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Noninvasive Assessment of Right Heart Function and Hemodynamics during Exercise in Patients with Pulmonary Arterial Hypertension

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Abstract

Objectives—Noninvasive assessment of right heart function and hemodynamics in patients with pulmonary arterial hypertension (PAH) is most often performed at rest, whereas the symptoms, in general, present with exertion. Assessment during exertion is limited to symptom assessment and the 6-minute walk distance. We investigated the feasibility of obtaining echocardiographic data that could accurately reflect pulmonary artery pressures (PAP), particularly mean PAP and right ventricular function during exercise in patients with PAH.

Methods—We investigated right ventricular function and hemodynamics using echocardiography during symptom-limited exercise in 10 consecutive patients undergoing right heart catheterization (RHC) as part of their clinical evaluation for PAH. We further assessed these measurements for correlation with known predictors of outcome in PAH in an exploratory analysis.

Results—We were able to successfully obtain complete right heart measurements by echocardiography, including mean PAP, in the majority (9 of 10) of the subjects. One patient had an incomplete tricuspid regurgitation jet at rest and with exercise. Echocardiographic pulmonary vascular resistance correlated with RHC cardiac output and brain natriuretic peptide level, whereas tricuspid annular plane systolic excursion during exercise correlated with right atrial pressure on RHC, brain natriuretic peptide, and 6-minute walk distance. Tricuspid regurgitation velocity and mean PAP with exercise correlated moderately with mean PAP and cardiac output by RHC.

Conclusions—Exercise echocardiography can provide meaningful data in patients with PAH, including measuring mean PAP. The presence of correlations in this small number of patients indicates promising targets for future investigation.

Keywords

pulmonary arterial hypertension; exercise echocardiography; right ventricular function

Pulmonary arterial hypertension (PAH) is a progressive disease of remodeling of the pulmonary vasculature that ultimately leads to right ventricular (RV) failure and death. In

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the last decade, we have seen significant advancement in treatment options and improved survival; nonetheless, noninvasive assessment of right heart function and hemodynamics in patients with PAH is most often performed at rest, whereas the symptoms generally present with exertion. Furthermore, clinical monitoring has remained limited to symptom assessment and the 6-minute walk distance (6MWD).^{1,2}

RV function and exercise capacity are important predictors of mortality and response to therapy in patients with PAH, but they are seldom assessed in concert. The 6MWD is the most commonly used test to assess exercise capacity and has been a primary endpoint in numerous therapeutic clinical trials.³ It is easy to perform, involves minimal risk, and does not require technical expertise. It does have important limitations, including variability in reports of its predictive value, variability in correlation with other assessments of functional status, and a “ceiling effect,” in which patients with a relatively long distance at baseline do not show statistically significant improvement after treatment.^{4–7}

In contrast, most prognostic markers for patients with PAH relate to an assessment of RV function while at rest, often by echocardiography or by right heart catheterization (RHC).³ Routine testing most often does not include measurement of the dynamic changes that occur during exercise. Typically, pulmonary artery pressure (PAP) increases modestly with maximal exercise because of the capacity of the lung to recruit and distend the pulmonary vasculature, thereby decreasing pulmonary vascular resistance (PVR) to accommodate the rise in pulmonary blood flow. In PAH, the pulmonary arteries are pathologically remodeled with reduced distensibility and are therefore less responsive to the normal increased blood flow with exercise. In addition, PAP can increase dramatically with exercise, resulting in impaired RV function, increased dead space, and decreased oxygenation of blood.^{8,9} Exercise echocardiography has been used to assess right heart function and pressures and examine pulmonary artery distensibility, with results consistent with previously reported invasively obtained hemodynamics; however, the study was in healthy volunteers and the mean PAP was calculated.¹⁰ Studies of patients at risk for PAH in association with collagen vascular disease have explored the measurement of PAP during exercise, but they have not measured mean PAP or assessed other parameters of RV function.^{11,12}

The primary objectives of the present study were to examine the feasibility of obtaining echocardiographic assessments of right heart pressures and function during exercise and compare those results to conventional measures of severity in patients with group 1 PAH.

Methods

Study Patients and Data Collection

Twelve consecutive patients from a pulmonary hypertension referral center who underwent planned RHC were approached to participate in this prospective feasibility study. Ten patients gave informed consent. Diagnosis of PAH was confirmed with RHC, defined as a mean PAP >25 mm Hg and PVR >240 dyne sec cm⁻⁵, with a pulmonary capillary wedge pressure <15 mm Hg. We included all of the potential patients in World Health Organization (WHO) functional group I. Patients with PAH caused by portal hypertension were excluded on the basis of differing hemodynamic profiles resulting from hepatic insufficiency and high cardiac output (CO). Patients also were excluded if they were unable to walk on a treadmill, were pregnant, or had decompensated right heart failure. For each patient, information was collected regarding demographics, WHO functional class, brain natriuretic peptide (BNP), 6MWD, RHC measurements and vasodilator response, resting transthoracic echocardiogram, and exercise transthoracic echocardiographic information. This study was approved by the institutional review board at our institution.

Exercise Echocardiography

A symptom-limited treadmill exercise test was performed using a Naughton protocol, as described in established guidelines for stress echocardiography,¹³ except that the focus of measurement was for right heart parameters rather than regional left ventricular function. All transthoracic echocardiograms were performed using a Philips iE 33 ultrasound and interpreted by experienced sonographers (C.L., R.E.S.) who were not involved in the clinical care of the subjects and were not aware of the results of the RHC.

The echocardiographic parameters at rest and following exercise were measured and calculated as follows: PVR in Wood units is $(TRV_{\max} \times 10)/TVIRVOT + 0.16$, where $TRV_{\max}$ is the maximum velocity of the tricuspid regurgitation velocity (TRV) profile from continuous-wave Doppler (meters per second)¹⁴; RV CO in milliliters per minute is RV stroke volume $\times$ heart rate; and RV stroke volume in milliliters is $(\pi \times D^2 \times TVIRVOT)/4$, where π is 3.1416, D is the diameter of the RV outflow tract just beneath the valve in centimeters, and TVIRVOT is the time velocity integral of the RV outflow tract (in centimeters) obtained with pulsed-wave Doppler.¹⁵ Mean PAP was calculated by adding the right ventricular–right atrial mean systolic gradient to right atrial pressure (RAP), as described by members of our group.¹⁶

Statistical Analysis

Numerical variables were summarized with the sample median, minimum, and maximum. Categorical variables were summarized with number and percentage. The proportion of patients for whom a measurable value was obtained for each exercise echocardiogram was estimated. Resting and exercise echocardiogram measures were compared using a Wilcoxon signed rank test. Associations of exercise echocardiogram measures with RAP, mean PAP, CO (all three measures by RHC), WHO functional class, BNP, and 6MWD were examined using the Pearson test of correlation, with the exception of associations with WHO functional class, where the Spearman test of correlation was used owing to the ordinal nature of this outcome; the correlation coefficient r was estimated along with a 95% confidence interval. $P < 0.05$ were considered statistically significant. Statistical analyses were performed using R statistical software (version 2.11.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1 summarizes patient demographics, PAH information, and RHC results for the 10 study patients. Median age was 47 years (range 29–78), female sex ($N = 8$, 80%), and median body mass index was 24.9 (range 20.1–37.2). Most of the patients were either idiopathic PAH ($N = 4$, 40%) or associated PAH–connective tissue disease ($N = 4$, 40%). The WHO functional class was class II for two patients (20%), IIIa for four patients (40%), IIIb for two patients (20%) and IV for two patients (20%). Median BNP was 231 pg/mL (range 8–1330 pg/mL) and median 6MWD was 1232 ft (range 602–1596 ft). The median measurement of mean PAP was 45 (range 19–61 mm Hg).

Rest and exercise echocardiographic measurements are displayed in Table 2. For the resting echocardiogram, measurements were successfully obtained for the majority of patients with the exception of TRV (9 of 10), mean PAP (9 of 10), PVR (9 of 10), and RV mid free wall strain (8 of 10). All eight echocardiographic variables were successfully obtained in the resting state for seven patients and with exercise in five patients. The success rate for measurement of specific variables with exercise was similar: TRV (9 of 10), mean PAP (9 of 10), PVR (9 of 10), lateral tissue Doppler imaging TV annulus (8 of 10) and RV mid free wall strain (7 of 10). One patient had an incomplete TR jet both at rest and with exercise;

therefore, the mean PAP could not be measured and PVR could not be calculated. Potential differences between resting and exercise echocardiographic measure occurred for mean PAP (median 49 vs 65 mm Hg, $P = 0.068$) and RV CO (median 5.2 vs 7.8 L/min, $P = 0.014$).

The correlation between exercise echocardiographic variables of right heart function with known RHC predictors of outcome (RAP, mean PAP, CO) are shown in Table 3, and associations of exercise echocardiogram measures with other known predictors of outcome (BNP, 6MWD, WHO functional class) are displayed in Table 4.

The exercise echocardiogram parameters of TRV mean PAP, RV free wall strain, and metabolic equivalent of task (MET) achieved were significantly correlated with the mean PAP by RHC. In addition, the exercise echocardiogram TRV, mean PAP, PVR, and MET also significantly correlated with the CO by RHC and the tricuspid annular plane systolic excursion (TAPSE) correlated with RAP by RHC. When compared with other known predictors of outcome, the exercise echocardiogram PVR and TAPSE were significantly correlated with both BNP and 6MWD; PVR additionally correlated with WHO functional class. A number of other nonsignificant trends toward correlation with relatively strong correlation r values were observed in this small sample (Tables 3 and 4).

Discussion

We examined 10 patients with established group 1 PAH who were undergoing RHC as part of their clinical evaluation. The patients performed a symptom-limited exercise echocardiogram focusing on right heart measurements, including mean PAP, in an exploratory analysis. We then assessed these measurements for correlation with known predictors of mortality in PAH.

We were able to successfully obtain right heart measurements in a majority of the subjects, with only one having an immeasurable TR jet. Published success rates for estimation and/or measurement of right heart pressures using the TR jet are similar.¹⁶ Only 3 of 10 achieved 85% of maximal predicted heart rate, with the remaining 8 subjects limited by symptoms before reaching target. Notably, there was not an observed statistical difference between the median resting and exercise measurements (Table 2). Echocardiographic-derived PVR and TAPSE during exercise were at least moderately correlated with BNP and WHO functional class. TRV and mean PAP with exercise moderately correlated with the predictors of mean PAP and CO on RHC. A significant proportion of patients (40%) had a 6MWD of <1000 ft and did not achieve much change in measured parameters with exercise. Despite this, the MET achieved correlated well, as would be expected with 6MWD and WHO functional class. Indeed, the fact that the RHC hemodynamic results, BNP, 6MWD, and WHO functional class correlated with the exercise parameters (heart rate achieved, MET) reflects consistent data.

This feasibility study suggests that the echocardiographic measurements achieved at symptom limitation may provide clinically useful information. Previous studies have likewise indicated that such measurements are obtainable and correlate with both normal and diseased pulmonary vasculature. Exercise echocardiography has been used to assess right heart function and pressures and to examine pulmonary artery distensibility, with results consistent with previously reported invasively obtained hemodynamics; however, the study was conducted in healthy volunteers and the mean PAP was calculated.¹⁰ In contrast, our study measured the mean PAP during exercise by echocardiogram in patients with PAH. Studies of patients at risk for PAH in association with collagen vascular disease have explored the measurement of PAP during exercise, but they also did not measure mean PAP or assessed other parameters of RV function.^{11,12} There are several speculative benefits of

accurate noninvasive assessment of right heart function and pressures with exercise. Those most clinically useful include assessment of PAH disease severity, response to treatment, and prognosis. Patients with WHO functional class III represent a broad range of symptom limitation, within which exercise-based assessment may serve to better delineate outcome.

Although no discernible physiologic patterns emerged from our small study, we did uncover some unexpected findings. One subject with a high calculated stroke volume caused by a massively dilated pulmonary artery was unable to augment stroke volume further during exercise; however, PVR did not change significantly with exercise. Another subject, a young woman, was able to exercise adequately; however, she developed ST elevations during exercise, which was suggestive of compression of the left main coronary artery by the pulmonary artery. One other finding of interest was that two subjects who demonstrated a significant response to vasodilator therapy during the RHC also exhibited a decrease in PVR during the exercise echocardiogram. The response to vasodilator may indicate a more compliant pulmonary vascular bed for the increased CO during exercise.

Several limitations of our study should be acknowledged. As expected in a feasibility study, the sample size is small and results in low power to detect differences and associations; the possibility of type II error (ie, a false-negative association) is important to consider. In addition, echocardiography has inherent inaccuracy in right heart pressure assessment, and we did not address reproducibility in this study.

Conclusions

Exercise echocardiography for the assessment of right heart function and hemodynamics appears feasible in patients with PAH, including measurement of mean PAP. The identified correlations also show promise for further investigation. Larger studies are needed to assess the correlation of exercise echocardiographic parameters with prognostic indices of PAH.

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Key Points

- Symptom-limited exercise echocardiography is feasible in patients with pulmonary arterial hypertension.
- Echocardiographic measurements of pulmonary vascular resistance and tricuspid annular plane systolic excursion during exercise moderately correlated with brain natriuretic peptide and World Health Organization functional class; tricuspid regurgitation velocity and mean PAP with exercise moderately correlated with mean pulmonary artery pressures and cardiac output by right heart catheterization.
- The presence of correlations between the exercise echocardiographic measurements and known predictors of outcome in pulmonary arterial hypertension indicates promising targets for future investigations.

Brief Description

Pulmonary arterial hypertension (PAH) is a progressive disease of remodeling of the pulmonary vasculature ultimately leading to right ventricular failure and death. Significant advances in treatment options and improved survival have been made in the last decade; however, clinical monitoring has remained limited to symptom assessment and the 6-minute walk distance. In this study, we showed that exercise echocardiography is feasible in patients with PAH. The presence of correlations among the exercise echocardiographic measurements and known predictors of outcome in PAH indicates promising targets for future investigations.

Table 1

Patient demographic, PAH, and RHC information

Variable	Summary (N = 10)
Demographic information	
Age, y	47 (29–78)
Female sex	8 (80%)
Race	
White	8 (80%)
African American	1 (10%)
Asian	1 (10%)
BMI	24.9 (20.1–37.2)
Smoking history	
Never smoked	6 (60%)
Former but not current smoker	4 (40%)
PAH information	
WHO group I subgroup	
IPAH	4 (40%)
APAH–connective tissue disease	4 (40%)
APAH–congenital systemic to pulmonary shunts	2 (20%)
WHO functional class	
II	2 (20%)
IIIa	4 (40%)
IIIb	2 (20%)
IV	2 (20%)
BNP, pg/mL	231 (8–1330)
6MWD, ft	1232 (602–1596)
Right heart catheterization information	
SPAP, mm Hg	73 (32–87)
DPAP, mm Hg	29 (12–40)
MPAP, mm Hg	45 (19–61)
PVR, dyne · sec · cm ⁻⁵	573 (175–1383)
PVR, Wood units	7.2 (2.2–17.3)
PAOP, mm Hg	8 (4–15)
RAP, mm Hg	4 (1–12)
RVSP, mm Hg	71 (32–87)
CO, L/min	5.3 (2.3–9.2)
Vasodilator response	2 (22%)

Numerical variables were summarized with the sample median (minimum– maximum). Information was unavailable regarding vasodilator response for 1 patient. APAH, pulmonary hypertension associated with other diseases; BMI, body mass index; BNP, brain natriuretic peptide; CO, cardiac output; DPAP, diastolic pulmonary artery pressure; IPAH, idiopathic pulmonary arterial hypertension; MPAP, mean pulmonary artery pressure; 6MWD, 6-minute walk distance; PAH, pulmonary arterial hypertension; PAOP, pulmonary arterial occlusion pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; RVSP, right ventricular systolic pressure; SPAP, systolic pulmonary artery pressure; WHO, World Health Organization.

Table 2

Resting and exercise echocardiogram information

Variable	No. (%) measures successfully obtained		Median (minimum–maximum)		P
	Resting echocardiogram	Exercise echocardiogram	Resting echocardiogram	Exercise echocardiogram	
TRV, m/s	9 (90%)	9 (90%)	4.5 (2.9–5.4)	4.6 (3.0–5.4)	0.29
MPAP, mm Hg	9 (90%)	9 (90%)	49 (28–84)	65 (30–87)	0.068
PVR, Wood units	9 (90%)	9 (90%)	3.1 (1.8–9.9)	3.5 (1.7–12.8)	1.00
TAPSE, mm	10 (100%)	10 (100%)	17 (8–27)	17 (9–30)	0.16
Lateral TDI TV annulus, cm/s	10 (100%)	8 (80%)	8 (4–13)	9 (7–13)	0.94
RV mid free wall strain, %	8 (80%)	7 (70%)	–12 (–28 to –5)	–17 (–35 to –5)	0.68
RV cardiac output, L/min	10 (100%)	10 (100%)	5.2 (2.2–17.7)	7.8 (2.6–17.9)	0.014
RV stroke volume, mL	10 (100%)	10 (100%)	65 (28–184)	62 (25–186)	0.68

P values result from a Wilcoxon signed rank test comparing echocardiogram-measured values between resting and exercise echocardiogram. MPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; TRV, tricuspid regurgitation velocity; TV, time velocity.

Table 3
Associations of exercise echocardiogram measures with known RHC predictors of outcome

Exercise echocardiogram measure	Association with RHC RAP		Association with RHC MPAP		Association with RHC CO	
	<i>r</i> (95% CI)	<i>P</i>	<i>r</i> (95% CI)	<i>P</i>	<i>r</i> (95% CI)	<i>P</i>
TRV, m/s	0.11 (−0.60–0.72)	0.78	0.77 (0.21–0.95)	0.016	−0.68 (−0.93 to −0.04)	0.042
MPAP, mm Hg	0.37 (−0.39–0.83)	0.32	0.73 (0.13–0.94)	0.026	−0.56 (−0.89–0.16)	0.11
PVR, Wood units	0.44 (−0.32–0.85)	0.24	0.36 (−0.40–0.83)	0.34	−0.68 (−0.93 to −0.03)	0.043
TAPSE, mm	−0.74 (−0.94 to −0.21)	0.014	−0.37 (−0.81–0.34)	0.30	0.31 (−0.40–0.79)	0.39
Lateral TDI TV annulus, cm/s	0.34 (−0.48–0.84)	0.41	−0.03 (−0.72–0.69)	0.94	0.33 (−0.48–0.84)	0.42
RV mid free wall strain, %	0.39 (−0.51–0.88)	0.38	0.78 (0.08–0.97)	0.037	−0.09 (−0.79–0.71)	0.85
RV CO, L/min	−0.03 (−0.65–0.61)	0.94	−0.10 (−0.69–0.56)	0.79	0.42 (−0.29–0.83)	0.23
RV stroke volume, mL	−0.12 (−0.70–0.55)	0.73	−0.08 (−0.67–0.58)	0.83	0.43 (−0.27–0.83)	0.21
Heart rate	−0.28 (−0.77–0.42)	0.43	0.05 (−0.60–0.66)	0.90	0.46 (−0.23–0.85)	0.18
Heart rate, % max predicted	−0.20 (−0.74–0.49)	0.58	0.09 (−0.57–0.68)	0.81	0.25 (−0.45–0.76)	0.49
MET	−0.75 (−0.94 to −0.23)	0.012	−0.74 (−0.93 to −0.21)	0.015	0.55 (−0.12–0.88)	0.099

P values result from the Pearson test of correlation. CI, confidence interval; CO, cardiac output; MET, metabolic equivalent of task; MPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; *r*, Pearson's correlation coefficient; RAP, right atrial pressure; RHC, right heart catheterization; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; TRV, tricuspid regurgitation velocity; TV, time velocity.

Table 4
Associations of exercise echocardiogram measures with other known predictors of outcome

Exercise echocardiogram measure	Association with BNP		Association with 6MWD		Association with WHO functional class	
	<i>r</i> (95% CI)	<i>P</i>	<i>r</i> (95% CI)	<i>P</i>	<i>r</i> (95% CI)	<i>P</i>
TRV, m/s	0.42 (−0.33–0.85)	0.25	−0.19 (−0.76–0.54)	0.62	0.24 (−0.50–0.78)	0.55
MPAP, mm Hg	0.49 (−0.26–0.87)	0.18	−0.19 (−0.76–0.54)	0.63	0.29 (−0.46–0.80)	0.46
PVR, Wood units	0.77 (0.21–0.95)	0.016	−0.58 (−0.90–0.14)	0.10	0.61 (−0.09–0.91)	0.097
TAPSE, mm	−0.65 (−0.91 to −0.04)	0.041	0.78 (0.28–0.94)	0.008	−0.44 (−0.84–0.26)	0.19
Lateral TDI TV annulus, cm/s	−0.06 (−0.73–0.67)	0.89	−0.25 (−0.81–0.55)	0.55	−0.50 (−0.89–0.31)	0.20
RV mid free wall strain, %	0.03 (−0.74–0.76)	0.96	−0.41 (−0.89–0.50)	0.36	0.38 (−0.52–0.88)	0.44
RV CO, L/min	−0.31 (−0.79–0.39)	0.38	0.08 (−0.58–0.67)	0.84	−0.28 (−0.77–0.43)	0.41
RV stroke volume, mL	−0.40 (−0.82–0.31)	0.25	0.12 (−0.55–0.70)	0.73	−0.25 (−0.76–0.45)	0.45
Heart rate	−0.37 (−0.81–0.34)	0.30	0.55 (−0.13–0.87)	0.10	−0.09 (−0.68–0.57)	0.79
Heart rate, % max predicted	0.09 (−0.57–0.68)	0.81	0.52 (−0.16–0.87)	0.16	−0.04 (−0.65–0.61)	0.89
MET	−0.46 (−0.84–0.24)	0.18	0.91 (0.66–0.98)	<0.001	−0.72 (−0.93 to −0.16)	0.020

For associations with BNP and 6MWD, *P* values result from the Pearson test of correlation, and *r* = Pearson's correlation coefficient. For associations with WHO functional class, *P* values result from the Spearman test of correlation, and *r* = Spearman's correlation coefficient. BNP, brain natriuretic peptide; CI, confidence interval; CO, cardiac output; MET, metabolic equivalent of task; MPAP, mean pulmonary artery pressure; 6MWD, 6-minute walk distance; PVR, pulmonary vascular resistance; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; TRV, tricuspid regurgitation velocity; TV, time velocity; WHO, World Health Organization.