E/A ratio was pseudonormal and other supportive parameters (pulmonary vein S/D ratio, PASP, tissue Doppler) suggested increased PCWP, we used 15 mm Hg. In patients with normal ejection fractions, we used 20 and 9 mm Hg for those with increased and normal filling pressures on the basis of tissue Doppler findings. In patients with inconclusive tissue Doppler findings in whom other supportive parameters (volume of the left atrium, PASP) suggested increased PCWP, we used 15 mm Hg.

Calculation of PVR on the Basis of Echocardiographic Data

Stroke volume was calculated as the product of the cross-sectional area of the left ventricular outflow tract and the velocity-time integral. Mean PA pressure was calculated as follows[10]:

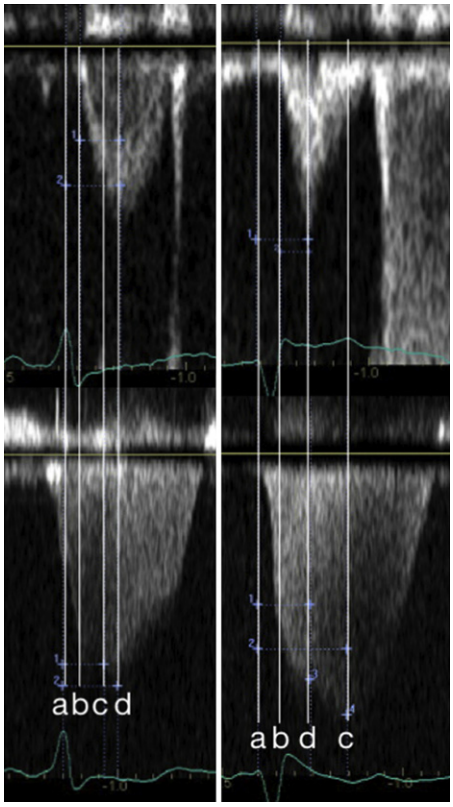

Figure 2 Pulsed Doppler in the RVOT (*top*) and continuous-wave Doppler of the tricuspid regurgitant jet (*bottom*) in two patients with cardiac amyloidosis. The patient on the *left* had normal PVR (1.8 WU), and the patient on the *right* had increased PVR (3.7 WU). The time intervals from the QRS to the opening (a-b) of the pulmonary valve, peak velocity (a-d) in the outflow tract, and the peak *right* ventricular pressure (a-c) are determined. The AcT is then [(a-d)−(a-b)], and tPV-PP is [(a-c)−(a-d)]. The interval (a-d) is superimposed on the tricuspid velocity envelope to determine the right ventricular pressure corresponding to peak velocity in the RVOT. Note that in the patient with normal PVR, tPV-PP is typically negative, and there is no pressure augmentation (AP = 0). In the patient with increased PVR (*right*), AcT was 78 msec, tPV-PP 102 msec, and AP 10 mm Hg.

$$\mathrm{PAMP_{Doppler}} = (0.65 \times \mathrm{PASP_{Doppler}}) - 1.2\ \mathrm{mmHg}.$$

PVR was calculated as follows:

$$\mathrm{PVR_{Doppler}} = (\mathrm{PAMP_{Doppler}} - \mathrm{PCWP_{Doppler}})/ \times (\mathrm{stroke\ volume} \times \mathrm{heart\ rate}).$$

The PVR surrogate proposed by Abbas *et al.*[17] was calculated. The peak velocity in the tricuspid regurgitant jet (TRV) is divided by the velocity-time integral in the RVOT ($\mathrm{VTI_{RVOT}}$). The following regression equation has been proposed to calculate PVR:

$$\mathrm{PVR_{Abbas}} = (\mathrm{TRV}/\mathrm{VTI_{RVOT}}) \times 10 + 0.16.$$

Statistical Analysis

Continuous variables with normal distributions are expressed as mean ± SD and when the distribution was not normal as median

(interquartile range). The degree of linear relationship between catheter measurements and echocardiography was assessed using correlation coefficients (R) if the data were continuous. Correlations between estimation of right atrial pressure and PCWP by echocardiography in categories and results from RHC were determined using Spearman's ρ. Possible determinants of pressure reflection variables were described using simple regression, and if significant ($P < .05$), the variables were entered into a multiple regression model. Paired Student's t tests or Wilcoxon's tests were used to compare continuous data. P values $< .05$ were considered statistically significant. Diagnostic utility was measured using sensitivity, specificity, the positive likelihood ratio, the negative likelihood ratio, and diagnostic odds ratios. The positive likelihood ratio is the ratio between the probability of a positive test result in those with disease and the probability of a positive test result in those without disease (sensitivity/[1−specificity]). The negative likelihood ratio is the ratio between the probability of a negative test result in a patient with disease and the probability of a negative test result in a patient without disease ([1−sensitivity]/specificity). The diagnostic odds ratio is the ratio between the positive and negative likelihood ratios. The study population was divided into a derivation group that comprised the first 59 patients investigated and a test group with the following 59 patients who underwent RHC. Receiver operating characteristic curve analysis was performed in the derivation group to establish cutoff values for the detection of pulmonary hypertension (PAMP >25 mm Hg) and increased PVR (>3 Wood units [WU]). The cutoff values from the derivation group aimed at determining levels that rule out (low negative likelihood ratio <0.1) or rule in (high positive likelihood ratio >10) pulmonary hypertension and increased PVR. These cutoff values were used in the test group.

RESULTS

Patient Characteristics

Echocardiographic investigations were performed simultaneously, on the same day but not simultaneously, and within 24 hours in 17%, 25%, and 76% of patients, respectively, and the investigations were on the same day or preceding RHC in 80%. The largest proportion of patients (75%) had left heart disease or were undergoing routine RHC with myocardial biopsy after heart transplantation (Table 1). Seventeen percent had pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. Six percent had severe and 17% moderate tricuspid regurgitation. Forty-one percent had left ventricular systolic dysfunction with left ventricular ejection fractions <50%. Forward failure with reduced cardiac index and backward failure with increased PCWP were common findings. Pulmonary hypertension and increased PVR were found in 55% and 39% of patients, respectively. Two patients were excluded from the calculation of PVR by Doppler because of left-to-right shunting and severe aortic regurgitation, making the Doppler cardiac output not representative for pulmonary flow.

Agreement between Catheterization and Echocardiography

In Table 2, we present the comparison between RHC and echocardiography for patients investigated simultaneously ($n = 20$) and nonsimultaneously ($n = 98$). The heart transplant recipients ($n = 28$) were excluded from grading of left ventricular filling pressure because of a lack of consensus in the literature on how this should be done.[24]

Table 1 Clinical, echocardiographic, and RHC characteristics (n = 118)

Variable	Value
Age (y)	53 ± 13
Women	42%
BSA (m^2)	1.9 ± 0.2
Diagnosis	
Left ventricular disease	51%
Dilated cardiomyopathy	19%
Amyloidosis	8%
Ischemic heart disease	3%
Valvular disease	9%
Other	12%
Heart transplantation	24%
Pulmonary arterial hypertension	16%
CTEPH	1%
Miscellaneous	8%
Echocardiography	
Left ventricular ejection fraction (%)	48 ± 18
<50%	41%
Left atrial volume/BSA (mL/m^2)	42 (30–58)
Right ventricular area change (%)	41 ± 14
TAPSE (mm)	14 ± 5
RHC	
Cardiac index ($L/min/m^2$)	2.44 ± 0.88
Right atrial pressure (mm Hg)	5 (2–11)
PASP (mm Hg)	41 (28–56)
PAMP (mm Hg)	28 (16–38)
Proportion with PAMP >25 mm Hg	55%
PCWP (mm Hg)	11 (7–19)
Transpulmonary gradient (mm Hg)	11 (8–18)
PVR (WU)	2.0 (2–4)
Proportion with PVR >3 WU	39%
Proportion with PVR >3 WU and PCWP >15 mm Hg	14%

BSA, Body surface area; *CTEPH*, chronic tromboembolic pulmonary hypertension; *TAPSE*, tricuspid annular plane systolic excursion. Data are expressed as mean ± SD for variables with normal distributions and as median (interquartile range) for variables with nonparametric distributions.

Eight patients did not have the data required for estimation according to ASE guidelines. Estimations of PCWP and PVR were performed in 83 patients. There was no significant difference between catheterization and echocardiography in patients investigated simultaneously except for PVR_{Abbas}. The linear relation was moderate to strong for all variables except PCWP. In patients investigated nonsimultaneously, the linear relation was still strong but less so compared with simultaneous investigation. The mean differences between catheterization and echocardiography in patients investigated nonsimultaneously were not significant except for right atrial pressure and PASP. The differences in absolute values were small. The limits of agreement (standard deviation of differences) were wide for all variables in both groups of patients.

PVR calculated according to the proposal of Abbas *et al.*[17] showed a weaker linear relation with $PVR_{Catheter}$ and larger limits of agreement compared with $PVR_{Doppler}$. Increased PCWP was a common finding in patients with pulmonary hypertension (Figure 3, *left*) also in those with increased PVR according to the Doppler method. The

Table 2 Agreement between RHC and Doppler echocardiography in patients investigated simultaneously (n = 20) or nonsimultaneously (n = 98) within 48 hours

Variable	RAP	PASP	PAMP	PCWP	Cardiac index	$PVR_{Doppler}$	PVR_{Abbas}
Simultaneously with catheterization							
RHC	9 (4.3 to 17.3)	53 (36 to 80)	39 (22 to 48)	15 (10 to 26)	2.0 (1.8 to 2.3)	6.0 (2 to 9.3)	6.0 (2 to 9.3)
Doppler echocardiography	15 (5 to 15)	46 (39 to 71)	28 (24 to 45)	15 (15 to 20)	1.7 (1.2 to 2.3)	5.2 (2.1 to 10.3)	3.6 (1.5 to 4.6)
Mean difference ± SD	−0.6 ± 4.8	2.5 ± 9.2	2.0 ± 6.9	3.2 ± 9.3	0.03 ± 0.4	0.1 ± 2.1	3.0 ± 3.6
Limits of agreement	−10.2 to 9.0	−15.9 to 20.9	−11.8 to 15.8	−15.4 to 21.8	−0.5 to 1.1	−4.1 to 4.3	−6.1 to 10.3
Correlation coefficient	0.87	0.95	0.90	0.55	0.80	0.92	0.70
P value	.47	.27	.13	.24	.55	.64	.02
Nonsimultaneously with catheterization							
RHC	4 (2 to 9.5)	39 (26 to 51)	26 (16 34)	12 (7 to 20)	2.0 (2 to 3)	3 (2 to 5)	3 (2 to 5)
Doppler echocardiography	5 (5 to 15)	40 (30 to 52)	25 (18 to 32)	15 (9 to 20)	2.3 (1.6 to 3.2)	3.4 (1.6 to 5.7)	2.9 (2.1 to 4.1)
Mean difference ± SD	−2 ± 3.5	−2.7 ± 10.8	−0.8 ± 8.0	−1.3 ± 6.6	−0.02 ± 0.7	0.1 ± 2.7	1.1 ± 3.4
Limits of agreement	−9 to 5	−24.3 to 18.9	−16.8 to 15.2	−14.5 to 11.9	−1.42 to 1.38	−5.3 to 5.5	−5.7 to 7.9
Correlation coefficient	0.73	0.84	0.79	0.57	0.74	0.73	0.52
P value	<.0001	.02	.35	.12	.90	.56	.12

RAP, Right atrial pressure.
Data are expressed as mean ± SD for variables with normal distributions and as median (interquartile range) for variables with nonparametric distributions. *P* values are for comparisons between catheterization and Doppler echocardiography.

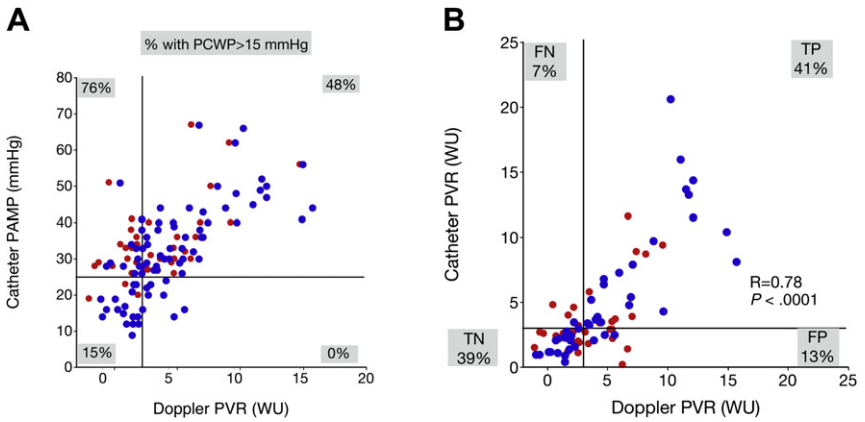

Figure 3 Scatterplot showing the relation between Doppler PVR and **(A)** catheter PAMP and **(B)** catheter PVR. The *red dots* show patients with PCWP > 15 mm Hg and the *blue dots* those with PCWP ≤ 15 mm Hg. The *horizontal lines* indicate the thresholds for increased PAMP (>25 mm Hg) and PVR (>3 WU), while the *vertical lines* indicate increased PVR (>3 WU) with the Doppler method. The percentage within each quadrant with PCWP > 15 mm Hg is shown in the *left* plot, and the percentages of true-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN) results are shown in the *right* plot.

linear relation between catheter and Doppler PVR was strong, and Figure 3 (*right*) demonstrates the diagnostic ability to identify individuals with PVR >3 WU. Increased PVR and increased PCWP often coexisted.

Detection of Pulmonary Hypertension

The receiver operating characteristic curve for the detection of PAMP >25 mm Hg using $PASP_{Doppler}$ in the derivation group had a large area under the curve (0.92; 95% confidence interval [CI], 0.85–0.99). The cutoff value selected with a high positive likelihood ratio to rule in pulmonary hypertension was >39 mm Hg, and the selected cutoff value with a low negative likelihood ratio to rule out pulmonary hypertension was >29 mm Hg. Table 3 shows the results when these values were used in the test group. $PASP_{Doppler}$ >39 mm Hg increased the likelihood of pulmonary hypertension in a mild to moderate degree, with a positive likelihood ratio of 4.7. On the contrary, $PASP_{Doppler}$ ≤29 mm Hg reduced the likelihood of pulmonary hypertension to a moderate degree, with a negative likelihood ratio of 0.12 (an 8.3-fold reduction in likelihood).

Detection of Increased PVR

The sensitivity, specificity, and positive and negative likelihood ratios for the detection of PVR >3 WU were for PVR_{Abbas} 77% (95% CI, 62%–87%), 77% (95% CI, 65%–87%), 3.4 (95% CI, 2.0–5.7) and

Table 3 Diagnostic performance regarding assessment of pulmonary hypertension (PAMP >25 mm Hg) and increased PVR (>3 WU) in the test group (n = 59) from pressure reflection variables with cutoff values from the derivation group

Variable	Cutoff	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)
Rule in pulmonary hypertension						
$PASP_{Doppler}$	>39 mm Hg	87 (71–95)	81 (63–92)	4.7 (2.1–10.5)	0.16 (0.06–0.40)	29.7 (7.1–124)
Rule out pulmonary hypertension						
$PASP_{Doppler}$	>29 mm Hg	97 (84–99)	26 (13–45)	1.3 (1.0–1.6)	0.12 (0.02–0.94)	10.5 (1.2–92)
Rule in increased PVR						
AcT	<85 msec	75 (55–88)	82 (66–92)	4.3 (2.0–9.1)	0.30 (0.2–0.6)	14.0 (39–50)
tPV-PP	>75 msec	75 (55–88)	88 (73–95)	6.4 (2.5–17)	0.28 (0.14–0.57)	22.5 (5.6–91)
AP	>4 mm Hg	81 (67–90)	86 (76–92)	5.7 (3.1–10.3)	0.22 (0.12–0.41)	26.3 (9.5–73)
Two positive		79 (60–91)	88 (73–95)	6.7 (2.6–17.3)	0.24 (0.11–0.5)	28.5 (6.8–120)
Three positive		58 (39–76)	94 (81–98)	9.9 (2.5–40)	0.44 (0.27–0.72)	22.4 (4.3–116)
Rule out increased PVR						
AcT	<110 msec	96 (80–99)	56 (39–71)	2.2 (1.5–3.2)	0.08 (0.01–0.5)	29 (3.5–241)
tPV-PP	>50 msec	83 (64–93)	75 (58–87)	3.3 (1.8–6.2)	0.22 (0.04–0.56)	15 (3.9–57)
AP	>1 mm Hg	92 (74–98)	71 (54–83)	3.1 (1.8–5.3)	0.12 (0.03–0.45)	26.4 (5.2–134)
Two positive		88 (71–96)	73 (58–84)	3.3 (2.0–5.6)	0.16 (0.05–0.5)	21 (5.2–84)
Three positive		85 (66–94)	85 (72–93)	5.8 (2.7–12.3)	0.18 (0.07–0.4)	32 (8.1–127)

AP, Augmented pressure.

0.30 (95% CI, 0.17–0.53) and for $PVR_{Doppler}$ 86% (95% CI, 71%–94%), 76% (95% CI, 61%–86%), 3.5 (2–6.1), and 0.18 (0.08–0.42), respectively.

The relations between pressure reflection variables and possible determinants are shown in Table 4. The linear relation between PVR and augmented pressure was strong, whereas the relations with AcT and tPV-PP were moderate. There were no significant or only weak relations with PCWP and cardiac index. The pressure reflection variables were moderately related to right ventricular function. In a multiple regression model, only PVR showed an independent relation to the pressure reflection variables, except for a weak independent relation between tPV-PP and right ventricular fractional area change. The three pressure reflection variables had large areas under the receiver operating characteristic curves in the derivation group (Figure 4).

The cutoff values in the derivation group were selected aiming at either ruling in or ruling out increased PVR (Table 3). Using the cutoff values for ruling in increased PVR showed positive likelihood ratios indicating an increase in the likelihood to a mild to moderate extent (4.3-fold to 6.4-fold). With two or three positive pressure reflection variables, the likelihood of PVR >3 WU was increased to a moderate to large extent (6.7-fold to 9.9-fold). Using the cutoff values aiming at ruling out increased PVR decreased the likelihood to a moderate to large extent. With AcT >110 msec, the likelihood of increased PVR was reduced 12.5-fold. Twenty-four patients in the test group had increased PVR, and only one had AcT >110 msec. On the other hand, with all three of these rule-out criteria positive, the likelihood of increased PVR increased to a moderate extent.

Patients with pulmonary hypertension had to a large extent increased PCWP (Figure 4). This was also true for patients with signs of pressure reflection indicating high likelihood of increased PVR. The plots in Figure 5 show the relation between catheter PVR and pressure reflection variables and demonstrate the good ability to identify patients with PVR >3 WU and that increased PVR is often combined with increased PCWP.

DISCUSSION

In the present study, we found that echocardiography can provide a comprehensive functional assessment comparable with that of invasive hemodynamic measurements in a representative cohort of patients who undergo RHC. Furthermore, in this patient population with a variety of cardiovascular diseases, echocardiography. including assessment of pressure reflection, can be used to rule in and rule out pulmonary hypertension and increased PVR.

Pulmonary hypertension is a common finding in patients undergoing echocardiography. An abnormal rise in PA pressure can be caused by pulmonary venous hypertension, increased PVR, increased pulmonary flow, or a combination of these mechanisms. It is of great importance to recognize pulmonary hypertension as well as a pathologic increase in PVR, because this is associated with adverse prognosis[5,25] and influences treatment strategies.

In the present study, we investigated to what degree echocardiography can provide information otherwise obtained by RHC. Overall, there were no significant differences between echocardiographic and catheter measurements. Our results regarding the correlation between catheterization and echocardiography are superior compared with those presented in a meta-analysis by Janda *et al.*[26] reporting on the diagnostic accuracy of echocardiography for pulmonary hypertension but are in agreement with a recent study on echocardiographic assessment of hemodynamics in patients with heart failure.[27] The overall correlation between catheterization and echocardiographic assessment of PASP in the meta-analysis was 0.70, compared with 0.84 in the present study, and the sensitivity, specificity, and positive likelihood ratio were 83%, 72%, and 3.0, respectively, compared with 87%, 81%, and 4.7. The enhanced diagnostic accuracy observed in the present study could be due to a combination of using multiple echocardiographic windows in the search for the highest velocity (avoiding underestimation) and a high sweep speed to differentiate the true velocity envelope from artifacts (avoiding overestimation). The estimation of PCWP was

Table 4 Relation between variables describing pressure reflection and possible determinants

Variable	AcT			tPV-PP			Augmented pressure		
	R	*P*	Slope	*R*	*P*	Slope	*R*	*P*	Slope
Simple regression									
PCWP	0.20	.04	−0.75	0.14	.14	—	0.02	.83	—
Cardiac index	0.17	.06	—	0.20	.03	−15.0	0.10	.22	—
PVR	0.47	<.0001	−3.7	0.57	<.0001	9.3	0.73	<.0001	1.7
TAPSE	0.39	<.0001	2.2	0.14	.26	—	0.06	.55	—
FAC	0.42	<.0001	0.94	0.42	<.0001	−1.9	0.36	<.0001	−0.25
Multiple regression									
R for entered variables	0.57			0.59			0.71		
PCWP		.07	—		—	—		—	—
Cardiac index		—	—		.83	—		—	—
PVR		<.0001	−3.1		<.0001	7.1		<.0001	1.6
FAC		.06	—		.04	−0.93		.36	−0.05

FAC, Fractional area change of the right ventricle; *TAPSE*, tricuspid annular plane systolic excursion.

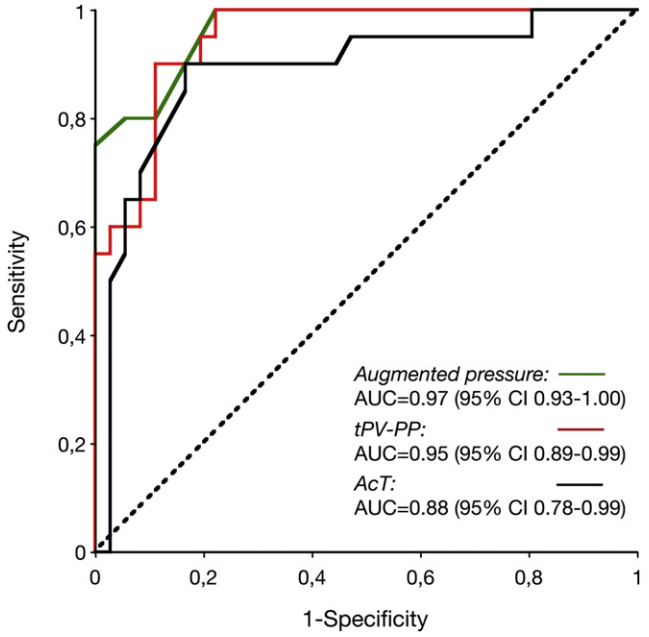

Figure 4 Receiver operating characteristic curves for the detection of increased PVR (> 3 WU) for AcT, tPV-PP, and augmented pressure from the derivation group ($n = 59$). *AUC*, Area under the curve.

based on the recent ASE guidelines.[24] It is recommended to distinguish between patients with normal and reduced left ventricular ejection fractions and to use several variables. The outcome of this assessment is that we can identify patients likely to have PCWP >15 mm Hg. In the guidelines, there are no recommendations on how to estimate PCWP as a continuous variable. Therefore, to calculate PVR on the basis of echocardiographic data, we used a categorical scale, with PCWP being 9 mm Hg in patients with normal findings, 20 mm Hg in patients with high E/A or E/E′ ratios, and 15 mm Hg in patients with inconclusive mitral or tissue Doppler findings but positive supportive signs. The weakest linear relation and widest limits of agreement were observed for this estimation of PCWP. Our findings are in agreement with recent reports on the assessment of filling pressure in patients with reduced as well as preserved ejection fractions.[28-30] The reliability of the echocardiographic assessment of left ventricular filling pressure is under debate, and the results of recent studies conflict with some that underline the limitations[28-30] but also those claiming that the method is accurate.[27,31,32] It is important in every patient with increased PA pressure to evaluate the filling pressure in the left ventricle. The assessment of filling pressure might identify patients with PCWP >15 mm Hg, but the limits of agreement are wide, and it is difficult to distinguish passive pulmonary hypertension solely due to pulmonary venous hypertension from reactive pulmonary hypertension with increased PVR. We calculated PVR using two different methods, but the wide limits of agreement should discourage from using such estimations in individual patients. In groups of patients and for research purposes, however, estimation of PVR can be done and we recommend calculation on the basis of assessment of cardiac output, PAMP, and PCWP rather than the simplified method proposed by Abbas *et al.*[17] We can argue from the observation in our patient cohort, in which PVR_{Abbas} was less accurate compared with $PVR_{Doppler}$, but foremost from a theoretical standpoint. The ratio between peak velocity in the tricuspid regurgitant jet and the RVOT velocity-time integral is a surrogate for PA pressure and cardiac output. The method does not take filling pressure on the right or left side into consideration, and therefore, this is a surrogate not for PVR but rather for the total pulmonary resistance.

Assessment of pressure reflection in the pulmonary circulation is an alternative method to detect increased PVR in individual patients. The method is based on a well-known phenomenon in the pulmonary circulation that the propagating pressure wave will be reflected back toward the right ventricle in patients with precapillary increased resistance or decreased compliance.[20,21] We did not find any important relation between PCWP and the pressure reflection variables, and this supports the basic assumption that pressure reflection is related to conditions in the precapillary part of the pulmonary circulation. Indeed, the method allows us to identify patients with both increased PCWP and increased PVR (Figure 4). The echocardiographic measurements required are part of routine practice in every patient with increased tricuspid regurgitation velocity. In our previous studies, a large proportion of the patients had severe pulmonary hypertension and severely increased PVR.[10,15,19] A high prevalence of pulmonary vascular disease could have introduced a bias toward higher predictive values.[26] Therefore, in the present study, we included patients undergoing RHC after the

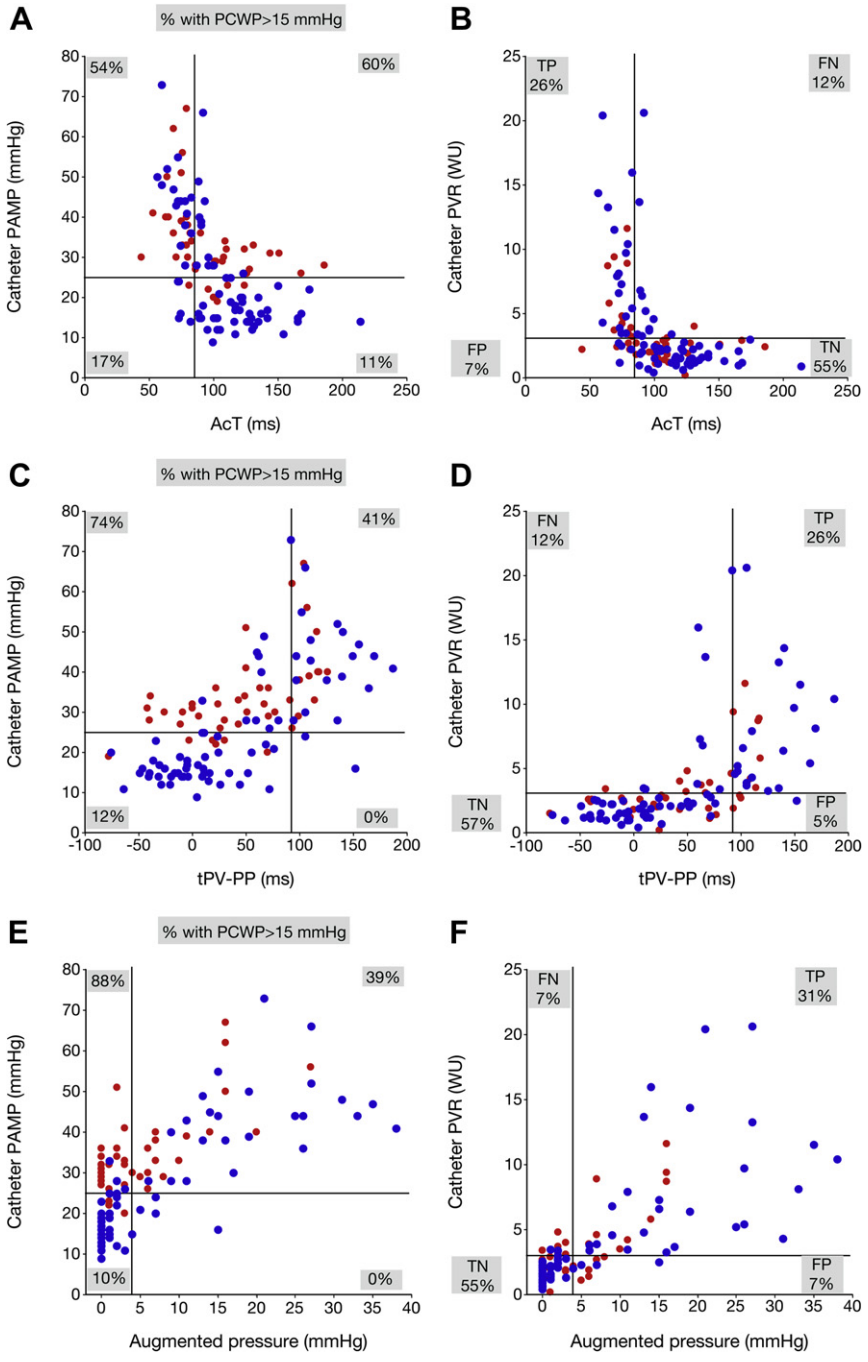

Figure 5 Scatterplot showing the relation between the pressure reflection variables and **(A, C, E)** catheter PAMP and **(B, D, F)** catheter PVR. The *red dots* show patients with PCWP > 15 mm Hg and the *blue dots* those with PCWP ≤ 15 mm Hg. The *horizontal lines* indicate the thresholds for increased PAMP (>25 mm Hg) and PVR (>3 WU), while the *vertical lines* indicate increased PVR with the cutoff value aimed at ruling in increased PVR. The percentage within each quadrant with PCWP > 15 mm Hg is shown in the *left* plots, and the percentages of true-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN) results are shown in the *right* plots.

previous study period.[19] The selection was based on quality criteria regarding echocardiography, regular rhythm, and the time between the two investigations. Therefore, this population should be representative of patients undergoing RHC at a tertiary referral center. The proportion with pulmonary hypertension (PAMP >25 mm Hg) was reduced from 78% to 55% and the proportion with increased PVR from 68% to 39% compared with our previous report.[19] We still found that the agreement between echocardiographic and catheter measurements from previous studies[10,15] was comparable. The concern about selection bias in the first description of the method was confirmed. We could not reproduce the same simultaneous high specificity and sensitivity levels. Sensitivity, specificity, and positive and negative predictive values describe how a diagnostic test performs in a group of patients. It is difficult to translate these values to the assessment of risk in an individual patient.[33] For that purpose, we report the

positive and negative likelihood ratios. Positive and negative likelihood ratios are independent of disease prevalence. Likelihood ratios are a useful and practical way of expressing the power of a diagnostic test in increasing or decreasing the likelihood of disease. We determined two different cutoff values for ruling in and ruling out pulmonary hypertension and increased PVR. The cutoff value for ruling in pulmonary hypertension ($PASP_{Doppler}$ >39 mm Hg) increases the likelihood to a mild to moderate extent, and for ruling out pulmonary hypertension and increased PVR ($PASP_{Doppler}$ ≤29 mm Hg), the likelihood is reduced to a moderate extent. The corresponding values for PVR on the basis of pressure reflection variables had an even larger impact on the likelihood of disease. With two positive pressure reflection variables aiming at ruling in disease, the presence of increased PVR is 6.7 times more likely, and with three positive variable 9.9 times more likely, than a positive test result in the absence of increased PVR.[33] The negative likelihood ratios for the individual pressure reflection variables for ruling out increased PVR ranged from 0.22 to 0.08, which implies that a negative test result is 4.5 to 12.5 times more likely to be truly negative than falsely negative. Importantly, in patients without tricuspid regurgitation and assessment of augmented pressure and tPV-PP, AcT can be helpful to rule out increased PVR. In the presence of AcT >110 msec, increased PVR is highly unlikely.

Several specific treatment options are currently available for patients with pulmonary arterial hypertension (class I), and more patients are submitted to diagnostic RHC. Echocardiography can be used to identify patients with high and low likelihoods of increased PVR. We therefore suggest that the assessment of pressure reflection might serve as a gatekeeper for RHC, when the issue is whether PVR is increased or not and the patient is not a candidate for left ventricular assist device implantation or heart transplantation. As with any diagnostic test, it is crucial to make a pretest assessment of the likelihood of disease (according to Bayes's theorem).[33] If symptoms and other findings indicate an intermediate or high probability of pulmonary vascular disease, RHC should be performed regardless of the pressure reflection findings.

Study Limitations

The catheter and echocardiographic investigations were performed simultaneously in only a small proportion (17%) of the study patients. The main object of the study was to investigate the diagnostic ability of echocardiography to detect pulmonary hypertension and increased PVR. Patients were investigated within 48 hours and 76% within 24 hours. This time interval between echocardiography and catheterization introduces inaccuracies due to biologic variation. Therefore, it is conceivable that the time interval can give both erroneously false-negative and false-positive results but less likely that it contributes to a false impression of good diagnostic performance.

The echocardiographic assessment of filling pressure was performed according to ASE guidelines.[24] However, the study design was retrospective, and in some patients, the variables provided were either missing ($n = 8$) or scarce. More data related to diastolic function might have improved the relation between catheterization and echocardiography. RHC as the gold standard in the present study, but the measurement of PCWP as a surrogate for left ventricular filling pressure[34] and the assessment of cardiac output are known to introduce errors. Some of the diagnostic discrepancies between catheterization and echocardiography might therefore be due to errors in invasive measurements.

In the calculation of augmented pressure, we assumed that the right atrial pressure was constant. This is a simplification, and in some patients with significant delays in right ventricular peak pressure compared with the timing of peak RVOT velocity, the augmented pressure might have been underestimated. However, it is less likely that these patients would be missed, because they will have large tPV-PP values, indicating pressure reflection.

CONCLUSIONS

In the present study, we have shown that echocardiography can provide a comprehensive cardiopulmonary assessment, including PVR, comparable with the results of RHC. The findings suggest that echocardiographic data corresponding to RHC can be used for research purposes to monitor hemodynamic changes. The limits of agreement between echocardiography and catheterization are, however, wide, and therefore findings in individual patients should be interpreted with caution. For the detection of increased PVR, we recommend assessment of pressure reflection. We describe separate cutoff values to rule in and rule out pulmonary hypertension and increased PVR. The findings suggest that echocardiography can serve as a gatekeeper to RHC.

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