Pulmonary Arterial Hypertension

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

Annelieke C.M.J. van Riel, MD; Alexander R. Opotowsky, MD, MMS; Mário Santos, MD; Jose M. Rivero, MD, RDCS; Andy Dhimitri, RDCS; Barbara J.M. Mulder, MD, PhD; Berto J. Bouna, MD, PhD; Michael J. Landzberg, MD; Aaron B. Waxman, MD, PhD; David M. Systrom, MD; Amil M. Shah, MD, MPH

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±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±8.0 mm Hg) and peak exercise ($r=0.75$, P<0.001; bias, −1.9±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.1–5 Stressing the pulmonary circulation during exercise can unmask abnormal pulmonary hemodynamic response in patients with normal or borderline resting hemodynamics and has important clinical implications.6–8 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.9,10 Second, the presence of exercise-induced PH corresponds with worse prognosis and exercise capacity in left-sided valvular heart disease.11,12 Finally, evaluation of pulmonary hemodynamics during exercise can enhance early diagnosis of heart failure with preserved ejection fraction.13,14

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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.15,16 Furthermore, pulmonary pressures

Received September 21, 2016; accepted February 6, 2017.

From the Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands (A.C.M.J.v.R., B.J.M.M., B.J.B.); Netherlands Heart Institute, Utrecht (A.C.M.J.v.R., B.J.M.M.); Department of Cardiology, Boston Children’s Hospital, and Harvard Medical School, MA (A.R.O., M.J.I.L.); Cardiovascular Medicine, Department of Medicine (A.R.O., J.M.R., A.D., M.J.I.L., A.M.S.) and Pulmonary and Critical Care Medicine, Department of Medicine, (A.B.W., D.M.S.), Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; and Department of Physiology and Cardiothoracic Surgery, Cardiovascular R&D Unit, Faculty of Medicine, University of Porto, Portugal (M.S.).

Guest Editor for this article was Christopher M. Kramer, MD.


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Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org DOI: 10.1161/CIRCIMAGING.116.005711
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. 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. 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 arterial pressure (PAP), and pulmonary arterial wedge pressure were measured using a hemodynamic monitoring system (Xper Cardio Physiomonitoring 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 O₂ 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 (VE), pulmonary gas exchange, heart rate, arterial oxygen saturation, cardiac output 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. 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. 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 PASP measurements by echocardiography equaled invasively derived PAP minus RA pressure. If the TR envelope was of inadequate quality, only the PASP was measured.

Results

Demographics and Clinical Characteristics
Of the 65 patients included in this analysis, 31% were male, and mean age was 62±13 years (Table 1). Mean body mass index was 26.0±4.9 kg/m², and 14% of patients were obese (body mass index ≥30 kg/m²). 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±8.5%. All patients performed spirometry at rest, with a mean forced expiratory volume in 1 second of 2.2±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±6.7 mL/kg per minute (71±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.

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...
In contrast, agreement at rest for both systolic and mean B and C TR envelopes was poor (Table 2B and 2D). In addition, the mean bias tended to be modestly lower with echocardiography for quality A TR envelopes. Agreement in patients with quality A TR envelopes was good, both for change in PASP ($r=0.75$, $P<0.001$; bias, $-2.9 \pm 8.0$ mmHg; Figure 2C and 2F; Table 2) and for change in 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 PASP 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 ($r=0.77$, $P<0.001$; bias, $4.0 \pm 11.3$ mmHg; Figure 2B and 2E) and for MPAP at peak ($r=0.77$, $P<0.001$; bias, $4.0 \pm 11.3$ mmHg; Figure 2B and 2E). 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). 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 $>3.0$ mm Hg/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
Accuracy of Exercise Echocardiography

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
d 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% (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
(ΔMPAP/W ratio), a threshold of 1.4 mm Hg/10 W dem-
strated 91% sensitivity and 82% specificity (AUC, 0.90;
95% CI, 0.77–1.0; P<0.001) to detect an abnormal pulmo-
nary 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 1. Baseline Characteristics

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<td>Height, cm</td>
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<td>Weight, kg</td>
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<td>BSA, m²</td>
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<td>BMI, kg/m²</td>
<td>26±4.9</td>
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<td>Medical history</td>
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<td>Hypertension</td>
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<td>Congestive heart failure</td>
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<td>Cerebrovascular accident</td>
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<td>ERA or PDE-5 inhibitor</td>
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<td>Systolic blood pressure, mm Hg</td>
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<td>Diastolic blood pressure, mm Hg</td>
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<td>Atrial fibrillation</td>
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<td>Paced</td>
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<td>Hemoglobin, g/dL</td>
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<td>LV ejection fraction, %</td>
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<td>E/A ratio</td>
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<td>E′ (septal)</td>
<td>7.56±3.27</td>
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<td>E/E′ ratio</td>
<td>10.13±4.13</td>
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<td>LA volume, mL</td>
<td>58.7±33.6</td>
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<td>RVOT AccT, ms</td>
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<td>MPI-RV</td>
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<td>AR≥mild-to-moderate</td>
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Table 1. Continued

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<td>PS≥mild</td>
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<td>TR≥mild-to-moderate</td>
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<td>Peak VO₂, % predicted</td>
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<td>RER</td>
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<td>FEV₁, % predicted</td>
<td>81.7±22.2</td>
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<td>FEV₁/FVC ratio</td>
<td>76.9±10.2</td>
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<td>Watts</td>
<td>85±46</td>
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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; FEV₁, 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 VO₂ oxygen consumption.
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.32–34 Furthermore, the presence of exercise-induced PH, assessed by exercise

| 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 |
| PASP at rest |     |      |      |      |           |                     |         |         |                     |
| 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               |
| PASP at peak |     |      |      |      |           |                     |         |         |                     |
| 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               |
| ΔPASP       |     |      |      |      |           |                     |         |         |                     |
| 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               |
| MPAP rest   |     |      |      |      |           |                     |         |         |                     |
| 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±5.5  | 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               |
| MPAP peak   |     |      |      |      |           |                     |         |         |                     |
| 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               |
| ΔMPAP       |     |      |      |      |           |                     |         |         |                     |
| 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.
van Riel et al. Accuracy of Exercise Echocardiography

Echocardiography, independently associated with reduced survival in patients with valvular disease and could be useful to identify a high-risk subset of asymptomatic patients. 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. 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. Table 4 summarizes findings of selected previously published papers on the accuracy of echocardiography versus RHC that include Bland–Altman analysis. 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. 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. CO assessment by echocardiography is
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. 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., 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., 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. Furthermore, the use of contrast enhancement may also increase the yield of exercise echocardiography.

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
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,7,25 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 noninvasive hemodynamic assessment at rest and with exercise are necessary to confirm these findings. These limitations

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

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

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.

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/CO, mean pulmonary arterial pressure per 10 W; MPAP/CO, mean pulmonary arterial pressure to cardiac output ratio; and PASP, systolic pulmonary arterial pressure.
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 catherization 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.

Sources of Funding

The work in this study was supported by a fellowship grant provided by Netherlands Heart Institute (Dr van Riel), a travel grant provided by ZonMW (Dr van Riel), a grant from the National Heart, Lung, and Blood Institute K08HL16792 (Dr Shah), an American Heart Association grant 14CRP20380422 (Dr Shah), and a Watkins Discovery Award from the Brigham and Women’s Heart and Vascular Center (Dr Shah). Drs Opotowsky and Landzberg are supported by the Dunlevie Family Fund.

Disclosures

Dr Shah reports receiving research support from Actelion and consulting fees from Myocardia. Dr Opotowsky reports receiving research support from Novartis, Gilead, and consulting fees from Myocardia. Drs Opotowsky and Landzberg are supported by the Brigham and Women’s Heart and Vascular Center (Dr Shah). Drs Opotowsky and Landzberg are supported by the Dunlevie Family Fund.

References


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

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Delay</th>
<th>Position During Measurements</th>
<th>Exercise</th>
<th>n</th>
<th>r</th>
<th>Bias</th>
<th>SD</th>
<th>Limits of Agreement</th>
<th>r</th>
<th>Bias</th>
<th>SD</th>
<th>Limits of Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al**</td>
<td>2009</td>
<td>Within 1 h</td>
<td>Supine</td>
<td>59</td>
<td>0.66</td>
<td>−0.6</td>
<td>20.1</td>
<td>−40.0 to 38.8</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Kovacs et al**</td>
<td>2010</td>
<td>Unknown</td>
<td>Semisupine</td>
<td>28</td>
<td>...</td>
<td>0.3</td>
<td>7.6</td>
<td>−14.6 to 15.2</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Rich et al**</td>
<td>2011</td>
<td>Within 30 days</td>
<td>Supine</td>
<td>160</td>
<td>0.68</td>
<td>2.2</td>
<td>18.6</td>
<td>−34.2 to 38.6</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Rich et al**</td>
<td>2011</td>
<td>Simultaneous</td>
<td>Supine</td>
<td>23</td>
<td>0.71</td>
<td>8.0</td>
<td>18.6</td>
<td>−28.4 to 44.4</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>D’Alto et al**</td>
<td>2013</td>
<td>Within 1 h</td>
<td>Supine</td>
<td>152</td>
<td>0.77</td>
<td>−0.5</td>
<td>9.0</td>
<td>−19.0 to 18.0</td>
<td>0.66</td>
<td>−0.5</td>
<td>9.0</td>
<td>−19.0 to 18.0</td>
</tr>
<tr>
<td>Claessen et al</td>
<td>2016</td>
<td>Within 24 h</td>
<td>Semisupine (echo)+supine (RHC)</td>
<td>57</td>
<td>0.92</td>
<td>1.7</td>
<td>10.0</td>
<td>−17.9 to 21.2</td>
<td>0.91</td>
<td>4.1</td>
<td>6.1</td>
<td>−7.9 to 16.0</td>
</tr>
<tr>
<td>Amsallem et al</td>
<td>2016</td>
<td>Within 5 days</td>
<td>Supine</td>
<td>187</td>
<td>0.96</td>
<td>3.3</td>
<td>8.2</td>
<td>−12.6 to 19.3</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>van Riel et al*</td>
<td>2016</td>
<td>Simultaneous</td>
<td>Upright</td>
<td>44</td>
<td>0.72</td>
<td>−2.9</td>
<td>8.0</td>
<td>−18.6 to 12.7</td>
<td>0.61</td>
<td>1.3</td>
<td>7.6</td>
<td>−13.6 to 16.1</td>
</tr>
</tbody>
</table>

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

*Present study data.


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 Noninvasive Comparison

Circ Cardiovasc Imaging. 2017;10:
doi: 10.1161/CIRCIMAGING.116.005711

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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

First author: van Riel

Short title: Accuracy of exercise echocardiography

Annelieke CMJ van Riel1,2 MD, Alexander R Opotowsky3,4 MD, MMSc, Mário Santos5 MD, Jose M Rivero6 MD, RDCS, Andy Dhimitri4 RDCS, Barbara JM Mulder1,2 MD, PhD, Berto J Bouma1 MD, PhD, Michael J Landzberg3,4 MD, Aaron B Waxman6 MD, PhD, David M Systrom6 MD, Amil M Shah4 MD, MPH.

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

<table>
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<tr>
<th></th>
<th>N</th>
<th>Echo</th>
<th>Cath</th>
<th>Bias</th>
<th>SD of bias</th>
<th>limits of agreement</th>
<th>r</th>
<th>p value</th>
<th>coefficient of variation</th>
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<td>PASP at rest</td>
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<tr>
<td>Overall</td>
<td>63</td>
<td>24.6 ± 9.6</td>
<td>22.7 ± 12.6</td>
<td>-1.9</td>
<td>10.6</td>
<td>-22.7 - 18.9</td>
<td>0.57</td>
<td>&lt;0.001</td>
<td>0.43</td>
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<tr>
<td>A</td>
<td>42</td>
<td>24.4 ± 9.3</td>
<td>20.7 ± 8.9</td>
<td>-3.6</td>
<td>7.2</td>
<td>-17.7 - 10.5</td>
<td>0.68</td>
<td>&lt;0.001</td>
<td>0.30</td>
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<tr>
<td>B</td>
<td>17</td>
<td>25.7 ± 9.8</td>
<td>27.4 ± 18.9</td>
<td>1.7</td>
<td>15.8</td>
<td>-29.3 - 32.7</td>
<td>0.55</td>
<td>0.02</td>
<td>0.60</td>
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<tr>
<td>C</td>
<td>4</td>
<td>22.7 ± 14.7</td>
<td>23.8 ± 10.2</td>
<td>1.1</td>
<td>12.6</td>
<td>-23.6 - 25.8</td>
<td>0.54</td>
<td>0.46</td>
<td>0.54</td>
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<tr>
<td>PASP at peak</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>63</td>
<td>40.2 ± 15.8</td>
<td>41.4 ± 18.4</td>
<td>1.2</td>
<td>16.0</td>
<td>-30.2 - 32.6</td>
<td>0.57</td>
<td>&lt;0.001</td>
<td>0.39</td>
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<tr>
<td>A</td>
<td>22</td>
<td>48.8 ± 19.6</td>
<td>46.9 ± 23.5</td>
<td>-1.9</td>
<td>15.6</td>
<td>-32.3 - 28.6</td>
<td>0.75</td>
<td>&lt;0.001</td>
<td>0.33</td>
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<tr>
<td>B</td>
<td>26</td>
<td>37.6 ± 12.0</td>
<td>39.0 ± 13.0</td>
<td>1.5</td>
<td>14.4</td>
<td>-26.7 - 29.7</td>
<td>0.34</td>
<td>0.09</td>
<td>0.36</td>
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<tr>
<td>C</td>
<td>15</td>
<td>32.1 ± 8.5</td>
<td>37.5 ± 17.0</td>
<td>5.4</td>
<td>19.3</td>
<td>-32.5 - 43.3</td>
<td>-0.05</td>
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<td>ΔPASP</td>
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<tr>
<td>Overall</td>
<td>63</td>
<td>15.6 ± 12.6</td>
<td>18.7 ± 10.2</td>
<td>3.1</td>
<td>11.2</td>
<td>-18.9 - 25.1</td>
<td>0.53</td>
<td>&lt;0.001</td>
<td>0.66</td>
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<tr>
<td>A</td>
<td>22</td>
<td>19.6 ± 15.2</td>
<td>19.6 ± 11.9</td>
<td>0.0</td>
<td>11.0</td>
<td>-21.5 - 21.5</td>
<td>0.7</td>
<td>&lt;0.001</td>
<td>0.56</td>
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<tr>
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<td>15.8 ± 10.3</td>
<td>20.3 ± 10.0</td>
<td>4.4</td>
<td>11.7</td>
<td>-18.5 - 27.3</td>
<td>0.34</td>
<td>0.09</td>
<td>0.67</td>
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<td>14.7 ± 6.8</td>
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<td>10.3</td>
<td>-14.6 - 25.6</td>
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<td>0.32</td>
<td>0.86</td>
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<td>MPAP rest</td>
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<tr>
<td>Overall</td>
<td>60</td>
<td>15.8 ± 6.1</td>
<td>17.1 ± 8.7</td>
<td>1.6</td>
<td>7.6</td>
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<td>16.1 ± 7.3</td>
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<td>6.6</td>
<td>-12.5 - 13.3</td>
<td>0.52</td>
<td>&lt;0.001</td>
<td>0.39</td>
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<tr>
<td>B</td>
<td>16</td>
<td>16.2 ± 6.5</td>
<td>19.4 ± 11.8</td>
<td>3.7</td>
<td>9.8</td>
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<td>5.2 - 12.0</td>
<td>-</td>
<td>-</td>
<td>0.10</td>
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<td>MPAP peak</td>
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<td>Overall</td>
<td>53</td>
<td>26.1 ± 11.2</td>
<td>31.0 ± 13.6</td>
<td>5.4</td>
<td>11.6</td>
<td>-17.3 - 28.1</td>
<td>0.6</td>
<td>&lt;0.001</td>
<td>0.40</td>
</tr>
<tr>
<td>A</td>
<td>22</td>
<td>31.2 ± 13.8</td>
<td>35.2 ± 17.7</td>
<td>4.0</td>
<td>11.3</td>
<td>-18.2 - 26.2</td>
<td>0.77</td>
<td>&lt;0.001</td>
<td>0.34</td>
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</tr>
<tr>
<td>B</td>
<td>22</td>
<td>23.7 ± 7.8</td>
<td>29.0 ± 10.0</td>
<td>4.6</td>
<td>11.3</td>
<td>-17.5 - 26.7</td>
<td>0.1</td>
<td>0.65</td>
<td>0.40</td>
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<tr>
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<td>9</td>
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<td>28.4 ± 11.4</td>
<td>10.6</td>
<td>12.6</td>
<td>-14.0 - 35.3</td>
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<td>Δ MPAP</td>
<td>Overall</td>
<td>51</td>
<td>10.2 ± 8.2</td>
<td>13.9 ± 7.7</td>
<td>3.8</td>
<td>7.1</td>
<td>-10.1 - 17.7</td>
<td>0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A</td>
<td>22</td>
<td>12.5 ± 9.3</td>
<td>14.9 ± 10.0</td>
<td>2.4</td>
<td>6.9</td>
<td>-11.0 - 15.8</td>
<td>0.75</td>
<td>&lt;0.001</td>
<td>0.50</td>
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<td>B</td>
<td>20</td>
<td>10.2 ± 7.2</td>
<td>14.5 ± 7.0</td>
<td>4.4</td>
<td>8.4</td>
<td>-12.1 - 20.9</td>
<td>0.19</td>
<td>0.41</td>
<td>0.68</td>
</tr>
<tr>
<td>C</td>
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<td>4.6 ± 3.9</td>
<td>11.2 ± 3.9</td>
<td>6.2</td>
<td>3.3</td>
<td>-0.2 - 12.6</td>
<td>0.66</td>
<td>0.06</td>
<td>0.35</td>
</tr>
</tbody>
</table>

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.

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

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.