Pulmonary hypertension (PHT) is an important and often fatal visceral complication of systemic sclerosis (scleroderma; SSc) [1] which can occur in both the limited (lcSSc) and diffuse (dcSSc) cutaneous subsets of the disease [2, 3]. In lcSSc, it typically occurs in the absence of significant interstitial lung fibrosis [4] and generally develops after at least 10 yr from disease onset. Affected patients often have other pronounced vascular features such as severe Raynaud’s phenomenon or widespread telangiectasias [4]. The precise prevalence is difficult to determine, but ultimately it may complicate up to 15% of cases of lcSSc [5]. By contrast, in dcSSc, PHT always occurs secondary to advanced interstitial lung disease, causing additional cardiorespiratory symptoms. Clinical features of PHT in SSc are often elusive, especially in its early stages; progressive breathlessness generally occurs, but may be ignored by patients, especially in dcSSc with pre-existing fibrotic lung disease. In advanced pulmonary vascular disease, there may be symptoms of right heart failure, but such features are of little use for the early detection of PHT. Clinical signs of right ventricular strain may be present, such as a loud pulmonary component of the second heart sound on auscultation or a left parasternal heave. However, such signs are variable, tend to occur late and cannot be readily quantified. Investigations are more reliable for identifying pulmonary vascular pathology. The earliest abnormality is usually a reduction in carbon monoxide transfer factor on pulmonary function testing. When this occurs in the absence of substantially reduced lung volumes, then PHT should be strongly suspected, although such a pattern is found in ~20% of the SSc population, many of whom do not develop PHT [6]. More specific diagnostic tests are therefore needed. An ECG may show characteristic abnormalities such as a peaked P-wave or signs of right ventricular strain but, until relatively recently, confirmation of PHT has depended on the findings at right heart catheterization (RHC) with direct pressure measurement.

Echocardiography can also be used to diagnose elevated pulmonary arterial pressure, particularly when employing the Doppler technique. This approach has proven reliable in practice [7] and has been used to provide an estimate of pulmonary artery pressure in a variety of chronic lung diseases [8]. The use of this modality should facilitate the identification of PHT in connective tissue diseases, and hopefully lead to earlier diagnosis of mild PHT cases in SSc when the condition would be expected to be most amenable to treatment. However, there have been no studies specifically addressing the validity of echocardiography for diagnosing PHT in SSc. A reliable, non-invasive technique would be particularly useful because SSc patients represent an ‘at risk’ group in which regular screening for PHT, and monitoring of response to treatment, could be of considerable benefit. We have undertaken a study to compare estimated PAP by Doppler echocardiogram with the actual measurements obtained at RHC in a group of SSc patients in whom PHT had been clinically suspected.

COMPARISON OF DOPPLER ECHOCARDIOGRAPHY AND RIGHT HEART CATHETERIZATION TO ASSESS PULMONARY HYPERTENSION IN SYSTEMIC SCLEROSIS

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Academic Rheumatology and Connective Tissue Diseases Unit, Royal Free Hospital Medical School, London and
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SUMMARY

Pulmonary hypertension (PHT) is an important complication of systemic sclerosis (SSc). Echocardiography can be used to detect PHT and, with Doppler echocardiography, the pulmonary arterial systolic pressure (PASP) can often be estimated. We have undertaken a study to compare echocardiographic assessment with right heart catheterization (RHC) in 33 SSc patients in whom clinical assessment [including ECG, chest X-ray, lung function tests and high-resolution computed tomography (HRCT)] had raised strong suspicion of PHT. The mean (s.d.) interval between echocardiography and RHC was 1.8 (2.3) months. Twenty-one patients (64%) had PHT (PASP ≥ 30 mmHg) on RHC, and echocardiography correctly identified 19 of these (sensitivity 90%). Of the 12 patients without PHT on RHC, nine were correctly identified by echocardiography (specificity 75%). The five incorrectly classified patients all had PASP in the borderline normal/abnormal range. The presence of tricuspid regurgitation allowed Doppler measurement of PASP in 20 patients (61%) and this correlated significantly with RHC values (r = 0.83, P < 0.001). We conclude that echocardiography is a reliable method for detecting PHT and it may be particularly useful for the early detection and monitoring of this potentially fatal complication in SSc.

Key words: Systemic sclerosis, Pulmonary hypertension, Echocardiography, Pulmonary artery, Right heart catheter.
METHODS

The study population consisted of 33 consecutive patients, with confirmed SSc as defined by the American College of Rheumatology Preliminary Criteria [9], who were clinically suspected of having PHT [10 male, 23 female, mean (s.d.) age 48.6 (11.7) yr]. Twenty-three patients fulfilled the criteria for lcSSc, the remainder had diffuse cutaneous disease according to the two-subset classification [10]. Patients were referred to our unit between 1987 and 1993. Clinical details are given in Table I. Pulmonary hypertension was suspected in these patients on the basis of the findings on clinical examination, lung function testing, plain chest radiography and thin-section high-resolution computed tomography (HRCT) of the lungs. The most frequent reason for suspecting the diagnosis was depression of carbon monoxide gas transfer (DLCO) which was considered to be disproportionately great for the degree of depression of lung volume. Echocardiography and RHC were performed as part of the routine evaluation of these patients. Patients underwent Doppler echocardiography and RHC within 6 months of each other, with a mean (s.d.) interval of 1.8 (2.3) months between investigations. All studies were performed as part of the normal clinical evaluation for these patients at the Royal Brompton Hospital.

Echocardiography

M-mode and cross-sectional echocardiography were performed with the patient in the left lateral position using a Hewlett Packard (Andover, MA, USA) echocardiogram. Non-imaging continuous-wave Doppler signals were recorded with a Doptek (Southampton) 2.0 MHz transducer. Tricuspid regurgitant flow was identified in continuous-wave mode at the apex. The peak instantaneous systolic pressure drop from right ventricle to atrium was calculated from the peak signal velocity of the tricuspid regurgitant signal by the simplified Bernoulli equation. The final estimation of pulmonary artery systolic pressure (PASP) was obtained by adding the patient's jugular venous pressure to the estimate of PASP.

Definitions

At RHC, PHT was taken to be present if PASP was \( \geq 30 \text{mmHg} \), providing pulmonary capillary wedge pressure was normal [11]. Similarly, at echocardiography, PHT was considered to be present if a Doppler PASP was \( \geq 30 \) or, if a Doppler estimate was not available, there was evidence of right ventricular dilatation or hypertrophy with a structurally normal left ventricle. These criteria were selected because they are the least equivocal echocardiographic features of PHT and we were keen to avoid over-diagnosis in these patients; however, wherever possible, Doppler measurements were used as the non-invasive criterion for PHT due to its quantitative nature.

Data analysis

Values refer to means with standard deviations in parentheses unless otherwise stated. Comparisons between groups were examined by the Mann–Whitney U-test, and relationships between sets of data by least squares linear regression analysis. The relationship between RHC PASP and Doppler echo PASP was also investigated by the method of Altman and Bland [12]. The sensitivity [true positives/(true positives + false negatives)], specificity [true negatives/(true negatives + false positives)], positive predictive value [true positives/(true positives + false positives)] and negative predictive value [true negatives/(true negatives + false negatives)] were investigated. The relationship between RHC PASP and Doppler echo PASP was also investigated by the method of Altman and Bland [12]. The sensitivity [true positives/(true positives + false negatives)], specificity [true negatives/(true negatives + false positives)], positive predictive value [true positives/(true positives + false positives)] and negative predictive value [true negatives/(true negatives + false negatives)] were investigated.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>SSc subset</th>
<th>FVC % predicted</th>
<th>DLCO % predicted</th>
<th>HRCT suggesting fibrosing alveolitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>48.6</td>
<td>10 M (30%)</td>
<td>23 limited</td>
<td>80</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>11.7</td>
<td>23 F (70%)</td>
<td>10 diffuse</td>
<td>21</td>
<td>18</td>
</tr>
</tbody>
</table>

DLCO, carbon monoxide gas transfer; FVC, forced vital capacity; HRCT, high-resolution computed tomography.
TABLE II
Comparison of right heart catheter and echocardiogram results for all 33 patients studied

<table>
<thead>
<tr>
<th></th>
<th>Right heart catheter</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo</td>
<td>Normal</td>
<td>PHT</td>
</tr>
<tr>
<td>Normal</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>PHT</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>21</td>
</tr>
</tbody>
</table>

Echo, echocardiogram; PHT, pulmonary hypertension.

TABLE III
Comparison of right heart catheter and Doppler assessment for patients with tricuspid regurgitation (A) and echocardiography results for those without tricuspid regurgitation (B)

<table>
<thead>
<tr>
<th></th>
<th>Right heart catheter</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>PHT</td>
</tr>
<tr>
<td>(A) Patients with tricuspid regurgitation</td>
<td>Doppler echo</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PHT</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>(B) Patients without tricuspid regurgitation</td>
<td>M-mode echo</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>PHT</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

Doppler echo, Doppler echocardiogram; PHT, pulmonary hypertension.

RESULTS

Twenty-one patients (64%) were found to have PHT at RHC. Echocardiography correctly identified 19 of these patients, giving a sensitivity for the diagnosis of PHT of 90% (Table II). The two incorrectly classified patients had PASP in the range 32–42 mmHg. Nine of the 12 patients without PHT on RHC were correctly identified by echocardiography, giving a specificity for the diagnosis of 75% (Table II). The three incorrectly classified patients had PASP in the range 27–29 mmHg. The positive and negative predictive values for echocardiography in assessing the presence or absence of PHT were 86 and 82%, respectively. The interval between the two procedures in the misdiagnosed patients was not significantly different from the interval in the correctly assigned patients.

A Doppler measurement of PASP was possible in 20 patients (61%). The RHC PASPs in these patients were significantly higher than in the 13 patients in whom a Doppler measurement was not possible [mean 54.5 (23.7) vs 33.6 (16.8) mmHg; \( P = 0.009 \)]. The values for PASP obtained by Doppler echocardiography correlated highly with the values obtained at RHC \( (r = 0.83, P < 0.001) \) (Fig. 1). The mean absolute difference between RHC and Doppler measurements of PASP was 11.4 (9.8) mmHg. Although there was a tendency for greater discrepancy between the two measurements with increasing PASP (Fig. 2), there was no correlation between this difference and the time interval between the two procedures. Of the 20 patients in whom a Doppler measurement was possible, 18 (90%) were correctly diagnosed as having, or not having, PHT. The sensitivity and specificity for Doppler echocardiography in the diagnosis of PHT were 100 and 60%, respectively (Table III). The two incorrectly classified patients both had normal PASP at RHC, but were determined to have PHT on Doppler echocardiography. Their RHC values for PASP were 28 and 29 mmHg, compared with 38 and 35 mmHg, respectively, on echocardiography.

Doppler measurement was not possible in 13 cases because there was no tricuspid regurgitation. However, our data suggest that the presence of tricuspid regurgitation does not reflect the presence or absence of PHT, because the range of pulmonary arterial pressures measured by RHC in the 6/13 patients with PHT and no TR was similar (30–80 mmHg) to that...
seen in the 15/20 patients with PHT in whom a Doppler measurement was possible (34–109 mmHg). For all 33 patients, there was a significant negative correlation between RHC PASP and DLCO (r = 0.60, P < 0.001). There was no correlation between RHC or Doppler measurement of PASP and forced vital capacity (FVC).

**DISCUSSION**

In this study, we have shown that echocardiography is both sensitive and specific for the diagnosis of PHT in patients with SSc and clinical suspicion of PHT. Overall, five of the 33 patients were incorrectly classified (15%), but these all had PASP in the range 27–42 mmHg, the upper end of the normal range or in the mild PHT range [11]. If Doppler echocardiography suggested the presence of PHT of at least moderate severity (PASP > 40 mmHg), values obtained at RHC were always abnormal. Only two patients had a normal echocardiogram but an abnormal RHC, and both had PASP ≤ 40 mmHg (36 and 32 mmHg).

Doppler quantification of the degree of PHT by echocardiography was possible in approximately two-thirds of the patients studied. When a Doppler assessment was possible, echocardiography was even more accurate in determining the presence or absence of PHT, incorrectly classifying only 2/20 patients; both had normal RHC PASP, but were thought on Doppler echocardiography to have mild (< 40 mmHg) PHT. There was a close correlation between PASP as measured by RHC and Doppler echocardiography. Doppler measurement was not possible in 13 cases because no tricuspid regurgitation (TR) was detectable. However, it is unlikely that PHT will be missed in cases where the Doppler cannot be performed; the M-mode echo correctly predicted PHT in 11 of 13 cases even without Doppler estimation of pulmonary artery pressure.

Although our results reveal a highly significant correlation between the pressure measures obtained at RHC and Doppler echocardiography, in some cases the difference between the two was up to 29 mmHg. This may be due to inaccuracy in the Doppler measurement as the direction of flow of the regurgitant tricuspid jet of blood is variable and even a skilled operator may have difficulty in identifying the maximal velocity. We feel, however, that it is more likely that the differences in the measured PASP between the two techniques are due to real changes in the systolic pressures between the two tests. In primary PHT, PASP has been shown to fluctuate widely in a single patient over the course of 6 h [13] due to spontaneous variability of cardiac output and pulmonary vascular resistance; a similar phenomenon is likely to occur in patients with SSc. The dynamic nature of the pulmonary circulation in these patients has been demonstrated not only after pharmacological interventions [14, 15], but also during Raynaud’s phenomenon [16], perhaps making SSc patients especially prone to fluctuations in PASP.

The pulmonary complications of SSc are a major cause of morbidity and mortality [1]. The prognosis of PHT due to primary vessel disease is poor with a 2 yr survival of 40% [5]. Treatment of the condition is at present unsatisfactory and advances are only likely if the disease can be more easily identified at any early stage. Our results suggest that echocardiography is a useful tool in this regard, although other methods are still needed to identify SSc pulmonary vasculopathy, ideally prior to the development of sustained PHT, when it may be most feasible to modify the disease process. It is possible that markers of vascular perturbation, such as soluble adhesion molecules [17] or circulating levels of endothelin-1 [18], may prove useful in the early diagnosis of pulmonary vasculopathy in SSc, although results so far are inconclusive. It is also possible that immunogenetic markers might usefully predict those patients most at risk of PHT, as they have in SSc-associated lung fibrosis [19], but no definite MHC associations have yet been identified for pulmonary vascular disease in SSc.

This is the first study focusing on the usefulness of Doppler echocardiography in identifying the presence or absence of PHT in this unique patient group. In one retrospective study of 49 patients with SSc undergoing RHC, the predictive value of a number of non-invasive tests, including echocardiography (without Doppler estimates of pulmonary artery pressure), for the diagnosis of PHT was examined. Only 67% of patients with PHT were correctly identified non-invasively and, in fact, a reduction in gas transfer below 43% of predicted was the most sensitive test [3]. The addition of Doppler estimates of PASP used in this study therefore considerably improves the accuracy of echocardiography in both the diagnosis and exclusion of PHT in patients with SSc.

Although our patients were highly selected, in that in all cases there was clinical suspicion of PHT, it is precisely this group of subjects in whom RHC is performed to diagnose PHT, and in whom echocardiography would be most useful in obviating the need for invasive investigative procedures. Our results are, therefore, representative of usual clinical practice despite the selected nature of the study population. Furthermore, the Doppler echocardiogram gives additional information regarding structural and functional cardiac abnormalities which cannot be obtained from RHC. Thus, myocardial diastolic dysfunction (suggesting myocardial fibrosis) or pericardial effusion [20, 21], which may complicate SSc, can be detected by echocardiography. It is unlikely that PHT will be missed in cases where the Doppler cannot be performed—none of our cases with normal M-mode echo had PHT by Doppler. The main advantage of the Doppler examination over standard echocardiography is its quantitative nature for monitoring disease progression or response to therapeutic intervention.

In conclusion, our results demonstrate that M-mode and cross-sectional echocardiography are sensitive and specific tools for identifying PHT in SSc. When Doppler estimation of PA pressure is possible, the values obtained correlate well with those from right heart catheterization, and so Doppler studies can be
used to assess and monitor the severity of PHT in SSc. Although the need to perform RHC in some cases remains, e.g. to determine its severity in those patients without tricuspid regurgitation, we believe that our study has confirmed the usefulness of echocardiography for assessing PHT in SSc. It should, therefore, be included in the routine investigation of SSc patients in whom PHT is clinically suspected, or those particularly at risk. Currently, this would include patients with long-standing (over 5 yr duration) lcSSc or those dcSSc cases with established lung fibrosis. By screening in this way, the true frequency of this complication can be determined, and detection of asymptomatic cases of PHT should permit new potential therapies to be evaluated earlier in the disease. Doppler echocardiography is also likely to be invaluable in serial assessment of PHT in SSc to determine the efficacy of such treatments.

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REFERENCES