CHEST

Original Research

PULMONARY VASCULAR DISEASE

Delay in Recognition of Pulmonary Arterial Hypertension

Factors Identified From the REVEAL Registry

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Background: **Pulmonary arterial hypertension (PAH) is a progressive and fatal disorder. Despite the emergence of effective therapy, PAH is commonly at an advanced stage when recognized. Factors associated with a prolonged symptomatic period before the recognition of PAH have not been fully evaluated.**

Methods: **The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry) enrolled 2,967 US adult patients with PAH from March 2006 to September 2007. Patients were considered to have delayed disease recognition if > 2 years elapsed between symptom onset and the patient receiving a PAH diagnosis, starting on PAH-specific therapy, or receiving a diagnosis by right-sided heart catheterization.**

Results: **In 21.1% of patients, symptoms were experienced for > 2 years before PAH was recognized. Patients with onset of PAH symptoms before age 36 years showed the highest likelihood of delayed disease recognition (OR, 3.07; 95% CI, 2.03-4.66). History of obstructive airways disease (OR, 1.93; 95% CI, 1.5-2.47) and sleep apnea (OR, 1.72; 95% CI, 1.33-2.22) were independently associated with delayed PAH recognition. Six-minute walk distance < 250 m (OR, 1.91; 95% CI, 1.16-3.13), right atrial pressure < 10 mm Hg (OR, 1.77; 95% CI, 1.26-2.48), and pulmonary vascular resistance < 10 Wood units (OR, 1.28; 95% CI, 1.02-1.60) were also associated with delayed disease recognition, but sex, race/ethnicity, and geographic region showed no association.**

Conclusions: **One in five patients in the REVEAL Registry who were diagnosed with PAH reported symptoms for > 2 years before their disease was recognized. Younger individuals and patients with histories of common respiratory disorders were most likely to experience delayed PAH recognition.**

Trial registry: **ClinicalTrials.gov; No.: NCT00370214; URL: www.clinicaltrials.gov**

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Abbreviations: 6MWD = 6-min walk distance; LVEDP = left ventricular end-diastolic pressure; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; REVEAL = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; RHC = right-sided heart catheterization

Pulmonary arterial hypertension[1] (PAH) is an uncommon disorder characterized by abnormal increases in pulmonary artery pressure (PAP), normal pulmonary capillary wedge pressure (PCWP), and increased pulmonary vascular resistance (PVR).[2] PAH results in right ventricular pressure/volume overload leading to right ventricular failure and death.[3] Patients with PAH are often diagnosed late in the course of the disease when the pathologic changes are advanced and irreversible.[4-7] Diagnosis of PAH at this stage is associated with poor prognosis for survival,[8,9] underscoring the importance of early disease recognition and treatment.

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In 1987, National Institutes of Health Registry investigators identified the common presenting symptoms of PAH as dyspnea on exertion, edema, fatigue, and chest pain; in this registry, the median time between

the onset of these symptoms and the performance of a right-sided heart catheterization (RHC) was 1.3 years.[6] More recently, patients enrolled in the ongoing Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL Registry) had a median time from PAH symptom onset to the performance of an RHC of 1.1 years.[10] Multiple effective treatments have been developed utilizing the National Institutes of Health and REVEAL Registries,[11-15] and rapid diagnosis maximizes these new opportunities to improve survival. Studies published to date have provided little insight regarding which patients are at greatest risk for delayed recognition of PAH. Studies in other disease states indicate that patient characteristics such as age, sex, and race can result in delays in diagnosis and treatment initiation.[16-19] Whether similar characteristics exist among patients with PAH has not been examined. Such information is crucial if interventions to promote earlier disease recognition and treatment are to be successfully implemented in the PAH population. The purpose of this study is to identify factors associated with a >2-year interval between the onset of PAH-attributable symptoms to recognition of the disease.

The Bottom Line

How does this work advance the field?

Despite progress in understanding the cellular and genetic basis of pulmonary arterial hypertension, the time to recognition of the disease has not improved over the past 2 decades. This article builds upon previous research by identifying factors that are associated with delayed recognition of pulmonary arterial hypertension.

What are the clinical implications?

Research suggests that younger patients and those with common respiratory disorders are more likely to experience delayed recognition of pulmonary arterial hypertension. Interventions to promote earlier disease recognition should focus on these populations. Clinicians caring for younger patients and those diagnosed with common respiratory illnesses should consider pulmonary arterial hypertension if a patient's severity of symptoms or response to therapy are inadequately explained by the existing diagnosis.

Materials and Methods

Design Overview

We conducted a cohort study among patients enrolled in the REVEAL Registry between March 1, 2006, and September 30, 2007. The study was approved by the institutional review board at each participating center (e-Appendix 1). Subjects provided written informed consent for collection of baseline and follow-up data. The design of the REVEAL Registry has been described in detail previously.[20] Briefly, patients with PAH who were either previously diagnosed or newly diagnosed (defined as having a diagnostic RHC within 90 days of enrollment) were included. Patients were excluded if RHC was not performed, hemodynamic criteria were not met, or the clinical presentation was inconsistent with the diagnosis of PAH. Data collection was Web-based and was performed by a trained research associate at each site who reviewed medical records and recorded prespecified variables electronically.

The hemodynamic criteria necessary for enrollment into the REVEAL Registry differed from those conventionally required for a diagnosis of PAH. A mean PAP >25 mm Hg (>30 mm Hg with exercise) and a PVR ≥3 Wood units were compulsory. However, the PCWP and left ventricular end-diastolic pressure (LVEDP) requirements were liberalized to include patients with values >15 to ≤18 mm Hg. The cohort for this analysis excluded patients with PCWP >15 mm Hg. Analysis of the entire population, including patients with PCWP >15 mm Hg, is available in e-Tables 1-5. The designation of patients as having primarily group 1 PAH (rather than group 2-4 pulmonary hypertension)[1] was at the discretion of the principal investigator at each of the participating sites.

Time to Disease Recognition

Time to disease recognition was measured from the date of the onset of symptoms attributable to PAH (ascertained from the medical record) to the earliest of three indicators for disease recognition: physician announcement to a patient of a diagnosis of PAH, initiation of PAH-specific therapy, or RHC confirmation of the diagnosis. The REVEAL Registry records each of these indicators of enrollment.

Statistical Analysis

Among many covariates, the REVEAL Registry records PAH subgroup classification, demographic variables, physician

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