Screening for PAH in patients with systemic sclerosis: focus on Doppler echocardiography

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It is well established that patients with CTDs such as SSC carry a considerable risk of developing pulmonary arterial hypertension (PAH). Such SSC-PAH patients have an even worse prognosis than patients with only one of these two conditions. In view of the high incidence and prevalence of PAH in SSC, and the available treatment options that improve quality of life, exercise capacity and possibly survival, systematic screening has been recommended. The present article reviews current recommendations from PAH guidelines, focusing on studies that used Doppler echocardiography for screening, and describes limitations associated with the procedure. Furthermore, characteristics and parameters used to identify patients at high risk of developing PAH are summarized.

**KEY WORDS:** Doppler echocardiography, Screening, Pulmonary arterial hypertension, Guidelines, Predictors.

**Background**

Pulmonary arterial hypertension (PAH), currently defined as a mean pulmonary artery pressure (PAP) >25 mmHg at rest or >30 mmHg during exercise with a pulmonary capillary wedge pressure <15 mmHg measured by right heart catheterization, is a frequent complication in patients with SSC. Estimates based on echocardiographic screening (confirmed by right heart catheter) suggest that 8% (French centres in the ItinéraIR Sclérodermie Survey) up to 15% (UK) of SSC patients develop PAH [1]. Patients with SSC-PAH have a considerably poorer prognosis than individuals with other forms of PAH. Early studies showed a median survival of only 12 months in untreated symptomatic patients, and the risk of death was increased 3-fold [2].

However, with the advent of various disease-specific drugs (prostanoids, endothelin receptor antagonists, phosphodiesterase-5 inhibitors), evidence-based treatment of SSC-PAH patients has become the standard, resulting in improvements in exercise capacity, quality of life and possibly survival.

**Screening recommendations in PAH guidelines**

The high incidence and prevalence of PAH in SSC, together with the devastating course if untreated, and the possibility of treating this complication, form the basis for recommendations to systematically and regularly screen this at-risk patient population.

The British Cardiac Society guidelines issued in 2001 recommend annual Doppler echocardiography in SSC patients to identify PAH patients [3]. The PAH guidelines of the European Society of Cardiology (ESC), while acknowledging that some experts advise screening of asymptomatic SSC patients, in 2004 recommended a complete and careful echocardiographic assessment of patients in the presence of a PAH-related symptom [4]. The WHO Venice guidelines (2004) advise periodic screening for PAH using Doppler echocardiography, among other techniques, in the scleroderma spectrum of disease (but provide no guidance on specific time intervals for screening) [5]. The updated guidelines of the American College of Chest Physicians (ACCP) recommend Doppler echocardiographic screening in asymptomatic patients at high risk (quality of evidence: expert opinion; benefit: intermediate; strength of recommendation: moderate, based on expert opinion only) [6]. In patients with SSC, ACCP recommends pulmonary function testing with diffusing capacity for carbon monoxide (DLCO) performed periodically (every 6–12 months) to improve detection of pulmonary vascular or interstitial disease (quality of evidence: fair; benefit: intermediate; strength of recommendation: moderate) [6]. Finally, the National Pulmonary Hypertension Centres of the UK and Ireland recommend in their 2008 guidelines, that screening should be performed annually in patients with lcSSc or MCTD with U1 RNP antibodies, using echocardiography and DLCO. Furthermore, right heart catheterization (RHC) should be performed in all cases with a peak velocity of tricuspid regurgitation (VTR) of >2.8 m/s on echocardiography or a reduction in DLCO of 50% in the absence of interstitial lung disease. In contrast, patients with other CTDs should only be screened in the presence of symptoms [7].

**Choice of echocardiographic parameters**

The guidelines agree on the use of echocardiography as the screening tool of choice in the SSC patient group. However, there is currently no unequivocal guidance about the choice of parameters and thresholds to be used to identify PAH. Several groups performed screening studies using various Doppler parameters (in some cases, with subsequent confirmation of the diagnosis with RHC). An overview is provided in Table 1.

The studies used the VTR to estimate systolic PAP. This parameter is *sensu stricto* not measured, but calculated based on a formula using VTR plus right atrial pressure, which represents right ventricular systolic pressure (RVSP). In the absence of a pulmonary valve gradient, RVSP equals systolic PAP.

**Validation of echocardiographic parameters**

It is well known that there is substantial variation among echocardiographers in their technique, as well as the accuracy of measurements and interpretation of results. Little effort has been made to validate the use of echocardiography in SSC-PAH. In contrast to RHC, echocardiography cannot distinguish between elevated PAP resulting from PAH or from post-capillary causes such as diastolic dysfunction of the left heart. Moreover, it is not possible to obtain PAP values in up to 20–30% of patients because of technical and patient-related problems such as obesity [8].

Further, although the accuracy of echocardiography has been tested against RHC (the gold standard), its retest reliability has
not been validated in SSc [8]. The sensitivity, specificity and predictive value of this screening technique depend on the thresholds used, with the sole use of echocardiography considered to be of limited value (a combination of non-invasive techniques is possibly more useful) [9].

In the most comprehensive and current systematic literature review to date (2008), Kowal-Bielecka et al. [10] summarized the validation status of Doppler echocardiography in SSc-PAH on the basis of 35 studies including significant subgroups of SSc-PAH patients. While echo was considered feasible and to have face validity, it was considered only partially validated with respect to criterion validity based on significant correlations between echocardiographic measures and RHC in SSc patients considered to be at high risk of pulmonary hypertension. No controlled studies enabling evaluation of the discriminant capacity of echo in PAH/SSc-PAH were found. Good inter- and intra-observer reliability was reported for a limited number of parameters (e.g. right ventricular ejection fraction) in a more general SSc population [10].

Consequently, while Doppler echocardiography is regularly being used in SSc-PAH patients and according to a recent Delphi study, regarded as a key tool in the assessment of PAH in SSc [11], rheumatologists and others need to be cautious about the validity and credibility of studies using Doppler echo to screen for, or to follow-up, PAH in SSc patients.

Further characteristics to define SSc patients at high risk of PAH

Despite these limitations, there is presently no alternative to echocardiography in daily clinical practice. It should be noted that on the basis of multivariate analyses, a number of characteristics or parameters have been reported that might be useful to identify those SSc patients who have a particularly high risk of developing PAH. Schachna et al. (2003) identified only late age at onset of SSc as a risk factor. Steen and Medsger [12] found in lcSSc, over a 15-yr time period that patients who subsequently developed isolated PAH, showed a progressive deterioration in the DLCO, severity of RP and of digital tip ulcers, and a potential protective role of calcium channel blocking agents. In SSc, Allanoire et al. [13] have demonstrated that elevated levels of natriuretic peptides [N-terminal pro-brain natriuretic peptide (NT-proBNP)] were associated with an early increase of PAP in echocardiography. Very recently, in a prospective follow-up of 101 SSc patients initially free of PAH, these authors identified eight patients who developed PAH after a mean of 28 months [14]. On multivariate analysis, a decrease in DL\textsubscript{CO} and an increase in NT-proBNP levels measured at baseline after wash-out of vasodilators, both were independent predictors for the occurrence of PAH. The combination of an increased NT-proBNP level (a reflection of cardiac wall stress) together with a decreased DL\textsubscript{CO}/alveolar volume (DL\textsubscript{CO}/VA) ratio of <70% (as the reflection of limited capillary gas exchange) predicted the occurrence of PAH during follow-up with a hazard ratio of 47 (95% CI 5, 450).

Prospective studies are needed to confirm the predictive value of the various proposed factors for PAH.

### Rheumatology key messages

- SSc patients have a high incidence and prevalence of PAH.
- Despite important limitations, Doppler echocardiography currently represents the screening method of choice according to recent PAH guidelines.
- A RHC is mandatory to confirm the diagnosis.
- A number of predisposing factors may help to identify SSc patients at particularly high risk of developing PAH.

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### References


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**Table 1. Overview on echo Doppler parameters used for PAH screening in SSc patients**

<table>
<thead>
<tr>
<th>Author</th>
<th>Source</th>
<th>Setting</th>
<th>SS patients</th>
<th>Doppler parameter primarily used for screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murata</td>
<td>Jpn Circ J 1992;56:983</td>
<td>Univ. centre Japan</td>
<td>71</td>
<td>VTR</td>
</tr>
<tr>
<td>Battle</td>
<td>Chest 1996;110:1515</td>
<td>Univ. centre USA</td>
<td>34</td>
<td>sPAP &gt;30 mmHg</td>
</tr>
<tr>
<td>Murata</td>
<td>Chest 1997;111:36</td>
<td>Univ. centre Japan</td>
<td>135</td>
<td>sPAP &gt;40 mmHg</td>
</tr>
<tr>
<td>Denton</td>
<td>Br J Rheumatol 1997;36:239</td>
<td>Univ. centre UK</td>
<td>33</td>
<td>sPAP &gt;30 mmHg</td>
</tr>
<tr>
<td>Mukerjee</td>
<td>Ann Rheum Dis 2003;62:1088</td>
<td>Univ. centre UK (mostly)</td>
<td>794</td>
<td>sPAP &gt;35 mmHg (or DLCO &lt;50% predicted, or precipitous fall in DLCO &gt;20% over 1 yr)</td>
</tr>
<tr>
<td>Mukerjee</td>
<td>Rheumatology 2004;43:461</td>
<td>Univ. centre UK</td>
<td>137</td>
<td>Tricuspid gradient (range 30–40 mmHg); elevated sPAP</td>
</tr>
<tr>
<td>Rachella</td>
<td>Arthritis Rheum 2005;52:3792</td>
<td>21 Univ. centres France (‘ItinéR AIR Sclérodermie’)</td>
<td>599</td>
<td>VTR ≥ 3 m/s or VTR 2.5–3 m/s (plus unexplained dyspnoea)</td>
</tr>
<tr>
<td>Wylie</td>
<td>Arthritis Rheum 2005;52:2125</td>
<td>50 Rheumatol. practises USA</td>
<td>669 de novo</td>
<td>(Estimated) RVSP &gt;40 mmHg</td>
</tr>
<tr>
<td>Kiatchoosakun</td>
<td>J Med Assoc Thai 2007;90:2024</td>
<td>Univ. centre Thailand</td>
<td>129</td>
<td>RVSP &gt;36 mmHg</td>
</tr>
<tr>
<td>Hsu</td>
<td>J Rheumology 2008; online first</td>
<td>Univ. centre USA</td>
<td>49</td>
<td>RVSP &gt;47 mmHg (optimal cutpoint compared with RHC)</td>
</tr>
</tbody>
</table>


