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

To the Editor:

The contemporary population of patients with pulmonary arterial hypertension (PAH) are older, with a 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 behaviour of pulmonary artery 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 the 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 pulmonary artery pressures and RC-time.

Adults with PAH aged >45 years referred for right heart catheterisation were recruited. Exclusion criteria included left ventricular systolic dysfunction (left ventricular ejection fraction <50%) or ≥ moderate left-sided valvular heart disease. The local research ethics board approved the study protocol. Participants provided written informed consent.

A balloon-tipped fluid-filled catheter was positioned in the pulmonary artery *via* internal jugular venous access. Right atrial pressure (RAP), pulmonary artery pressures (PAP) 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 15 mL·kg⁻¹ of 0.9% sodium chloride solution at 100 mL·min⁻¹. Haemodynamic data were recorded 1 min after completing Volume. Afterwards, participants were transferred to a cycle ergometer in a semi-upright position. Haemodynamic data were acquired at 1, 3 and 5 min at rest (Control) and averaged. Participants then pedalled at self-selected cadence between 60 and 80 xg at constant a work-rate of 15 watts. Haemodynamic data were obtained at 3 min after onset of cycling (Exercise).

Analysis intervals consisted of ≥10 consecutive beats free from premature beats. Calculations included: pulmonary pulse pressure (pulmonary PP; mmHg) = pulmonary artery systolic pressure (PASP) – pulmonary artery diastolic pressure (PADP); transpulmonary gradient (TPG; mmHg) = mean pulmonary artery pressure (mPAP) – PAWP; diastolic pressure difference (DPD; mmHg) = PADP – PAWP; 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×PP). Changes in RAP and PAWP, relative to volume infused, were assessed by the slopes of RAP/volume infused and PAWP/volume infused relations.

Data were analysed 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.

@ERSpublications

In this study, among patients with pulmonary arterial hypertension, exercise was more potent in eliciting pulmonary vascular abnormalities and demonstrated paradoxical increase in RC-time
<https://bit.ly/35Mb0dv>

Cite this article as: Valle FH, Esfandiari S, Jang H-J, *et al.* Contrasting haemodynamic effects of exercise and saline infusion in older adults with pulmonary arterial hypertension. *ERJ Open Res* 2021; 7: 00183-2020 [<https://doi.org/10.1183/23120541.00183-2020>].

Copyright ©ERS 2021. This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.

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 by 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⁻¹ and 8 (4) mmHg·L⁻¹, respectively. HR, RAP, systolic pulmonary artery pressure (SPAP), diastolic pulmonary artery pressure (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.

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 PAP and HR. We also examined the behaviour of the pulmonary vasculature as characterised 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 pulmonary artery pressure responses.

We explored the relationship between the changes in PAWP and the pulmonary vascular behaviour as characterised 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 the 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.

TABLE 1 Haemodynamic changes induced by Exercise *versus* Volume

Variable	Δ Exercise	Δ Volume	p-value
Heart rate beats·min ⁻¹	37 [24]	6 [13]	0.04
RAP mmHg	7 [6]	7 [12]	1.00
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 pulse pressure 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

Data are presented as median [interquartile range], unless otherwise stated. RAP: right atrial pressure; PASP: pulmonary artery systolic pressure; PADP: pulmonary artery diastolic pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; DPD: diastolic pressure difference; TPG: transpulmonary gradient; RC-time: resistance-compliance relationship.

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 haemodynamic criteria alone may be insufficient to differentiate both) [2, 8–10]. Our observations are complementary to the study by ANDERSEN *et al.* [11], in which exercise was a more sensitive stimulus compared to volume expansion in heart failure with preserved ejection fraction, 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, haemodynamic 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 physiological PAWP responses. However, exercise more potently elicited pulmonary vascular abnormalities and demonstrated a paradoxical increase in RC-time during exercise.

Felipe H. Valle¹, Sam Esfandiari¹, Ho-Jun Jang², Felipe C. Fuchs³, Stephen P. Wright¹, John Granton⁴ and Susanna Mak¹

¹Division of Cardiology, Mount Sinai Hospital/University Health Network, Toronto, Canada. ²Division of Cardiology, Sejong General Hospital, Bucheon-si, Republic of Korea. ³Division of Cardiology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. ⁴Division of Respiriology, University Health Network, Toronto, Canada.

Correspondence: Susanna Mak, Division of Cardiology, Mount Sinai Hospital, Rm 18-365, 600 University Avenue, Toronto, Ontario, Canada, M5G 1X5. E-mail: susanna.mak@sinahealthsystem.ca

Received: 10 April 2020 | Accepted: 5 Nov 2020

Conflict of interest: F.H. Valle has nothing to disclose. S. Esfandiari has nothing to disclose. H-J. Jang has nothing to disclose. F.C. Fuchs has nothing to disclose. S.P. Wright has nothing to disclose. J. Granton has received support through his foundation from unrestricted grants from Bayer and Janssen Pharmaceuticals to support research, quality improvement projects and development of educational tools. He has also received payment for participation in steering and adjudication committees of clinical trials sponsored by United Therapeutics and Bellerophon. S. Mak reports grants from the Heart and Stroke Foundation of Canada and the Ontario Research Fund during the conduct of the study, and philanthropic donations for equipment from the Sinai Foundation outside the submitted work.

References

- 1 Badesch DB, Raskob GE, Elliott CG, *et al.* Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest* 2010; 137: 376–387.
- 2 Hoeper MM, Lam CSP, Vachiery J-L, *et al.* Pulmonary hypertension in heart failure with preserved ejection fraction: a plea for proper phenotyping and further research. *Eur Heart J* 2017; 38: 2869–2873.
- 3 D'Alto M, Romeo E, Argiento P, *et al.* Clinical relevance of fluid challenge in patients evaluated for pulmonary hypertension. *Chest* 2017; 151: 119–126.
- 4 Berry NC, Manyoo A, Oldham WM, *et al.* Protocol for exercise hemodynamic assessment: performing an invasive cardiopulmonary exercise test in clinical practice. *Pulm Circ* 2015; 5: 610–618.
- 5 Wright SP, Granton JT, Esfandiari S, *et al.* The relationship of pulmonary vascular resistance and compliance to pulmonary artery wedge pressure during submaximal exercise in healthy older adults. *J Physiol* 2016; 594: 3307–3315.
- 6 Tedford RJ, Hassoun PM, Mathai SC, *et al.* Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. *Circulation* 2012; 125: 289–297.
- 7 Bellofiore A, Dinges E, Naeije R, *et al.* Reduced hemodynamic coupling and exercise are associated with vascular stiffening in pulmonary arterial hypertension. *Heart* 2017; 103: 421–427.
- 8 Galiè N, Barberà JA, Frost AE, *et al.* Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 834–844.
- 9 Guazzi M. Pulmonary hypertension in heart failure preserved ejection fraction. *Circ Heart Fail* 2014; 7: 367–377.
- 10 Vachiery J-L, Tedford RJ, Rosenkranz S, *et al.* Pulmonary hypertension due to left heart disease. *Eur Respir J* 2019; 53: 1801897.
- 11 Andersen MJ, Olson TP, Melenovsky V, *et al.* Differential hemodynamic effects of exercise and volume expansion in people with and without heart failure. *Circ Heart Fail* 2015; 8: 41–48.
- 12 Esfandiari S, Wolsk E, Granton D, *et al.* Pulmonary arterial wedge pressure at rest and during exercise in healthy adults: a systematic review and meta-analysis. *J Card Fail* 2019; 25: 114–122.