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

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Abstract

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 (PAP) 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 PAP 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 PAP correlated reasonably well with invasive measurement at rest ($r=0.72$, $p<0.001$; bias=−2.9±8.0 mmHg) and peak exercise ($r=0.75$, $p<0.001$; bias=−1.9±15.6). Lower quality TR signals (grade B and C) correlated poorly with invasive measurements overall. In patients with grade A TR signals, mean PAP-to-workload ratio at a threshold of 1.4mmHg/10W, was able to identify abnormal pulmonary hemodynamic response during exercise (>3.0 mmHg/L/min increase), with 91% sensitivity and 82% specificity (AUC 0.90 [95% CI 0.77–1.0], $p=0.001$).

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DISCLOSURES

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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.

Keywords

exercise echocardiography; catheterization; pulmonary hypertension; exercise testing

Regardless of etiology, pulmonary hypertension (PH) is associated with increased mortality, morbidity and cardiac events[1–5]. 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[6–8]. First, it may facilitate early detection of pulmonary vascular disease (e.g. pulmonary arterial hypertension, PAH). 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].

Exercise echocardiography provides a non-invasive approach to screen for and detect exercise induced PH, but its accuracy when compared to invasive pressure measurements is not well established[15,16]. Furthermore, pulmonary pressures are known to vary dynamically within an individual over time, and information on simultaneous noninvasive compared to invasive measurement of pulmonary hemodynamics during exercise is limited [6,17–23]. This study aimed to determine the accuracy of echocardiographic estimation of pulmonary pressures during exercise compared to 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[24]. Patients in whom tricuspid regurgitation spectral Doppler signal (TR) was not available at rest and peak exercise (either due to 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 pressures (PAP), and pulmonary arterial wedge pressure (PAWP) 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 VO_2, arterial and mixed venous O_2 content.

Exercise protocol

All exercise tests were performed on an upright cycle ergometer with the subject breathing room air. Two minutes of rest were 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 (HR), radial arterial pressure, RA pressure, RV pressure, and PAP were measured continuously, whereas PAWP was obtained at rest and during each minute of exercise. Aerobic capacity expressed as percentage of predicted was calculated using the Wasserman equation[25]. 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 (A.vR.) blinded to invasive hemodynamic data, using a computerized off-line analysis station as previously described[26]. Both at rest and during exercise TR velocity was measured, using the apical 4-chamber view and the right ventricular inflow from a parasternal window, and traced to obtain the peak and mean systolic right-ventricular-right-atrial (RV-RA) gradient. The systolic PAP (PASP) was calculated using the highest RV-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 two predefined criteria: (1) extension of the signal for at least half of systole, and (2) well defined border[27]. Envelopes were graded as quality A if all criteria were applicable, quality B if one criterion was missing and quality C if both criteria were missing (Figure 1). The quality grading was performed independently by two readers (A.vR. and A.R.O.) and in case of disagreement a third reader (A.S.) 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 (ROC) 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 mmHg/L/min by invasive evaluation, following recent consensus documents and taken into account the mean age of our population[28–30]. Cut-points were chosen closest to the top-left corner of ROC 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±13 years (Table 1). Mean body mass index was 26.0±4.9 kg/m^2 and 14% were obese (body mass index ≥30 kg/m^2). 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 (FEV1) of 2.2±0.7 L and a median FEV1/forced vital capacity of 0.79 (25th to 75th percentile: 0.74 – 0.84). The mean peak VO_2, a measure of functional capacity, was 15.9±6.7 mL/kg/min (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[31].

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%) grade B and 4 patients (6%) 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±14 mmHg and average MPAP was 18±10 mmHg by RHC, and 25±10 mmHg and 16±6 mmHg respectively by echocardiography for quality A TR spectral Doppler tracings. Mean values were 25±11 mmHg and 16±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 non-invasive and invasive measures of

PASP (r=0.72, p<0.001; bias=−2.9±8.0 mmHg; Figure 2, panels A and D; Table 2) and MPAP (r=0.61, p<0.001; bias=1.3±7.6 mmHg; Figure 3, panels A and D) 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±22 mmHg and MPAP was 32±14 mmHg by RHC, and 49±20 mmHg and 31±14 mmHg respectively by echocardiography for quality A TR envelopes. Mean values were 36±11 mmHg and 23±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±15.6 mmHg; Figure 2, panels B and E; Table 2) and MPAP at peak (r=0.77, p<0.001; bias 4.0±11.3 mmHg; Figure 3, panels B and E). 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±12 mmHg and the average change in MPAP was 14±8 mmHg by RHC. By echocardiography, for quality A TR envelopes, the average change in PASP was 20±15 mmHg and the average change in MPAP was 13±9 mmHg. For quality B and C studies average values by echocardiography were 13±11 mmHg and 8±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±11.0 mmHg; Figure 2, panels C and F; Table 2) and change in MPAP (r=0.75, p<0.001; bias 2.4±6.9 mmHg; Figure 3, panels C and F). 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 (Supplemental Table 1). In addition, similar findings were noted for the relationship between resting, peak exercise, and change in MPAP when calculated using the Chemla formula (Supplemental Table 2).[7,17] Of note, echocardiography-based assessment of MPAP was available in a larger number of participants using the Chemla formula compared to the VTI method, particularly for peak exercise values (n of 65 vs 55, respectively) and change values from rest to peak exercise (n of 65 vs 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/min. This was present in 22 patients (34%) and was associated with a significantly lower peak VO_2, expressed as percentage of predicted (61.6±15.5% vs. 77.5±24.5% p=0.008). The RER was significantly lower in patients with an abnormal pulmonary hemodynamic response (1.1±0.2 vs. 1.0±0.1, p=0.01) and these patients achieved a lower amount of watts during exercise (98±47 W vs. 63±36 W,

p=0.004). ROC analysis was employed 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 mmHg, with a sensitivity of 82% and a specificity of 36% (AUC 0.78 [95% 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 mmHg, 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 mmHg, 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 (W; ΔMPAP/W ratio), a threshold of 1.4 mmHg/10W 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 mmHg/10W 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 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 non-invasively 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 pulmonary hypertension 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 pulmonary hypertension, assessed by exercise 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[35,36]. 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[18,27,37–41]. 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[42]. Table 4 summarizes findings of selected previously published papers on the accuracy of echocardiography versus RHC that include Bland-Altman analysis [17–19,40,43,44]. 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[43], 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 to 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 to 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 cut-off values for echo-based PASP and MPAP to predict and abnormal pulmonary vascular reserve in our analysis compared to 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 cutpoint selection. However, we believe use of the peak RV-to RA pressure gradient is more clinically relevant as 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 pathologic response[9,28]. Cardiac output 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 cardiac output with exercise[45]. 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 and colleagues, which suggested that PASP/W ratio at a cutoff value of >0.47 mmHg/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], $p<0.001$) [17].

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.[44], who demonstrated reliable estimation of right ventricular systolic pressure by echocardiography at rest when careful attention is paid to signal quality. Notably, the feasibility of obtaining high quality TR envelops (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 semi-supine bicycle ergometers[46]. Furthermore, the use of contrast enhancement may also increase the yield of exercise echocardiography[47]. 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 employed 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 non-invasive 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 (i.e. upright versus recumbent). As the purpose of this study was to evaluate the accuracy of non-invasive estimation of pulmonary pressure with exercise in a diverse sample of patients with dyspnea, resting-state pre-capillary pulmonary hypertension was present in only a very small subset. While multipoint MPAP/CO or MPAP/W slopes may be more robust and accurate than the ‘single-point’ measures reported here[7,29], echo-based TR velocity was only collected uniformly at rest and peak exercise in this study, and data at intermediate timepoints was insufficient for calculation of a multipoint slope. Furthermore, direct comparison of the invasive versus echocardiographically determined MPAP/CO slope was not feasible as 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 notwithstanding, we believe 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.

CONCLUSION

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. While 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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 (PAP) during exercise. We compared echocardiography-based measures of PAP 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 non-invasively assessed change in mean PAP (MPAP) to change in work rate (expressed as watts [W]; ΔMPAP/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.

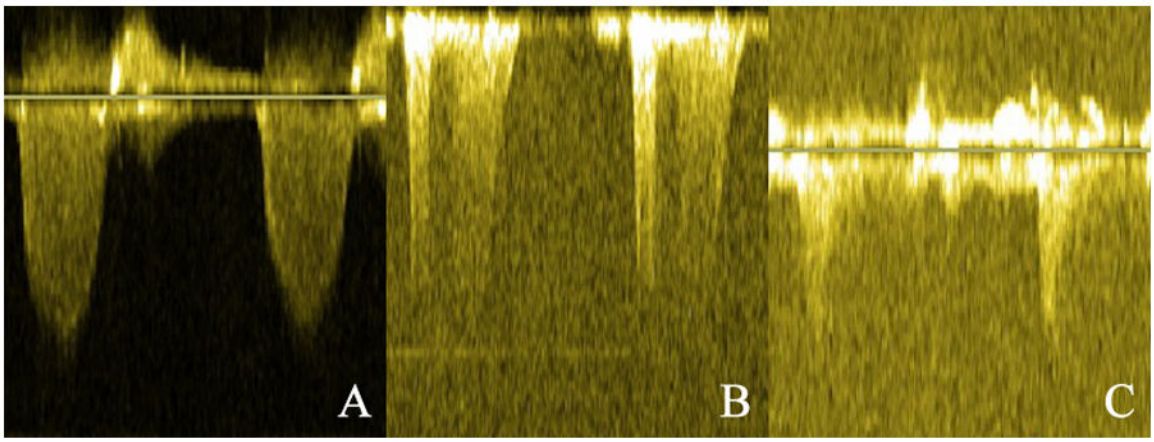

Figure 1. Examples of quality grade A, B and C tricuspid regurgitation Doppler envelopes

The TR spectral Doppler envelopes were assessed for quality using two 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 one 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.

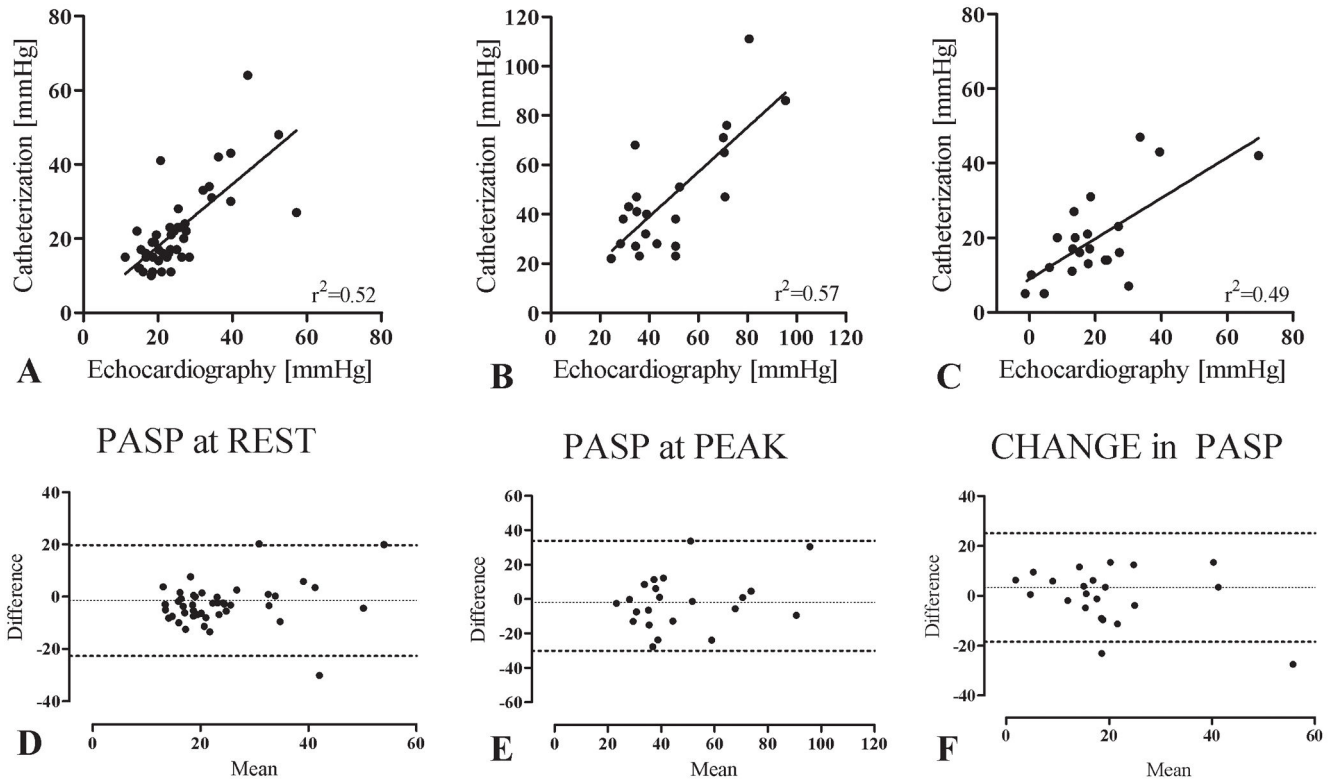

Figure 2.

Relationship between pulmonary artery systolic pressure 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 (C; n=22) and the change during exercise (E; n=22). Corresponding Bland-Altman plots demonstrate the bias and limits of agreement at rest (B), at peak (D) and change during exercise (F).

PASP – systolic pulmonary arterial pressure; TR – tricuspid regurgitation

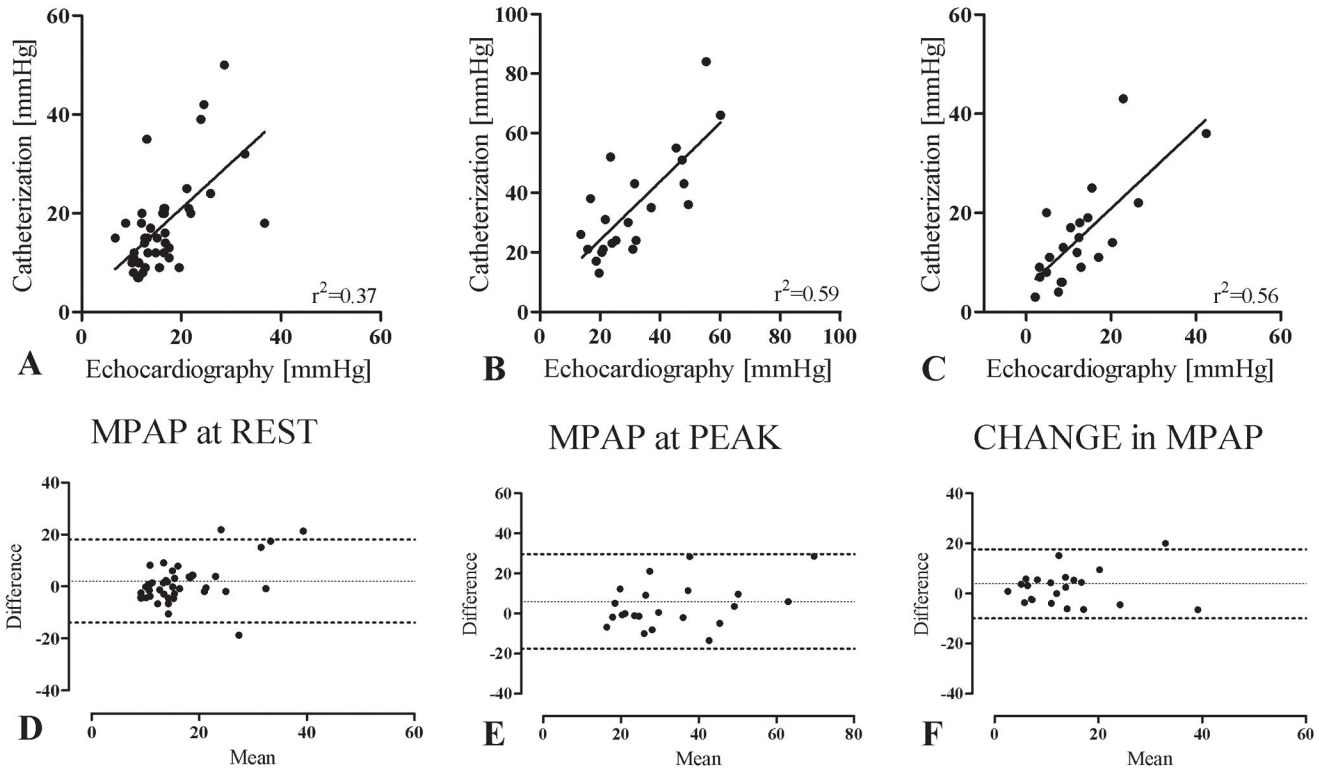

Figure 3.

Relationship between mean pulmonary arterial pressure 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 (C; n=22) and the change during exercise (E; n=22). Corresponding Bland-Altman plots demonstrate the bias and limits of agreement at rest (B), at peak (D) and change during exercise (F).

MPAP – mean pulmonary arterial pressure; TR – tricuspid regurgitation

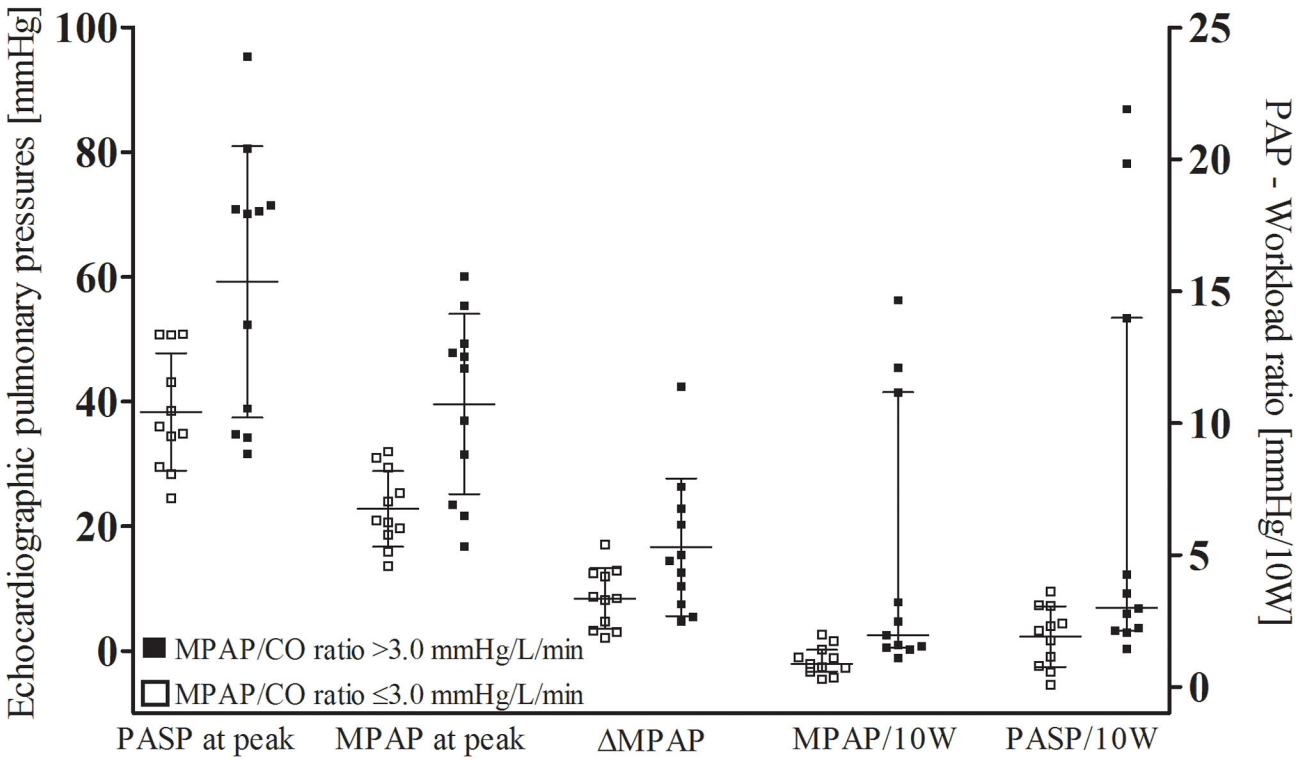

Figure 4.

Hemodynamic variables obtained by echocardiography among patients with and without abnormal pulmonary hemodynamic response during exercise based on a MPAP-CO slope >2.5 mmHg/L/min by RHC.

Scatterplots represent individual values. The bars represent mean and SD in PASP at peak, MPAP at peak and ΔMPAP. In MPAP/10W, plotted on the right y-axis, the bars represent the median with interquartile range.

PASP – systolic pulmonary arterial pressure; MPAP – mean pulmonary arterial pressure; MPAP/CO – mean pulmonary arterial pressure to cardiac output ratio; ΔMPAP – change in mean pulmonary arterial pressure; MPAP/10W – mean pulmonary arterial pressure per 10 Watts.

Table 1

Baseline characteristics

	n=65
Demographics	
Age [years]	62.1 ± 13
Male sex	20 (31)
Height [cm]	165 ± 8.5
Weight [kg]	70.2 ± 13
BSA [m2]	1.78 ± 0.2
BMI [kg/m2]	26 ± 4.9
Medical history	
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)
Current medication use	
Beta blocker	23 (35)
ACE inhibitor / ARB	15 (23)
Diuretic	23 (35)
Digoxin	3 (5)
ERA or PDE-5 inhibitor	2 (3)
Clinical characteristics	
Systolic blood pressure [mmHg]	143 ± 23
Diastolic blood pressure [mmHg]	76 ± 12
Rhythm	
Sinus rhythm	57 (87)
Atrial fibrillation	3 (5)
Paced	5 (8)
Hemoglobin [g/dL]	13.5 ± 1.7
Echocardiographic characteristics	
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

	n=65
MPI-RV	0.41 ± 0.21
Valvular disease	
AR ≥ mild-to-moderate	2 (3)
MR ≥ mild-to-moderate	7 (12)
MS ≥ mild-to-moderate	0
PS ≥ mild	0
TR ≥ mild-to-moderate	13 (25)
Test performance characteristics	
peak VO_2 [% predicted]	71.4 ± 23.2
RER	1.1 ± 0.2
FEV_1 [% predicted]	81.7 ± 22.2
FEV_1/FVC ratio	76.9 ± 10.2
Watts [W]	85 ± 46

Values are presented as mean±SD or as count with (percentage).

ACE - angiotensin converting enzyme; AR - aortic valve regurgitation; ARB - angiotensin receptor blocker; BMI - body mass index; BSA - body surface area; FEV_1 - forced expiratory volume in 1 second; FVC - forced vital capacity; ERA - endothelin receptor antagonist; LA - left atrium; LV - left ventricle; MPI-RV - myocardial performance index of the righ 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.

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 – 19.7	0.62	<0.001	0.44
A	44	25.2 ± 9.8	22.2 ± 11.4	−2.9	8.0	−18.6 – 12.7	0.72	<0.001	0.34
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 – 25.7	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 – 33.9	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	28	38.2 ± 12.0	41.2 ± 15.6	3.0	15.1	−26.7 – 32.6	0.42	0.03	0.38
C	15	32.1 ± 8.5	37.5 ± 17.0	5.4	19.3	−32.5 – 43.3	−0.05	0.87	0.55
Δ PASP									
Overall	65	15.3 ± 12.6	18.6 ± 10.1	3.4	11.1	−18.4 – 25.2	0.54	<0.001	0.66
A	22	19.6 ± 15.2	19.6 ± 11.9	0.0	11.0	−21.5 – 21.5	0.70	<0.001	0.56
B	28	15.0 ± 10.5	19.9 ± 10.0	4.9	11.4	−17.5 – 27.3	0.38	0.05	0.65
C	15	9.2 ± 9.8	14.7 ± 6.8	5.5	10.3	−14.6 – 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 – 18.1	0.59	<0.001	0.48
A	44	16.2 ± 6.3	17.4 ± 9.5	1.3	7.6	−13.6 – 16.1	0.61	<0.001	0.45
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
MPAP peak									
Overall	55	26.3 ± 11.0	31.8 ± 14.1	6.1	12.0	−17.4 – 29.6	0.59	<0.001	0.41
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	24	24.3 ± 7.8	30.9 ± 12.0	6.4	12.4	−17.8 – 30.6	0.24	0.25	0.44
C	9	19.5 ± 2.9	28.4 ± 11.4	10.6	12.6	−14.0 – 35.3	0.35	0.35	0.50
Δ MPAP									
Overall	53	10.0 ± 8.1	13.7 ± 7.6	3.9	7.0	−9.8 – 17.7	0.61	<0.001	0.58
A	22	12.5 ± 9.3	14.9 ± 10.0	2.4	6.9	−11.0 – 15.8	0.75	<0.001	0.50

	N	Echo	Cath	Bias	SD of bias	limits of agreement	r	*p* value	coefficient of variation
B	22	9.6 ± 7.2	14.2 ± 6.8	4.6	8.1	−11.3 – 20.4	0.24	0.29	0.65
C	9	4.6 ± 3.9	11.2 ± 3.9	6.2	3.3	−0.2 – 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 - 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.

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 mmHg/L/min						
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
Δ MPAP		≥ 10	73	64	0.76 (0.56 – 0.96)	0.04
Δ MPAP / 10 Watts		≥ 1.4	91	82	0.90 (0.77 – 1.00)	0.001
Δ PASP / 10 Watts		≥ 1.9	91	46	0.75 (0.55 – 0.96)	0.04
Quality B or C TR envelope	43					
MPAP / CO ratio > 3 mmHg/L/min						
PASP at peak		-	-	-	0.63 (0.46 – 0.81)	0.19
MPAP at peak		-	-	-	0.55 (0.36 – 0.75)	0.66
Δ MPAP		-	-	-	0.40 (0.19 – 0.61)	0.38
Δ MPAP / 10 Watts		-	-	-	0.48 (0.25 – 0.70)	0.72
Δ PASP / 10 Watts		-	-	-	0.54 (0.36 – 0.73)	0.69

AUC - area under the curve; CI - confidence interval; CO - cardiac output; MPAP - mean pulmonary arterial pressure; PASP - systolic pulmonary arterial pressure; TR - tricuspid regurgitation. 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.

Table 4

Studies evaluating pulmonary arterial pressure by echocardiography and right heart catheterization at rest and during exercise

					PASP				MPAP			
Author	**Year**	**Delay**	**Position during measurements**	**n**	**r**	**bias**	**SD**	**limits of agreement**	**r**	**bias**	**SD**	**limits of agreement**
Rest												
Fisher et al[40]	2009	within 1h	supine	59	0.66	−0.6	20.1	−40.0 to 38.8	-	-	-	-
Kovacs et al[19]	2010	unknown	semisupine	28	-	0.3	7.6	−14.6 to 15.2	-	-	-	-
Rich et al[43]	2011	within 30 days	supine	160	0.68	2.2	18.6	−34.2 to 38.6	-	-	-	-
Rich et al[43]	2011	simultaneous	supine	23	0.71	8.0	18.6	−28.4 to 44.4	-	-	-	-
D'Alto et al[18]	2013	within 1h	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[17]	2016	within 24h	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[44]	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[19]	2010	unknown	semisupine	28	-	−5.6	19.0	−42.8 to 31.6	-	-	-	-
Claessen et al[17]	2016	within 24h	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

* Present study data

Echo - echocardiography; MPAP - mean pulmonary arterial pressure; PASP - systolic pulmonary arterial pressure; RHC - right heart catheterization