Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis

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Objective. A prospective study to evaluate echocardiography and gas transfer (DLCO) by comparison with cardiac catheterization in discriminating between patients with and without systemic sclerosis-associated pulmonary arterial hypertension (SScPAH).

Method. A total of 137 (52 with and 85 without pulmonary fibrosis) had echocardiography and lung function tests within 3 months of their definitive invasive study.

Results. At cardiac catheterization 99 of these patients were found to have PAH, while PAH was excluded in 38. Echocardiographically estimated tricuspid gradient (TG) showed a moderate positive correlation ($r^2 = 0.44$, $P < 0.005$) with both mean pulmonary pressure and invasively determined tricuspid gradient. DLCO showed a weak correlation ($r^2 = 0.09$, $P = 0.006$), when compared with mean pulmonary arterial pressure. In total, 97% of patients with an echocardiographically determined TG of $>45$ mmHg were found to have pulmonary hypertension at catheterization. However, no threshold could be defined with either screening test that safely excluded PAH.

Conclusions. The positive predictive accuracy of currently used non-invasive tests are adequate for the diagnosis of advanced PAH provided sufficiently high thresholds (TG $>45$ mmHg or DLCO $<$55% predicted) are used. These tests cannot be relied upon to exclude pulmonary hypertension where pre-test probability is high.

Key words: Pulmonary arterial hypertension, Echocardiography, Tricuspid gradient, DLCO, Cardiac catheterization, Systemic sclerosis.

Idiopathic pulmonary hypertension (IPH), previously known as primary pulmonary hypertension, is a progressive disorder historically associated with a poor prognosis [1]. In the setting of systemic sclerosis (SSc) the outlook for patients with pulmonary arterial hypertension (PAH) was reported to be even worse [2] than IPH. Recently, effective therapies have become available [3–7] and recent registries suggest that with treatment the prognosis has improved relative to historical controls [8, 9].

Most authorities recommend non-invasive testing as part of a screening programme for those at risk of developing PAH [10]. SSc is the best known example of an ‘at-risk’ group with a prevalence of PAH of up to 10–15% [11]. Other at-risk populations are known to exist. These include relatives of patients with familial PAH [12], patients with other connective tissue diseases [13, 14] and patients with pulmonary embolic disease [15], all of whom may benefit from regular screening. The accuracy of echocardiography or pulmonary function testing has not been formally assessed against the gold standard diagnostic technique of cardiac catheterization in any of these at-risk populations. Although echocardiography has been evaluated in populations where the diagnosis of pulmonary hypertension has already been established, these are very different groups from ones where mild pulmonary hypertension may or may not be present.

Both echocardiography [16] and pulmonary function testing [17] appear to perform adequately in identifying patients with advanced PAH related to systemic sclerosis (SScPAH). There is a scarcity of published data on the reliability of these techniques in instances where PAH is not clinically evident. In the context of SScPAH, Denton et al. [18] performed Doppler echocardiography to estimate the tricuspid gradient (TG), an indirect and observer-dependent measure of pulmonary artery pressure elevation, on 33 consecutive SSc patients clinically suspected to have PAH. They subsequently confirmed the diagnosis in 21 of these patients (64%) on cardiac catheterization (where the mean pulmonary artery pressure was directly measured). Echocardiography correctly identified 19 of these patients, giving a sensitivity of 90% and specificity of 75%. Interestingly, they noted a difference of up to 29 mmHg between echo and catheter findings, the authors concluded that echocardiography is a useful non-invasive, initial screening tool. The role of carbon monoxide diffusing capacity (DLCO) as a non-invasive measure of PAH is less certain. Stupi et al. [16] and Ungerer et al. [17] have demonstrated an association between DLCO $<$40–55% and isolated SSc PAH in a total of 87 patients. Steen et al. [19] found that an isolated reduction in DLCO is a frequent abnormality in SSc. Of their 73 patients followed-up for a mean 5.4 yr, five developed PAH. In a smaller population of predominantly IPH patients, Burke et al. [20] and Jezek and Widimsky [21] were unable to confirm a clear link between a low DLCO and PAH. Krowka [22] and Capomolla et al. [23] have recommended that DLCO should be added to echocardiography
as the initial diagnostic screen for PAH. These authors had small cohorts of patients with PAH resulting from a mixture of causes (including SSc, systemic lupus erythematosus, IPH and chronic thromboembolism). They found that a fall in DLCO in addition to a rise in echo TG correlated with the onset of PAH at cardiac catheterization.

Thus, though widely used in screening programmes, the positive and negative predictive values and thresholds for diagnosis on echocardiography and pulmonary function testing are unknown. Establishing the accuracy of non-invasive tests in the setting of SSc is important. It will facilitate the development of robust PAH screening programmes in the SSc population, while providing insights to the limits of these techniques when applied to other disease states where the prevalence of PAH is lower.

The aims of this study, therefore, were: (i) to evaluate the reliability of echo-estimated TG or DLCO in predicting the presence of pulmonary hypertension at cardiac catheterization; (ii) to determine threshold values which reliably establish or exclude the diagnosis of pulmonary hypertension; and (iii) to determine whether echocardiography or DLCO abnormalities were predictive of the severity of SScPAH in terms of the degree of haemodynamic impairment abnormality seen at catheterization.

Patients and methods

An active screening programme for the early identification of SScPAH has been in operation at the Royal Free Hospital (RFH) since 1998. To evaluate the efficacy of this programme, standardized criteria for invasive evaluation were instituted in 1998. Cardiac catheterization was performed in all patients in a background SSc population who met the following criteria:

(1) The tricuspid gradient on transthoracic echocardiography exceeded 35 mmHg or, if the gradient could not be determined, the pulmonary acceleration time was less than 100 ms.

(2) The corrected DLCO was less than 50% of predicted in patients without advanced (grade 3 or 4 on high-resolution CT) pulmonary fibrosis, or any patient in whom the corrected DLCO fell by more than 20% in the previous 2 yr.

(3) Any patient with unexplained exercise limitation.

Patients were drawn from the population attending the Royal Free Scleroderma Unit, the Interstitial Lung Disease Unit at the Royal Brompton Hospital (RBH) and from external referral sources. Full written informed consent was obtained from all patients who underwent invasive cardiac catheterization.

Population

Between 1998 and 2002, 219 patients have met these criteria and proceeded to cardiac catheterization; 148 were found to have pulmonary arterial hypertension and in 71 patients the diagnosis was excluded. These patients are considered in another publication [11]. However, not all these patients had pulmonary function testing and echocardiography prior to catheterization and in many (especially asymptomatic patients) the investigation leading to catheterization had been performed more than 3 months prior to invasive evaluation.

From this population we identified all patients in whom pulmonary function testing and echocardiography had been performed in the 3 months before cardiac catheterization. We examined the predictive power of these non-invasive tests for the identification of patients who are found to have pulmonary hypertension on catheterization. For the purposes of standardization we only included patients whose tests had been performed at the RFH or RBH.

Clinical review

At the RFH site, annual clinical review was performed in clinics directed by CB, using a standard proforma. The presence or absence and grade of dyspnoea [modified New York Heart Association (NYHA) grading] were established at each review. Patients were identified as having unexplained dyspnoea if severe pulmonary fibrosis on high-resolution CT (HRCT) or significant airway disease on pulmonary function testing were not found.

Patients from either site (RFH, RBH) meeting the criteria for catheterization were formally reviewed in the pulmonary hypertension clinic led by JC, and the dyspnoea grade, clinical findings and results of investigations evaluated. Catheterization was scheduled for all patients within 1 month of review, where possible, if the patient agreed and was considered fit for the procedure.

Pulmonary function testing

Annual pulmonary function testing was performed in the two institutions (Dr P. Dillworth at RFH and Prof. Du Bois at RBH). Patients with a total lung capacity (TLC) of <70% underwent high-resolution CT unless they were already known to have advanced interstitial lung disease. Patients with a corrected DLCO of <50% in the absence of advanced interstitial lung disease were invited for cardiac catheterization irrespective of echocardiographic findings. All patients in whom DLCO had fallen by more than 20% since the previous examination were invited for catheterization, unless active fibrosis (falling lung volumes or ground-glass appearance on high-resolution CT) explained the change.

Echocardiography

Annual echocardiography was performed either at the Royal Free Hospital (under the direction of JD) or at the Royal Brompton Hospital (under the direction of Dr Henein) using standardized templates for the evaluation of right ventricular dimensions, tricuspid gradients (TG) and, more recently, pulmonary acceleration times. All patients in whom a TG of greater than 35 mmHg, or in whom right ventricular dilatation or shortened pulmonary acceleration times were found, were invited for cardiac catheterization, irrespective of symptoms or pulmonary function test findings.

Cardiac catheterization

Right heart catheterization was performed from a right femoral approach using a 7 French Bard thermodilution catheter under local anaesthesia. Patients were allowed to rest for 5 min after catheter insertion, and then baseline haemodynamics were performed on two occasions over a period of 5 min. If pulmonary arterial pressure, heart rate or pulmonary vascular resistance varied by more than 10%, further assessments were performed until stability was established. Patients with a mean pulmonary pressure of less than 25 mmHg underwent benchly exercise for 2 min if the resting pulmonary vascular resistance exceeded 200 dynes per cm⁻⁵. Where exercise mean pulmonary pressure exceeded 30 mmHg, patients were defined as having PAH. Patients with PAH underwent vasodilator testing using a graded iloprost infusion regime (2, 6 and 12 ng/kg per min at 5-min intervals).

Pulmonary angiography was performed in patients with non-low risk ventilation perfusion scans unless CT pulmonary angiography had already excluded pulmonary embolic disease. Left heart catheterization was additionally performed in all patients with angina-like chest pain, or in whom dyspnoea remained unexplained on the basis of pulmonary function testing and right heart pressures. The catheterization operators were not
blinded to the echocardiographic and lung function test information as these investigations were performed prior to this procedure.

**Statistical analysis**

The statistical software package Microsoft Excel was used. The echo-estimated tricuspid gradients (otherwise known as the pulmonary artery systolic pressures) were correlated with the baseline mean systolic pulmonary artery pressure (mPAP) minus the right atrial pressure (RAP) on cardiac catheterization. The mean PAP was correlated with the DLCO and an r² value derived for patients with no pulmonary fibrosis. The patients with advanced fibrosis were not included in the DLCO correlation as it was felt that the presence of fibrosis might be a confounding factor.

To determine the predictive capacity of the screening tests for the diagnosis of PAH, threshold tricuspid gradient levels (30, 35, 40 and 45 mmHg) and corrected %DLCO (50, 55 and 60%) were analysed for positive and negative predictive values; 4 × 4 tables were constructed for each threshold and the sensitivity, specificity, positive and negative predictive values calculated.

**Results**

During the 4-yr period of the study serial echocardiography, pulmonary function testing and clinical evaluation were performed on 574 patients at either the RFH or RBH. During this period 137 patients had cardiac catheterization performed within 3 months of screening; 85 of these patients had no or mild fibrosis, while 52 had grade III or IV fibrosis on high-resolution CT scanning. Table 1 shows the differences between the populations with and without pulmonary fibrosis.

**Total population**

As pulmonary fibrosis does not influence the accuracy of echocardiography, the whole population was considered in assessing the accuracy of tricuspid gradient in identifying patients with PAH (Table 2). Echocardiography showed good specificity at high thresholds (TG ≥45 mmHg) associated with a high false-negative rate, and poor specificity at lower thresholds.

These findings suggest that echocardiography using TG and pulmonary acceleration time lacks the sensitivity required to exclude PAH. A positive correlation was found between TG and mean PAP (Fig. 1), and additional abnormalities on echocardiography (right ventricular dilation in 23, reversed septal motion in 16) were found only in those with a TG of >40 mmHg, thus abnormal echocardiographic findings are increasingly found as pulmonary hypertension reaches advanced stages.

**Patients without pulmonary fibrosis**

Indications for catheterization included unexplained dyspnoea in 74 out of 85 (as an isolated abnormality in 26 patients, of whom 12 had PAH). The echo-estimated TG was over 35 mmHg in 49 out of 85 (as an isolated abnormality in six of whom one had PAH). The corrected DLCO was <50% in 25 out of 85 patients (isolated abnormality in none). Eight patients had a fall in their corrected DLCO >20% over the previous 2 yr as their reason for cardiac catheterization (this was an isolated finding in two patients). None of these eight patients had PAH. A single patient was catheterized based only on pulmonary acceleration time and PAH was excluded.

PAH was found in 54 of the 85 studied, 33 had NYHA grade 3 or 4 dyspnoea. Two patients were NYHA grade 1, and identified purely on the basis of the screening tests (TG >35 mmHg in both, plus a falling DLCO in one). However, 11 patients with mild dyspnoea (NYHA grade 2) had not been identified as symptomatic until rigorously questioned.

Twenty-two of the 31 patients in whom PAH was excluded were also symptomatic. Eight of these patients were NYHA grade 3. Specific diagnoses (diastolic dysfunction and coronary disease) were found in five of these patients. Thus, with rigorously applied questioning most patients in whom isolated PAH was found were symptomatic. However, a third of symptomatic patients did not have PAH.

The tricuspid gradient exceeded 45 mmHg in 21 of the 54 patients with isolated PAH, while only one patient in whom PAH was excluded at catheterization had a TG of >45 mmHg. Eighteen patients who had isolated PAH had a TG of <35 mmHg, and eight patients with a TG of <30 mmHg on echocardiography had pulmonary hypertension at catheterization.

The corrected DLCO was <50% predicted in 21 of the 54 patients with isolated PAH, and less than 55% in 31, while similarly impaired gas transfer was found in only three and nine, respectively, of the 31 patients in whom PAH was excluded. Nevertheless, PAH was found in 23 patients with a predicted corrected DLCO of greater than 55%, again suggesting that

**Table 1.** Characteristics of 137 SSc patients undergoing cardiac catheterization for suspected PAH within the 3-month period after screening with echocardiography and lung function tests, including DLCO estimation, between 1998 and 2002

<table>
<thead>
<tr>
<th>Variables</th>
<th>SSc with no pulmonary fibrosis (excluded on HRCT chest)</th>
<th>SSc with pulmonary fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>85</td>
<td>52</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>62 ± 11</td>
<td>64 ± 7</td>
</tr>
<tr>
<td>Duration of SSc (yr)</td>
<td>12 ± 8</td>
<td>14 ± 7</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>ACA = 41, SCL70 = 8,</td>
<td>ANA = 22, other ENA = 14, SCL70 = 28, ANA = 24</td>
</tr>
<tr>
<td>mPAP - catheter (mmHg)</td>
<td>39 ± 12</td>
<td>36 ± 11</td>
</tr>
<tr>
<td>PASP - RAP on catheter (mmHg)</td>
<td>45 ± 22</td>
<td>49 ± 19</td>
</tr>
<tr>
<td>PASP on echo (mmHg)</td>
<td>39 ± 15</td>
<td>46 ± 18</td>
</tr>
<tr>
<td>Corrected DLCO</td>
<td>57 ± 12</td>
<td>39 ± 12</td>
</tr>
</tbody>
</table>

Corrected DLCO, % corrected transfer factor for carbon monoxide; mPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressure; RAP, right atrial pressure.
preserved gas transfer is insufficiently sensitive for the exclusion of PAH. Table 3 demonstrates the relationship between lower thresholds of DLCO (60, 55 and 50%) and the positive and negative predictive values at each threshold in this group of 85 SSc patients. Among patients with PAH, a lower DLCO was associated with more advanced PAH. The average mPAP was 42 mmHg in patients with a DLCO of less than 55%, but only 32 mmHg in patients with PAH and a DLCO of greater than 55%. However, the strength of the relationship between mPAP and DLCO is weak (Fig. 2) with an $r^2$ value of 0.09. Thus, as with echocardiography, the test performs best in advanced rather than early PAH, but the relationship with severity is less secure.

**Patients with pulmonary fibrosis**

Thirty-eight of the 52 patients with pulmonary fibrosis had a tricuspid gradient of $\geq$35 mmHg. All but one were breathless on exertion. Fourteen patients with TG $<35$ mmHg were studied, six because of a falling DLCO, and eight with increasing dyspnoea unexplained on lung function tests and high-resolution CT changes. Five of the eight with increasing symptoms had PAH on catheterization, while two of the six whose symptoms had not deteriorated had PAH.

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**Table 3.** Relationship between falling DLCO thresholds and sensitivity, specificity, negative and positive predictive values in 85 SSc patients, in whom significant pulmonary fibrosis had been excluded, undergoing cardiac catheterization for suspected PAH

<table>
<thead>
<tr>
<th>% DLCO thresholds</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&gt;60$ vs $\leq60$</td>
<td>74</td>
<td>45</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>$&gt;55$ vs $\leq55$</td>
<td>57</td>
<td>71</td>
<td>78</td>
<td>49</td>
</tr>
<tr>
<td>$&gt;50$ vs $\leq50$</td>
<td>39</td>
<td>90</td>
<td>88</td>
<td>46</td>
</tr>
</tbody>
</table>

**Fig. 1.** Relationship between systolic pulmonary pressures on cardiac catheter and echocardiographically determined tricuspid gradient (echo TG) in 137 patients. A clear positive correlation is evident ($r^2=0.45$); however, PAH is evident in many patients with low tricuspid gradients.

**Fig. 2.** Relationship between mean pulmonary pressures (mPAP) on cardiac catheter and corrected DLCO in 85 SSc patients without significant pulmonary fibrosis. A weak negative correlation is seen ($r^2=0.09$), but few patients with very low gas transfer do not have PAH.
The tricuspid gradient exceeded 45 mmHg in 25 of the 45 patients with pulmonary fibrosis-associated PAH, while no patient in whom PAH was excluded had a TG of >35 mmHg. Pulmonary hypertension was found in seven of the 14 patients with a TG of <35 mmHg. Fewer patients with low tricuspid gradients were studied in the pulmonary fibrosis group, as breathlessness alone was rarely considered unexplained in this population.

Discussion

The main findings of this study are that echo-estimated TG (or systolic pulmonary artery pressure) and DLCO, the most commonly used screening tools for SScPAH, perform well only in the diagnosis of advanced pulmonary hypertension. Using conservative thresholds (TG > 40 mmHg or DLCO < 55%) nearly half the patients with symptomatic PAH are left without a firm diagnosis. With lower echo TGs or higher DLCO thresholds the number of false-positive diagnoses increases progressively.

The importance of screening programmes for SScPAH has long been recognized [10]. With advances in our understanding of genetics [24], and the ability to undertake complex procedures in patients at risk of PAH [25], it is increasingly important that we understand the strengths and limitations of our diagnostic and screening tools. From our data it would appear that echo-estimated TG and DLCO cannot be regarded as adequate for the exclusion of pulmonary hypertension in breathless patients. How these tests perform in asymptomatic populations cannot be determined from this study as very few patients had asymptomatic pulmonary hypertension.

Contrary to previous authors [26], we did not find that DLCO was a useful method of identifying patients with early pulmonary vasculopathy associated with SSc. Rather, this technique appeared to identify patients with advanced PAH.

SScPAH patients are unusual in that they become symptomatic and develop reduced cardiac output at relatively low pulmonary pressures. As a consequence we have been able to analyse the impact of using lower thresholds of TG on false-positive rates of diagnosis of pulmonary hypertension. As one uses TG thresholds below 40 mmHg the issue of false positives becomes prohibitive, and thus we cannot recommend resting echocardiographic examination as a method for identifying populations with early PAH in the setting of SSc. In addition it is evident from our data that resting echocardiography may not reliably exclude PAH in breathless patients. Whether modifications such as exercise echocardiography [12], pulmonary vascular resistance estimation by colour-flow Doppler [27], or the use of new contrast media such as sonicated albumin [28] can fill this role requires further study.

Echocardiography performed better in identifying patients who require urgent referral and treatment for advanced disease. Patients suspected of having advanced IPH (formerly known as PPH—modified NYHA grade III/IV, cardiac index <2.11/min per m², right atrial pressure >11 mmHg) have a 35% annual mortality without therapy [1]. In SSc the annual mortality in this PAH population is 40% even with therapy [11]. Patients in this group need urgent invasive assessment and institution of effective therapy as proposed by Gibbs [10]. Relying on echocardiography alone to identify these patients results in a false-negative rate of 42% (patients with PAH and echo TG < 45 mmHg). However, combining echocardiography and clinical findings (modified NYHA dyspnoea grade) identifies >90% of patients with advanced PAH. Thus, any patient with SSc who has developed breathlessness while walking on the flat at a normal pace within the preceding 6-12 months should be regarded as potentially having advanced pulmonary hypertension irrespective of echocardiographic findings. Many of these patients will have lung fibrosis or other cardiac diseases as the cause of their symptoms, but urgent investigation is mandatory.

Echocardiographic assessment of TG is traditionally regarded as an extremely accurate technique [29]. However, under- and overestimations of TGs are well known to occur. Overestimates are rarely reported [30]. Underestimation of the pressure difference is expected in a minority of cases, due either to the absence of tricuspid regurgitation or inability to obtain full alignment with the regurgitant jet [31, 32]. Not surprisingly, therefore, the bulk of the inaccuracy associated with echocardiographic estimation is due to underdiagnosis of mild to moderate PAH. The frequency of overestimation of the pressure difference identified in this study is not currently well recognized, though this has been reported by other investigators [31–33]. Hinderleiter [32] found that Doppler echo estimates and invasive catheter measurements of pulmonary artery systolic pressure were significantly correlated ($r = 0.57, P < 0.001$) in 70 out of 81 patients with IPH. However, where regurgitant velocity was measurable, Doppler estimates exceeded invasive measurements in 35% of cases. These investigators concluded that echocardiography is useful in estimating the severity of PAH, but may not quantify small changes in tricuspid gradients in individual patients. The reason for this discrepancy is unknown, but several explanations have been proposed. Valchieri et al. [34] explained the lack of agreement between catheter and echo measurements by a variety of factors. These include clinical estimate instead of direct measurement of right atrial pressure, an unavoidable discrepancy between sonic beam to flow angle, and uncertainty in the assignment of the maximum velocity of the regurgitant jet. Similarly, Rich et al. [35] and Richards et al. [36] have demonstrated variations of up to 30% within 24 h in pulmonary artery pressures. Again, they concluded that this variation might lead to the overestimation recorded by the one-off echo measurement.

Limitations

Our study had several limitations. Only one aspect of the echocardiographic study has been considered in detail. During evaluation pulmonary artery acceleration times, right ventricular diameters and estimates of left ventricular diastolic dysfunction were also recorded. The former two are essentially confirmatory measures for advanced pulmonary hypertension rather than useful in diagnosing early PAH, the latter only important for excluding post-capillary causes of PAH.

Multiple operators in two institutions performed the echocardiograms and despite strict quality control at both institutions there may be significant intra-observer variability between operators’ results. This may explain some of the spread of results obtained. There was a maximum 3-month delay between the screening tests and cardiac catheterization. This may have caused bias towards the null, but none of the patients deteriorated in their functional state during this time period, suggesting disease stability. This limitation represents real-life screening rather than the ideal, which can only be occasionally achieved outside research situations.

We did not routinely investigate patients with a DLCO of 50–55% in the absence of symptoms or echocardiographic abnormalities. The significant number of symptomatic patients with PAH whose DLCO exceeded 50–55% strongly suggests that a sizeable asymptomatic population of patients with PAH and a DLCO of 50–55% has not been overlooked.

Conclusion

Resting echocardiography and pulmonary function testing are less sensitive than clinical history in identifying patients with early pulmonary hypertension in SSc patients. Both techniques identify patients with advanced PAH with moderate specificity in the setting of SSc, though echocardiography correlates better with severity of pulmonary hypertension. Neither technique has the characteristics that make it a good screening test for early
pulmonary hypertension (high sensitivity and high specificity). Echocardiography as an adjunct to clinical evaluation is the optimal current screening approach, as patients with a high mortality will be identified with a greater degree of certainty.

<table>
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<th>Key message</th>
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<td>Echocardiography as an adjunct to clinical evaluation is the optimal current screening approach to identify patients with PAH.</td>
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References