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Performance under pressure: The relevance of pulmonary vascular response to exercise challenge in scleroderma

Silvia Ulrich¹, Stephen C. Mathai²

¹Clinic of Pulmonology, University Hospital Zurich, Zurich, Switzerland

²Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, USA

Corresponding Author:

Prof. Dr. med. Silvia Ulrich

Clinic of Pulmonology

University Hospital Zurich

Raemistrasse 100

8091 Zürich, Switzerland

silvia.ulrich@usz.ch

Pulmonary arterial hypertension (PAH) affects up to 10% of patients with systemic sclerosis (SSc) and is a leading cause of morbidity and mortality in this devastating disease.(1, 2) PAH in SSc has an even worse prognosis than idiopathic PAH and targeted therapies are less effective.(3, 4) Efforts have been directed towards early diagnosis of PAH in SSc with the idea that starting treatment prior to extensive pulmonary vascular remodelling may slow or prevent right ventricular dysfunction, which is the primary determinant of outcomes in PAH. (5-7) As shown by Hsu and colleagues, SSc patients with mildly elevated pulmonary arterial pressures (PAP) have impaired myocardial sarcomere function compared to idiopathic PAH patients, suggesting RV dysfunction occurs with early pulmonary vascular disease and may be more profound in SSc patients. (8)Further, recent studies have demonstrated the impact of mildly elevated pulmonary pressures on outcomes in various disease states, including SSc. These findings have led to recent revisions in the diagnostic criteria for PAH, lowering the mean PAP threshold to 20 mmHg. (9-11) However, in SSc, mildly elevated pulmonary vascular resistance (PVR) also seems to portend a poor prognosis, but this has not yet been incorporated into diagnostic guidelines.(12) While screening programs including different measures and algorithms have been established in many centres caring for SSc patients worldwide in order to detect PAH earlier (6, 7, 13), none of these have been designed to detect mildly elevated PAP (mPAP > 20 mmHg) or PVR (PVR > 2 Wood units) that have important clinical impact. A potentially valuable tool to early detect pulmonary vascular disease in patients at risk for PAH, such as SSc, is to assess pulmonary hemodynamics during exercise(14-16).

Exercise stresses the pulmonary vasculature by progressively increasing cardiac output and consequently pressure with augmenting pulmonary vascular load(17). Nature elegantly addressed this vital challenge by equipping the pulmonary circulation with sufficiently low resistance and high compliance to accommodate the entire cardiac output even with maximal exercise (18). Recruitment and distension of the pulmonary vessels lead to decreased PVR with exercise (17, 19), however, the exact underlying mechanisms regulating these responses are still unknown. These adaptive responses are designed to overcome additional escalation of PVR related to stretching of the pulmonary vasculature from increasing lung volume at exercise (18). PAH is characterized by vasoconstriction of pulmonary artery smooth muscles, vascular remodelling, and endothelial cell proliferation (20) leading to elevated PVR at rest. With exercise, PVR increases further, most likely due to

insufficient distention and recruitment of the diseased vessels(14). An abnormal pulmonary hemodynamic response on exercise has been defined as an increase of the $mPAP > 30$ mmHg combined with an $mPAP/CO$ (total pulmonary resistance, TPR) > 3 WU at peak exercise (15, 16). An increase in $mPAP/CO$ on exercise has been found to be associated with impaired survival in a large cohort of dyspnoeic patients assessed by RHC(21) and in patients with pulmonary arterial and distal chronic thromboembolic pulmonary hypertension(22). SSc-patients fulfilling the above diagnosis of exercise PAH have a similarly impaired survival as SSc with PAH diagnosed according to resting hemodynamics (23).

In the current issue of the CHEST, Zeder K et al. further add to this growing body of evidence emphasizing the clinical importance of exercise pulmonary hemodynamics in SSc. The authors show that both the PVR and TPR at maximal exercise and the pressure-flow slopes during exercise were independent predictors of mortality, whereas respective resting measures were not. From a physiological standpoint, these findings are plausible as it hypothesized that more than 50-70% of the pulmonary vasculature needs to be affected in order to raise the mean PAP > 25 mmHg. (24) Thus, it may be expected that early pulmonary vascular remodelling in SSc would not necessarily impact resting PAP but that increasing vascular load during exercise challenge might unmask dysfunctional pulmonary vasculature in earlier stages of disease progression. Thus, the observation that this abnormal pulmonary vascular response to exercise predicts outcomes in SSc is inherently important and suggests that more routine assessment with exercise hemodynamics may be warranted in this population. However, the larger question will be whether an early detection of pulmonary vascular disease using exercise hemodynamics and subsequent early treatment with pulmonary vasodilators will delay or prevent the progression of pulmonary vascular disease. Unfortunately, despite data suggesting efficacy of initial combination therapy in SSc-PAH,(25, 26) to date we have limited data which show that initiating PAH-targeted therapy in SSc-patients with suspected pulmonary vascular disease based upon abnormal pulmonary vascular response to exercise or borderline resting hemodynamics improves outcomes.(23, 27-29) Further, since none of currently approved therapies for PAH have been shown to affect pulmonary vascular remodelling in humans, the role of pulmonary vasodilators in early pulmonary vascular disease remains unclear. Importantly, assessing response to therapy will be challenging as outcome measures for this disease state have yet to be defined and it is unlikely that measures employed in current PAH trials, such as time to

clinical worsening, will be applicable and practical in early pulmonary vascular disease. Still, the results of this study by Zeder et al support the clinical utility of exercise RHC for the early detection of pulmonary vascular disease in SSc and highlight the need for future investigations that will identify and validate appropriate outcome measures to be employed in randomized clinical trials of therapy for SSc patients with early pulmonary vascular disease.

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