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Left Ventricular Function Before and After Aerobic Exercise Training in Women With Pulmonary Arterial Hypertension

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Abstract

Background: Pulmonary arterial hypertension (PAH) is a chronic debilitating illness. The effects of vigorous aerobic exercise training (AET) on heart function in PAH are poorly understood.

Methods: 18 women with PAH (age 56.2 ± 8.8 yr, BMI 28.8 ± 7.3 kg/m²) underwent 10 wk of vigorous AET. Cardiac function was observed at rest and peak exercise using bioelectrical impedance cardiography before and after the AET. Cardiac function was observed in a small PAH subset ($n = 7$) for 10 wk prior to beginning the AET. A cohort of sedentary women ($n = 19$) served as healthy controls.

Results: Left ventricular ejection fraction (EF; 48 ± 9.2 vs. 61.5 ± 13.3 %, $P = .034$) and the systemic vascular resistance index (SVRI; 2258 ± 419.1 vs 2939 ± 962.4 dyn·s/cm⁵·m², $P = .008$) were lower at supine rest in the baseline PAH group vs healthy group, as were peak exercise heart rate (HR; 140 ± 13.3 vs 170 ± 13.8 beats/min, $P < .001$) and SVRI (828 ± 141.1 vs 824 ± 300.9 dyn·s/cm⁵·m², $P = .050$) after controlling for age and HR. SVRI measured at peak exercise decreased in the PAH group after AET (828 ± 141.1 vs 766 ± 139.6 dyn·s/cm⁵·m², $P = .020$). Early diastolic left ventricular filling ratio (EDFR) worsened in the PAH subset prior to AET (95.9 ± 19.4 vs 76.2 ± 18.9 %, $P = .043$) and remained unchanged after AET.

Conclusion: Vigorous AET was not associated with significant declines in left ventricular systolic or diastolic function in women with PAH. AET may be beneficial for reducing afterload and may preserve left ventricular diastolic function.

Abstract

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Left ventricular filling dynamics (LVFD) were measured in patients with pulmonary hypertension during cardiopulmonary exercise testing before and after a cardiopulmonary rehabilitation program. Noninferiority analysis revealed that LVED were unaltered after the program, implying that vigorous exercise did not adversely influence right ventricular or pulmonary vascular function.

Keywords

cardiopulmonary rehabilitation; pulmonary arterial hypertension; aerobic exercise training; left ventricular function

Pulmonary arterial hypertension (PAH) is a debilitating condition resulting in pathologic and irreversible elevation of pulmonary artery pressure¹ caused by increased smooth muscle tone and endothelial cell proliferation within the distal pulmonary microvasculature.² Patients with PAH experience elevated afterload at the right ventricle (RV) due to increased pulmonary vascular resistance that contributes to progressive RV dilation and dysfunction (Figure 1).^{3,4} This often results in right-sided heart failure,⁵ which is the leading cause of death in PAH.⁶ Prior to eventual mortality, changes in RV function can diminish function of the left ventricle (LV) through shifts in interventricular septal architecture^{7–10} and alterations in the pericardium.^{11,12} Chronic dyspnea, poor exercise tolerance, and decreased activity participation are often exacerbated.^{13,14}

Historically, patients with PAH were advised to avoid exercise training over concern that exercise participation may worsen right ventricular function and precipitate right ventricular failure.¹⁵ Despite this concern, 2 randomized clinical trials^{16,17} demonstrated that aerobic exercise training (AET) benefitted patients with PAH. AET improved exercise capacity and select health-related quality of life domains; findings which may have important implications for longevity in patients with PAH.^{18,19} These studies reported improvements without any serious adverse events or decrease in cardiac output.¹⁷

Previous studies on cardiac function in patients with PAH have generally focused on right ventricular function at rest⁴ providing little information associated with left ventricular hemodynamics and total body oxygen delivery. A recent echocardiographic analysis of LV function in a group of 128 patients with PAH elucidated left ventricular diastolic dysfunction in 64% of the subjects, with early relaxation abnormalities in 48%.²⁰ At rest, increased pulmonary artery resistance can be compensated by inotropic shifts, Frank-Starling mechanism-mediated increases in right ventricular contractile force, and encroachment on the pulmonary microvascular reserve, leaving resting left ventricular filling unaffected. Measuring left ventricular function during an exercise challenge may unmask these compensatory mechanisms.

LV filling is dependent on adequate RV ejection and blood flow through the pulmonary vasculature (Figure 1). Thus, measuring LV systolic and diastolic function during an intense exercise challenge could provide information from which inferences in overall cardiac functional status can be made. The present study employed a strenuous exercise challenge to characterize LV hemodynamics with an emphasis on diastolic filling in a small sample of

women with PAH before and after a regimen of AET. This study was aimed at determining the safety of AET in these subjects with respect to the potential provocation of cardiac functional decline. Thus, a noninferiority design was used to test the hypothesis that vigorous AET would not exacerbate left ventricular filling or hemodynamic dysfunction in these subjects.

METHODS

Subjects for this study participated in the National Institutes of Health (NIH) Exercise Therapy for Advanced Lung Disease Trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00678821) identifier: NCT00678821). Subjects were recruited from the greater Washington, DC area between 2008 and 2014. A sedentary, but otherwise healthy control group without PAH, was recruited from a database maintained by the NIH Clinical Center in Bethesda, MD. All participating institutional review boards approved this study (NIH: 08-CC-0133; Inova Fairfax Hospital: 08.129; and George Mason University: 6057) and informed consent was obtained from each participant pursuant to the Declaration of Helsinki.²¹ Medical records for subjects with PAH were obtained from referring clinics and all subjects were evaluated by a physician prior to enrollment. Primary findings from this study have been previously reported.¹⁷

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are presented in Table 1. Once enrolled in the study, participants were dismissed if they had any disease exacerbation requiring hospitalization, an onset of any exclusion criteria, an alteration of PAH medication regimen, were noncompliant with the intervention (failure to participate in 80% of the AET sessions), or voluntarily withdrew. No PAH medications were adjusted or added during the study.

Tests and Procedures

All subjects completed a treadmill graded exercise test (GXT) to volitional exhaustion using a modified Naughton protocol.¹⁷ Left ventricular function during rest and peak exercise was assessed using bioelectrical impedance cardiography ([ZCG]; PhysioFlow, Manatec Biomedical). Data acquired from ZCG were measured continuously and averaged over each 15 sec. No data were included in more than 1 of the 15-sec numbers bins. Table 2 contains a list of variables obtained from ZCG and their methods of derivation. All subjects with PAH participated in an identical AET regimen. Using 2×2 block randomization, half were assigned to immediately begin training (START) while the other half participated in a 10-wk, delayed-entry group (WAIT). The START group participated in 10 wk of AET, 3 times/wk, followed by a repeat GXT. The WAIT group maintained normal daily activities for the first 10 wk followed by a second GXT, and then participated in the 10-wk AET intervention, followed by a third GXT. The healthy control group performed the initial GXT and did not participate in the AET regimen.

The AET regimen included treadmill walking 3 times/wk for 10 wk. The target heart rate range was calculated from the pre-exercise GXT as 70–80% of the heart rate reserve, using the method of Karvonen.²² Sessions were initially 30 min and progressively added 1 min each session up to 45 min, with 5 min of warmup and 5–10 min of cooldown walking.

Statistical Analysis

Given the small sample size, variables were assessed visually for normality using histograms. Levene's test was used to assess equality of variances. Two-tailed independent or paired *t*-tests were used to compare group means. Multiple regression was used to assess confounding effects of covariate factors, with subsequent analysis of covariance to test for significant differences between group measures of cardiac function after controlling for these covariates. Due to the paucity of work detailing meaningful clinical changes in the indices of cardiac function listed in Table 2, a noninferiority design was considered appropriate. A decline 10% from baseline was used for all noninferiority null hypotheses in each measure of left ventricular function. One-tailed paired *t*-tests were used for the noninferiority analyses. An alpha-level of 0.05 was considered statistically significant for all tests. Data were analyzed using SPSS Macintosh version 22 (IBM).

RESULTS

Figures 2 and 3 depict CONSORT diagrams for the healthy control and PAH groups. Subjects from the randomized controlled trial were included in the current study if they had interpretable baseline ZCG recordings. Through random chance, only women were enrolled in the PAH group in this study. The 10 subjects with PAH from the WAIT group and 8 from the START group were combined into 1 larger PAH group ($n = 18$) after finding no significant differences in physical characteristics, left ventricular function, or GXT performances at baseline or post-AET treatment. Nineteen women were included in the healthy control group (Figure 2). Baseline data from all 18 of the subjects with PAH were compared to the healthy controls. Seven of the 10 participants in the WAIT subgroup were used in the training portion of this study examining left ventricular diastolic function over the 10-wk period of free-living activity. The 3 omitted subjects had noisy or missing data on their postcontrol nonexercise regimen. All 8 participants in the START subgroup were included in the training portion of the study. No significant differences in physical characteristics were observed between the PAH and control groups other than age (Table 3).

Stability of ZCG Indices of Left Ventricular Function in Patients with PAH

Seven participants from the WAIT group had both baseline and pre-exercise ZCG data adequate for analysis. Bland Altman plots were developed to determine stability of the core left ventricular function measurements over 10-wk of free living with no participation in AET (Figure 4). No significant differences over the 10-wk period between the baseline and pre-AET time points were observed when measured during supine or standing rest. Early diastolic filling ratio (EDFR) at peak exercise significantly declined from the baseline to pre-AET ($95.9 \pm 19.4\%$ vs $76.2 \pm 18.9\%$, $P = .043$) over the initial 10-wk period, then remained stable during the 10-wk AET period (Figure 5).

Comparison of Subjects with PAH and Healthy Controls

After controlling for age, left ventricular ejection fraction (EF) and systemic vascular resistance index (SVRI) were significantly lower in the patients with PAH than in the controls during supine rest (Table 4). At peak exercise, heart rate (HR) was significantly lower in the patients with PAH than in the healthy controls, as was SVRI after controlling

for both age and HR. No significant differences in left ventricular function existed between groups at peak exercise.

Comparison of ZCG Indices of Left Ventricular Function Before and After Training

No significant worsening of left ventricular systolic or diastolic function was observed following AET (Table 5). During standing rest, HR, cardiac output, cardiac index, left ventricular ejection time, left cardiac work index (LCWI) and acceleration index (AI) were statistically different. SVRI measured during peak exercise was significantly reduced following AET. Figure 6 depicts the 95% confidence intervals for mean changes over time for all variables assessed before and after the AET regimen.

DISCUSSION

The 18 patients with PAH in this study were a subset of the 29 participants included in the previous RCT. Primary outcomes of this trial were previously reported and include a 56 ± 45 m improvement in 6-min walk distance, a 1.9 ± 1.3 min increase in treadmill GXT duration, a 26 ± 23 watt increase in peak work rate, and improvement in 6 of the 8 scales on the 36-item Short Form Health Survey version 2 and 5 of the 6 scales on the Cambridge Pulmonary Hypertension Outcome Review questionnaire. No adverse events were reported. The current study added that despite a diminution in left ventricular function during supine rest in the overall sample of women with PAH, PAH and control group differences were not observed at peak exercise. After 10 wk of vigorous AET, no significant disturbances in left ventricular diastolic or systolic function were observed in the subjects with PAH. Subanalyses revealed a decline in EDVR over 10 wk of free-living activity, in which participants engaged in no regular aerobic exercise, in the WAIT subset. However, no further decline was observed following AET in the WAIT subset and no exercise training induced decline was observed in the START subset. The results indicated that, for subjects with PAH, neither maximal aerobic exercise testing nor AET appeared to adversely affect left ventricular diastolic or systolic function. The results further suggested that AET could possibly play a role in offsetting or delaying what might possibly be an impending decline in early diastolic filling in these patients.

To date, the long-held concerns that exercise training may worsen cardiac function in PAH has not been completely dispelled.²³ This study found no evidence of significant decrease in left ventricular function at rest in the patients with PAH and left ventricular function at peak exercise was maintained similar to healthy controls before and after AET. The AET regimen used in this study was substantially more intense and prolonged compared to other studies in patients with severe chronic illnesses,^{24–26} including PAH,^{27–32} or individuals who are sedentary but otherwise healthy.³³ While significant benefits of participating in AET for people with PAH have been reported previously,^{16,17} the current findings suggest that participation in AET appears to be safe and without adverse consequences on left ventricular function.

At baseline, SVRI was lower during peak exercise in the subjects with PAH than in the healthy controls. The effects of PAH on left ventricular afterload have not been previously reported. It is possible that the reduction in baseline SVRI could have been associated with

systemic effects of targeted vasodilators used to treat PAH. SVRI was reduced even further following AET in the women with PAH, suggesting that AET might be an effective afterload-reducing adjunct in this population. In addition, the concomitant reductions in LVET and LCWI during standing rest may suggest greater left ventricular inotropy. This inference was further supported by the increase in standing rest AI. The approximate 6% decrease in HR appeared to facilitate an approximate 11% decrease in Qt at standing rest. The drop in HR in concurrence with the reduction in LVET and the apparent increase in inotropy implied that left ventricular filling time was prolonged. However, the observation of no significant change in EDFR further implied that any prolongation of LV filling time was likely distributed over both the early and late phases during standing rest.

Diastolic filling occurs in 2 phases, the early and late stages. EDFR is the ZCG analog for the early to late ventricular filling velocity ratio (E/A ratio) obtained through echocardiography. Decreases in the E/A ratio have been associated with impaired ventricular relaxation during diastole or reductions in blood flow through the pulmonary veins to the left ventricle.³⁴ In a retrospective study,³⁵ 53 of 61 women with PAH had impaired left ventricular relaxation. The diastolic filling ratio was determined to be a pervasive marker of left ventricular diastolic dysfunction and a significant predictor of mortality after controlling for pulmonary artery pressure, right atrial pressure, and cardiac index.³⁵ While echocardiography is presently the principle method for measuring the diastolic filling ratio, echocardiographic measures are typically obtained at rest and are methodologically difficult when attempted during exercise. Echocardiography is virtually impossible to perform during submaximal or maximal exercise on the treadmill. The present study suggested that, as an alternative, ZCG measurement of diastolic function during an intense exercise challenge might be useful in detecting early declines in diastolic function.

This work has some limitations. The sample used in this study may be underpowered for some indices of cardiac function. Our sample was comprised entirely of women, which may prohibit broader generalization to men who have PAH. It is possible that patients with more severe PAH, who were omitted by our exclusion criteria, might have more overtly impaired right and left ventricular dysfunction.^{36,37}

While ZCG technology permits measurements of left ventricular function during peak exercise, it can be noisy in some subjects and cannot be used to evaluate right ventricle function directly. Moreover, the number of available indices of diastolic function is limited. Further development of this technology may expand its usage. Despite this limitation, ZCG currently offers what may be the only practical method for obtaining select left ventricular diastolic and systolic function measures during intense exercise on a treadmill. ZCG validation studies have focused on measures of left ventricular cardiac output and stroke volume.^{38–46} The ZCG method has been compared to the direct Fick method,^{38,39,41,43,46} pulse contour analysis,^{43,46} nitrous oxide rebreathing,⁴⁶ carbon dioxide rebreathing,⁴⁰ acetylene rebreathing,⁴⁵ dye dilution,⁴² and Doppler echocardiography.⁴⁴ Good agreement has been demonstrated between ZCG and these methods.^{38,39,42} Conversely, deviation from manufacturer guidelines, antiquated signal filtering methods and older versions of software have been implicated⁴⁷ in studies that report poor agreement^{41,43–45} and findings that were equivocal with other methods.^{40,46} Measures such as cardiac output and left ventricular

stroke volume are calculated using waveform derived algorithms⁴⁸ which may reduce, under some conditions, the accuracy of these calculations. Other measures such as left ventricular ejection time, EDVR, and dz/dt are measured directly from the waveform.⁴⁸ Overall the ZCG waveform is very similar to the waveform obtained through a Doppler echocardiogram and good correlations have been reported for many of the same cardiac cycle events.⁴⁹ ZCG technology can be negatively affected by small stroke volume,⁴³ lung hyperinflation,⁴¹ movement artifact,⁵⁰ and fluid in the lungs.⁵¹ Studies have demonstrated a high degree of accuracy for ZCG measured changes in left ventricular function when assessed over time.⁴³ The PhysioFlow ZCG system used in this study has been previously used in subjects with PAH.⁵²

CONCLUSION

The results of this study suggest that, in patients with PAH, vigorous exercise training that is sufficient for eliciting clinically important improvements in exercise tolerance and quality of life does not appear to be associated with significant declines in either left ventricular systolic or diastolic function. To the contrary, left ventricular afterload was reduced after AET in these subjects with PAH. This study also provides some preliminary data that appears to suggest that vigorous AET may play a role in preserving left ventricular diastolic function, which may decrease over time as an effect of disease progression. Further studies are needed to explore this potential interaction between AET and left ventricular diastolic dysfunction as the progression of left ventricular diastolic dysfunction has been shown to contribute to impending mortality in populations with PAH.³⁵

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Figure 1.
Influence of attenuation of right ventricular ejection and pulmonary microvascular reactivity and reserve on left ventricular filling and cardiac function.

Figure 2. Consort diagram for the healthy control group. Abbreviation: ZCG, bioelectrical impedance cardiography.

Figure 3.

Consort diagram for the PAH group. Abbreviations: PAH, pulmonary arterial hypertension; WHO, World Health Organization; ZCG, bioelectrical impedance cardiography.

Figure 4.

Bland-Altman plots for 7 subjects with PAH before and after 10 wk of free-living activity. Panel A: Heart rate plots during peak exercise; Panel B: stroke volume plots during peak exercise; Panel C: end-diastolic volume plots during peak exercise; Panel D: end diastolic filling ratio plots at peak exercise. Zero on the Y-axis represents the group mean and the horizontal dashed lines represent ± 2 standard deviations from the group mean. Abbreviation: EDVR, early diastolic filling ration; EDV, end-diastolic volume; SV, stroke volume.

Figure 5. Changes in the early diastolic filling ratio (EDFR) at peak exercise. Data points connected by a single line represent EDFR measures for 1 participant before and after 10 wk of free-living activity, followed by a 3rd time point measured after 10 wk of aerobic exercise training (AET). ^aIndicates a statistically significant difference between the 2 time periods.

Figure 6.

Data reports 95% confidence intervals for the mean change from baseline for various indices of cardiac function. The full height of each bar represents the full range of the 95% confidence interval, with the mean at the exact vertical center point of each bar (unmarked).

^aDenotes statistically significant differences between the pre-exercise and postexercise values for the variable. Panel A: Changes in cardiac function during supine rest; Panel B: changes in cardiac function during standing rest; Panel C: changes in cardiac function at peak exercise. Abbreviations: AI, acceleration index; CI, cardiac index; CTI, contractility

index; EDFR, early diastolic filling ratio; EDV, end-diastolic volume; EF, left ventricular ejection fraction; HR, heart rate; LCWI, left cardiac work index; LVET, left ventricular ejection time; Qt, cardiac output; SV, stroke volume; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index.

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Table 1.**Study Inclusion and Exclusion Criteria**

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • WHO Group I PAH • Resting mean pulmonary arterial pressure 25 mm Hg as measured by RHC • Age 21–82 yr old • Physically sedentary, defined as no structured exercise for >20 min/day, 3 times/wk • Stable PAH medication regime for 3 mo 	<ul style="list-style-type: none"> • Ischemic heart disease • EF <40% or a documented PCWP 18 mm Hg • Documented cor pulmonale • Prior participation in a formal pulmonary rehabilitation program within 6 mo • WHO/NYHA functional class I and most recent 6MWT distance >400 m • WHO/NYHA functional class IV and most recent 6MWT distance <50 m • Severe hepatic disease • Severe renal disease • Mitochondrial dysfunction of any etiology • Obstructive lung disease with documented FEV₁/FVC ratio 65% • Severe psychiatric disease • Current use of tobacco • Current use of illicit or recreational drugs • Use of any medication not typically used in the management of PAH that alters response and adaptation to exercise (eg, antiretroviral therapy) • Pregnancy

Abbreviations: EF, left ventricular ejection fraction; FEV₁, forced expiratory volume in 1 sec; FVC, forced vital capacity; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; WHO, World Health Organization; RHC, right heart catheterization; 6MWT, 6-min walk test.

Table 2.Description of ZCG Variables Used in Analyses^a

	Abbreviation	Description	Equation
Acceleration index, No unit	AI	Force generation of the heart unaffected by preload; peak velocity of blood in the aorta	$(dZ/dT_{\max})/LVET$
Cardiac index, L/min/m ²	CI	Cardiac output normalized to the total body surface area	Qt/BSA where $BSA = 0.007184 * \text{Height}^{0.725} * \text{Weight}^{0.425}$
Cardiac output, L/min	Qt	Quantity of blood pumped by the heart systemically each minute	$SV * HR/1000$
Contractility index, no unit	CTI	Overall force generation of the heart; accounts for both contractility and preload	$dZ/dT_{\max}$
Early diastolic filling ratio, %	EDFR	The ratio of early diastolic filling time to late diastolic filling time	$O \text{ wave}/S \text{ wave} * 100$
End-diastolic volume, mL	EDV	Volume of blood remaining in ventricle after systole	SV/EF
Center cardiac work index, kg-m/m ²	LCWI	Force generation of center ventricle normalized to body surface area	$0.0144 * CI * (MAP - PAOP)$
Center ventricular ejection fraction, %	EF	The percentage of blood ejected from the ventricle at the end of systole	$0.84 - (0.64 * PEP)/LVET^b$
Center ventricular ejection time, msec	LVET	The interval of time between the opening and closing of the aortic valve	Directly measured
Stroke volume, mL	SV	Quantity of blood pumped from the center ventricle with each heartbeat	$SVI_{\text{cal}} * ((dZ/dT_{\max})/(dZ/dT_{\max})_{\text{cal}} * (TFIT_{\text{cal}}/TFIT)^{1/3} * BSA^c$ where $SVI_{\text{cal}} = k * [(dZ/dT_{\max})/(Z_{\max} - Z_{\min})] * W(TFIT_{\text{cal}})$
Systemic vascular resistance, dyn-s/cm ⁵	SVR	The resistance provided by systemic circulation that must be overcome by the ventricle during systole	$80 * (MAP - CVP)/Qt$
Systemic vascular resistance index, dyn-s/cm ⁵ .m ²	SVRI	The resistance provided by systemic circulation that must be overcome by the ventricle during systole normalized to body surface area	$80 * (MAP - CVP)/CI$

Abbreviations: BSA, body surface area; CVP, central venous pressure; $dZ/dT_{\max}$, first derivative of impedance signal; HR, heart rate; MAP, mean arterial pressure (mm Hg); PAOP, pulmonary artery occlusive pressure; PEP, pre-ejection period; SVI, stroke volume index; TFIT, time interval recorded from the first zero value after the cardiac cycle initiation and the first signal nadir following the peak ejection velocity; $W(TFIT_{\text{cal}})$, a weighting algorithm incorporating $TFIT_{\text{cal}}$, HR, and pulse pressure; Z, impedance; ZCG, bioelectrical impedance cardiography.

^aSome information and equations adapted from Charloux²⁴ and from correspondence with the manufacturer.

^bCapan³⁹ equation listed in this table has been modified by the manufacturer in a proprietary manner, therefore the original equation was included in this table.

^cSubscript “cal” identifies measurements obtained during system calibration.

Table 3.Physical Characteristics of PAH and Healthy Control Groups^a

	WAIT PAH Group (n=10)	START PAH Group (n=8)	PAH Combined Group (n=18)	Healthy Control Group (n=19)
Age, yr	56.4 ± 5.8	56.0 ± 12.0	56.2 ± 8.8	47.9 ± 7.9 ^b
Height, cm	165.5 ± 4.8	159.9 ± 6.5	163.0 ± 6.1	165.2 ± 4.2
Weight, kg	80.3 ± 21.8	72.3 ± 20.0	76.7 ± 20.8	85.6 ± 18.4
BMI, kg/m ²	29.3 ± 7.9	28.1 ± 7.1	28.8 ± 7.3	31.3 ± 6.6
Race/Ethnicity				
Black	6 (60)	2 (25)	8 (44)	10 (53)
White	3 (30)	4 (50)	7 (39)	7 (37)
Asian	1 (10)	2 (25)	3 (17)	2 (10)
Disease duration, yr	6.5 ± 4.6	5.0 ± 4.5	5.9 ± 4.5	---
PAH etiology				
SS	3 (30)	3 (37.5)	6 (33)	---
Drug-induced	2 (20)	---	2 (11)	---
SLE	1 (10)	2 (25)	3 (18)	---
Sjögren's syndrome	1 (10)	1 (12.5)	2 (11)	---
CTD	1 (10)	1 (12.5)	2 (11)	---
Idiopathic	1 (10)	1 (12.5)	2 (11)	---
RA	1 (10)	---	1 (5)	---
Number of PAH medications/patient	2.2 ± 1.0	1.9 ± 1.0	2.1 ± 1.0	---
PAH medication class				
None	1 (10)	---	1 (5.5)	---
PDE5 alone	-	3 (37.5)	3 (17)	---
PA alone	1 (10)	1 (12.5)	2 (11)	---
ERA + PDE5	2 (20)	1 (12.5)	3 (17)	---
PDE5 + PA	1 (10)	---	1 (5.5)	---
ERA + PDE5 + PA	5 (50)	3 (37.5)	8 (44)	---
WHO/NYHA functional classification	2.2 ± 0.4	2.4 ± 0.7	2.3 ± 0.6	---
I	1 (12)	---	1 (6)	---
II	3 (38)	8 (80)	11 (61)	---
III	4 (50)	2 (20)	6 (33)	---
IV	---	---	---	---
Supplemental oxygen use	2 (20)	2 (25)	4 (22)	---
6MWD, m	401 ± 85.9	400 ± 77.5	401 ± 79.9	563 ± 96.2 ^b

Abbreviations: BMI, body mass index; CTD, connective tissue disorder; ERA, endothelin receptor antagonist; PA, prostacyclin analogue; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5 inhibitor; RA, rheumatoid arthritis; SS, systemic sclerosis/scleroderma; SLE, systemic lupus erythematosus; 6MWD, 6-min walk distance.

^aData reported as mean ± standard deviation or number (%).

^b P value <.01 comparing the difference between the PAH Combined Group and the Healthy Control Group using an independent sample t -test.

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Table 4.

Indices of Baseline Cardiac Function for PAH and Healthy Control Groups

4-A. Supine Rest^a			
	PAH Group	Healthy Control Group	P Value
HR, beats/min	76 ± 11.4	72 ± 16.5	.427
SV, mL	70 ± 19.7	73 ± 17.3	.698
Qt, L/min	5.3 ± 1.5	5.1 ± 1.5	.794
CI, L/min/m ²	2.8 ± 0.6	2.6 ± 0.7	.376
EF, %	48 ± 9.2	61.5 ± 13.3	.034 ^b
LVET, msec	293 ± 72.1	300 ± 52.2	.085
CTI, no unit	140 ± 75.5	197 ± 100.0	.06
EDV, mL	151 ± 50.0	124 ± 44.2	.094
SVR, dyn-s/cm ⁵	1226 ± 279.1	1466 ± 430.5	.058
SVRI, dyn-s/cm ⁵ -m ²	2258 ± 419.1	2939 ± 962.4	.008 ^b
LCWI, kg-m/m ²	3.0 ± 0.9	3.2 ± 1.0	.473
EDFR, %	76 ± 63.3	61 ± 24.0	.347
AI, no unit	0.5 ± 0.2	0.7 ± 0.5	.122

4-B. Standing Rest			
	PAH Group	Healthy Control Group	P Value
HR, beats/min	83 ± 9.8	81 ± 14.9	.658
SV, mL	75 ± 19.4	74 ± 16.5	.8
Qt, L/min	6.3 ± 1.7	5.9 ± 1.3	.469
CI, L/min/m ²	3.3 ± 0.7	3.0 ± 0.6	.125
EF, %	54 ± 10.2	64 ± 12.2	.089 ^c
LVET, msec	346 ± 74.1	306 ± 51.0	.072
CTI, no unit	229 ± 188.3	228 ± 102.8	.981
EDV, mL	145 ± 43.9	121 ± 41.3	.105
SVR, dyn-s/cm ⁵	1200 ± 330.0	1274 ± 316.1	.512
SVRI, dyn-s/cm ⁵ -m ²	2186 ± 436.3	2545 ± 670.5	.083
LCWI, kg-m/m ²	4.1 ± 1.4	3.8 ± 0.9	.402
EDFR, %	46 ± 25.0	54 ± 30.9	.423
AI, no unit	0.7 ± 0.8	0.8 ± 0.6	.747

4-C. Peak Exercise			
	PAH Group	Healthy Control Group	P Value
HR, beats/min	140 ± 13.3	170 ± 13.8	<.000 ^d
SV, mL	109 ± 24.4	107 ± 29.0	.798

4-C. Peak Exercise			
	PAH Group	Healthy Control Group	P Value
Qt, L/min	15.2 ± 3.4	18.0 ± 4.2	.163 ^e
CI, L/min/m ²	8.0 ± 1.1	9.0 ± 2.0	.062
EF, %	67 ± 11.2	75 ± 10.9	.064
LVET, msec	180 ± 35.3	186 ± 40.0	.636
CTI, no unit	559 ± 279.3	501 ± 241.9	.504
EDV, mL	166 ± 45.0	144 ± 51.0	.167
SVR, dyn-s/cm ⁵	451 ± 108.4	411 ± 134.6	.328
SVRI, dyn-s/cm ⁵ ·m ²	828 ± 141.1	824 ± 300.9	.050 ^f
LCWI, kg-m/m ²	9.3 ± 1.8	11.1 ± 3.3	.056
EDFR, %	92 ± 46.7	70 ± 28.7	.086
AI, no unit	3.2 ± 1.7	3.0 ± 2.0	.721

Abbreviations for Tables 4-A, 4-B and 4-C: AI, acceleration index; ANCOVA, analysis of covariance; CI, cardiac index; CTI, contractility index; EDV, end-diastolic volume; EDFR, early diastolic filling ratio; EF, left ventricular ejection fraction; HR, heart rate; LCWI, left cardiac work index; LVET, left ventricular ejection time; PAH, pulmonary arterial hypertension; Qt, cardiac output; SV, stroke volume; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index.

^a All data in all tables are reported as mean ± standard deviation. *P* values derived from independent sample *t*-tests unless otherwise noted.

^b *P* value obtained from ANCOVA using age as a covariate were statistically significantly different both in the independent sample *t*-tests and in the ANCOVA model while all other variables were not significantly different in either test.

^c *P* value obtained from ANCOVA using age as a covariate was statistically significantly different in the independent sample *t*-tests but not in the ANCOVA model. All other variables were not significantly different in either test.

^d *P* value obtained from ANCOVA using age as a covariate was statistically significantly different both in the independent sample *t*-test and in the ANCOVA model.

^e *P* value obtained from ANCOVA using age as a covariate was statistically significantly different in the independent sample *t*-test but not in the ANCOVA model.

^f *P* value obtained from ANCOVA using age and HR as covariates was not statistically significantly different in the independent sample *t*-test, or when using age alone as a covariate.

Note: All other variables were not significantly different using any of the 3 tests.

Table 5.

Indices of cardiac function for the PAH group before and after AET

A – Supine Rest			
	Pre-AET	Post-AET	P-value
HR, bpm	75 ± 11.2	72 ± 12.0	0.146
SV, ml	69 ± 19.2	71 ± 19.0	0.246
Qt, l.min	5.1 ± 1.4	5.0 ± 1.2	0.446
CI, L/min/m ²	2.7 ± 0.6	2.7 ± 0.6	0.473
EF, %	48 ± 9.4	48 ± 8.3	0.396
LVET, msec	264 ± 74.3	271 ± 74.9	0.359
CTI, no unit	140 ± 77.8	135 ± 72.0	0.368
EDV, ml	149 ± 50.4	153 ± 44.0	0.298
SVR, dyn-s/cm ⁵	1257 ± 257.3	1258 ± 287.8	0.494
SVRI, dyn-s/cm ⁵ .m ²	2295 ± 403.1	2294 ± 526.7	0.496
LCWI, kg-m/m ²	2.9 ± 0.9	2.9 ± 0.7	0.491
EDFR, %	78 ± 65.0	70 ± 33.0	0.279
AI, no unit	0.5 ± 0.2	0.5 ± 0.2	0.456

B – Standing Rest			
	Pre-AET	Post-AET	P-value
HR, bpm	83 ± 9.8	78 ± 9.1	0.023
SV, ml	75 ± 19.4	73 ± 14.1	0.206
Qt, l.min	6.3 ± 1.7	5.6 ± 1.1	0.006
CI, L/min/m ²	3.3 ± 0.7	3.0 ± 0.5	0.012
EF, %	54 ± 10.1	51.2 ± 6.1	0.151
LVET, msec	346 ± 74.1	317 ± 57.2	0.027
CTI, no unit	229 ± 189.0	179.6 ± 56.3	0.11
EDV, ml	145 ± 43.9	143 ± 37.4	0.404
SVR, dyn-s/cm ⁵	1200 ± 330.0	1211 ± 297.0	0.408
SVRI, dyn-s/cm ⁵ .m ²	2186 ± 436.3	2186 ± 334.0	0.5
LCWI, kg-m/m ²	4.1 ± 1.4	3.5 ± 0.9	0.021
EDFR, %	46 ± 25.0	57 ± 34.7	0.14
AI, no unit	0.7 ± 0.8	0.6 ± 0.2	0.023

C – Peak Exercise			
	Pre-AET	Post-AET	P-value
HR, bpm	140 ± 13.3	139 ± 15.4	0.392
SV, ml	109 ± 24.5	110 ± 24.7	0.353
Qt, l.min	15.2 ± 3.4	15.4 ± 3.9	0.377
CI, L/min/m ²	8.0 ± 1.1	8.2 ± 1.5	0.271

<i>C – Peak Exercise</i>			
	Pre-AET	Post-AET	P-value
EF, %	67 ± 11.2	65 ± 10.6	0.197
LVET, msec	180 ± 35.3	176 ± 36.3	0.342
CTI, no unit	559 ± 279.3	489 ± 265.5	0.163
EDV, ml	166 ± 45.0	172 ± 38.1	0.134
SVR, dyn-s/cm ⁵	451 ± 108.4	424 ± 117.6	0.057
SVRI, dyn-s/cm ⁵ ·m ²	828 ± 141.1	766 ± 139.6	0.02
LCWI, kg-m/m ²	9.4 ± 1.8	9.3 ± 2.8	0.456
EDFR, %	92 ± 46.7	81 ± 34.5	0.201
AI, no unit	3.2 ± 1.7	2.9 ± 1.7	0.267

Data are presented as mean ± standard deviation. P-values derived from 1-tailed paired t-tests.