Clinical Profile and Underdiagnosis of Pulmonary Hypertension in US Veteran Patients

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Background—Pulmonary hypertension (PH) is a key contributor to cardiovascular morbidity and early mortality; however, reports are lacking on the epidemiology of PH in at-risk patient populations.

Methods and Results—The echocardiography registries from 2 major Veterans Affairs hospitals were accessed to identify patients with at least moderate PH, defined here as a pulmonary artery systolic pressure ≥60 mm Hg detected echocardiographically. From a total of 10,471 individual patient transthoracic echocardiograms, we identified moderate or severe PH in 340 patients (332 men; mean, 77 years; mean pulmonary artery systolic pressure, 69.4±10.5 mm Hg), of which PH was listed as a diagnosis in the medical record for only 59 (17.3%). At a mean of 832 days (0–4817 days) following echocardiography diagnosing PH, 150 (44.1%) patients were deceased. PH was present without substantial left heart remodeling: the mean left ventricular ejection fraction was 0.50±0.16, left ventricular end-diastolic dimension was 5.0±0.9 cm, and left atrial dimension was 4.4±0.7 cm. Cardiac catheterization (n=122, 36%) demonstrated a mean pulmonary artery pressure of 40.5±11.4 mm Hg, pulmonary capillary wedge pressure of 22.6±8.9 mm Hg, and pulmonary vascular resistance of 4.6±2.9 Wood units. Diagnostic strategies for PH were variable and often incomplete; for example, only 16% of appropriate patients were assessed with a nuclear ventilation/perfusion scan for thromboembolic causes of PH.

Conclusions—In an at-risk patient population, PH is underdiagnosed and associated with substantial mortality. Enhanced awareness is necessary among practitioners regarding contemporary PH diagnostic strategies. (Circ Heart Fail. 2013;6:906-912.)

Key Words: diagnosis ■ epidemiology ■ pulmonary hypertension

Pulmonary hypertension (PH) is the principal intermediate pathophenotype responsible for right-sided congestive heart failure.1 When present, even subclinical pathological changes to cardiovascular function mediated by untreated PH are associated with increased morbidity and decreased longevity.2 Observations from epidemiological reports have indicated that compared with other community-based populations, the US military veteran patient population has an increased prevalence of PH-associated primary lung and cardiovascular disease3; however, the epidemiology of PH for this population is not known. In the current study, we leveraged the unique strengths of the VA clinical database, which is a universal and centralized electronic medical record, to test our hypothesis that PH is a prevalent form of cardiovascular disease in a cohort of veteran patients. We further aimed to investigate the clinical profile and diagnostic strategies used for PH in this patient population.

Methods

The study was approved by the VA investigational review board for patient safety and privacy and complies with the Declaration of Helsinki. Databases hosting echocardiogram results were analyzed for all studies performed at the Veterans Affairs Boston Health Care System (Boston, MA) and the Providence Veterans Affairs Medical Center (Providence, RI) from July 1, 2008, through July 1, 2011. These institutions function as referral centers for US military veterans residing in New Hampshire, Maine, Massachusetts, Vermont, and Rhode Island.

Echocardiographic Definition of PH

At both Veterans Affairs Boston Health Care System and Providence Veterans Affairs Medical Center, the Crystal Reports software program was used to catalog transthoracic echocardiography data.
Focused studies to evaluate specific cardiovascular diseases (eg, cardiac tamponade), exercise or dobutamine stress echocardiograms, and transesophageal echocardiograms were excluded from the analysis. PH is defined as pulmonary artery systolic pressure (PASP) ≥40 mm Hg, which was calculated by the sum of the transtricuspid gradient plus estimated right atrial pressure.

Electronic Medical Record

The centralized Veterans Health Information System and Technology Architecture electronic medical record was accessed to acquire patients’ medical information and clinical data. Active medications at the time of analysis were recorded. In the event patients were deceased at the time of analysis, then the most complete medication list before death was used for analysis.

Diagnostic Testing

Patients underwent a 2-dimensional transthoracic echocardiogram as clinically indicated using standard ultrasound equipment by 3 major vendors (GE Healthcare, Milwaukee, WI; Philips, Bothel, WA; and Siemens, Erlanger, Germany). A cardiologist experienced in echocardiography interpreted all studies using the Phillips Xcelera Cardiac Reporting system. Left atrial and left ventricular (LV) dimensions were measured in the parasternal long axis view. The LV ejection fraction was assessed using the biplane Simpson’s method, and diastolic functional classification was performed as outlined in the American Society of Echocardiography document for LV functional analysis. All right heart catheterizations were performed in the supine position according to standard, previously published methods for acquiring invasive cardiopulmonary hemodynamic measurements. The cardiopulmonary hemodynamic criteria used to consider patients for a diagnosis of World Health Organization (WHO) Group 1 PH (ie, pulmonary arterial hypertension [PAH]) or chronic thromboembolic pulmonary hypertension (CTEPH) were: mean pulmonary artery pressure ≥25 mm Hg, pulmonary vascular resistance ≥3.0 Wood units, and pulmonary capillary wedge pressure ≤16 mm Hg. Ultimately, the determination of WHO Group classification was adjudicated by 2 cardiologists and a pulmonologist, each with substantial clinical experience in the clinical management of patients with pulmonary vascular disease.

Statistical Analysis

All statistical analyses were performed using Origin 9.0 (Northampton, MA). Categorical variables are reported as frequencies with percentages. Unless otherwise indicated, continuous data are expressed as the mean±SD. Normality was tested by using the Shapiro–Wilk test. When samples were normally distributed, an unpaired Student t test was used to compare 2 independent groups. When data were not normally distributed, comparisons between 2 groups were made with use of the Mann–Whitney test. Statistical significance was defined as P<0.05.

Results

From a total of 10471 individual patient echocardiograms screened, 1437 (13.7%) patients met the predefined PH search criteria. We next elected to focus further analyses on patients with an estimated PASP ≥60 mm Hg, a subpopulation of the cohort most likely to meet conventional clinical criteria for severe PH, and thereby express a representative profile of clinically meaningful PH in veterans (Figure 1). We identified 343 patients with echocardiographically assessed PASP ≥60 mm Hg; of these patients, 3 were excluded from further analysis due to the unavailability of clinical information. The remaining patient cohort (n=340) was largely male (97.6%; mean age, 78 years; range, 52–100); at a mean of 832 days (0–4817 days) following echocardiography demonstrating evidence of moderate or severe PH, 150 (44.1%) patients were deceased (Table 1). The mean number of comorbidities per patient listed in the problem list was 13.8±6.1, with cardiovascular and pulmonary diseases accounting for 5.3±2.7 and 1.3±1.3 comorbidities per patient, respectively. Despite this, PH was reported as a diagnosis in the problem list for only 59 (17.3%) patients.

Diagnostic tests recommended to evaluate the cause of PH that were performed in this cohort are illustrated in Figure 2. Among the entire cohort (n=340), a minority of patients underwent pulmonary function testing with lung diffusivity capacity (40.5%), right heart catheterization (35.8%), or pulmonary thromboembolic assessment with ventilation/perfusion scan or thoracic computed tomographic angiography (25.8%). For patients with a clinical and cardiopulmonary hemodynamic profile that was compatible with CTEPH (n=18), a ventilation/perfusion scan to diagnose CTEPH occurred in only 3 (16%) patients. Seventeen patients meeting hemodynamic criteria for WHO Group 1 PH (ie, PAH) had an appropriate diagnostic evaluation including an echocardiogram and pulmonary function test. Of these, 4 patients did not have any evidence of...
significant cardiopulmonary disease (ie, LV ejection fraction <0.50, significant left-sided valvular disease, ratio of forced expiratory volume 1 second to forced vital capacity <0.7, or pulmonary fibrosis) and, thus, may represent WHO Group 1 PH.

Of the 10 most prevalent comorbidities in the overall PH cohort, 9 were primary diseases of the cardiovascular or pulmonary system (Figure 3), which is reflected in the distribution of patients’ medications that emphasize pharmacotherapies commonly used for the treatment of systemic hypertension, congestive heart failure, coronary artery disease, and/or chronic obstructive lung disease (Figure 4). Pulmonary circulation-specific pharmacotherapies were reported for 8 (2.3%) and 3 (0.8%) patients prescribed a phosphodiesterase type-V-inhibitor or endothelin receptor antagonist, respectively.

Echocardiographic and Hemodynamic Characteristics

Analysis of echocardiography data in this cohort demonstrated a mean PASP of 69.4±10.5 mm Hg without evidence of substantial left heart remodeling: the mean LV ejection fraction was 0.50±0.16, intraventricular septal thickness was 1.1±0.4 cm, LV end-diastolic dimension was 5.0±0.9 cm, and left atrial dimension was 4.4±0.7 cm (Table 2). This degree of left atrial enlargement has been previously identified as a marker of left atrial hypertension-associated PH.10 Therefore, the distribution of diastolic function in our cohort was assessed next. Interestingly, although class III (reversible restrictive) or class IV (fixed restrictive) diastolic dysfunction was present in 17.0% of patients, diastolic function was reported to be indeterminate in the majority of the cohort (57.6%) (Figure 5), indicating a potential limitation of this echocardiographic application for diagnosing PH due to diastolic dysfunction-induced left atrial hypertension in this patient population.

Complete hemodynamic data were recorded for 90 patients (Table 3). The mean pulmonary artery pressure was 40.5±11.4 mm Hg and pulmonary capillary wedge pressure was 22.6±8.9 mm Hg; despite elevations in pulmonary capillary wedge pressure, the mean pulmonary vascular resistance was 4.6±2.9 Wood units. Compared with patients not undergoing cardiac catheterization (n=218), patients in whom cardiac catheterization was performed (n=122) had a greater cardiovascular disease burden (4.9±2.6 versus 5.8±2.9 diagnosed cardiovascular comorbidities, P<0.01) and evidence of more severe left heart remodeling, including decreased LV ejection fraction (0.51±0.16 versus 0.47±0.17, P<0.03), increased LV end-diastolic dimension (4.9±0.9 versus 5.2±0.8 cm, P<0.01), as well as more severe PH assessed.

Table 1. Clinical and Diagnostic Profile of Pulmonary Hypertension in Veteran Patients

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, %</td>
<td>332 (97.6)</td>
</tr>
<tr>
<td>Deceased, %</td>
<td>150 (44.1)</td>
</tr>
<tr>
<td>Age in years, range</td>
<td>77 (52–100)</td>
</tr>
<tr>
<td>PH diagnosed in the medical record, %</td>
<td>59 (17.3)</td>
</tr>
<tr>
<td>Patient comorbidities, range</td>
<td>13.8 (0–40)</td>
</tr>
<tr>
<td>Cardiovascular comorbidities, range</td>
<td>5.3 (0–16)</td>
</tr>
<tr>
<td>Pulmonary comorbidities, range</td>
<td>1.3 (0–6)</td>
</tr>
<tr>
<td>Days from diagnosis, range</td>
<td>832 (0–4817)</td>
</tr>
</tbody>
</table>

The clinical characteristics of patients from 2 major Veterans Affairs hospitals undergoing transthoracic echocardiography demonstrating a pulmonary artery systolic pressure ≥60 mm Hg were analyzed. Values are presented as n (%) for the categories: men, deceased, and PH diagnosed in the medical record. Values are presented as mean (range) for the categories: age, patient comorbidities, and days from diagnosis. For each category, the total number of patients included in the analysis is n=340, except the category days from diagnosis (n=82), which indicates the time elapsed between initial detection of severe PH of any severity by echocardiography and patient death. PH indicates pulmonary hypertension.
by PASP on echocardiography (67.5±9.8 versus 72.0±12.4 mm Hg, P<0.002) (Table 4). By contrast, there was no difference between groups in pulmonary disease burden or performance on pulmonary function testing.

**Discussion**

We report that the prevalence of PH in an unselected cohort of veteran patients is ≈14%, which compares favorably to rates of PH reported previously for populations characterized by a high burden of comorbid diseases known to promote pulmonary vascular dysfunction.\textsuperscript{11–13} Our data demonstrate that despite the well-established relationship between PH and cardiovascular morbidity and mortality,\textsuperscript{2,14} this disease remains substantially under recognized in clinical practice. Evidence in support of this assertion was that less than one fifth of patients with echocardiographically assessed PASP ≥60 mm Hg had PH listed in the problem list in the medical record, and, when ultimately established, the diagnosis was delayed and associated with substantial mortality.

Expert consensus guideline statements recommend a multidisciplinary strategy to assess PH classification and prognosis,\textsuperscript{9,15} and that the identification of one pathophysiological mechanism accounting for patients’ PH phenotype does not exclude alternative mediators of disease expression.\textsuperscript{9} This is particularly salient to our study population, in which multiple cardiovascular, pulmonary, and hematologic comorbidities were present that adversely affect pulmonary artery pressure. Nevertheless, we observed that only a minority of patients with evidence of PH on echocardiography underwent at least one consensus guideline-recommended test\textsuperscript{9} to assess disease etiology or severity. For example, despite sound clinical evidence indicating that PH due to chronic thromboembolic disease is a treatable form of PH,\textsuperscript{16,17} evaluating for this was uncommon in our study cohort.

Although the available cardiac catheterization and pulmonary function test data indicate that PH due to left atrial hypertension (WHO Group 2 PH) and/or chronic lung disease (WHO Group 3) was well represented in this study cohort, the high proportion of patients in whom a PH diagnostic
evaluation was incomplete confounded an accurate determination of PH prevalence by disease mechanism. Interestingly, findings demonstrating that right heart catheterization tended to occur in patients with more severe left heart remodeling on echocardiography suggest that this, rather than PH severity per se, may be a key factor in the decision to undergo diagnostic right heart catheterization.

Despite the elderly nature of our cohort, we identified 4 patients with a clinical profile consistent with PAH. This observation is in concert with reports indicating that PAH is increasingly diagnosed initially in older patients. Indeed, the mean age of our patients with PAH (68 years) is well within the age range reported for other cohorts in which this form of PH diagnosis was late in life.

Findings from this study are in agreement with those of previous reports, indicating the limitations to echocardiography as a central method by which to assess the extent and cause of PH, and this may be of particular importance to the veteran patient population. For example, our observation that diastology was indeterminate in a majority of the cohort despite enlargement of the left atrium illustrates a potential limitation to the effectiveness of using this echocardiographic strategy to implicate impaired diastolic function as a pathophysiological mechanism by which to account for PH. Atrial fibrillation and mitral valvular disease, which are established confounders to the echocardiographic assessment of diastolic function and PASP, and which were present in a sizeable proportion of our cohort, are likely to have hindered the diagnostic utility of echocardiography for these purposes.

Collectively, these observations provide support to future endeavors using novel echocardiography scoring systems that do not rely solely on PASP or left atrial dimension for predicting PH severity.

This study has numerous limitations that merit consideration when interpreting our findings. First, selection and referral bias, which are inherent to our retrospective study design, are likely to have confounded the accurate determination of PH prevalence in veteran patients. Second, the identification of an appropriate control group necessary to assess the consequences accurately of PH on key outcome measures, such as hospitalization or survival, was not possible due to unavailability of these data in veteran patients without PH or only mild PH. Third, our study was not designed to assess appropriateness of treatment, and,
therefore, any speculation relating to the quality of care for PH within the VA healthcare system cannot be supported. Fourth, the possibility exists that certain PH diagnostic tests, particularly right heart catheterization, were deferred due to clinically sound reasons (eg, test contraindication(s) and patient refusal). Thus, although the implementation of appropriate diagnostic testing was suboptimal for some forms of PH, such as CTEPH, the generalizability of this trend to all WHO PH Groups cannot be determined definitively from results in the current study.

Conclusions

Our data support recently published findings from others 21,22 suggesting that in at-risk patients, PH is prevalent yet largely underdiagnosed. Although it is unresolved if pulmonary vasodilator therapy alters morbidity or mortality in forms of PH other than PAH,23–25 our work highlights the need for enhanced awareness among the practicing cardiovascular community regarding contemporary strategies for identifying treatable forms of PH, particularly CTEPH, or assessing PH severity.

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Disclosures

Dr Bhatt discloses the following relationships—Advisory Board: Medscape Cardiology; Board of Directors: Boston VA Research Institute, Society of Chest Pain Centers; Chair: American Heart Association Get With The Guidelines Science Subcommittee; Honoraria: American College of Cardiology (Editor, Clinical Trials, Cardiosource), Duke Clinical Research Institute (clinical trial steering committees), Slack Publications (Chief Medical Editor, Cardiology Today Intervention), WebMD (CME steering committees); Other: Senior Associate Editor, Journal of Invasive Cardiology; Research Grants: Amarim, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, The Medicines Company; Unfunded Research: FlowCo, PLx Pharma, Takeda. The other authors have no conflicts to report.

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Pulmonary hypertension (PH) is associated with increased morbidity across the spectrum of cardiopulmonary diseases. Yet, despite the large population of patients at increased risk for PH, reports are lacking on the epidemiology, clinical profile, and extent to which guideline-based recommendations for the diagnosis of PH are implemented into clinical practice. In this study, we report that among an unselected population of at-risk patients, the prevalence of PH is 14%. However, even in patients with severe PH (3.2% of population), the diagnosis of PH is largely under-recognized, and, when ultimately established, is delayed and associated with substantial mortality. We observed that practice patterns for the diagnosis of PH are variable and often incomplete: a minority of patients with echocardiographically assessed severe PH underwent pulmonary function testing, right heart catheterization, ventilation/perfusion scan, or thoracic computed tomography to determine the etiology of pulmonary vascular disease, despite guideline-based recommendations indicating appropriateness of these tests. Shortcomings in the determination of PH etiology are particularly evident for chronic thromboembolic pulmonary hypertension, which is a form of pulmonary vascular disease that is potentially amenable to treatment. Among patients with a clinical profile compatible with chronic thromboembolic pulmonary hypertension, the diagnosis was pursued appropriately in only 16% of patients. Overall, our work highlights the need for enhanced awareness among the practicing cardiovascular community regarding contemporary strategies for identifying treatable forms of PH, particularly chronic thromboembolic pulmonary hypertension, as well as assessing PH severity.
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