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To stress or not to stress? Exercise pulmonary haemodynamic testing in systemic sclerosis

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Exercise pulmonary hypertension may have prognostic significance in patients with systemic sclerosis http://ow.ly/qkpx304uPZE

Pulmonary arterial hypertension (PAH) is a leading cause of morbidity and mortality in systemic sclerosis (SSc) [1], and patients have a ∼10% lifetime risk of developing this devastating complication [2]. Despite targeted PAH therapy, outcomes of SSc-associated PAH (SSc-PAH) remain unsatisfactory, with a median survival of only 3–4 years from time of diagnosis [3, 4]. In the hope of further improving outcomes in SSc-PAH, early disease detection has been a major focus of research in the past decade [5–9]. One important and highly debated topic is the utility of exercise pulmonary haemodynamic testing for the early diagnosis of pulmonary vascular disease [10–12].

From a physiological viewpoint, exercise stress testing for the unmasking of early or silent pathology appears a worthwhile pursuit. The pulmonary circulation is unique in that >60% of its circulation must be obstructed before the resting mean pulmonary artery pressure (mPAP) rises above 25 mmHg [13], a value which represents the consensus threshold for the diagnosis of pulmonary hypertension (PH) [14]. Thus, there is the potential that clinically important pulmonary vascular disease is left undiagnosed using the current diagnostic criterion. Reliance on resting measurements may be very specific, but is perhaps not sensitive enough for the early diagnosis of pulmonary vascular disease. Furthermore, there is also now ample evidence to support that patients with normal resting mPAP but an abnormal pulmonary haemodynamic response during exercise (also known as exercise PH) develop symptoms of exertional dyspnoea [15–18]. So why do some experts remain circumspect or even oppose the concept of exercise haemodynamics testing of the pulmonary circulation?

Many readers will know that exercise haemodynamics were part of the definition of PH (exercise mPAP >30 mmHg) until this was officially abandoned during the Fourth World Symposium on PH (Dana Point, USA, 2008) [19] due to uncertainties regarding the upper limits of normal exercise mPAP [20]. Exercise mPAP is also dependent on age, exercise type and exercise intensity [20]. A fundamental problem of the old definition of exercise PH was related to the fact that mPAP is a flow-dependent variable. Therefore, exercise mPAP must be adjusted for cardiac output in order to avoid false positive diagnoses of exercise PH [21], where elevated mPAP is simply driven by large cardiac output increases during exercise (as would occur in athletic individuals). To address this issue, new data have been accumulated in recent years and

there is now broad agreement that a normal subject should not exceed an mPAP >30 mmHg and an mPAP/cardiac output ratio (total pulmonary resistance, TPR) >3 WU during exercise [22, 23]. Therefore, the combination of mPAP >30 mmHg and TPR >3 WU has been proposed by various authors as a suitable "interim" definition of exercise PH [16, 22–24], with perhaps the exception of elderly individuals (age >70 years) where normative data remains limited. However, high quality longitudinal studies on the natural history of exercise PH are lacking and there remains no proof, to date, that exercise PH is of prognostic importance. Notwithstanding that exercise PH is a real pathophysiological entity; current guidelines have remained very cautious and do not support the use of any haemodynamic thresholds to define exercise PH [14], until more evidence is gathered to validate any proposed new criteria.

In the current issue of the *European Respiratory Journal*, STAMM *et al.* [25] provide provocative data from their single centre study on the prognostic relevance of exercise PH in SSc. A total of 72 consecutively eligible SSc patients with a clinical suspicion of PH (due to exertional dyspnoea and/or reduced diffusing capacity of the lung for carbon monoxide (D_{LCO}) and/or a forced vital capacity (FVC)/D_{LCO} ratio >1.6) underwent diagnostic exercise right heart catheterisation (RHC) with supine incremental cycle ergometry. It was usual clinical practice in the authors' institution to perform exercise haemodynamics in all patients undergoing RHC, unless they were physically unable to exercise. Patients were stratified into three groups according to resting and exercise haemodynamic findings: 1) resting precapillary PH (mPAP ⩾25 mmHg and pulmonary artery wedge pressure (PAWP) ⩽15 mmHg at rest; n=17); 2) exercise PH (mPAP <25 mmHg at rest with mPAP >30 mmHg and TPR >3 WU at peak exercise; n=28); and 3) no PH (not fulfilling any of the former criteria; n=27). Patients with a post-capillary PH component (resting PAWP >15 mmHg or exercise PAWP >20 mmHg) and those with severe lung function impairment (FVC <60% predicted) were excluded. Patients were followed for a median of 33 months and transplant-free survivals of the three groups were compared.

The main finding of the study was that among SSc patients with normal mPAP at rest, the presence of exercise PH, using the recently proposed criteria of mPAP >30 mmHg and TPR >3 WU at peak exercise, was associated with a reduced survival compared to those with normal resting and exercise haemodynamics (no PH group). The estimated 1-, 3- and 5-year transplant-free survival rates were 100%, 93% and 82% in the exercise PH group *versus* 100%, 93% and 93% in the no PH group (p=0.043). Surprisingly, no survival difference was observed between the exercise PH and resting precapillary PH groups. Supporting the concept that progressive pulmonary vascular disease might have accounted for the worse prognosis in the exercise PH group, four out of the five deaths at follow-up in this group were due to right heart failure *versus* none in the no PH group. These results imply that exercise PH in SSc is not a benign disorder and mirror the findings of a previous UK multicentre study, which showed that 19% of patients with SSc-related exercise PH developed resting PAH at a mean follow-up of 2.3 years [4].

Although the present study by STAMM *et al.* [25] is the first demonstration that exercise PH in SSc confers prognostic significance and provides external validation of the proposed exercise PH criteria, there are important caveats. This was a relatively small, retrospective, single centre study and systematic follow-up was not part of the study protocol. Therefore, we have no knowledge of the true rate of conversion to manifest PAH (proven with RHC) in the exercise PH group. The survival curves of the exercise PH and no PH groups diverged at a follow-up time when there were only a small number of at-risk subjects remaining, which may limit the robustness of the results. The no PH group was significantly younger than the exercise PH group, which could have influenced the observed survival difference. The results of this study strictly pertain to a selected population of SSc patients who underwent RHC for clinical suspicion of PH, and are not generalisable to other population groups. Importantly, it is likely that the natural history and outcomes of exercise PH are disease specific. For example, we do not know whether the same abnormal exercise pulmonary haemodynamic response has different prognostic implications in SSc, chronic thromboembolic disease, lung disease or asymptomatic carriers of a PAH-causing mutation.

The haemodynamic findings of the study warrant some discussion. By definition, the no PH group did not reach mPAP >30 mmHg and TPR >3 WU at peak exercise. However, when analysed by multipoint mPAP–cardiac output plots, the no PH group displayed unusually steep mPAP–cardiac output slopes with an average slope of 3.7 WU. A subject with an mPAP–cardiac output slope of >3 WU will usually reach exercise mPAP >30 mmHg and TPR >3 WU, unless exercise is curtailed prematurely before peak exercise [26]. Another important observation is that the exercise PH group displayed a higher median exercise PAWP compared with the no PH group (16 *versus* 11 mmHg), despite comparable resting PAWP values. Occult left heart disease is common in SSc [27] and although patients with an exercise PAWP >20 mmHg were excluded from the present study, an exercise-induced rise in PAWP contributed, in part, to the abnormal mPAP response seen in the exercise PH group. This is a salient point since exercise PH can result from increased pulmonary vascular resistance (due to pulmonary vascular disease) and/or increased

left atrial pressure (due to left heart disease). This can be especially problematic in SSc where both mechanisms may coexist and contribute to the development of exercise PH.

Although SSc has been the most studied population, exercise haemodynamics are of potential relevance in other at risk groups. Of particular interest are asymptomatic carriers of PAH-causing mutations. Carriers of bone morphogenetic protein receptor type 2 (BMPR2) gene mutation, the most common cause of heritable PAH, have a ∼20% lifetime risk of developing PAH [28]. A prospective screening study of asymptomatic BMPR2 mutation carriers has now completed recruitment (DELPHI-2 study; clinicaltrials. gov identifier number: NCT01600898) and will inform on the predictive value of invasive exercise haemodynamics for the future occurrence of PAH in this population.

Should patients with exercise PH be offered PAH therapy? Interestingly, targeted PAH treatment was administered to 16 (57%) patients with exercise PH in the present study. No significant improvement in 6-min walking distance was observed at 3-month follow-up, and the authors acknowledge that PAH therapy was used strictly off-label at the discretion of the treating physicians. Based on the lack of high-quality efficacy data [29, 30], the use of PAH therapy for exercise PH cannot be recommended at present.

STAMM et al. [25] are to be congratulated for executing a study that provides evidence, for the first time, that exercise PH in SSc is of potential prognostic relevance. Clinicians and researchers who believe in the importance of exercise pulmonary haemodynamics have eagerly awaited such studies. In recognition of the ongoing interest and unresolved questions in this field, the European Respiratory Society has formed an expert multidisciplinary task force to evaluate the scientific knowledge and evidence base for exercise pulmonary haemodynamic testing, and to identify priority areas for future research. A particular focus of the task force is to evaluate the methodology of invasive haemodynamic testing, since a uniform testing methodology is a prerequisite for any future definition of exercise PH and is fundamental for multicentre collaborations, which are likely to be needed to achieve major scientific advancement.

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