Pulmonary hypertension in lung diseases: Survey of beliefs and practice patterns

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Received 25 September 2009; accepted 30 December 2009
Available online 21 January 2010

KEYWORDS
Bosentan; Lung disease; Pulmonary fibrosis; Pulmonary hypertension; Sarcoidosis; Sildenafil

Summary
Introduction: Pulmonary hypertension can be associated with decreased functional capacity and poor prognosis in patients with parenchymal lung diseases (PLD). Yet, little attention has been given to current beliefs and practice patterns.
Methods: An 18-question survey was submitted electronically to members of four Networks of the American College of Chest Physicians.
Results: Analyzable responses were received from 453 physicians. Most (95%) respondents reported testing for PH in patients with PLD using transthoracic echocardiography (TTE) or right-heart catheterization (RHC) and believed that PH could occur in the absence of severe compromise in pulmonary function (70%) and hypoxemia (50%). Approximately 30% of physicians reported not performing RHC to confirm a diagnosis of PH before initiating therapy.
Most respondents (92%) felt that medical therapy was effective and the medication of first choice was either bosentan or sildenafil. Most respondents believed that treating PH in these patients improves quality of life (63%) and dyspnea (67%), but were less sure about the impact on functional capacity and survival.
Conclusions: Approximately 30% of physicians do not perform RHC to confirm this diagnosis prior to initiating therapy. Despite relatively little supportive evidence, most physicians treat with vasoactive medications and believe that medical therapy confers benefit.

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Introduction

Pulmonary hypertension (PH) is defined by the presence of a resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg. 1-3 PH may occur as an ‘idiopathic’ disease of the pulmonary vasculature or may be the result of underlying cardiac and/or pulmonary diseases. 1-3 In fact, PH associated with underlying pulmonary diseases is far more common than idiopathic PH. 4-5 Several reports 6-10 in patients with various forms of advanced parenchymal lung diseases (PLD) have shown a high prevalence of PH. These and other studies have also indicated that the occurrence of PH in patients with advanced PLD (PLD-PH) is associated with increased functional limitation and mortality. 6-8,11-13

It is, however, less clear whether pharmacotherapy for PLD-PH results in significant functional or survival benefit. No prospective, randomized trials evaluating this approach have yet been published and the literature on the subject remains largely limited to case series or case reports. 14-17 Several recent reports have highlighted important limitations in benefit obtained either due to continued progression of the underlying PLD or worsening of associated hypoxemia. In addition, consensus guidelines only address treatment of patients with pulmonary arterial hypertension (PAH) and do not address PLD-PH. 9 Given this lack of objective evidence and the continued need to provide relief to patients, we conducted a survey to assess beliefs of physicians involved in caring for these patients regarding pulmonary hypertension, parenchymal lung disease. Identi-

Methods

Survey creation

Survey components were initially identified by searching MEDLINE and EMBASE from 1998-2008 using the following key words: COPD, interstitial lung disease, pulmonary fibrosis, pulmonary hypertension, parenchymal lung disease. Identified references were reviewed to determine medications commonly used for PLD-PH and any reports on therapy including randomized trials, cohort studies, case reports or any guidelines or treatment algorithms. The survey was structured into three sections (Appendix 1). The first section focused on demographic and epidemiologic data, the second characterized the diagnostic approach, and the third focused on beliefs regarding treatment and its efficacy. A draft survey was then distributed to clinicians with a known interest and expertise in PH (i.e., all coauthors). These experts were asked to comment on the relevance of each survey item and the clarity of each response option. The feedback and results of this pre-pilot survey were used to further refine the survey instrument. The final survey instrument was further examined for face validity, content validity, internal consistency, and construct validity by an expert with formal training in survey development.

Survey population and administration

The survey was approved by the Steering Committee of the Pulmonary Vascular Disease Network of the American College of Chest Physicians (ACCP) and was submitted to the members of four Networks: the Pulmonary Vascular Disease, Interstitial and Diffuse Lung Disease, Cardiovascular Disease and Hypertension, and the Clinical Pulmonary Medicine Networks. To maximize response, the survey was administered electronically by the ACCP 3 times biweekly between January and March 2008. The survey was accompanied by a brief introduction of the purpose of the survey. All responses were anonymous, respondents were allowed a partial response, and only one response per respondent was permitted.

Data analysis

Individual survey responses were compiled for overall analysis. Categorical measures were summarized using frequencies and percentages. Subsequently, responses were stratified by physician respondents characterizing themselves as being in private practice [Group 1] vs. those working in academic medical centers or university hospitals [Group 2]. Categorical measures were summarized using frequencies and percentages. Pearson Chi-square test was used unless listed otherwise. Values of p < 0.05 were considered statistically significant. SAS 9.1.3 software (SAS Institute, Cary, NC) was used for all analyses.

Results

Characteristics of survey respondents

The survey was sent to a total of 2941 physicians; 20 (0.6%) were not deliverable and 453 (16%) responded. Of these, 426 (94%) were pulmonologists, 8 (1.7%) were cardiologists, 1 was a rheumatologist, and 21 (4.6%) did not identify their specialty. Among pulmonologists, 219 (51.5%) were in private practice [Group 1] and 207 (48.5%) worked in an academic setting [Group 2]. Sixty-six percent of respondents saw <6 patients of PLD-PH per month and 34% saw ≥6.

PH prevalence, significance, and hemodynamic characteristics

Twenty-two percent of respondents felt that ≤10% patients with COPD in their practice had PH whereas only 5% of respondents felt this was true of patients with IPF (Fig. 1). Sixteen percent of the respondents felt that PH occurred in ≥30% patients with COPD, whereas 40% of respondents felt >30% of patients with IPF had PH. Ten percent of respondents felt that >50% of patients with IPF had PH.

Forty eight percent of respondents thought that patients with PLD-PH have a normal cardiac index (48%), and most thought that right atrial pressure (73%) and pulmonary vascular resistance (84%) are elevated, and that wedge pressure is normal (76%). Six percent of respondents felt that severe PH did not occur in association with PLD. 70% felt that severe PH could be seen in PLD patients with mild or moderate lung disease, and 50% felt severe PH could occur in the absence of hypoxemia (Fig. 2). Most respondents were of the opinion that the presence of PH was an indicator of poor prognosis (Fig. 3), and an important determinant of functional limitation, dyspnea, and hypoxemia in patients with PLD.
Screening and diagnosis

Five percent of respondents do not screen PLD patients for PH (Fig. 4) and 18% of respondents screen all PLD patients for PH. The most common reasons for screening were unexplained shortness of breath, abnormally low diffusion capacity for carbon monoxide, and associated hypoxemia.

The tests most commonly used for screening of PH included right-heart catheterization (RHC; 62%) and transthoracic echocardiography (TTE; 35.6%). Only a minority found spirometry, diffusion capacity for carbon monoxide, PaO2, brain natriuretic peptide measurement, or radiographic imaging useful in screening for PH.

Regarding the need for RHC, 33% of respondents felt that a RHC was not required to make a diagnosis of PH in a patient suspected to have PH by TTE. In the presence of right ventricular dilatation on TTE, 55% of physicians performed RHC if the right ventricular systolic pressure (RVSP) exceeded 40 mmHg and 72% performed RHC if the RVSP exceeded 45 mmHg (Table 1). In the absence of right ventricular dilatation, only 19% performed a RHC with a RVSP ≤40 mmHg and 62% performed a RHC only if the RVSP was >50 mmHg.

Treatment of PH in patients with PLD

Most respondents (92%) felt that currently available treatment modalities are effective in treating PLD-PH. Sixteen percent of respondents treated all patients with PLD-PH with vasoactive medications, whereas others treated patients in selected situations including: significant functional limitation (40%), severe PH (34%), PH out of proportion to the degree of compromise in pulmonary function (40%), and persistent PH despite oxygen supplementation (37%). Only 15% of respondents did not treat any patients with IPF-associated PH, while 38% of respondents treated 11% or more of patients, and 6% treated >50% of patients with IPF-associated PH with vasoactive medications (Fig. 5). In contrast, a much higher proportion of respondents did not treat PH related to COPD (36%), sarcoidosis (30%), and cystic fibrosis (59%) with vasoactive medications.

Seventy one percent of respondents felt that oxygen therapy was the most effective treatment of PLD-PH (Fig. 6). Parenteral prostanoids, endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE5 inh), and inhaled prostanoids were all felt to be effective modalities in treating PLD-PH patients. The least effective forms of treatment were felt to be immunosuppressive agents (such as azathioprine, cyclosporine, and imatinib), systemic corticosteroids, and calcium channel antagonists. Ninety percent of physicians reported treating patients with supplemental oxygen in the case of desaturation to <90% during exertion or sleep. However, only 50% of respondents performed nocturnal oximetry studies to look for nocturnal desaturation in these patients.

First-line therapy was bosentan or sildenafil for PH associated with IPF or sarcoidosis and sildenafil for PH associated with COPD (Fig. 7). A significant proportion of respondents felt that PH-specific vasoactive therapy improved six-minute walk distance (44%), quality of life (64%), and dyspnea (67%) among patients with PLD. However, only a minority (24%) felt that such therapy resulted in improved survival. Thirty three percent of respondents felt that an increase in 6MWD and functional capacity, even in the presence of worsening hypoxemia on PH-specific vasoactive therapy, represented an adequate therapeutic response; 33% disagreed with this statement, and 34% were unsure. Surprisingly, only 12% of respondents were concerned about the potential for worsening hypoxemia.
hypoxemia with the use of parenteral prostanoids in patients with PLD-PH.

The most useful methods for monitoring treatment response (in descending order of perceived accuracy) were: RHC followed by TTE, WHO/NYHA functional class assessment, 6MWD, and brain natriuretic peptide levels.

Comparing respondents by location of practice

Overall, there was a remarkable degree of concordance in practice patterns between the physicians in private practice (Group 1) and those in academic institutions (Group 2). Approximately 37% of respondents in Group 1 and 27% in Group 2 felt that a RHC was not needed to make a diagnosis of PH prior to initiating therapy. Physicians in Group 2 were more likely to view pulmonary rehabilitation as important in the management of their patients (32% vs. 19%; p = 0.02) and physicians in Group 1 were more likely to perform nocturnal oximetry studies (49% vs. 39%; p = 0.04). A significant proportion of physicians in both groups (30% in Group 1 and 40% in Group 2) did not provide oxygen supplementation to their patients if they desaturated to <90% during sleep. Regarding treatment of PLD-PH, physicians in Group 2 were more likely to only treat patients with "PH out of proportion to the degree of lung dysfunction" (p = 0.01) or "severe PH" (p = 0.09) compared to Group 1. Choice of first-line agents was not significantly different between the groups, irrespective of

Table 1   Results in response to the question: at what level of echocardiographic abnormality do you ask your patient to undergo right-sided heart catheterization if there is no evidence of left-sided cardiac dysfunction?

<table>
<thead>
<tr>
<th>Right ventricular systolic pressure</th>
<th>Normal RV (cumulative % respondents)</th>
<th>Dilated or dysfunctional RV (cumulative % respondents)</th>
</tr>
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<tbody>
<tr>
<td>&gt;35 mmHg</td>
<td>7</td>
<td>29</td>
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<tr>
<td>&gt;40 mmHg</td>
<td>19.5</td>
<td>55</td>
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<td>&gt;45 mmHg</td>
<td>38</td>
<td>72.5</td>
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<td>&gt;55 mmHg</td>
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<td>&gt;60 mmHg</td>
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underlying disease. In terms of treatment response, more physicians in Group 1 felt that vasoactive therapy significantly improved 6MWD, functional capacity (48% vs. 37%; \( p < 0.01 \)), and survival (25% vs. 18%; \( p = 0.09 \)) compared to physicians in Group 2.

**Discussion**

This study represents the first large-scale assessment of beliefs and self-reported clinical practice patterns of physicians caring for patients with PLD-PH. This survey was able to capture a large sample of pulmonary specialists in academic centers as well as in private practice and thus includes perspectives from both settings. The salient findings of our study are as follows: (1) physicians believe that PH occurs in a significant proportion of patients with PLD and that PH in these patients is an indicator of poor prognosis and significant functional limitation; (2) despite its limitations, TTE remains the most commonly used screening test for PH in this setting; (3) approximately 30% of physicians in practice do not perform RHC to confirm the diagnosis of PH prior to initiating therapy; and (4) despite relatively little supportive evidence, most physicians treat these patients with vasoactive medications and believe that these medications can confer significant benefit.

Notably, most respondents felt that >10% of patients with various forms of PLD have associated PH. We suspect that this perception may be colored by the fact that most publications relating to this subject have included patients being evaluated for surgical procedures such as lung volume reduction surgery and/or lung transplantation. By definition, these patients have more advanced PLD and are therefore more likely to have significant hypoxemia and PH. The true prevalence of PH in an unselected sample of patients with any form of PLD remains unknown but is likely to be lower than that in a subgroup of patients with advanced PLD. Another point of interest is that, in contrast to available

**Figure 5** Percentage of patients with PLD-associated PH receiving PH-specific vasoactive therapy.

**Figure 6** Perceptions regarding the most and least efficacious options in treating PLD-associated PH. O2, oxygen; ERA, endothelin receptor antagonist; PDE, phosphodiesterase-5 inhibitor; PP, parenteral prostanoid analogue; IP, inhaled prostanoid analogue; PR, pulmonary rehabilitation; AZA/cyclo, azathioprine/cyclophosphamide; SCS, systemic corticosteroids; CCB, calcium channel blockers.
data, respondents felt that PH was more prevalent in patients with IPF than in any other form of PLD. Most respondents appreciated that severe PH can occur in patients with PLD, including, on occasion, in those with relatively mild to moderate PLD. In addition, the survey respondents typically knew that the presence of PH is an indicator of poor functional capacity and shortened survival in these patients. These findings have been extensively reported in the literature in association with IPF, COPD, and sarcoidosis. On the other hand, approximately 20% of respondents did not indicate that PH is an important determinant of gas exchange, functional limitation, and survival in these patients.

Most survey respondents reported using TTE to screen for PH in patients with PLD despite numerous studies that have highlighted the significant limitations of TTE in this regard. Nonetheless, TTE remains the most commonly used method to screen for PH due to its non-invasiveness, widespread availability, and relatively low cost. Some survey respondents reported using pulmonary function tests, PaO₂, and brain natriuretic peptide levels to diagnose PH. Several studies have shown that the severity of pulmonary function abnormality (including diffusing capacity) and PaO₂ correlate loosely with the presence or absence of PH; however, their value in screening for PH remains unclear.

One of the most surprising findings of this survey was that approximately 30% of physicians from both groups were not using RHC to confirm or refute the diagnosis of PLD-PH patients before initiating therapy. We find this perplexing in view of the extensive literature regarding the limitations of non-invasive diagnostic methods, including TTE, in making a diagnosis of PH in these patients. Establishing the correct diagnosis in PH is extremely important because its presence has significant prognostic implications. In addition, vasoactive medications are expensive and may have significant side effects. Although, the role of RHC in PLD has not been well-defined, we believe that it is an important diagnostic tool in these patients and should always be performed before any vasoactive therapy is considered.

Most respondents felt that oxygen supplementation is the most effective treatment for PLD-PH. In several studies, a low diffusion capacity for carbon monoxide and the presence of hypoxemia were the abnormalities most closely associated with the presence of PH. Hypoxic pulmonary vasoconstriction is also felt to play an important role in the development of PH in patients with PLD; the duration and severity of hypoxemia required remain poorly defined and might vary on a case by case basis. Minai et al. reported that 70% of patients with PAH alone have nocturnal hypoxemia and among these patients, evaluating for exertional hypoxemia was not a good screening test for the presence of nocturnal hypoxemia. Current recommendations suggest providing patients with supplemental oxygen to keep oxygen saturation >90% during sleep or with activity. Most physicians in our survey reportedly followed these recommendations; still, only 50% of respondents reported performing nocturnal oximetry testing on patients with PLD-PH.

In contrast to available data, 92% of respondents felt that currently available treatments were effective in treating PLD-PH. To our knowledge, none of the currently available treatment modalities has been sufficiently tested in patients with PLD-PH to establish efficacy. Recent case series have pointed to short-term improvement in functional capacity with vasoactive medications, but none report a sustained benefit. Perhaps the strongest case for an effective intervention can be made for oxygen supplementation in COPD-associated PH, for which some studies have suggested stabilization or improvement in pulmonary hemodynamics. Overall, we submit that the benefits of oxygen supplementation in the treatment of PLD-PH requires further study.

Notwithstanding the lack of evidence for efficacy, physicians reported treating a significant proportion of patients with PLD-PH with various vasoactive medications. Oral vasoactive agents remained those most commonly used, likely due to ease of availability, cost, and the concern for worsening hypoxemia from the use of parenteral prostanooid analogues. Most respondents only treated selected subgroups of patients with PLD-PH. These groups included those with significant functional limitation, severe PH, PH out of proportion to the degree of compromise in pulmonary function, and persistent PH despite oxygen supplementation. However, these subgroups remain
very poorly defined in the literature and therefore subject to personal bias. Such subjective patient selection reflects a lack of evidence in the field and the need for more studies, some of which are currently underway and may help provide clarity going forward.

Several limitations of our study warrant comment. First, notwithstanding the large absolute number of respondents (N = 453), we cannot exclude the possibility of a sample bias in that only 16% of all physicians who were approached responded. Still, this response rate is typical of on-line surveys and systematic biases between responders and non-responders have not been reported. Also, the survey was only sent to selected networks of the ACCP thought to have an interest in the subject matter and therefore, results might not be representative of the community of general pulmonologists. Furthermore, as neither cardiologists nor rheumatologists were represented in the survey, our results may not apply to them.

In summary, respondents to this survey of ACCP members regarding the diagnosis and management of PH associated with PLD indicated that PH is common in PLD, that they did not always perform RHC to confirm the diagnosis before therapy was initiated, and that therapy with vasoactive medications confers benefit. To the extent that these impressions are discordant with data from the available literature, our findings point out the need for further research and for better methods to disseminate known findings to the clinical community.

Conflict of interest

Omar A. Minai is a member of the Scientific Advisory Board and Speakers Bureau for Actelion, Gilead, and United Therapeutics.

Steven D. Nathan is on the speakers bureau, has consulted for and received research funding from Gilead, United Therapeutics and Actelion Pharmaceuticals.

David B. Badesch has received honoraria for service on Steering Committees or Advisory Boards from Actelion/Cotherix, Gilead/Myogen, Encysive, Pfizer, United Therapeutics/Lung Rx, Lilly/ICOS, MondoBiotech, MondoGEN, and GlaxoSmithKline. Nicholas Hill and James K. Stoller do not report any conflicts of interest.

Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.rmed.2009.12.015.

References


