Does left heart disease cause most systemic sclerosis associated pulmonary hypertension?

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In systemic sclerosis we should ask what, in this individual patient, is the driver for elevated pulmonary pressures? http://ow.ly/nwLNM

In this issue of the *European Respiratory Journal*, Fox *et al.* [1] present data that suggest most pulmonary hypertension (PH) in systemic sclerosis is post-capillary and that many patients are receiving pulmonary vasodilator therapy inappropriately. Of 53 patients identified as having PH, nearly half (24) had elevated wedge pressures, a further five had elevated left ventricular end-diastolic pressure and another six were "exposed" as having occult post-capillary abnormalities in response to a 500-mL fluid challenge administered over 5–10 min. Thus, in total, 35 (67%) out of 53 PH patients did not have pulmonary arterial hypertension (PAH). The number of patients with elevated pulmonary artery occlusion pressures (PAOP) is high when compared with other studies [2, 3] and there is no "threshold" wedge pressure that differentiates normality from cardiac disease during fluid challenge [4, 5], but this misses the bigger point. Their work illustrates the flaws in the accepted diagnostic benchmark.

These issues may seem of relevance only to rheumatologists, but as the average age of patients with idiopathic PAH increases [6], requiring diagnosis of PAH in the presence of diastolic dysfunction, and as increased numbers of patients with diastolic heart failure and PH [7] are referred for consideration of pulmonary vasodilator therapy, the same issues must be addressed by all clinicians with an interest in PH.

A haemodynamic definition of PAH was agreed by consensus in 1973 [8] to obviate the need for high risk lung biopsies it was modified in 2009 in recognition of the high variability of measured pulmonary vascular resistance to a simple requirement of mean pulmonary arterial pressure (PAP) $\geqslant$25 mmHg, plus a PAOP and/or left ventricular end-diastolic pressure (LVEDP) $\leqslant$15 mmHg, with a normal or reduced cardiac output [9].

This definition works well for classical cases, given that the average LVEDP in heart failure associated PH has been reported at 23 mmHg for a mean PAP of 34 mmHg [10], while in PAH, the PAOP is on average normal (mean of eight) for a mean PAP of >50 mmHg [6]. For borderline cases, common sense indicates that rare conditions (idiopathic PAH incidence less than four per million [11]) can be dismissed in favour of common conditions (heart failure or lung disease associated PH account for 80% of all PH).

In systemic sclerosis, no such common sense algorithm exists, as group 1 and 2 PH are both common. Cardiac magnetic resonance [12] and *post mortem* [13] studies show that the majority of systemic sclerosis patients have some cardiac involvement; thus, PAH in systemic sclerosis could become virtually impossible to diagnose if exclusion of any left heart abnormality is a prerequisite for diagnosis. The question we should be asking is what, in this individual patient, is the driver for elevated pulmonary pressures?

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Mechanistically, post-capillary PH originates from elevated left atrial pressures. The PAOP is generally slightly higher than the mean left atrial pressure [14]. PAOP and LVEDP are not identical and discrepancies occur [15]. A compliant left atrium can protect the pulmonary vasculature from elevated LVEDP, while a stiff left atrium can result in post capillary PH in the setting of a normal LVEDP [16].

Poor practice may also explain many of the discrepancies reported. In many centres, mean pressure rather than end expiratory pressure is reported. Currently, most centres report post a-wave LVEDP, which correlates with end diastolic left atrial pressure and is higher than the mean left atrial pressure [17]. In wedge position confirmation, using contrast and/or saturations are rarely mentioned, and such measures may be reassuring despite over-wedging.

A further issue is that filling pressures vary over time, yet we work with single measures as a gold standard. In the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) database, 10% of patients with an initial PAOP $\leqslant$12 mmHg had a follow-up PAOP $\geqslant$16 mmHg, while 50% of patients with an initial PAOP $\geqslant$16 mmHg had a follow-up PAOP $\leqslant$12 mmHg [18]. Diuretics may have played some role in the latter observation but we do not have any definition of optimal fluid status in patients at the time of catheterisation.

NAEIJE *et al.* [19] have proposed using the diastolic-wedge gradient as a more reliable method of distinguishing PAH from PH. This is based on evidence that as PAOP increases in experimental situations, diastolic PAP and PAOP remain nearly identical [17]. Two studies provide indirect support for this concept. TATEBE *et al.* [20] studied 676 patients with symptomatic heart failure of various causes; of these, 100 had ''passive PH'' (PAOP 21 mmHg, diastolic PAP 20 mmHg and mean PAP 30 mmHg) and 58 had reactive PH, defined as a transpulmonary gradient (TPG) >12 mmHg or pulmonary vascular resistance >2.5 Wood units (PAOP 21 mmHg, diastolic PAP 24 mmHg and mean PAP 35 mmHg). LEUNG *et al.* [10] studied patients with an LVEDP >15 mmHg and preserved left ventricular systolic function. 216 had no PH (mean PAP 20$\pm$4.1 mmHg; TPG 3.2$\pm$2.4 mmHg, suggesting a PAOP of 17.8 mmHg; LVEDP was 20$\pm$4.3 mmHg, thus higher than wedge in those without PH; in this group the diastolic PAP was 12.6 mmHg, below either wedge or LVEDP) and 239 had PH (mean PAP 34.2$\pm$7.8 mmHg; TPG 12.4$\pm$8.1 mmHg, suggesting a PAOP of 21.8 mmHg; LVEDP was 22.7$\pm$5.8 mmHg; and the diastolic PAP was 22.2$\pm$6.8 mmHg) suggesting that diastolic-wedge gradient would continue to discriminate left heart from precapillary PH. These data also suggest that where LVEDP exceeds the PAOP, this is due to preserved left atrial function protecting the pulmonary vascular tree from the impact of raised left-sided filling pressures.

We have only begun to get to grips with the complexities of diagnosing pulmonary vascular disease in the presence of left heart abnormalities. Further studies to elucidate the role of the left atrium, to understand the impact of acute fluid loading and the variability of haemodynamics over time are required.

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