Identifying early pulmonary arterial hypertension in patients with systemic sclerosis

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Pulmonary arterial hypertension (PAH) is a life-shortening complication of systemic sclerosis (SSc) with a life-time prevalence of approximately 10% [1, 2]. It is currently defined by the presence of a mean pulmonary arterial pressure (mPAP) ⩾25 mmHg with a pulmonary arterial wedge pressure (PAWP) ⩽15 mmHg and a pulmonary vascular resistance (PVR) >3 WU, in the absence of significant lung disease or chronic thromboembolic disease. Other forms of pulmonary hypertension (PH) may also quite commonly exist in SSc patients, including PH due to left heart disease or lung disease. It is widely agreed that identifying patients with SSc who also have PAH (SSc-PAH) earlier in their disease process is likely a good idea with the presumption that earlier diagnosis leads to earlier treatment, which hopefully leads to better outcomes. Certainly, previous data have demonstrated superior survival in patients with SSc-PAH identified by screening when compared with patients presenting due to symptoms [3]. Over the past few years several groups have investigated the optimal way of screening SSc patients for the presence of PAH, most notably the DETECT investigators [4]. The DETECT study demonstrated that in a population of SSc patients enriched for the likely presence of PAH (by including patients only with a diffusion coefficient for carbon monoxide, *D*LCO, <60% predicted), a two-step algorithm including electrocardiographic, echocardiographic and laboratory biomarkers selecting patients to undergo right heart catheterisation (RHC) had greater sensitivity than echocardiography alone in identifying patients with PH. Superiority in clinical practice in non-enriched populations of SSc patients when compared to approaches combining echocardiography, trends in *D*LCO and clinical history has not been clearly demonstrated [5]. Nevertheless, the DETECT algorithm has been a welcome introduction in stimulating efforts to identify SSc-PAH patients at an earlier stage.

If a patient with suspected SSc-PAH does undergo RHC and is found to have a mean pulmonary arterial pressure (mPAP) below the current threshold for diagnosing PH (25 mmHg) then how should they be screened in the future? The answer to this question will depend on several factors, including the annual incidence of PAH in patients known to have mPAP <25 mmHg and whether any factors which convey an increased risk of the development of PAH can be identified. In the current edition of the *European Respiratory Journal*, Coghlan *et al.* [6] explore this issue in more detail. In their study, 76 patients found to have mPAP <25 mmHg in the original DETECT cohort from two centres (London and Heidelberg)

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were followed and reassessed after 3 years. To augment study numbers, 20 further DETECT-eligible SSc patients without PH were also enrolled, producing an initial study number of 96. 13 patients were lost to follow-up while a further 12 patients refused repeat RHC, leaving 71 patients with follow-up RHC at 3 years. Several findings of note were observed. First, 18/71 patients (25%) developed PH during follow-up with an annual incidence of 6.1%. This is significantly higher than the annual incidences of between 0.75% and 1.85% identified by three previous groups [7–9]. As the authors point out, these studies repeated RHC only in patients in whom symptoms or TRV suggested the development of PH. Furthermore, the mean *D*LCO in these previous studies (71–82%) was significantly higher than in the current study (49%). It is likely that patients referred to renowned tertiary specialist centres are a pre-selected group of patients at higher risk of PH than in more unselected cohorts of SSc patients. The figure of 6.1% should therefore be taken as the upper limit of the annual incidence of PH in patients and specifically relates to patients known to have a reduced *D*LCO.

Second, of the 18 patients who developed PH at repeat RHC, only five were deemed to have developed PAH, with five patients developing PH due to left heart disease and eight PH due to lung disease. Although in clinical practice distinguishing between PAH and PH due to lung disease in a condition in which a degree of pulmonary fibrosis is common is difficult, these data suggest that evaluation both of features suggestive of possible post-capillary PH (such as enlargement of the left atrium and estimates of left atrial filling pressure at echocardiography) and of the severity of lung disease may affect the decision to repeat the RHC.

Third, worsening in several parameters reflecting progressive pulmonary vascular disease (including exercise capacity, *D*LCO, N-terminal pro-brain natriuretic peptide (NT-proBNP), tricuspid regurgitant velocity measured at echocardiography (TRV), mPAP and PVR) was observed during the study period. A recent study involving 58 SSc patients with baseline and follow-up assessment (28 of whom also had follow-up RHC) observed worsening in NT-proBNP and peak oxygen uptake but no change in mPAP or cardiac output at rest [9]. The more pronounced deterioration in parameters reflecting pulmonary vascular disease in the current study may reflect the fact that this cohort was enriched for patients with a low *D*LCO, as well as the larger number of patients assessed.

Fourth, the important predictors of the subsequent development of PH were identified as higher pulmonary vascular resistance at baseline RHC as well as higher TRV, lower *D*LCO and a dilated inferior vena cava.

Although current European Respiratory Society/European Society of Cardiology guidelines use a threshold of $\geqslant$25 mmHg to define PH [10], there has been increasing recognition that patients with mPAP 21–24 mmHg, especially those with SSc, may represent a distinct group of patients with an increased likelihood of underlying pulmonary vascular disease (and increased mortality) compared to patients with mPAP $\leqslant$20 mmHg [11–14]. In keeping with this, patients with mPAP 21–24 mmHg in the current study had a lower exercise capacity and *D*LCO and worse pulmonary haemodynamics than patients with mPAP $\leqslant$20 mmHg.

COGHLAN *et al.* [6] are to be congratulated for their study which provides further evidence for the presence of progressive pulmonary vascular disease in a proportion of SSc patients who do not meet current diagnostic criteria for PH. On the basis of their data the clinician should have a low threshold for recommending interval RHC in patients with baseline features (such as high PVR and low *D*LCO) suggestive of an increased risk of future PAH. This decision should be influenced by any progression in noninvasive investigations over time (such as *D*LCO, TRV and NT-proBNP) as well as an assessment of both symptoms and the presence of lung and left heart disease. Given that a mPAP >20 mmHg is abnormal [15], the question remains as to whether carefully selected SSc patients with mPAP 21–24 mmHg and features suggestive of a higher risk of progression to PAH (as currently defined) may benefit from PAH-specific therapy. This question needs to be answered by future prospective clinical trials.

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