Unmasking hidden disease: exercise pulmonary haemodynamics in systemic sclerosis

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Although pulmonary arterial hypertension (PAH) is a rare condition in the general population, it is not uncommon in systemic sclerosis (SSc), with a prevalence of 9% [1]. Furthermore, survival in patients with PAH associated with SSc (SSc-PAH) is worse than in those with idiopathic PAH, even when accounting for their older age [2–4]. As a result, patients with SSc are the main "at-risk" patient group who undergo widespread screening for the presence of PAH. Patients identified with SSc-PAH as a result of screening appear to have less severe disease and better survival than those who are diagnosed following symptomatic presentation [5]. If PAH results from progressive loss of the pulmonary arterial bed, and over 50% of this vasculature needs to be obstructed before pulmonary hypertension (PH; as defined by a resting mean pulmonary arterial pressure (mPAP) $\geqslant$25 mmHg) develops, then there is a good rationale for the use of exercise to unmask hidden pulmonary vascular disease.

Prior to the 4th World Symposium on Pulmonary Hypertension (2008, Dana Point, CA, USA), exercise-induced PH was defined as a mPAP during exercise of >30 mmHg. A review of exercise haemodynamics of 404 healthy volunteers demonstrated that mPAP at exercise exceeded 30 mmHg at maximal exercise in 21% of volunteers <50 yrs old, and at slight exercise in 47% of volunteers >50 yrs old [6]. Thus, the diagnosis of exercise-induced PH was dropped. Over the last few years several papers have been published which have increased our understanding of normal and abnormal pressure responses to exercise. Pressure is flow-dependent, and a review of published literature up to 2013 demonstrated that the relationship between mPAP and cardiac output (CO) does not exceed 3 mmHg·min·L^{-1} in normal subjects, equivalent to a total pulmonary resistance (TPR=mPAP/CO) of <3 Wood units (WU) [7, 8]. Herve *et al.* [9] subsequently studied 169 patients and found that a combination of mPAP >30 mmHg and TPR >3 WU at maximal exercise was highly sensitive for distinguishing between healthy subjects and those with pulmonary vascular disease or left heart disease. Kovacs *et al.* [10] applied these new proposed criteria for exercise PH to a cohort of 1187 healthy volunteers from the literature, and observed a fall in false positive rates from 13.7 to 2.5%. Stamm *et al.* [11] subsequently studied 72 SSc patients and observed poorer transplant-free survival in those patients with TPR >3 WU and mPAP >30 mmHg at peak exercise, compared with those with normal haemodymics at rest and on exercise. Their observations that exercise PH in SSc is not a benign condition were consistent with previous data from the UK registry, which observed progression to resting PAH in 19% of patients with mPAP >30 mmHg on exercise [12].

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It appears, therefore, that exercise is useful in revealing the *presence* of hidden "sub-clinical" pulmonary vascular disease. Can exercise also provide an insight into the *progression* of sub-clinical pulmonary vascular disease? In the current issue of the *European Respiratory Journal*, Kovacs *et al.* [13] present data on 99 patients with scleroderma-spectrum disease who underwent exercise echocardiography during cardiopulmonary exercise testing. 58 patients underwent repeat exercise echocardiography (after a mean of 3.9 years) while 28 of these also underwent baseline and follow-up right heart catheterisation. Patients with left ventricular systolic and diastolic dysfunction, significant valvular disease or uncontrolled systemic hypertension were excluded. The primary end-point was the change in systolic pulmonary arterial pressure (sPAP) at 50 W between baseline and follow-up exercise echocardiography. Patients had resting sPAP well within normal limits (median (interquartile range) 25 (22–27) mmHg) and relatively well-preserved diffusing capacity of the lung for carbon monoxide (*D*LCO) (median 82% (65–94%)). Although there was no change in resting sPAP between baseline and follow-up echocardiography, there was a significant increase in the primary end-point of sPAP at 50 W exercise. Furthermore, at follow-up exercise testing, peak oxygen consumption fell significantly while ventilatory equivalent for CO_2 (a marker of dead space ventilation) and N-terminal pro-brain natriuretic peptide rose significantly. In the subgroup of patients who also underwent follow-up right heart catheterisation, there was similarly no change in resting haemodynamics, while mPAP and pulmonary vascular resistance at 50 W and the mPAP/CO slope all rose at follow-up catheterisation. Three of 99 patients were diagnosed with PAH during the follow-up period, equivalent to an incidence of 0.75 per 100 patient years, which is similar to that observed elsewhere [14].

There are some important limitations to this new data. The overall sample size was quite small and only 58 out of 99 patients underwent follow-up exercise echocardiography, although the baseline characteristics of those who did not undergo follow-up investigations were similar to the 58 who did. The number of patients undergoing repeat right heart catheterisation was even smaller. Exaggerated increases in PAP on exercise may occur not only as a result of increased pulmonary vascular resistance (due to pulmonary arterial disease), but also due to increased left atrial pressure (due to left heart disease). Interestingly, the number of patients with a pulmonary arterial wedge pressure (PAWP) >20 mmHg at exercise rose from seven out of 28 at baseline to 12 of 28 at follow-up right heart catheterisation, raising the possibility of progression of left heart disease. However, although the mPAP/CO slope increased significantly between baseline and follow-up there was no change in the PAWP/CO slope, suggesting that the progression in exercise PAP over time was indeed likely driven by progression in pulmonary vascular disease.

In general the findings of the current study reinforce the notion that assessing haemodynamic and physiological response to exercise can unmask abnormalities not appreciated by merely assessing resting variables. They also suggest a tendency to progressive pulmonary vascular disease in patients with SSc, even in those with unremarkable resting echocardiography and *D*LCO.

When discussing exercise haemodynamics in SSc a further group of patients merit mention. Although a threshold of 25 mmHg is used to define PH, a review of 1187 healthy volunteers in the literature identified the upper limit of normal resting mPAP (as defined by mean +2 standard deviations) of 20.6 mmHg [6]. Patients with a resting mPAP of 21–24 mmHg may, therefore, be described as having borderline pulmonary haemodynamics [15]. It would appear that presence of borderline pulmonary haemodynamics is also not a benign condition. Valerio *et al.* [16] observed that SSc patients with borderline haemodynamics had a significantly increased risk of developing PAH when compared with those with resting mPAP of ⩽20 mmHg and had a 3-year mortality of 18%. Perhaps not surprisingly, there is significant overlap between those patients with borderline haemodynamics and exercise PH. Lau *et al.* [17] studied 290 patients with mPAP <25 mmHg. They observed increasing rates of exercise PH with increasing resting mPAP, with 86% of patients with resting mPAP 21–24 mmHg fulfilling the proposed criteria of exercise PH.

Currently there are limited and conflicting data regarding the efficacy of PAH-specific therapy in SSc patients with evidence of pulmonary vascular disease who do not meet current criteria for PAH [11, 18, 19]. Given the data published in recent years, an adequately powered multicentre randomised controlled trial of PAH therapy in SSc patients with exercise PH and/or borderline pulmonary haemodynamics using exercise physiology, symptoms and development of PAH as end-points is warranted. Before this can happen an agreement on what constitutes an abnormal left atrial pressure response to exercise is needed. This definition may include a combination of a threshold for PAWP on exercise, the PAWP/CO slope and echocardiographic features of left ventricular diastolic and systolic function. The European Respiratory Society has formed a task force on exercise pulmonary haemodynamics and it is hoped that their recommendations will help stimulate agreement on a suitable definition.

In summary, the current study adds to our understanding of the natural history of pulmonary vascular disease in SSc and further highlights the ability of exercise to unmask hidden physiological abnormalities.

The time is now ripe for a randomised trial of PAH-specific therapy in patients with evidence of pulmonary vascular disease (exercise PH and/or borderline haemodynamics) who do not meet the current definition of PAH.

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