

## Accuracy of Echocardiography to Estimate Pulmonary Artery Pressures With Exercise A Simultaneous Invasive–Noninvasive Comparison

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**Background**—Exercise echocardiography is often applied as a noninvasive strategy to screen for abnormal pulmonary hemodynamic response, but it is technically challenging, and limited data exist regarding its accuracy to estimate pulmonary arterial pressure during exercise.

**Methods and Results**—Among 65 patients with exertional intolerance undergoing upright invasive exercise testing, tricuspid regurgitation (TR) Doppler estimates and invasive measurement of pulmonary arterial pressure at rest and peak exercise were simultaneously obtained. TR Doppler envelopes were assessed for quality. Correlation, Bland–Altman, and receiver-operating characteristic curve analyses were performed to evaluate agreement and diagnostic accuracy. Mean age was  $62\pm 13$  years, and 31% were male. High-quality (grade A) TR Doppler was present in 68% at rest and 34% at peak exercise. For grade A TR signals, echocardiographic measures of systolic pulmonary arterial pressure correlated reasonably well with invasive measurement at rest ( $r=0.72$ ,  $P<0.001$ ; bias,  $-2.9\pm 8.0$  mm Hg) and peak exercise ( $r=0.75$ ,  $P<0.001$ ; bias,  $-1.9\pm 15.6$  mm Hg). Lower quality TR signals (grade B and C) correlated poorly with invasive measurements overall. In patients with grade A TR signals, mean pulmonary arterial pressure-to-workload ratio at a threshold of 1.4 mm Hg/10 W was able to identify abnormal pulmonary hemodynamic response during exercise ( $>3.0$  mm Hg/L per minute increase), with 91% sensitivity and 82% specificity (area under the curve, 0.90; 95% confidence interval, 0.77–1.0;  $P=0.001$ ).

**Conclusions**—Agreement between echocardiographic and invasive measures of pulmonary pressures during upright exercise is good among the subset of patients with high-quality TR Doppler signal. While the limits of agreement are broad, our results suggest that in those patients, sensitivity is adequate to screen for abnormal pulmonary hemodynamic response during exercise. (*Circ Cardiovasc Imaging*. 2017;10:e005711. DOI: 10.1161/CIRCIMAGING.116.005711.)

**Key Words:** arterial pressure ■ catheterization ■ exercise echocardiography ■ exercise testing ■ pulmonary hypertension

Regardless of pathogenesis, pulmonary hypertension (PH) is associated with increased mortality, morbidity, and cardiac events.<sup>1–5</sup> Stressing the pulmonary circulation using exercise can unmask abnormal pulmonary hemodynamic response in patients with normal or borderline resting hemodynamics and has important clinical implications.<sup>6–8</sup> First, it may facilitate early detection of pulmonary vascular disease (eg, pulmonary arterial hypertension). Early detection may allow for more adequate and timely treatment in this progressive disease with the result of better outcomes.<sup>9,10</sup> Second, the presence of exercise-induced PH corresponds with worse

prognosis and exercise capacity in left-sided valvular heart disease.<sup>11,12</sup> Finally, evaluation of pulmonary hemodynamics during exercise can enhance early diagnosis of heart failure with preserved ejection fraction.<sup>13,14</sup>

### See Editorial by Claessen and La Gerche See Clinical Perspective

Exercise echocardiography provides a noninvasive approach to screen for and detect exercise-induced PH, but its accuracy when compared with invasive pressure measurements is not well established.<sup>15,16</sup> Furthermore, pulmonary pressures

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are known to vary dynamically within an individual over time, and information on simultaneous noninvasive compared with invasive measurement of pulmonary hemodynamics during exercise is limited.<sup>6,17–23</sup> This study aimed to determine the accuracy of echocardiographic estimation of pulmonary pressures during exercise compared with simultaneous invasive pressure measurements by right heart catheterization (RHC).

## Methods

### Study Population and Design

We studied consecutive patients with unexplained exertional intolerance referred for an invasive cardiopulmonary exercise test at Brigham and Women's Hospital between May 2013 and October 2015. The test consisted of concomitant invasive hemodynamic and echocardiographic evaluation at rest and during exercise in the upright position as previously described.<sup>24</sup> Patients in whom tricuspid regurgitation (TR) spectral Doppler signal was not available at rest and peak exercise (either because of not being assessed or not detectable) were excluded. This study complies with the Declaration of Helsinki, and the Partners Human Research Committee approved this retrospective chart review and waived the requirement for informed consent.

### Invasive Hemodynamic Evaluation

A flow-directed, balloon-tipped, 4-port pacing pulmonary artery catheter (Edwards Lifesciences, Irvine, CA) was placed with ultrasound and fluoroscopic guidance. A sheath was inserted into the radial artery. End expiratory systemic arterial, right atrial (RA), right ventricular (RV), pulmonary artery pressure (PAP), and pulmonary arterial wedge pressure were measured using a hemodynamic monitoring system (Xper Cardio Physiomonitring System; Philips, Andover, MA) calibrated before each study. The pressure transducer was leveled using as reference 5 cm below the axillary fold. Cardiac output (CO) was determined by true Fick method, with direct measurement of oxygen consumption, arterial, and mixed venous O<sub>2</sub> content.

### Exercise Protocol

All exercise tests were performed on an upright cycle ergometer, with the subject breathing room air. Two minutes of rest was followed by 2 minutes of unloaded cycling at 55 to 65 rpm. Thereafter, work rate was continuously increased using a 5, 10, 15, or 20 W/min ramp protocol, chosen on the basis of exertional tolerance history, to a symptom-limited maximum. Minute ventilation ( $V_E$ ), pulmonary gas exchange, heart rate, radial arterial pressure, RA pressure, RV pressure, and PAP were measured continuously, whereas pulmonary arterial wedge pressure was obtained at rest and during each minute of exercise. Aerobic capacity expressed as percentage of predicted was calculated using the Wasserman equation.<sup>25</sup> Breath-by-breath pulmonary gas exchange was measured using a commercially available metabolic cart (MGC Diagnostics, St. Paul, MN).

### Exercise Echocardiography

Transthoracic echocardiography was performed with the patient in the upright position, seated on the cycle ergometer, and simultaneous with the invasive hemodynamic measurements. Images were obtained with the patient at rest, prior to exercise, and at maximal exercise. All quantitative echocardiographic measurements were performed by a single reader (Dr van Riel) blinded to invasive hemodynamic data, using a computerized offline analysis station as previously described.<sup>26</sup> Both at rest and during exercise, TR velocity was measured, using the apical 4-chamber view and the RV inflow from a parasternal window, and traced to obtain the peak and mean systolic right ventricular-to-right atrial (RV-to-RA) gradient. The systolic PAP (PASP) was calculated using the highest RV-to-RA gradient. Estimation of PAP by echocardiography did not include addition of RA pressure such that PAP measurements by echocardiography equaled invasively derived PAP minus RA pressure. If the TR envelope was of inadequate quality, only the PASP was measured.

The TR spectral Doppler envelopes were assessed for quality using 2 predefined criteria: (1) extension of the signal for at least half of systole, and (2) well-defined border.<sup>27</sup> Envelopes were graded as quality A if all criteria were applicable, quality B if 1 criterion was missing, and quality C if both criteria were missing (Figure 1). The quality grading was performed independently by 2 readers (Drs van Riel and Opatowsky), and in case of disagreement, a third reader (Dr Shah) made a final decision. The mean gradient (MPAP) was calculated by tracing the TR time-velocity integral in all patients. All echocardiographic quantitative measurements were performed in triplicate, and the average value was used for analysis.

### Statistical Analysis

Data are expressed as numbers with percentages for categorical variables, as means with standard deviations for normally distributed continuous variables, or as medians with interquartile ranges for non-normally distributed continuous variables. Correlations between echocardiographic and invasive hemodynamics were determined using Pearson correlation. Bland-Altman analysis was used to assess the accuracy and precision of echocardiography-derived hemodynamics compared with simultaneously obtained invasive measurements. The bias, standard deviation of the difference, and 95% limits of agreement were reported. Coefficient of variation was calculated as the standard deviation of the difference divided by the mean value between RHC and echocardiography. Receiver-operating characteristic curves were constructed to determine the diagnostic accuracy of echocardiography-derived pulmonary vascular pressures and pressure/workload relationships to detect an abnormal pulmonary vascular reserve. This was defined as a mean PAP-CO slope >3.0 mm Hg/L per minute by invasive evaluation following recent consensus documents and taken into account the mean age of our population.<sup>28–30</sup> Cut points were chosen closest to the top-left corner of receiver-operating characteristic space. SPSS Statistics 23.0 (IBM, Chicago, IL) was used for statistical analyses. A 2-tailed  $P < 0.05$  was used as a criterion for statistical significance.

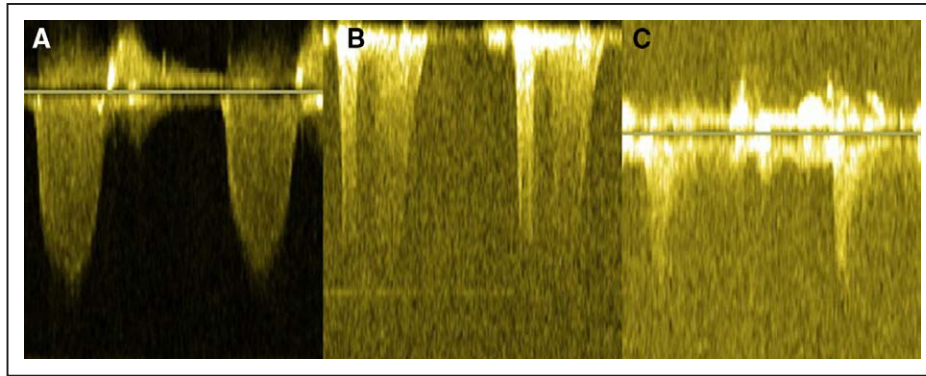
## Results

### Demographics and Clinical Characteristics

Of the 65 patients included in this analysis, 31% were male, and mean age was  $62 \pm 13$  years (Table 1). Mean body mass index was  $26.0 \pm 4.9$  kg/m<sup>2</sup>, and 14% of patients were obese (body mass index  $\geq 30$  kg/m<sup>2</sup>). Hypertension (54%) and dyslipidemia (40%) were the most prevalent cardiovascular risk factors. Only 2 patients (3%) were using targeted pulmonary arterial hypertension medications, 2 patients (3%) had severe TR, and 3 patients (5%) were in atrial fibrillation at the time of testing. Average left ventricular ejection fraction was normal at  $59.3 \pm 8.5\%$ . All patients performed spirometry at rest, with a mean forced expiratory volume in 1 second of  $2.2 \pm 0.7$  L and a median forced expiratory volume in 1 second/forced vital capacity of 0.79 (25th to 75th percentile, 0.74–0.84). The mean peak oxygen consumption, a measure of functional capacity, was  $15.9 \pm 6.7$  mL/kg per minute ( $71 \pm 23\%$  predicted). The primary limit to exercise was attributed to a central cardiac cause in approximately half of the study population ( $n=34$ , 52%), with (exercise-induced) PH ( $n=20$ , 31%) and (exercise-induced) heart failure with preserved ejection fraction ( $n=12$ , 19%) as the most frequent underlying diagnoses, according to a diagnostic algorithm which was previously published.<sup>31</sup>

### Agreement of Echocardiographic and Invasive Measures of PAP in the Upright Position at Rest

Forty-four patients (68%) had grade A TR quality at rest, 17 patients (26%) had grade B, and 4 patients (6%) had



**Figure 1.** Examples of quality grade A, B, and C tricuspid regurgitation Doppler envelopes. The tricuspid regurgitation (TR) spectral Doppler envelopes were assessed for quality using 2 predefined criteria: (1) extension of the signal for at least half of systole, and (2) well defined border. Envelopes were graded as quality A if all criteria were applicable, quality B if 1 criterion was missing, and quality C if both criteria were missing. Grade A demonstrates both extension of signal through all of systole and well-defined spectral Doppler envelope border. Grade B demonstrates clear extension of the regurgitant signal throughout systole, although the spectral envelope border is poorly defined. Grade C shows only an early systolic spike, without signal persistence through at least half of systole and extremely poor spectral Doppler envelope border definition.

grade C. As previously noted, estimation of PAP by echocardiography did not include addition of RA pressure and, therefore, corresponded to the RV-to-RA peak systolic pressure gradient. At rest, average systolic PASP was  $24 \pm 14$  mmHg and average MPAP was  $18 \pm 10$  mmHg by RHC and  $25 \pm 10$  and  $16 \pm 6$  mmHg, respectively, by echocardiography for quality A TR spectral Doppler tracings. Mean values were  $25 \pm 11$  and  $16 \pm 7$  mmHg, respectively, by echocardiography for quality B and C TR spectral Doppler tracings. Agreements between the simultaneous invasive measurement and echocardiographic estimation of PAP are depicted in Table 2. For quality A signals, moderately good agreement was found between noninvasive and invasive measures of PASP ( $r=0.72$ ,  $P<0.001$ ; bias,  $-2.9 \pm 8.0$  mmHg; Figure 2A and 2D and Table 2) and MPAP ( $r=0.61$ ,  $P<0.001$ ; bias,  $1.3 \pm 7.6$  mmHg; Figure 3A and 3D) at rest. In contrast, agreement at rest for both systolic and mean PAP was poor for quality B and C TR envelopes (Table 2).

### Agreement of Echocardiographic and Invasive Measures of PAP at Peak Upright Exercise

Twenty-two out of 65 patients (34%) had grade A TR quality with exercise. Average PASP was  $49 \pm 22$  mmHg and MPAP was  $32 \pm 14$  mmHg by RHC and  $49 \pm 20$  and  $31 \pm 14$  mmHg, respectively, by echocardiography for quality A TR envelopes. Mean values were  $36 \pm 11$  and  $23 \pm 7$  mmHg, respectively, by echocardiography for quality B and C TR envelopes. Agreement among patients with quality A TR envelopes was good, both for PASP at peak exercise ( $r=0.75$ ,  $P<0.001$ ; bias,  $-1.9 \pm 15.6$  mmHg; Figure 2B and 2E and Table 2) and for MPAP at peak ( $r=0.77$ ,  $P<0.001$ ; bias,  $4.0 \pm 11.3$  mmHg; Figure 3B and 3E). In contrast, agreement in patients with quality B and C TR envelopes was poor (Table 2).

### Agreement of Echocardiographic and Invasive Measures of Change in PAP During Upright Exercise

The average invasively measured change in PASP was  $22 \pm 12$  mmHg and the average change in MPAP was  $14 \pm 8$

mmHg by RHC. By echocardiography, for quality A TR envelopes, the average change in PASP was  $20 \pm 15$  mmHg and the average change in MPAP was  $13 \pm 9$  mmHg. For quality B and C studies, average values by echocardiography were  $13 \pm 11$  and  $8 \pm 7$  mmHg, respectively. Agreement among patients with quality A TR envelopes was good, both for change in PASP ( $r=0.70$ ,  $P<0.001$ ; bias,  $0.0 \pm 11.0$  mmHg; Figure 2C and 2F; Table 2) and for change in MPAP ( $r=0.75$ ,  $P<0.001$ ; bias,  $2.4 \pm 6.9$  mmHg; Figure 3C and 3F). Agreement in patients with quality B and C TR envelopes was poor (Table 2).

Similar findings for the agreement of echocardiographic and invasive measures of PAP both at rest and peak exercise in the upright position were noted after excluding 2 patients with severe TR (Table I in the Data Supplement). In addition, similar findings were noted for the relationship between resting, peak exercise, and change in MPAP when calculated using the Chemla formula (Table II in the Data Supplement).<sup>7,17</sup> Of note, echocardiography-based assessment of MPAP was available in a larger number of participants using the Chemla formula compared with using the velocity time integral method, particularly for peak exercise values (n of 65 versus 55, respectively) and change values from rest to peak exercise (n of 65 versus 53, respectively). In addition, the mean bias tended to be modestly lower with the Chemla formula.

### Predicting Abnormal Pulmonary Hemodynamic Response During Exercise With Echocardiography

Presence of an abnormal pulmonary hemodynamic response during exercise was defined as an invasively measured MPAP/CO ratio  $>3.0$  mmHg/L per minute. This was present in 22 patients (34%) and was associated with a significantly lower peak oxygen consumption, expressed as percentage of predicted ( $61.6 \pm 15.5\%$  versus  $77.5 \pm 24.5\%$ ;  $P=0.008$ ). The respiratory exchange rate was significantly lower in patients with an abnormal pulmonary hemodynamic response ( $1.1 \pm 0.2$  versus  $1.0 \pm 0.1$ ;  $P=0.01$ ), and these patients achieved a lower amount of watts during

Table 1. Baseline Characteristics

	n=65
<b>Demographics</b>	
Age, y	62.1±13
Male sex	20 (31)
Height, cm	165±8.5
Weight, kg	70.2±13
BSA, m <sup>2</sup>	1.78±0.2
BMI, kg/m <sup>2</sup>	26±4.9
<b>Medical history</b>	
Hypertension	35 (54)
Dyslipidemia	26 (40)
Diabetes mellitus	9 (14)
Coronary artery disease	9 (14)
Congestive heart failure	9 (14)
Pulmonary hypertension	8 (12)
Cerebrovascular accident	2 (3)
Connective tissue disease	8 (13)
Lung disease	27 (42)
Malignancy	12 (19)
<b>Current medication use</b>	
Beta blocker	23 (35)
ACE inhibitor/ARB	15 (23)
Diuretic	23 (35)
Digoxin	3 (5)
ERA or PDE-5 inhibitor	2 (3)
<b>Clinical characteristics</b>	
Systolic blood pressure, mm Hg	143±23
Diastolic blood pressure, mm Hg	76±12
<b>Rhythm</b>	
Sinus rhythm	57 (87)
Atrial fibrillation	3 (5)
Paced	5 (8)
Hemoglobin, g/dL	13.5±1.7
<b>Echocardiographic characteristics</b>	
LV ejection fraction, %	59.3±8.5
E/A ratio	1.11±0.47
E' (septal)	7.56±3.27
E/E' ratio	10.13±4.13
LA volume, mL	58.7±33.6
RVOT AccT, ms	120±38
MPI-RV	0.41±0.21
<b>Valvular disease</b>	
AR≥mild-to-moderate	2 (3)

(Continued)

Table 1. Continued

	n=65
MR≥mild-to-moderate	7 (12)
MS≥mild-to-moderate	0
PS≥mild	0
TR≥mild-to-moderate	13 (25)
<b>Test performance characteristics</b>	
Peak V <sub>O<sub>2</sub></sub> , % predicted	71.4±23.2
RER	1.1±0.2
FEV <sub>1</sub> , % predicted	81.7±22.2
FEV <sub>1</sub> /FVC ratio	76.9±10.2
Watts	85±46

Values are presented as mean±SD or as count with (percentage). ACE indicates angiotensin-converting enzyme; AR, aortic valve regurgitation; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; ERA, endothelin receptor antagonist; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; LA, left atrium; LV, left ventricle; MPI-RV, myocardial performance index of the right ventricle; MR, mitral valve regurgitation; MS, mitral valve stenosis; PDE-5, phosphodiesterase type 5; PS, pulmonary valve stenosis; RER, respiratory exchange rate; RVOT AccT, right ventricular outflow tract acceleration time; TR, tricuspid valve regurgitation; and V<sub>O<sub>2</sub></sub>, oxygen consumption.

exercise (98±47 versus 63±36 W;  $P=0.004$ ). Receiver-operating characteristic analysis was used to determine the ability of echocardiographic measures to detect an abnormal pulmonary hemodynamic response (Table 3 and Figure 4). Among patients with quality A TR envelopes, PASP at peak exercise performed best at a cutoff value of 34 mm Hg, with a sensitivity of 82% and a specificity of 36% (area under the curve [AUC], 0.78; 95% confidence interval [CI], 0.57–0.98;  $P=0.03$  for test of whether AUC is significantly different from an AUC of 0.50). MPAP at peak performed best at the cutoff value of 21 mm Hg, with a sensitivity and specificity of 91% and 55%, respectively (AUC, 0.84; 95% CI, 0.66–1.0;  $P=0.008$ ). Change in MPAP from rest to peak exercise performed best using the cutoff of 10 mm Hg, with a sensitivity of 73% and a specificity of 64% (AUC, 0.76; 95% CI, 0.56–0.96;  $P=0.04$ ). Indexing the change in MPAP to exercise intensity reflected in watts ( $\Delta$ MPAP/W ratio), a threshold of 1.4 mm Hg/10 W demonstrated 91% sensitivity and 82% specificity (AUC, 0.90; 95% CI, 0.77–1.0;  $P=0.001$ ) to detect an abnormal pulmonary hemodynamic response during exercise. When using PASP indexed to watts, a threshold of 1.9 mm Hg/10 W demonstrated a 91% sensitivity and 46% specificity (AUC, 0.75; 95% CI, 0.55–0.96;  $P=0.04$ ). In patients with quality B and C TR envelopes, echocardiographic measures were not able to identify an abnormal pulmonary hemodynamic response during exercise (Table 3).

## Discussion

This study is the first, to our knowledge, to simultaneously assess pulmonary pressures at rest and with exercise by both RHC and echocardiography and demonstrates 3 major novel findings. First, while pulmonary pressure assessment by echocardiography demonstrates good correlation with

**Table 2. Comparison of Pulmonary Arterial Pressures Estimated by Echocardiography Versus Catheterization**

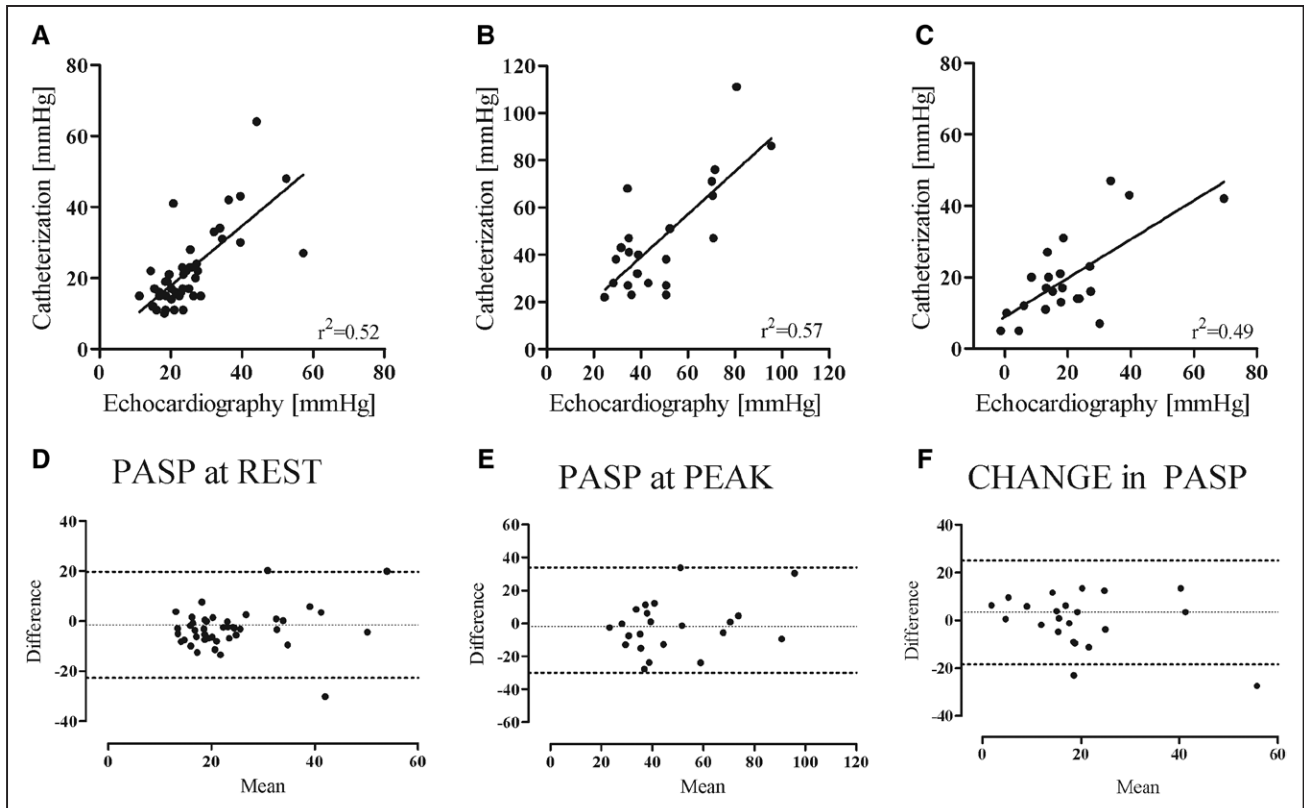
	N	Echo	Cath	Bias	SD of Bias	Limits of Agreement	r	P Value	Coefficient of Variation
<b>PASP at rest</b>									
Overall	65	25.1±9.9	23.7±13.6	-1.5	10.8	-22.7 to 19.7	0.62	<0.001	0.44
A	44	25.2±9.8	22.2±11.4	-2.9	8.0	-18.6 to 12.7	0.72	<0.001	0.34
B	17	25.7±9.8	27.4±18.9	1.7	15.8	-29.3 to 32.7	0.55	0.02	0.60
C	4	22.7±14.7	23.8±10.2	1.1	12.6	-23.6 to 25.7	0.54	0.46	0.54
<b>PASP at peak</b>									
Overall	65	40.4±15.6	42.3±19.0	1.9	16.3	-30.1 to 33.9	0.57	<0.001	0.39
A	22	48.8±19.6	46.9±23.5	-1.9	15.6	-32.3 to 28.6	0.75	<0.001	0.33
B	28	38.2±12.0	41.2±15.6	3.0	15.1	-26.7 to 32.6	0.42	0.03	0.38
C	15	32.1±8.5	37.5±17.0	5.4	19.3	-32.5 to 43.3	-0.05	0.87	0.55
<b>ΔPASP</b>									
Overall	65	15.3±12.6	18.6±10.1	3.4	11.1	-18.4 to 25.2	0.54	<0.001	0.66
A	22	19.6±15.2	19.6±11.9	0.0	11.0	-21.5 to 21.5	0.70	<0.001	0.56
B	28	15.0±10.5	19.9±10.0	4.9	11.4	-17.5 to 27.3	0.38	0.05	0.65
C	15	9.2±9.8	14.7±6.8	5.5	10.3	-14.6 to 25.6	0.28	0.32	0.86
<b>MPAP rest</b>									
Overall	62	16.1±6.3	18.0±10.0	2.1	8.2	-13.9 to 18.1	0.59	<0.001	0.48
A	44	16.2±6.3	17.4±9.5	1.3	7.6	-13.6 to 16.1	0.61	<0.001	0.45
B	16	16.2±6.5	19.4±11.8	3.7	9.8	-15.5 to 22.9	0.58	0.02	0.56
C	2	14.9±9.5	19.0±7.0	8.6	1.7	5.2 to 12.0	-	-	0.10
<b>MPAP peak</b>									
Overall	55	26.3±11.0	31.8±14.1	6.1	12.0	-17.4 to 29.6	0.59	<0.001	0.41
A	22	31.2±13.8	35.2±17.7	4.0	11.3	-18.2 to 26.2	0.77	<0.001	0.34
B	24	24.3±7.8	30.9±12.0	6.4	12.4	-17.8 to 30.6	0.24	0.25	0.44
C	9	19.5±2.9	28.4±11.4	10.6	12.6	-14.0 to 35.3	0.35	0.35	0.50
<b>ΔMPAP</b>									
Overall	53	10.0±8.1	13.7±7.6	3.9	7.0	-9.8 to 17.7	0.61	<0.001	0.58
A	22	12.5±9.3	14.9±10.0	2.4	6.9	-11.0 to 15.8	0.75	<0.001	0.50
B	22	9.6±7.2	14.2±6.8	4.6	8.1	-11.3 to 20.4	0.24	0.29	0.65
C	9	4.6±3.9	11.2±3.9	6.2	3.3	-0.2 to 12.6	0.66	0.06	0.35

Values are presented as mean±SD. Correlation (r) is based on Pearson correlation. P values represent results of a test of whether the correlation is significantly different from 0. A indicates quality A tricuspid regurgitation (TR) envelope; B, quality B TR envelope; C, quality C TR envelope; Cath, catheterization; Echo, echocardiography; MPAP, mean pulmonary arterial pressure; PASP, systolic pulmonary arterial pressure; and SD, standard deviation.

invasive measures during upright exercise, its accuracy is highly dependent on the quality of the TR spectral Doppler envelope. In patients with high-quality TR envelopes, agreement between invasive and noninvasive measurements was good, with low bias and reasonable limits of agreement. Second, echocardiographic measures of pulmonary pressure with exercise demonstrate high sensitivity to detect abnormal pulmonary hemodynamic response among the subset of patients in whom high-quality TR signals can be obtained at rest and peak exercise. Finally, indexing noninvasively assessed change in MPAP to change in work rate

(ΔMPAP/W ratio) demonstrated clinically acceptable sensitivity (91%) and specificity (82%) to identify an abnormal pulmonary hemodynamic response to exercise. Together, these findings suggest that exercise echocardiography is an adequate screening test for exercise PH in the subset of cases where high-quality TR spectral Doppler envelopes can be obtained.

PH can complicate many cardiovascular and pulmonary conditions and is consistently associated with worse quality of life, exercise capacity, and survival.<sup>32-34</sup> Furthermore, the presence of exercise-induced PH, assessed by exercise



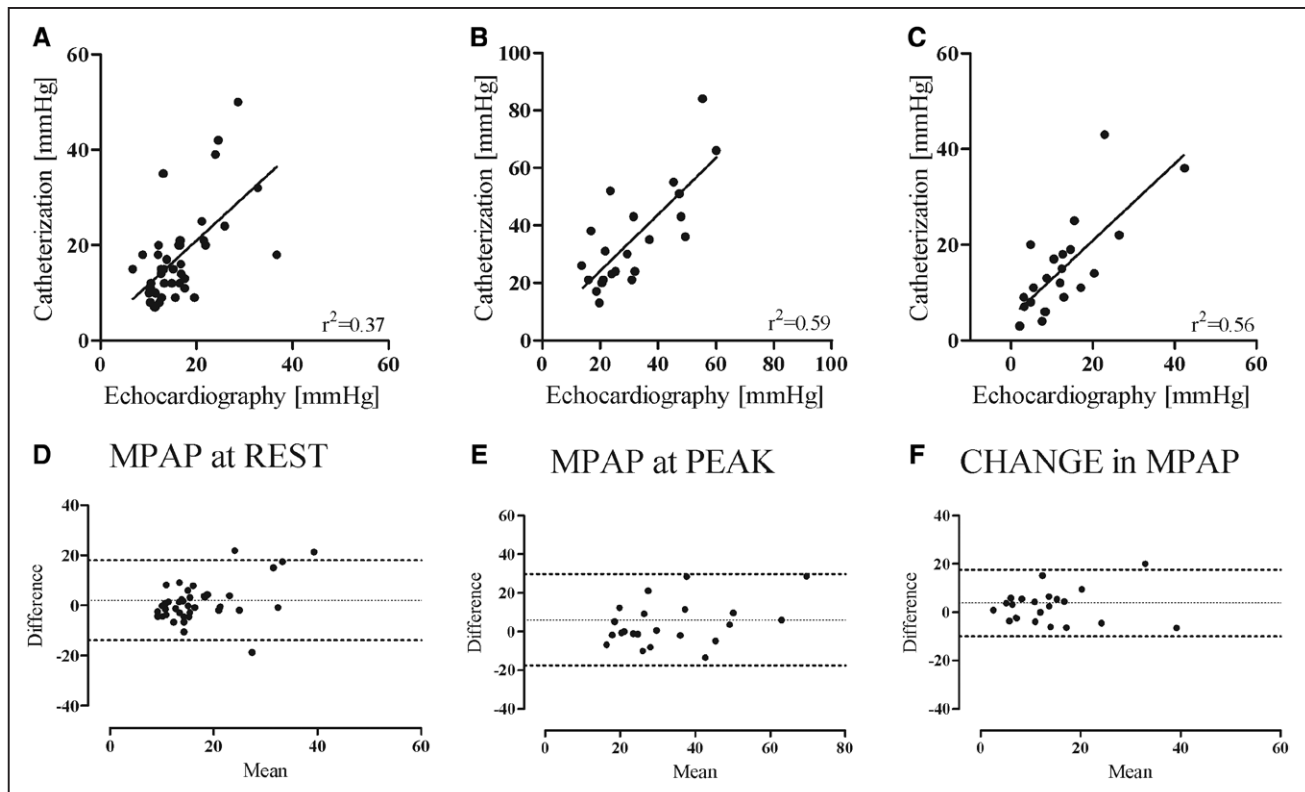
**Figure 2.** Relationship between pulmonary artery systolic pressure (PASP) measured by right heart catheterization and estimated by echocardiographic measurement of peak tricuspid regurgitation (TR) velocity. Plots represent patients with quality A TR envelope only. The correlations are shown at rest (**A**;  $n=44$ ), at peak (**B**;  $n=22$ ), and the change during exercise (**C**;  $n=22$ ). Corresponding Bland–Altman plots demonstrate the bias and limits of agreement at rest (**D**), at peak (**E**), and change during exercise (**F**).

echocardiography, is independently associated with reduced survival in patients with valvular disease and could be useful to identify a high-risk subset of asymptomatic patients.<sup>35,36</sup> While RHC is the gold standard to assess pulmonary pressures and is required to confirm the diagnosis of PH, there is a need for safe and practical noninvasive clinical tests to screen at-risk patients for PH. The correlation of echocardiography and RHC is good, as many studies have reported.<sup>18,27,37–41</sup> High correlation is, however, not necessarily associated with good patient-level agreement, and Bland–Altman analysis is more appropriate in determining the accuracy of echocardiography in this respect.<sup>42</sup> Table 4 summarizes findings of selected previously published papers on the accuracy of echocardiography versus RHC that include Bland–Altman analysis.<sup>17–19,40,43,44</sup> Similar to our findings, these studies demonstrated a good correlation of PASP at rest, with correlation coefficients ranging from 0.66 to 0.92. Systematic bias is minimal in most studies (range  $-2.9$  to  $2.2$  mmHg), although this is not universally the case,<sup>43</sup> while the standard deviation of the bias and corresponding limits of agreement are wide by clinical standards, with studies reporting standard deviations ranging from 7.6 to 20.1 mmHg. Our results are consistent with these previous reports on resting echocardiography.

Only 2 previous studies have reported the accuracy of echocardiography compared with RHC during exercise (Table 4), although the assessments in these studies were not simultaneous. Including our own data, the correlation with

invasive PASP was good (0.75 and 0.91), with modest systematic bias (range from  $-5.6$  to  $2.9$  mmHg). However, the standard deviation of the echocardiography–RHC difference was rather large (13.6–19.0 mmHg), leading to broad limits of agreement. MPAP is only reported by 2 previous studies, with results similar to that reported for PASP, namely good correlation, little systematic bias but wide limits of agreement (Table 4).

Despite the relatively wide limits of agreement of peak exercise pulmonary pressure assessments by echocardiography and RHC, our findings suggest that exercise echocardiography is able to detect an abnormal pulmonary hemodynamic response, using various hemodynamic cutoffs, with good sensitivity, but only among patients in whom good-quality TR envelopes can be consistently obtained at rest and during exercise. The lower cutoff values for echo-based PASP and MPAP to predict and abnormal pulmonary vascular reserve in our analysis compared with prior reports is likely related to both our use of the RV-to-RA gradient, exclusive of RA pressure, and to our emphasis on high sensitivity in cut point selection. However, we think that use of the peak RV-to RA pressure gradient is more clinically relevant because estimates of RAP are rarely available during exercise echocardiography. As the increase in PAP during exercise is dependent on both flow and resistance, many studies have proposed change in PAP-to-CO ratio as better indicator of pathological response.<sup>9,28</sup> CO assessment by echocardiography is



**Figure 3.** Relationship between mean pulmonary arterial pressure (MPAP) measured by right heart catheterization and estimated by echocardiographic tracing of tricuspid regurgitation (TR) velocity. Plots represent patients with quality A TR envelope only. The correlations are shown at rest (**A**;  $n=44$ ), at peak (**B**;  $n=22$ ), and the change during exercise (**C**;  $n=22$ ). Corresponding Bland–Altman plots demonstrate the bias and limits of agreement at rest (**D**), at peak (**E**), and change during exercise (**F**).

technically challenging at rest and more so during exercise. Work rate, expressed as watts, is a more uniformly available measure that is highly correlated to CO with exercise.<sup>45</sup> In our study, the change in MPAP-to-workload ratio demonstrated the highest sensitivity in determining an abnormal pulmonary hemodynamic response during exercise. This finding supports previously published data by Claessen et al,<sup>17</sup> which suggested that PASP/W ratio at a cutoff value of  $>0.47$  mm Hg/W had a sensitivity of 86% and specificity of 94% to detect abnormal pulmonary vascular reserve (AUC, 0.94; 95% CI, 0.88–1.01;  $P<0.001$ ).

Our study is one of the few to quantify the impact of the quality of the TR spectral Doppler envelope, categorized by prospectively defined criteria, on the accuracy of echocardiographic estimates at rest and with exercise. Our estimation of PAP by echocardiography did not include addition of RA pressure and, therefore, corresponded to the RV-to-RA peak systolic pressure gradient. Only in patients with high-quality TR signals did we find reasonable accuracy for echocardiography as a screening method for pulmonary vascular disease. This finding is concordant with the results of Amsallem et al,<sup>44</sup> who demonstrated reliable estimation of RV systolic pressure by echocardiography at rest when careful attention is paid to signal quality. Notably, the feasibility of obtaining high-quality TR envelopes (quality grade A) at both rest and peak exercise was low (34%) in our study. All exercise tests in our study were performed using a cycle ergometer in the upright position, which may have contributed to the

low observed feasibility. It is possible that the feasibility of obtaining high-quality TR envelopes is higher with alternative approaches, such as supine or semisupine bicycle ergometers.<sup>46</sup> Furthermore, the use of contrast enhancement may also increase the yield of exercise echocardiography.<sup>47</sup> Although no single measure is sufficient to separate disease presence from absence, exercise echocardiography may be a reasonable tool to screen for an abnormal pulmonary hemodynamic response during exercise. However, good-quality TR signals are essential and have major impact on accuracy. Indeed, our findings suggest that echocardiographic estimates of PAP based on suboptimal TR envelopes are inaccurate and may be misleading.

This study has several limitations that warrant consideration. The sample size is relatively small, although substantial for a comparison of simultaneous RHC and echocardiography with exercise. This was a retrospective analysis of clinically indicated invasive cardiopulmonary tests, and therefore, TR signals were not uniformly assessed, and contrast enhancement for TR signal was not performed. This may have led to potential selection bias, given the exclusion of patients without a measured or obtainable TR signal. Respirophasic variation in TR velocity measurement may be exaggerated during exercise. The use of average values of triplicate measures should mitigate the influence of respirophasic variation in our analysis. Additionally, peak TR velocity is typically used in current interpretation of exercise echocardiography, and use

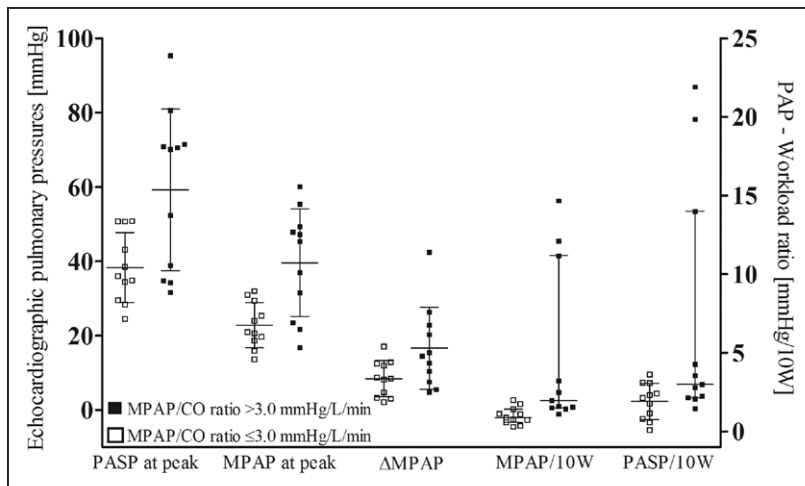
**Table 3. Sensitivity and Specificity of Echocardiography in Determining Pulmonary Vascular Disease During Exercise**

	n	Cutoff Value	Sensitivity	Specificity	AUC (95% CI)	P Value
Quality A TR envelope	22					
MPAP/CO ratio >3 mm Hg/L per minute						
PASP at peak		≥34	82	36	0.78 (0.57–0.98)	0.03
MPAP at peak		≥21	91	55	0.84 (0.66–1.00)	0.008
ΔMPAP		≥10	73	64	0.76 (0.56–0.96)	0.04
ΔMPAP/10 W		≥1.4	91	82	0.90 (0.77–1.00)	0.001
ΔPASP/10 W		≥1.9	91	46	0.75 (0.55–0.96)	0.04
Quality B or C TR envelope	43					
MPAP/CO ratio >3 mm Hg/L per minute						
PASP at peak		...	...	...	0.63 (0.46–0.81)	0.19
MPAP at peak		...	...	...	0.55 (0.36–0.75)	0.66
ΔMPAP		...	...	...	0.40 (0.19–0.61)	0.38
ΔMPAP/10 W		...	...	...	0.48 (0.25–0.70)	0.72
ΔPASP/10 W		...	...	...	0.54 (0.36–0.73)	0.69

Area under the curve (AUC) is based on receiver-operating characteristic curve analysis. P values represent results of a test of whether the AUC is significantly different from an AUC of 0.50. CI indicates confidence interval; CO, cardiac output; MPAP, mean pulmonary arterial pressure; PASP, systolic pulmonary arterial pressure; and TR, tricuspid regurgitation.

of the peak detected TR velocity, therefore, provided the most clinically relevant results regarding the comparability of invasive and noninvasive measurements of pulmonary pressures with exercise. Echocardiography during exercise was performed in an upright position, which may have further limited feasibility. However, we could not compare the feasibility and accuracy of echocardiography in different exercise positions (ie, upright versus recumbent). As the purpose of this study was to evaluate the accuracy of noninvasive estimation of pulmonary pressure with exercise in a diverse sample of patients with dyspnea, resting-state precapillary PH was present in only a small subset. While multipoint MPAP/CO or MPAP/W slopes may be more robust and accurate than the single-point measures

reported here,<sup>7,29</sup> echo-based TR velocity was only collected uniformly at rest and peak exercise in this study, and data at intermediate time points was insufficient for calculation of a multipoint slope. Furthermore, direct comparison of the invasive versus echocardiographically determined MPAP/CO slope was not feasible because adequate data on echo-based CO at peak exercise was not available in this study sample. Quantitative measures of RV function were not available with exercise. Finally, the sample size precludes confirmation of our estimates of sensitivity and specificity of exercise echocardiography versus RHC in a validation cohort. Future studies with simultaneous invasive and non-invasive hemodynamic assessment at rest and with exercise are necessary to confirm these findings. These limitations



**Figure 4.** Hemodynamic variables obtained by echocardiography among patients with and without abnormal pulmonary hemodynamic response during exercise based on a MPAP–CO slope >2.5 mm Hg/L per minute by right heart catheterization (RHC). Scatterplots represent individual values. The bars represent mean and SD in PASP at peak, MPAP at peak, and ΔMPAP. In MPAP/10 W, plotted on the right y axis, the bars represent the median with interquartile range. MPAP indicates mean pulmonary arterial pressure; ΔMPAP, change in mean pulmonary arterial pressure; MPAP/10 W, mean pulmonary arterial pressure per 10 W; MPAP/CO, mean pulmonary arterial pressure to cardiac output ratio; and PASP, systolic pulmonary arterial pressure.



**Table 4. Studies Evaluating Pulmonary Arterial Pressure by Echocardiography and Right Heart Catheterization at Rest and During Exercise**

Author	Year	Delay	Position During Measurements	n	PASP				MPAP			
					r	Bias	SD	Limits of Agreement	r	Bias	SD	Limits of Agreement
Rest												
Fisher et al <sup>40</sup>	2009	Within 1 h	Supine	59	0.66	-0.6	20.1	-40.0 to 38.8	...	...	...	...
Kovacs et al <sup>19</sup>	2010	Unknown	Semisupine	28	...	0.3	7.6	-14.6 to 15.2	...	...	...	...
Rich et al <sup>43</sup>	2011	Within 30 days	Supine	160	0.68	2.2	18.6	-34.2 to 38.6	...	...	...	...
Rich et al <sup>43</sup>	2011	Simultaneous	Supine	23	0.71	8.0	18.6	-28.4 to 44.4	...	...	...	...
D'Alto et al <sup>18</sup>	2013	Within 1 h	Supine	152	0.77	-0.5	9.0	-19.0 to 18.0	0.66	-0.5	9.0	-19.0 to 18.0
Claessen et al <sup>17</sup>	2016	Within 24 h	Semisupine (echo)+supine (RHC)	57	0.92	1.7	10.0	-17.9 to 21.2	0.91	4.1	6.1	-7.9 to 16.0
Amsallem et al <sup>44</sup>	2016	Within 5 days	Supine	187	0.96	3.3	8.2	-12.6 to 19.3	...	...	...	...
van Riel et al*	2016	Simultaneous	Upright	44	0.72	-2.9	8.0	-18.6 to 12.7	0.61	1.3	7.6	-13.6 to 16.1
Exercise												
Kovacs et al <sup>19</sup>	2010	Unknown	Semisupine	28	...	-5.6	19.0	-42.8 to 31.6	...	...	...	...
Claessen et al <sup>17</sup>	2016	Within 24 h	Semisupine (echo)+supine (RHC)	42	0.91	2.9	13.6	-23.7 to 29.6	0.91	7.3	7.4	-7.1 to 21.7
van Riel et al*	2016	Simultaneous	Upright	22	0.75	-1.9	15.6	-32.3 to 28.6	0.77	4.0	11.3	-18.2 to 26.2

Echo indicates echocardiography; MPAP, mean pulmonary arterial pressure; PASP, systolic pulmonary arterial pressure; and RHC, right heart catheterization.

\*Present study data.

notwithstanding, we think that the strength of the study includes the simultaneous assessment of pulmonary hemodynamics during exercise by echocardiography and RHC and provides important clinical information on the accuracy of exercise echocardiography.

### Conclusions

The agreement between echocardiographic and invasive measures of pulmonary pressures during upright exercise is good among the subset of patients with high-quality TR Doppler signal. Although the limits of agreement between echocardiography and catheterization are broad, our results suggest that the sensitivity is adequate to screen for abnormal pulmonary hemodynamic response during exercise in patients with good TR quality.

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### CLINICAL PERSPECTIVE

Exercise echocardiography is commonly used to noninvasively screen for abnormal pulmonary hemodynamic response, but it is technically challenging, and limited data exist regarding its accuracy to estimate pulmonary arterial pressure during exercise. We compared echocardiography-based measures of pulmonary arterial pressure based on tricuspid regurgitation (TR) Doppler to invasive measurement at rest and during exercise in 65 patients with exertional intolerance undergoing upright invasive exercise testing. While pulmonary pressure assessment by echocardiography demonstrated good correlation with invasive measures, its accuracy is highly dependent on the quality of the TR spectral Doppler envelope. In patients with high-quality TR envelopes, agreement between invasive and noninvasive measurements was good, with low bias and reasonable limits of agreement. Echocardiographic measures of pulmonary pressure with exercise demonstrate high sensitivity to detect abnormal pulmonary hemodynamic response among the subset of patients in whom high-quality TR signals can be obtained at rest and peak exercise. Indexing noninvasively assessed change in mean pulmonary arterial pressure (MPAP) to change in work rate (expressed as watts;  $\Delta$ MPAP/W ratio) demonstrated clinically acceptable sensitivity (91%) and specificity (82%) to identify an abnormal pulmonary hemodynamic response to exercise. These findings suggest that exercise echocardiography is an adequate screening test for exercise pulmonary hypertension in the subset of cases where high-quality TR spectral Doppler envelopes can be obtained.

## Accuracy of Echocardiography to Estimate Pulmonary Artery Pressures With Exercise: A Simultaneous Invasive –Noninvasive Comparison

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**Accuracy of Echocardiography to Estimate Pulmonary Artery Pressures with Exercise: A Simultaneous Invasive – Non-invasive Comparison**

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Short title: Accuracy of exercise echocardiography

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**SUPPLEMENTAL MATERIAL**

**Supplemental Table 1. Comparison of pulmonary arterial pressures estimated by echocardiography versus catheterization excluding 2 patients with severe tricuspid regurgitation.**

	N	Echo	Cath	Bias	SD of bias	limits of agreement	r	p value	coefficient of variation
<b>PASP at rest</b>									
Overall	63	24.6 ± 9.6	22.7 ± 12.6	-1.9	10.6	-22.7 - 18.9	0.57	<0.001	0.43
A	42	24.4 ± 9.3	20.7 ± 8.9	-3.6	7.2	-17.7 - 10.5	0.68	<0.001	0.30
B	17	25.7 ± 9.8	27.4 ± 18.9	1.7	15.8	-29.3 - 32.7	0.55	0.02	0.60
C	4	22.7 ± 14.7	23.8 ± 10.2	1.1	12.6	-23.6 - 25.8	0.54	0.46	0.54
<b>PASP at peak</b>									
Overall	63	40.2 ± 15.8	41.4 ± 18.4	1.2	16.0	-30.2 - 32.6	0.57	<0.001	0.39
A	22	48.8 ± 19.6	46.9 ± 23.5	-1.9	15.6	-32.3 - 28.6	0.75	<0.001	0.33
B	26	37.6 ± 12.0	39.0 ± 13.0	1.5	14.4	-26.7 - 29.7	0.34	0.09	0.36
C	15	32.1 ± 8.5	37.5 ± 17.0	5.4	19.3	-32.5 - 43.3	-0.05	0.87	0.55
<b>Δ PASP</b>									
Overall	63	15.6 ± 12.6	18.7 ± 10.2	3.1	11.2	-18.9 - 25.1	0.53	<0.001	0.66
A	22	19.6 ± 15.2	19.6 ± 11.9	0.0	11.0	-21.5 - 21.5	0.7	<0.001	0.56
B	26	15.8 ± 10.3	20.3 ± 10.0	4.4	11.7	-18.5 - 27.3	0.34	0.09	0.67
C	15	9.2 ± 9.8	14.7 ± 6.8	5.5	10.3	-14.6 - 25.6	0.28	0.32	0.86
<b>MPAP rest</b>									
Overall	60	15.8 ± 6.1	17.1 ± 8.7	1.6	7.6	-13.3 - 16.5	0.53	<0.001	0.45
A	42	15.7 ± 6.0	16.1 ± 7.3	0.4	6.6	-12.5 - 13.3	0.52	<0.001	0.39
B	16	16.2 ± 6.5	19.4 ± 11.8	3.7	9.8	-15.5 - 22.9	0.58	0.02	0.56
C	2	14.9 ± 9.5	19.0 ± 7.0	8.6	1.7	5.2 - 12.0	-	-	0.10
<b>MPAP peak</b>									
Overall	53	26.1 ± 11.2	31.0 ± 13.6	5.4	11.6	-17.3 - 28.1	0.6	<0.001	0.40
A	22	31.2 ± 13.8	35.2 ± 17.7	4.0	11.3	-18.2 - 26.2	0.77	<0.001	0.34

B	22	23.7 ± 7.8	29.0 ± 10.0	4.6	11.3	-17.5 - 26.7	0.1	0.65	0.40
C	9	19.5 ± 2.9	28.4 ± 11.4	10.6	12.6	-14.0 - 35.3	0.35	0.35	0.50
<b>Δ MPAP</b>									
Overall	51	10.2 ± 8.2	13.9 ± 7.7	3.8	7.1	-10.1 - 17.7	0.6	<0.001	0.59
A	22	12.5 ± 9.3	14.9 ± 10.0	2.4	6.9	-11.0 - 15.8	0.75	<0.001	0.50
B	20	10.2 ± 7.2	14.5 ± 7.0	4.4	8.4	-12.1 - 20.9	0.19	0.41	0.68
C	9	4.6 ± 3.9	11.2 ± 3.9	6.2	3.3	-0.2 - 12.6	0.66	0.06	0.35

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Values are presented as mean ± SD.

A - Quality A tricuspid regurgitation (TR) envelope; B - Quality B TR envelope; C - Quality C TR envelope; Cath - catheterization; Echo - echocardiography; MPAP - mean pulmonary arterial pressure; PASP - systolic pulmonary arterial pressure; SD - standard deviation.

**Supplemental Table 2. Comparison of mean pulmonary arterial pressure by echocardiography using the Chemla formula versus catheterization.**

	N	Echo	Cath	Bias	SD of bias	limits of agreement	r	p value	coefficient of variation
<b>MPAP rest</b>									
Overall	65	17.3 ± 6.1	18.0 ± 10.0	0.7	8.0	-15.0 - 16.4	0.59	<0.001	0.45
A	44	17.3 ± 6.0	17.4 ± 9.5	0.1	7.4	-14.4 - 14.6	0.64	<0.001	0.43
B	17	17.6 ± 5.9	19.4 ± 11.8	1.7	9.7	-17.3 - 20.7	0.58	0.01	0.52
C	4	15.8 ± 9.0	19.0 ± 7.0	3.2	9.1	-14.6 - 21.0	0.37	0.63	0.52
<b>MPAP peak</b>									
Overall	65	26.6 ± 9.5	31.8 ± 14.1	5.1	11.9	-18.2 - 28.4	0.55	<0.001	0.41
A	22	31.7 ± 11.9	35.2 ± 17.7	3.4	12.1	-20.3 - 27.1	0.73	<0.001	0.36
B	28	25.3 ± 7.3	30.9 ± 12.0	5.6	11.5	-16.9 - 28.1	0.38	0.05	0.41
C	15	21.6 ± 5.2	28.4 ± 11.4	6.8	12.8	-18.3 - 31.9	-0.07	0.81	0.51
<b>Δ MPAP</b>									
Overall	65	9.3 ± 7.7	13.7 ± 7.6	4.4	7.5	-10.3 - 19.1	0.52	<0.001	0.65
A	22	12.0 ± 9.3	14.9 ± 10.0	2.9	7.6	-12.0 - 17.8	0.69	<0.001	0.57
B	28	9.2 ± 6.4	14.2 ± 6.8	5.0	7.7	-10.1 - 20.1	0.33	0.09	0.66
C	15	5.6 ± 6.0	11.2 ± 3.9	5.6	6.9	-7.9 - 19.1	0.07	0.79	0.82

Values are presented as mean ± SD.

A - Quality A tricuspid regurgitation (TR) envelope; B - Quality B TR envelope; C - Quality C TR envelope; Cath - catheterization; Echo - echocardiography; MPAP - mean pulmonary arterial pressure; PASP - systolic pulmonary arterial pressure; SD - standard deviation.