




Pulmonary arterial hypertension: screening challenges in systemic sclerosis and future directions

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Screening for PAH is significant in scleroderma as it may lead to early diagnosis and initiation of therapy <http://ow.ly/TR6230aqRgq>

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Despite the advent of multiple medical therapies for pulmonary arterial hypertension (PAH), there is currently no cure available for this disease which continues to impose a very heavy burden of morbidity and mortality on afflicted patients. Survival on medical therapy is at best 7 years in patients with idiopathic PAH [1] and significantly less in patients with associated PAH (APAH), such as those with connective tissue disease (CTD) and particularly with scleroderma-associated PAH (SSc-PAH), where median survival is about 4 years.

In this context and considering the unduly high delay (in the order of years) between initial symptoms and diagnosis (typically obtained by right-heart catheterisation (RHC)), it becomes important to find strategies to detect the disease as early as possible. For obvious reasons, early detection is only feasible in populations at risk for the disease, such as those with APAH (*e.g.*, PAH complicating CTD or HIV) and other diseases from groups 2 (*e.g.*, heart failure) and 3 (owing to lung disease) of the pulmonary hypertension (PH) classification. Among these “diseases at risk for PAH”, scleroderma (SSc) is quite unique in two important aspects: 1. the prevalence of PAH in a general cohort of SSc patients is quite high (8–12%) compared to other similar “at risk” diseases (*e.g.*, the prevalence of PAH in HIV is less than 1%) and, 2. when afflicted with PAH, the survival of these patients is significantly curtailed compared to SSc patients who remain free from pulmonary vascular disease. Deaths due to PAH and pulmonary fibrosis, often complicated by PH, together account for up to 60% of all SSc-related deaths [2].

The importance of PAH detection in SSc patients is thus obvious and early diagnosis and initiation of appropriate PAH-specific therapy might potentially limit disease progression and improve survival rates. The PHAROS [3] and the ItinerAIR [4] SSc registries have both demonstrated that screening of SSc patients allows for early detection and potentially results in a significantly higher 3-year survival rate [4]. Whilst the best screening approach for SSc-PAH remains debatable, there is general expert consensus that screening should be considered in SSc patients on their initial visit with re-evaluation during interval visits thereafter. The current 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines [5], as compared to the 2009 guidelines, recommend that all patients with SSc-spectrum disorders be screened

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for PAH at initial evaluation with pulmonary function tests including single-breath diffusing capacity of the lung for carbon monoxide ($DLCO$), transthoracic echocardiography and N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement. Guidelines for RHC now require either a tricuspid regurgitant velocity (TRV) of $>3.4 \text{ m}\cdot\text{s}^{-1}$ or of $2.8\text{--}3.4 \text{ m}\cdot\text{s}^{-1}$ in the presence of symptoms.

The DETECT study by COGHLAN [6] was the first to address the issue of missed PAH diagnoses in 466 high-risk SSc patients ($DLCO <60\%$; duration of disease >3 -years). A DETECT two-step-algorithm outperformed the earlier 2009 ESC/ERS guidelines as a screening tool for RHC and demonstrated the limited utility of two components of the 2009 guidelines: symptoms (dyspnoea) which did not discriminate between PAH and PH and TRV alone, which would have missed 20% of PAH patients when using a PAH suspicion threshold of $\geq 2.5 \text{ m}\cdot\text{s}^{-1}$, 36% of PAH patients with a threshold of $>2.8 \text{ m}\cdot\text{s}^{-1}$ and 63% of PAH patients with a threshold of $>3.4 \text{ m}\cdot\text{s}^{-1}$. When applied to the DETECT cohort, the 2009 ESC/ERS guidelines missed 29% of PAH diagnoses compared to 4% using the DETECT tool, a considerable difference in the false-negative rate [6].

In this issue of the *European Respiratory Journal*, VANDECASTEELE *et al.* [7] prospectively compare the 2009 ESC/ERS guidelines to the DETECT algorithm in an unselected consecutive cohort of SSc patients irrespective of their risk factors or extent of skin involvement, a real-life clinical situation of a diverse population followed at an SSc referral centre at Ghent University Hospital in Belgium. In their cohort of 195 patients, out of 63 patients referred for RHC, referral was 46 (73%) using the DETECT algorithm alone, four (6%) using the 2009 ESC/ERS guidelines alone, and 34 (17%) and 40 (21%) using the 2015 echo-screening and 2015 combined-screening guidelines, respectively, in a *post-hoc* analysis. Only three patients were diagnosed with PAH, with RHC recommended by all of the examined screening algorithms. The results demonstrated a positive predictive value of 6% using the DETECT algorithm compared to 18% using the 2009 guidelines (and 11% and 9% using the 2015 echo-screening and combined-screening guidelines, respectively). The authors demonstrate improved cost-effectiveness of the 2009 guidelines compared to the DETECT tool, concluding that echocardiography remains the preferred first step for PAH screening in SSc patients.

To date, the DETECT algorithm has not been validated in patients with a $DLCO$ value of $>60\%$ of predicted and such patients constitute more than 75% of the Vandecasteele cohort (median=76%; interquartile range: 63.25–87). It is therefore not surprising that the positive predictive values of patients referred for RHC by the 2009 guidelines and the 2015 echo-screening and combined-screening guidelines are greater than that of the DETECT algorithm in this unselected group of SSc patients. This study demonstrates the superior screening performance, from a cost-analysis point of view, of the 2009/2015 guidelines (compared to DETECT) regardless of SSc patients' risk status and also their reliability for specific detection of PAH. Some obvious limitations of the study include the lack of data on sensitivity, specificity and the negative predictive value of the screening algorithms (since RHC was not applied to the whole cohort), the paucity of patients diagnosed with PAH (a total of three), and the *post-hoc* analysis of the 2015 ESC/ERS guidelines (as these were only published after initiation of the study [5]).

This study further emphasises the value of echocardiography in screening patients with SSc. Echocardiography is readily available although it has its own important limitations, including high dependency on the operator/interpreter, over-estimation or under-estimation of systolic pulmonary arterial pressure (PAP) [8], and false-negative and false-positive results. In this respect, GLADUE [9] has demonstrated that the use of echocardiography alone fails to diagnose PAH in up 31% of subjects in a large cohort of SSc patients, half of whom were eventually captured by combining echocardiographic results with pulmonary function tests. Furthermore, tricuspid regurgitation may be absent in a number of patients with PH, as suggested by the DETECT study in which it was not appreciable for 7% of patients with SSc-PAH [6]. Finally, echocardiography in SSc-PAH evaluation cannot differentiate between different types of PH, an important step in treatment strategies.

One noteworthy finding by Vandecasteele *et al.* relates to the fact that 13 out of 14 cases (93%) of borderline elevated PAP were detected by RHC as recommended by the DETECT algorithm *versus* only four out of 14 cases (29%) being detected by RHC following the 2009 guidelines. In light of the PHAROS registry finding that 55% of patients with borderline elevated PAP on initial RHC go on to develop PH (but not necessarily PAH) over a follow-up period of 2 years [10], this may be an advantage in favour of the DETECT algorithm.

Finally, is early detection for more aggressive therapy in SSc-PAH justifiable? This question may have seemed overly futile just a few years ago as most large clinical trials for PAH therapies demonstrated at best a modest clinical response in SSc-PAH compared to idiopathic pulmonary arterial hypertension (IPAH). However, this state of affairs may have changed with more recent trials such as the phase III PATENT-1 study (PATENT: Pulmonary Arterial hyperTENSION sGC-stimulator Trial). In this trial riociguat, a guanylate

cyclase stimulator given to patients with CTD associated PAH, was found to improve primary end-point (6-min walk distance), World Health Organization (WHO) functional class, and haemodynamics compared to a placebo treatment [11]. In addition, the 2-year survival rate was similar (93%) for patients with CTD associated PAH compared to IPAH [12]. Of note is the fact that about 63% of patients with CTD associated PAH were on background therapy with an endothelin receptor antagonist or prostacyclin [12]. More recently, the AMBITION trial (a uniquely designed protocol which used upfront combination therapy with two U.S. Food & Drug Administration (FDA) approved drugs, ambrisentan and tadalafil, for PAH [13]) demonstrated that time to clinical worsening in patients with PAH was improved. This was mainly driven by differences in hospitalisation rates (due to worsening PAH) between either of the monotherapies and the combination therapy. In a post-hoc analysis, initial combination therapy reduced the risk of clinical failure *versus* pooled monotherapy in each subgroup of CTD associated PAH, including SSc-PAH [14].

In conclusion, efforts towards early detection of PH in SSc are worthwhile and further studies, such as the one elegantly performed by VANDECASTEELE *et al.* [7], are needed to validate the various algorithms available in the specific context of an unselected SSc population. While RHC is the gold-standard for the diagnosis of PH in SSc, echocardiography remains a well-anchored screening tool for pulmonary vascular disease under these circumstances [15].

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