Chapter 9
Increase in Pulmonary Artery Pressures

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Patient 1: Routine Follow-Up Patient

A 58-year-old female with a 10 year history of anti-centromere antibody (ACA) positive limited SSc and telangiectasias is seen for annual review. She does not volunteer a change in effort tolerance and has no new symptoms related to her SSc. Her echocardiogram report reveals an estimated pulmonary artery systolic pressure (estPASP) of 35 mmHg, the ECG shows ST depression and T-wave inversion in right precordial leads and on lung function testing she has a DLCO (diffusion capacity of carbon monoxide) of 38%. How would you manage this patient?

This is clearly a patient at risk of pulmonary arterial hypertension (PAH), while all patients with SSc are at increased risk of developing pulmonary hypertension PH, PAH domi-

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nates in limited SSc especially those that are ACA positive. In diffuse SSc PAH, post capillary PH and lung associated PH are all common [1].

This patient has been seen routinely, and we are not told of any exercise limitation. To date all trials of therapy have been in patients with at least some breathlessness on effort [2]. We have no reason to believe that the treatments are ineffective in the absence of symptoms. Most patients with SSc have some exercise limitation, but being tolerant of this simply do not exercise to the point of breathlessness [3]. Focused questioning will often reveal breathlessness and an exercise test (such as a 6-min walking test) can also be helpful. Even in the absence of symptoms, PAH is a relentless progressive disorder so unless co-morbidity is a reason one would not treat PAH, investigation should be undertaken [4] [5],.

The echocardiogram data provided seems relatively reassuring. But we are provided with minimal data. If correct a PASP of 35 mmHg would be associated with a mean pulmonary artery pressure of around 20 mmHg [6]—below the diagnostic threshold in current guidelines. However, we also know that the accuracy of estPASP is ± 40 mmHg—so pressures may be entirely normal or very elevated [7]. Cardiac involvement in SSc is common, we are not told about the size of the left atrium (LA) or diastolic or systolic parameters—so left heart issues remains on the cards.

The DLCO is very low, but no other lung function data has been provided. While low gas transfer is associated with PAH in the setting of SSc, this is also seen in lung fibrosis and emphysema—so if pressures are elevated this could be due to lung disease [8]. A low DLCO is also associated with pulmonary veno-occlusive disease [9]—which is common in SSc and rapidly lethal unless transplantation is an option.

There is therefore insufficient information to provide reassurance to this patient. Further information is required to determine the pre-test probability that the echo data supports or excludes PAH. From the ECG whether right axis deviation is present. We also need the urate and N terminal probrain natriuretic peptide (NT-proBNP) levels and FVC

(forced vital capacity), only then can we use the DETECT algorithm [10] to determine the pre-test probability of PAH for any given echocardiographic findings.

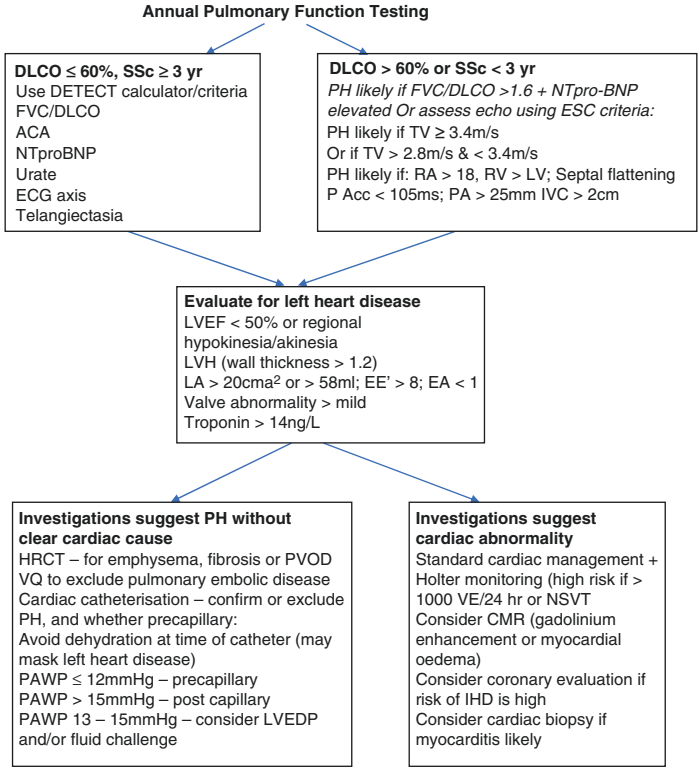
From the echocardiogram we need to know the right atrial area (the probability of PAH increases as right atrial area increases), and the triscuspid velocity (TV—estPASP includes an inaccurate estimate of right atrial pressure that increases the error significantly): above 2.3 m/s, or 22mmmHg the probability of PAH increases [10], above 3.4 m/s or est PAPS of 50 mmHg PH is highly probable irrespective of other findings [11]. It is important to also look at the left heart—reduced left ventricular ejection fraction (LVEF), left ventricular hypertrophy, valve disorders, left atrial enlargement or abnormal diastolic function all increase the likelihood that a left heart abnormality is present.

A flow-chart of how to screen and subsequently investigate for SSc PH is presented below (Fig. 9.1), an outline of management options is shown in Fig. 9.2.

Patient 2: Elevated Pulmonary Pressures with Breathlessness

A 55-year-old male with a 6 month history of diffuse Systemic Sclerosis, anti-Scl-70 positive and overlap myositis (CK 630iu) presents with breathlessness on modest exertion and palpitations. He denies any syncopal or presyncopal events. He is noted to have a persistent positive Troponin between 62 and 70 ng/L, an echocardiogram has reported LVEF of 55%, and estimated PASP of 55 mmHg. How should one proceed?

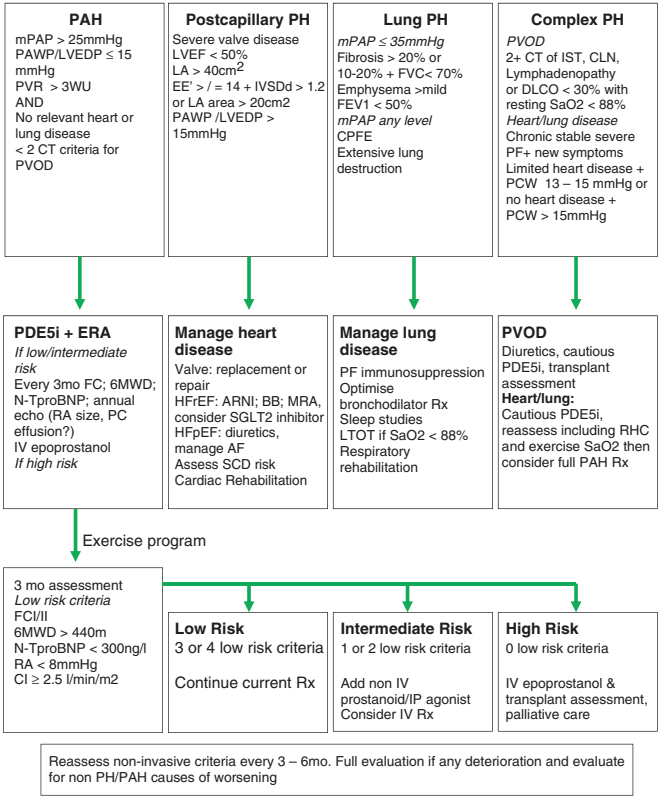
This patient may have a triscuspid velocity of 3.5 m/s and thus almost certain PH if the RA was estimated to be 5 mmHg, or <3.4 m/s if the RA is estimated as ≥10 mmHg, in which case supportive evidence of right heart abnormalities is recommended as detailed in Fig. 9.1 [2]. If PH is present, this may be due to PAH but there are pointers suggesting that postcapillary PH is more likely.



Legend. Flow chart illustrating the issues arising during screening. Patients may or may not meet criteria for DETECT, if not there is only consensus guidance on how to screen. Once echo is done as part of screening one may incidentally find cardiac abnormalities, that cannot be ignored.
ACA – anticentromere antibody status; LVEF left ventricular ejection fraction; LVH left ventricular hypertrophy; HRCT high resolution CT scanning; VQ – ventilation perfusion scan, PAWP – pulmonary artery wedge pressure; VE ventriculr ectopy; CMR cardiac magnetic resonance

FIGURE 9.1 Annual Pulmonary Function Testing

Patients with early DSSc and myositis are reported to be at higher risk of severe cardiac involvement, though it can occur in all SSc patients and at any time during the disease course [12]. Cardiac involvement is usually subclinical with minor ECG abnormalities (such as intraventricular conduction defects or loss of R wave in septal leads) [13], mild to



Legend: LVEDP - left ventricular end diastolic pressure; PVR – pulmonary vascular resistance; PAWP – pulmonary artery wedge pressure; IVSDd – interventricular septal diameter in diastole; CT computerised tomography; IST interlobular septal thickening; CLN – centrilobular nodules; PDE5i – phosphodiesterase type 5 inhibitor; ERA endothelin receptor antagonist; FC – functional class; RA – right atrium; 6MWD – six minute walking distance; ACEi – angiotensin converting enzyme inhibitors; BB – betablockers; CRT(D) – cardiac resynchronisation therapy (defibrillator); SCD – sudden cardiac death; PC – pericardial; AF – atrial fibrillation; LTOT – longterm oxygen therapy; ARNI - angiotensin receptor neprilysin inhibitor; MRA - mineralocorticoid receptor antagonist

FIGURE 9.2 Overview of SSc PH management

moderate diastolic impairment on echo [13], and cardiac magnetic resonance (CMR) scanning with wall thickness abnormalities or regional late gadolinium enhancement [14].

HFpEF (heart failure with preserved ejection fraction) is the most common form of symptomatic cardiac disease in SSc [12]. Previously this was called diastolic heart failure. In breathless patients the EE' is high (often >\=14), there is left

atrial dilation (usually >24 cm^2 or 69 mL) and atrial fibrillation is common [15]. Pulmonary hypertension is common and may be severe. NT-proBNP is usually elevated and often quite high (>1000 ng/L). Breathless occurs on effort and may progress to overt heart failure. Because systolic function is preserved and pulmonary hypertension develops gradually, the echo appearances can be almost indistinguishable from PAH—with a dilated poorly functioning right heart and even septal flattening in advanced HFpEF associated PH (mPAP >40 mmHg) [15]. In such cases LA enlargement usually provides the clue that the problem is left sided. Differentiating incidental left atrial dilation and PAH from HFpEF in patients with SSc is an art rather than a science and best done in expert centres. The only therapy that is established in HFpEF is diuretics [15].

Arrhythmias may or may not cause symptoms, in the setting of PH atrial arrhythmias worsen breathlessness and prognosis. Atrial fibrillation is strongly associated with HFpEF [15], in PAH atrial flutter is the more common atrial arrhythmia [16]. Sudden cardiac death due to ventricular tachyarrhythmias are strongly associated with high ventricular ectopic burden (>1000/24 h), NSVT and impaired systolic function with regional myocardial fibrosis [17]. In high risk cases an ICD is required [13], where the risk is uncertain, implantable monitors should be considered.

Coronary disease is believed to be more common in SSc than in the general population [18], though the data are inconsistent [19]. IHD should be considered where risk factors are identified or there is exertional chest discomfort. The presence of coronary disease complicates the management of PH.

HFrEF (heart failure with reduced ejection fraction) is relatively uncommon but important [12], PH is relatively less common in HFrEF but can occur. It is associated with male sex, older age, overlap myositis, and lung involvement [20], it may be driven by an inflammatory myocarditis with persistently elevated troponin. Once the diagnosis is established immunosuppressive therapy is recommended in addition to

all standard therapies for systolic heart failure [13]. In this population betablocker treatment is required despite the presence of Raynaud's, carvedilol is often well tolerated as a vasodilating betablocker. In patients that progress to end stage heart failure despite standard treatment cardiac transplantion is an option.

In this case we see high risk features (DSSc, overlap myositis, persistent Troponin elevation) but preserved ejection fraction. The elevated estPASP is a concern and cardiac catheterisation would be required to determine if PH is present. If postcapillary PH is confirmed, diuretics are required as stated above [15]. Confirmatory catheterisation is not required where PH is clearly postcapillary, for example the LA area is >40 cm^2 and there is no septal flattening [15]. A CMR and rhythm monitoring are essential in this case, if there is evidence of myocardial inflammation, then immunosuppression should be considered. If this is necessary from a non-cardiac perspective then one should simply proceed and monitor the Troponin and LVEF. If there is no non-cardiac indication, then we advise monitoring the Troponin and LVEF on a 6 monthly basis [13]. If the troponin escalates or the EF falls then immunosuppression should be considered, cardiac biopsy to exclude viral infection and confirm inflammatory cell infiltration and ideally chemokine drivers may help guide choice of therapy.

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