Expert consensus for performing right heart catheterisation for suspected pulmonary arterial hypertension in systemic sclerosis: a Delphi consensus study with cluster analysis

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ABSTRACT

Objective To establish an expert consensus on which criteria are the most appropriate in clinical practice to refer patients with systemic sclerosis (SSc) for right heart catheterisation (RHC) when pulmonary hypertension (PH) is suspected.

Methods A three stage internet based Delphi consensus exercise involving worldwide PH experts was designed. In the first stage, a comprehensive list of domains and items combining evidence based indications and expert opinions were obtained. In the second and third stages, experts were asked to rate each item selected in the list. After each of stages 2 and 3, the number of items and criteria were reduced according to a cluster analysis.

Results A literature search and the opinions of 47 experts participating in Delphi stage 1 provided a list of seven domains containing 142 criteria. After stages 2 and 3, these domains and tools were reduced to three domains containing eight tools: clinical (progressive dyspnoea over the past 3 months, unexplained dyspnoea, worsening of WHO dyspnoea functional class, any finding on physical examination suggestive of elevated right heart pressures and any sign of right heart failure), echocardiography (systolic pulmonary artery pressure >25 mm Hg in the presence of a pulmonary capillary wedge pressure ≤15 mm Hg), and pulmonary function tests (diffusion lung capacity for carbon monoxide <50% without pulmonary fibrosis).

Conclusions Among experts in pulmonary arterial hypertension–SSc, a core set of criteria for clinical practice to refer SSc patients for RHC has been defined by Delphi consensus methods. Although these indications are recommended by this expert group to be used as an interim tool, it will be necessary to formally validate the present tools in further studies.

INTRODUCTION

Pulmonary hypertension (PH) is a fatal disorder characterised by an increase in pulmonary vascular resistance, which leads to right heart failure. Among patients with systemic sclerosis (SSc), PH has a prevalence of about 9% according to a recent meta-analysis, and an estimated incidence of 0.61 cases per 100 patient years.1,2 Isolated pulmonary arterial hypertension (PAH) related to obstructive proliferative vasculopathy of the small and medium sized pulmonary arterial circulation and PH secondary to chronic hypoxaemia due to advanced lung disease are the two major causes of precapillary PH in SSc.3,4 PH has been associated with significantly high mortality and morbidity. One and 3 year survival rates were 78% and 47% for patients with isolated SSc–PAH. Survival is worse for those with lung disease associated SSc–PH (3 year survival 28%).5,6 In addition, 3 year survival was significantly lower in patients with SSc–PAH than in patients with idiopathic PAH (60% vs 77%).7

The gold standard for the diagnosis of PH is right heart catheterisation (RHC). Precapillary PH is defined at RHC as a mean resting pulmonary artery pressure (PAP) >25 mm Hg in the presence of a pulmonary capillary wedge pressure ≤15 mm Hg.8 The results of a recent study have supported the critical importance to systematically proceed with RHC when PH is suspected.9 Indeed, among 206 patients who were assessed by RHC for suspected PH, precapillary PH was confirmed in only 64 patients (31%) whereas 123 patients (60%) had normal haemodynamic measurements, 17 (8%) postcapillary PH and two (1%) pulmonary veno-occlusive disease. RHC is recommended in idiopathic PAH according to echocardiography parameters (tricuspid jet velocity >2.8 m/s or tricuspid insufficiency peak gradient >30 mm Hg).10 In SSc, although echocardiographic screening for the detection of PH in asymptomatic patients has been recommended by the European Society of Cardiology and the European Respiratory Society, no specific definition of PH suspicion that would lead to RHC has yet been elaborated.9 Thus in the case of suspected PH, echocardiography (increased systolic PAP (sPAP) or increased volume of tricuspid regurgitation), pulmonary function tests (reduced diffusion lung capacity for carbon monoxide (DLCO)), biomarkers (increased N terminal pro-brain natriuretic peptide (NT-proBNP) levels) or unexplained dyspnoea have been previously used alone or in combination as indications to refer patients for RHC.11–13 Thus determination of the most appropriate indications for RHC in SSc patients is still an unmet clinical need that should be addressed. This is of importance since accurate and regular screening for PH in high risk SSc patients is paramount to improve early PH diagnosis, which may improve prognosis and optimise therapy. This is highlighted by a recent study in which the 8 year survival rate was 64% in patients...
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included in a systematic detection programme, compared with 17% in patients diagnosed by routine care. In addition, RHC is an invasive technique that may be associated with complications in nearly 1% of procedures, and therefore it should be carried out in a specific well defined subset of patients.

The aim of the present study was to establish an expert consensus regarding which parameters are important and appropriate to refer patients with SSc for RHC in clinical practice. A Delphi exercise among experts in the treatment of PH–SSc was performed to identify the most appropriate and comprehensive tools and criteria for this referral process.

MATERIAL AND METHODS

Study participants

A panel of experts from the Expert Panel on Outcomes Measures in PAH related to Systemic Sclerosis (EPOSS) group represented the study steering committee. This interdisciplinary panel met in June 2010 to define the aims, scope and methodology of this study. In the next step, appropriate experts were identified and invited to participate in the Delphi exercise. To support the content validity of the process, these experts (rheumatologists, cardiologists and pulmonologists) had to have several years of experience in the diagnosis and treatment of PH, had published articles on PH in peer reviewed journals or had presented at major meetings, were study investigators in multicentre endpoint studies of PH–SSc and/or were members of consensus committees. Experts who participated in the first Delphi exercise that identified outcome measures in PH–SSc, undertaken by the EPOSS group, were invited by email and informed about the aims and scope of the Delphi study.

Delphi procedure

The Delphi method is a consensus method for medical and health service research. Such methods attempt to assess the extent of agreement (consensus measurement) and to resolve disagreement (consensus development). As opposed to the nominal group technique (NGT) and to a consensus development conference, a Delphi exercise enables the participation of experts without geographic limitations. In the Delphi procedure, participants can offer their opinions independently and confidentially without the pressure of face to face meetings. Thus many group dynamic problems are bypassed.

The three stage Delphi survey is described below.

Stage 1

The objective of the first stage was to obtain a comprehensive list of domains and parameters to be considered before referring an SSc patient for RHC. This list reflected both evidence based indications extracted from published reports on SSc–PH and expert opinions. First, members of the EPOSS steering committee (JA, OD and YA) conducted a non-systematic literature search. Two reviewers (JA and YA) independently searched articles published between 1966 and November 2010, and expanded on Pubmed, using the terms ‘systemic sclerosis’, ‘scleroderma’ or ‘CREST’, combined with ‘pulmonary hypertension’. The search was limited to studies in human adults. There was no language restriction. The medical subject heading (MeSH) terms were used for all databases, and a keyword search was substituted when the MeSH search was not available. All MeSH search terms were exploded. The results of the literature search were discussed at the first meeting of the steering committee. Based on this discussion, a preliminary list of domains and tools was set up to identify the most appropriate indications for RHC in order to improve the management of PH–SSc. Domains were defined as a grouping of highly related features that describe disease, function or physiology, and tools were defined as specific measures that help to define a domain. Then, the list of domains and tools was submitted for consideration by the whole group of 77 experts. They had the opportunity to add any domain or tool they considered potentially important in the decision to refer SSc patients for RHC in clinical practice. Newly proposed domains and tools were reviewed and categorised by members of the steering committee (JA, OD and YA). During this review, newly suggested tools/domains, if they were duplicates of already existing tools, were merged. All other newly proposed tools/domains were added to the list. Subsequent to this process, a final list of domains and tools was set up for the second stage of the Delphi exercise.

Stages 2 and 3

Stages 2 and 3 of this Delphi exercise were internet based and were completed between March and December 2011. Although web based and conventional Delphi processes have not been formally compared, internet based exercises have been shown to be feasible, cost and time saving, and better accepted by users than traditional paper based Delphi methods. To ensure security and confidentiality, each person received a personal email invitation, allowing individual access to the questionnaire on a web page specifically designed and programmed for the present Delphi study (http://questionpro.com/t/ACCsOZIwmt for stage 2 and http://questionpro.com/t/ACCsOZMKXp for stage 3). The survey was pilot tested among members of the EPOSS steering committee. Participants completed the questionnaires online. Participants included members of the steering committee who had no access to the primary data while responding to the questionnaires in each round. At the end of each round of the survey, participants could print an overview of their ratings.

The respondent group was asked to score each item, proposed after the first stage, to answer the following question: based on which parameters, performed on the basis of an annual screening of SSc patients in clinical practice, do you decide to refer patients for RHC? A 5 point scale, where a score of 1 indicating ‘not important/appropriate at all’ and 5 indicating ‘very important/appropriate’ was used for scoring. Participants did not have to provide a ranking of each individual tool to be able to finish the survey.

Before stage 3 of the Delphi survey, the number of items was reduced according to a cluster analysis based on the ratings of stage 2, as outlined below. All items in the upper cluster represented tools that were considered important in the previous stage. Then participants were asked to perform another, and final, rating of these items (stage 3 of the Delphi survey), using the same 5 point scale. When data from stage 3 were returned, a repeat cluster analysis was performed to further reduce the number of items to make it as practical as possible for clinical practice.

Refinement of the Delphi results

The final core set of items was refined after stage 3 to improve their real life applicability during a NGT webinar, including all of the coauthors of the present manuscript.

Statistical analysis

As specified above, a cluster analysis was performed by the biostatistician of the steering committee (DH) on the items of stages 2 and 3 to differentiate important/appropriate from
unimportant/inappropriate parameters. This analysis reduced the number of items in a statistically significant manner. Cluster analysis is an analysis of patterns in data by mathematical principles. It attempts to group measurement tools based on their rating patterns (categorical score 1–5). In the hierarchical cluster analysis performed in the present study, the two clusters were generated by the patterns defined by the cumulative frequency distribution of that categorical rating structure based on a squared Euclidean distance measure. All tools were included in the cluster analysis, including newly proposed items/domains from stage 1. The cluster analysis led to two clusters, with the upper cluster representing the more important and the lower cluster representing the less important items. Tools in the lower clusters were removed from further evaluation. After the mathematical analysis was completed, the steering committee carefully examined the data.

**RESULTS**

**Response rate and characteristics of participants**

Of 77 invited PAH–SSc experts, 47 (61%) participated in stage 1 of the Delphi exercise. Fifty experts (65%) participated in stage 2, 48 (62%) in stage 3 and 46 (60%) completed the three stages. Among the 50 participants responding in Delphi stage 2, 30 (60%) were rheumatologists, 15 were pulmonologists (30%) and five (10%) were cardiologists. Thirty-three experts (66%) were located in North America, 15 (30%) were from Europe, one was from Asia and one was from Australia.

**Domains and items after Delphi stage 1**

In stage 1 of the Delphi survey, a literature search allowed identification of five domains and 37 items (figure 1). The domains consisted of clinical findings, biomarkers, pulmonary function tests, echocardiography and cardiopulmonary exercise. Two domains (imaging and ECG) and 105 additional items were suggested by the respondent group of experts. Thus in stage 2, seven domains and 142 items were rated.

**Results of Delphi stages 2 and 3**

After stage 2, a cluster analysis was performed to reduce the high number of items in a rational manner based on the ratings by the respondent group. This procedure allowed discarding of 63 of the 142 initial items (figure 1, table 1). The number of domains and items had to be further reduced by repeating the cluster analysis after Delphi stage 3. In this second cluster analysis, four domains were excluded as all items belonging to these domains were categorised in the cluster of lower importance (table 1): biomarkers, cardiopulmonary exercise, imaging and ECG. The following three domains were considered, as specific items belonging to these domains were categorised in the cluster of high importance: clinical findings, echocardiography and pulmonary function tests (table 1).

The distribution of the ratings for individual tools by cluster analysis after stage 3 of the Delphi survey is shown in figure 2. Items in the upper cluster of high importance were progressive dyspnoea over the past 3 months, unexplained dyspnoea, worsening of WHO dyspnoea functional class, any finding on physical examination suggestive of elevated right heart pressures (jugular venous distension, accentuated P2, tricuspid regurgitation murmur), any sign of right heart failure, sPAP >45 mm Hg on echocardiography, dilation of the right ventricle on echocardiography and DLCO <50% predicted without pulmonary fibrosis. The experts judged this core set of indications as the most appropriate and comprehensive to refer SSc patients for RHC in the case of PH suspicion in clinical practice (table 2). These items were finally refined during a NGT webinar, leading to elaboration of a practical algorithm, approved by all of the

<table>
<thead>
<tr>
<th>Domain</th>
<th>Initial No of tools</th>
<th>Discarded after stage 2</th>
<th>Discarded after stage 3</th>
<th>Final core set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical findings</td>
<td>30</td>
<td>13</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>29</td>
<td>8</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td>33</td>
<td>16</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>11</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary exercise</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>17</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>No of tools</td>
<td>142</td>
<td>63</td>
<td>71</td>
<td>8</td>
</tr>
</tbody>
</table>

Figure 1  Flowchart of the Delphi survey showing the number of participants, and number of tools and domains from stages 1 to 3.
coauthors, that refined and prioritised the items included in the final core set, making them more practical to guide the physician towards a definite diagnosis of PH–SSc (figure 3).

**DISCUSSION**

The primary purpose of this report was to describe the process and results of a Delphi survey to develop a core set of indications to be used in clinical practice specifically for PH–SSc. This EPOSS instrument is the first pragmatic expert guideline for the detection of PH–SSc that is based on validated consensus methods. The background aim relates to the homogenisation of the management of SSc patients.

When interpreting the outcomes of this exercise, certain methodological considerations should be taken into account. We applied the usual elements of the Delphi technique, including a structured flow of information and anonymity for the participants during the exercise itself. In addition, the internet was used exclusively, thus allowing a larger number of participants to be included. Indeed, the participation rate obtained in this Delphi study was close or higher than the rate reported in other Delphi studies performed in SSc.12 14

We chose to apply a statistical procedure (cluster analysis) to differentiate between items and consequently domains of higher and lower importance. This procedure is useful because it...
Table 2  Final core set of domains and tools defined by the Delphi survey

<table>
<thead>
<tr>
<th>Domains</th>
<th>Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Dyspnoea (excluding other underlying causes of dyspnoea, not related to pulmonary hypertension); Unexplained dyspnoea; Worsening of WHO dyspnoea functional class; Right heart failure without apparent aetiology: Any finding on physical examination suggestive of elevated right heart pressures (jugular venous distension, accentuated P2, tricuspid regurgitation murmurs); Any sign of right heart failure.</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>sPAP &gt;45 mm Hg; Dilatation of right ventricle.</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td>DLCO &lt;50% without pulmonary fibrosis.</td>
</tr>
</tbody>
</table>

DLCO, diffusion lung capacity for carbon monoxide; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

Dyspnoea decreases bias. Another strength of the current study was inclusion of experts from different specialties for the Delphi survey. This reflects the routine clinical care of these patients, where experts from rheumatology, cardiology and pulmonology are required to cover the various clinical aspects of PH–SSc.

The final list of criteria included three clinical items related to dyspnoea: 'progressive dyspnoea over the past 3 months', 'unexplained dyspnoea' and 'worsening of WHO dyspnoea functional class'. Dyspnoea is a non-specific sign of PH, similar to fatigue, syncope and chest pain. Dyspnoea could be related to interstitial lung disease, myocardial involvement or anaemia. Thus the presence of one of these three symptoms requires, in part, the exclusion of other underlying causes of dyspnoea before referring patients for RHC. Dyspnoea, although non-specific, is critical in SSc–PAH and a major predictor of outcome. Of note, the item 'unexplained dyspnoea' has been previously reported for the non-invasive screening of PH–SSc in clinical practice. In a study performed on 1165 SSc patients, 206 were suspected of having PH: 145 (70%) on Doppler echocardiography, 47 (23%) on pulmonary function tests (DLCO <50% without pulmonary fibrosis) and 14 (7%) on unexplained dyspnoea. Among these 14 patients, two (14%) had confirmed PH on RHC, suggesting the usefulness of adding this item to other screening combination criteria and supporting its usefulness for early PH detection. Two additional clinical items and one echocardiographic parameter were related to right heart involvement: 'any finding on physical examination suggestive of elevated right heart pressures (jugular venous distension, accentuated P2, tricuspid regurgitation murmurs)', 'any sign of right heart failure' and 'dilation of right ventricle'. These clinical signs usually reflect advanced disease and are associated with a worse prognosis. Their presence requires rapid confirmation of PH diagnosis by RHC, after exclusion of other causes of right heart failure, such as pulmonary embolism or constrictive pericarditis. In addition, right ventricular dilation assessed by echocardiography or cardiac MRI has been identified as predictive of mortality and poor prognosis in PH.

Echocardiography is currently considered an effective screening tool for PAH in SSc. According to the WHO guidelines, baseline and annual Doppler echocardiography is recommended for early detection of PH. However, this examination is limited by its low specificity in the presence of left heart disease and elevated pulmonary capillary wedge pressure, leading to overestimation of PH prevalence. In addition, exclusion of left heart dysfunction may be challenging with echocardiography alone, and this examination cannot distinguish among the underlying causes of PAH. RHC is recommended in idiopathic PAH according to echo data. No consensus criteria have been set out for PAH–SSc, and thus different thresholds for sPAP or tricuspid jet velocity have been used in previous studies. For instance, mild PH was previously defined as tricuspid jet velocity ranging from 2.8 to 3.4 m/s, which corresponds to sPAP ranging from 36 to 51 mm Hg, if a fixed atrial pressure estimate of 5 mm Hg is used. In the French ItinerAIRstudy that enrolled 599 patients, RHC was performed regardless of symptoms in patients with a tricuspid jet velocity >3 m/s or with dyspnoea and tricuspid jet velocity of 2.5–3 m/s. In several other studies, sPAP >40 mm Hg was chosen as a threshold for PH suspicion as the negative predictive value of a Doppler echocardiographic threshold of 40 mm Hg was 92%. In our Delphi procedure, experts selected sPAP >45 mm Hg; in a recent study using a
threshold of 47 mm Hg, specificity was 96% and the positive predictive value was 93% for the detection of PH.3 The threshold of 45 mm Hg should be further validated, first as a single tool to refer SSc patients for RHC and then in combination with other parameters, including pulmonary function tests, unexplained dyspnoea and biomarkers.

The item DlCO <50% without pulmonary fibrosis was considered by the experts as an important and relevant criterion to refer a patient for RHC. This tool predicts the development of PAH at 3 years.16 In another study, decreased DlCO <50% identified a subset of patients with confirmed PH by RHC despite normal sPAP on echocardiography.1 Moreover, a retrospective case matched controlled study correlated progressive decline in DlCO and the subsequent development of isolated PAH.28 This study also showed that patients presenting with limited cutaneous SSc, who subsequently developed isolated PAH, had a progressive decrease in DlCO, starting >10 years before the diagnosis of PAH. These data, together with the results of our Delphi procedure, highlight the importance of this tool for suspicion of PH and support its further validation, alone or in combination with other tools, to refer SSc patients for RHC.

Taken together, this multidisciplinary Delphi survey defined, on a statistical basis, a core set of domains and tools that should be used to refer patients with SSc for RHC in clinical practice. It must be emphasised that the final list of domains and tools of this Delphi survey is the subjective opinion of experts in the field. Thus it is important to mention that the non-inclusion in the final core set does not mean that the excluded items cannot qualify as appropriate parameters to refer patient for RHC. As an example, a biomarker such as NT-proBNP might be considered as a research tool for the experts at the current time but may become a valid criterion to refer SSc patients suspected for PH for RHC. Indeed, growing evidence supports the use of NT-proBNP in screening algorithms for PH, as levels of this biomarker have been shown to predict the occurrence of pre-capillary PH in patients with SSc.10 29

This should not be confused with validation of particular domains and measurement tools, which was not the aim of the present study. The final core set defined by this Delphi survey can be seen as a priority list for measurement tools for which full validation should be achieved first in the following years, both for clinical practice and in terms of additional research.

Contributors Conception and study design: JA, DEF, OD and YA. Acquisition of the data: JA, DH, CFO, OD and YA. Analysis of the data: JA, DH, OD and YA. Preparation, drafting and final validation of the manuscript: JA, DH, DEF, CFO, OD and YA.

Competing interests None.

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