

Early View

Research letter

Contrasting hemodynamic effects of exercise and saline infusion in older adults with pulmonary arterial hypertension

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CONTRASTING HEMODYNAMIC EFFECTS OF EXERCISE AND SALINE INFUSION IN
OLDER ADULTS WITH PULMONARY ARTERIAL HYPERTENSION

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To the Editors:

The contemporary population of patients with pulmonary arterial hypertension (PAH) are older, with high prevalence of cardiovascular risk factors(1), and potentially at risk for left ventricular diastolic dysfunction (2). Accordingly, the effect of exercise or volume expansion may elicit augmented increases in pulmonary artery wedge pressure (PAWP) (3,4), in addition to abnormal behavior of pulmonary artery (PA) pressures.

In healthy older subjects, exercise-associated increases in PAWP are predictably coupled to decreases in pulmonary arterial compliance (PAC) and pulmonary vascular resistance (PVR), thereby systematically lowering the product of resistance-compliance relationship (RC-time)(5). We prospectively examined this physiology in older patients with PAH. Exercise and volume expansion were compared with respect to the response of the PAWP and relationships to PA pressures and RC-time.

METHODS

Adults with PAH aged > 45 years referred for right heart catheterizations were recruited. Exclusion criteria included LV systolic dysfunction (LVEF < 50%) or \geq moderate left-sided valvular heart disease. Local research ethics board approved the study protocol. Participants provided written informed consent.

Experimental protocol

A balloon-tipped fluid-filled catheter was positioned in the pulmonary artery (PA) via internal jugular venous access. Right atrial pressure (RAP), PA pressures and PAWP were recorded at *Baseline* in the supine position and heart rate (HR) was monitored continuously. After *Baseline*, *Volume* consisted of volume expansion challenge by

intravenous infusion of 15ml/Kg of 0.9% sodium chloride solution at 100ml/min rate. Hemodynamic data were recorded 1 minute after completing *Volume*. Afterward, participants were transferred to a cycle ergometer in semi-upright position. Hemodynamic data were acquired at 1, 3 and 5 minutes at rest (*Control*) and averaged. Participants then pedalled at self-selected cadence between 60–80 rpm at constant work-rate of 15 Watts. Hemodynamic data were obtained at 3 minutes after onset of cycling (*Exercise*).

Data analysis

Analysis intervals consisted of ≥ 10 consecutive beats free from premature beats. Calculations included: pulmonary pulse pressure (pulmonary PP; mmHg) = PASP - PADP; transpulmonary gradient (TPG; mmHg) = mPAP– PAWP; diastolic pressure difference (DPD; mmHg) = PADP – PAWP (DPD; mmHg); RC-time is calculated as the product of PVR (TPG/(stroke volume*HR)) and PAC (stroke volume/PP), which can be simplified to TPG/(HR x PP). Changes in RAP and PAWP, relative to volume infused, were assessed by the slopes of RAP/volume infused and PAWP/volume infused relations.

Statistical analysis

Data were analyzed using SPSS, version 21 (IBM Corp., Armonk, NY, USA.) and presented as median and interquartile ranges [IQR]. Comparisons of continuous variables between conditions were analysed using related-samples Wilcoxon Signed Rank Test. Two-tailed α level of 0.05 was considered statistically significant.

RESULTS

Five women, aged 60 [14] years, were studied. Four were receiving PAH-specific therapy. The mPAP was 38 [23] mmHg, PAWP was 4 [11] mmHg, TPG was 28 [27] mmHg and PVR was 9 [9] WU. After infusion of 1.1 [0.4] L of volume, HR did not change, but RAP and PAWP increased significantly from *Baseline*. The slopes of the RAP/volume infused and PAWP/volume infused were 6 [2] mmHg/L and 8 [4] mmHg/L, respectively. HR, RAP, SPAP, DPAP, pulmonary PP and TPG were significantly increased by *Exercise*. Patients tolerated the experimental protocol without adverse effects.

RAP and PAWP responses to *Volume* were not statistically different compared to *Exercise*. In contrast to the *Volume*, *Exercise* was associated with increased augmentation of HR, SPAP, DPAP, mPAP, pulmonary PP, DPD and TPG (**Table 1**).

Exercise increased RC-time significantly, while *Volume* did not. *Baseline* RC-time was 0.55 [0.29] seconds and 0.52 [0.19] seconds after *Volume* ($P = 0.89$). In contrast, RC-time was 0.51 [0.49] seconds at *Control* and increased significantly to 0.64 [0.62] seconds at *Exercise* ($P = 0.04$). The change in RC-time from *Control* to *Exercise* was 0.32 [0.26] seconds, compared to 0.02 [0.16] seconds, ($P = 0.04$) from *Baseline* to *Volume*. There was no relationship observed between PAWP and RC-time at any condition.

DISCUSSION

We examined the effect of exercise and volume expansion interventions amongst older adults with PAH. Despite similar effects on the PAWP response, exercise elicited

greater perturbations to PA pressures and HR. We also examined the behaviour of the pulmonary vasculature as characterized by the effect on RC-time. In health, we have observed that exercise-associated increases in PAWP are related to decreases in RC-time(5). In PAH subjects, we observed a paradoxical increase in RC-time with exercise, and no change with volume expansion, despite similar PAWP responses. Overall, for similar PAWP changes, exercise was more potent in eliciting the hallmarks of pulmonary vascular disease, compared to volume expansion. Therefore, exercise clearly differentiated the normal behaviour of the PAWP responses from the abnormal behaviour of the PA pressure responses.

We explored the relationship between the changes in PAWP and the pulmonary vascular behaviour as characterized by the RC-time product. Cross-sectional studies have demonstrated that PVR and PAC are coupled in a hyperbolic relationship(6,7). Tedford showed that higher PAWP is associated with lower RC-time and downward shift of RC-time hyperbolic relationship(6). Using a similar protocol, we have demonstrated that in health, RC-time decreased in direct correlation to exercise-mediated increases in PAWP(5). By contrast, in the present study we observed that *Exercise* resulted in increases in RC-time despite the increase in PAWP and HR, and no relationship was discernable between these variables. The paradoxical effect to increase RC-time was more notable with *Exercise* than with *Volume*. Pulmonary circulatory dysfunction in the patient population is a possible factor that underlies the lack of coupling between left heart filling pressures and the behaviour of RC-time. Our data are in contrast with a study in which RC-time declined with exercise in PAH (7). However, in contrast to our protocol, these investigators employed an estimation of left atrial pressure that did not

significantly change with exercise. More data would be needed to resolve this discrepancy.

Our preliminary findings may inform the understanding of using provocative manoeuvres to differentiate PAH from pulmonary hypertension due to left sided heart diseases (PH-LHD). There is considerable demographic overlap between PAH and PH-LHD (and resting hemodynamic criteria alone may be insufficient to differentiate both(2,8–10). Our observations are complementary to the study from Andersen (11), in which exercise was a more sensitive stimulus compared to volume expansion in HFpEF, eliciting greater increases in PAWP. In our study, PAWP responses to exercise were clearly normal(12), while exercise was a more potent stimulus of abnormal pulmonary vascular responses compared to volume. Hence, exercise can differentiate normal from abnormal PAWP responses, and also demonstrate whether PAWP responses remain coupled to pulmonary vascular responses.

Our study has limitations. Despite distinct pulmonary vascular responses elicited by the studied interventions, this sample is small and our study findings are hypothesis generating. *Volume* preceded *Exercise* in our study and this could potentially alter preload conditions. However, hemodynamic effects of *Volume* were no longer evident by the time participants were transferred to the cycle-ergometer. RC-time was calculated from a simplified equation, rather than from actual PVR and PAC measurements. Nonetheless, although we speculate that observed paradoxical RC-time during exercise is related to PVR increase at exercise, our data precludes definitive conclusion on this aspect.

In conclusion, in this pilot observation, among patients with PAH, exercise and volume challenges similarly confirmed physiologic PAWP responses. However, exercise more potently elicited pulmonary vascular abnormalities, and demonstrated a paradoxical increase in RC-time during exercise.

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Table 1. Hemodynamic Changes Induced by *Exercise* versus *Volume*

Variable	Δ Exercise	Δ Volume	p
HR (bpm)	37 [24]	6 [13]	0.04
RAP (mmHg)	7 [6]	7 [12]	1.0
PASP (mmHg)	42 [28]	6 [29]	0.04
PADP (mmHg)	19 [10]	4 [10]	0.04
mPAP (mmHg)	29 [15]	9 [20.5]	0.04
PAWP (mmHg)	7 [11]	9 [18]	0.34
Pulmonary PP (mmHg)	21 [18]	-1 [21]	0.04
DPD (mmHg)	5 [9]	-3 [7]	0.04
TPG (mmHg)	32 [16]	5 [11]	0.04
PAWP/RAP ratio	-0.22 [1.17]	0.42 [0.63]	0.14
RC-time (s)	0.32 [0.26]	0.02 [0.16]	0.04