Time to Diagnosis of Pulmonary Arterial Hypertension

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Substantial delays between the onset of pulmonary arterial hypertension (PAH) symptoms and diagnosis of the disease continue for the majority of PAH patients. The delays persist despite a growing number of effective treatments and the knowledge that early initiation of therapy is clinically beneficial. Patients need to be encouraged not to rationalize their symptoms when they do occur but to seek medical evaluation. Physicians should be alert to the common symptoms found at PAH presentation and recognize that patients may have comorbid conditions that mask the disease. The goal of identifying patients at the earliest stages of functional impairment will not be achieved unless PAH is considered as a possible diagnosis.

The pathway that patients negotiate between the onset of very common clinical symptoms to the diagnosis of a very rare disease is fraught with obstacles. The calls for shortening the time to diagnosis of PAH and the corollary of starting appropriate, disease-modifying treatments are ubiquitous throughout the literature. However, we continue to grapple with how best to accomplish the goal of timely, accurate diagnosis of PAH. Our registries detail the characteristics of PAH patients worldwide and are witness to the amount of time that exists between when a patient becomes symptomatic from evolving pulmonary vascular disease and when he or she is diagnosed with PAH. These periods that are devoid of a diagnosis often span greater than 1 to 2 years in US, French, German, Swiss, and Chinese registries of PAH patients.[1-5] The sequential US registries further document that despite intervening decades, there has been little progress made in achieving the goal of earlier diagnosis.[2,6] The median time from the onset of symptoms to PAH diagnosis was 1.3 years in the National Institutes of Health Registry that was published in 1987, and 1.1 years in the The Registry to EValuate Early And Long-term pulmonary arterial hypertension disease management (REVEAL Registry) first presented in press in 2010 (Figure 1).[2,6] Twenty percent of PAH patients enrolled in REVEAL had greater than 2 years between symptom onset and recognition of PAH.[7] We have progressed from the first description of primary pulmonary hypertension and the declaration that "there is no treatment" to the current period where a greater understanding of the pathobiology of PAH has evolved into the development of multiple effective therapies.[8] Starting PAH treatment at the earliest period of functional impairment is known to delay clinical progression.[9] Unfortunately, we continue to struggle with promptly uniting patients with the medication benefits of improved survival, increased 6-minute walk distances, and recovery of functional performance by diagnosing PAH only at its most advanced stages.[1,2] Early, accurate diagnosis of PAH is consequently imperative to providing patients with the best opportunity for quality and quantity of life.

PATIENT CONTRIBUTIONS TO DELAYED DIAGNOSIS

As practitioners specialized in the diagnosis and treatment of PAH, our patients frequently regale us with stories of what happened to them as they negotiated the medical community striving to find an explanation for their symptoms. There is a period of time, though, in which patients are cognizant of symptoms but have yet to seek medical attention. Armstrong and coworkers documented that patients report periods of perseverance through symptoms of PAH or avoidance of activities that precipitated symptoms prior to bringing their concerns to a physician.[10] The same authors also noted that family and friends could be instrumental in triggering the decision of a patient to seek help. How does the PAH community motivate patients and possibly the loved ones of symptomatic patients to communicate their concerns to a medical professional? There is limited research to quantitate the effectiveness of public awareness campaigns in minimizing the time to diagnosis of cancer and even less documentation of the effectiveness of educating the public about a rare disease such as PAH.[11] However, there are examples of successful campaigns. Susan Braun in recounting the history of breast cancer advocacy describes the steps in which a previously unmentionable disease became the target of a national campaign.[12] The process started with preparing the public for a message about breast cancer and later educating them about the extent and burden of the disease in terms accessible to all. Education about PAH is in its infancy, and we have begun similarly to how the breast cancer campaign began by publicizing stories of those affected by the disease. The traditional press has been utilized and there are now efforts to reach out through social media, which is increasingly becoming a means of communication about medical conditions.[13] Through these venues, patients are given

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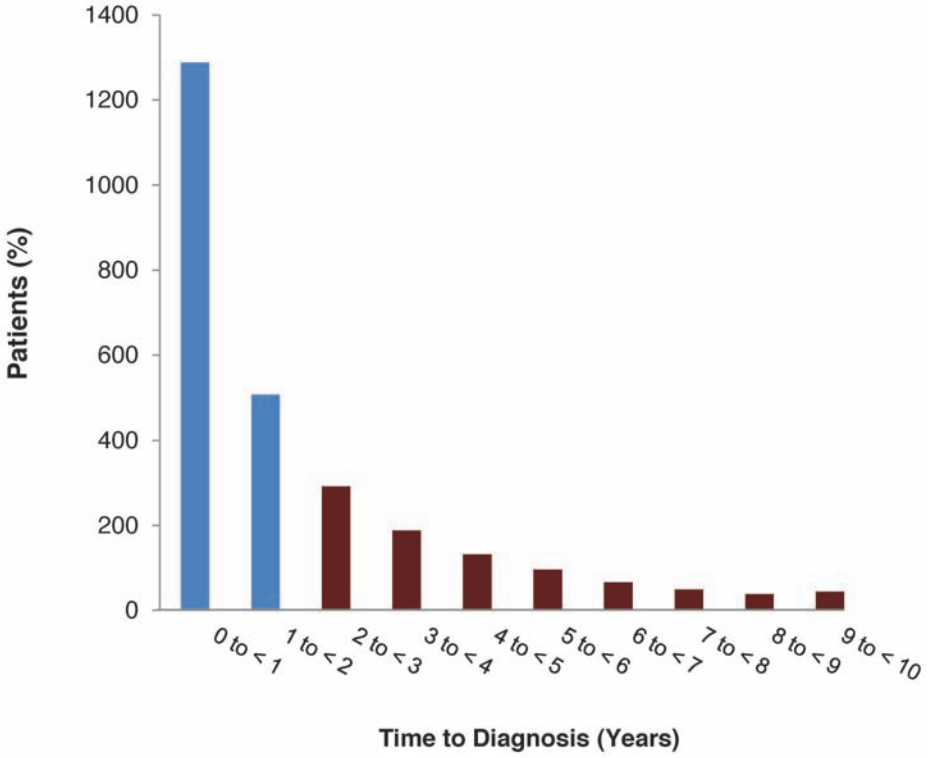

Figure 1: Time from first PAH symptom to diagnosis [2] 21% of patients (red columns) had >2 years of symptoms prior to being diagnosed with PAH.

the opportunity to share their experiences. They recount the insidious progression of their symptoms and share the less than flattering conditions that they initially thought were to blame: weight gain, deconditioning, or advancing age.[10] As our patients eventually learn, breathlessness may be a harbinger of a serious, yet treatable disease. It is only through interfacing with the medical community that a diagnosis of PAH can be made. We need to identify a process that will encourage patients to speak up about their symptoms and to help them recognize when their dyspnea and exercise tolerance are out of bounds from anything reasonably expected; it may not be asthma, obesity, or lack of exercise and it may not be just in your head.

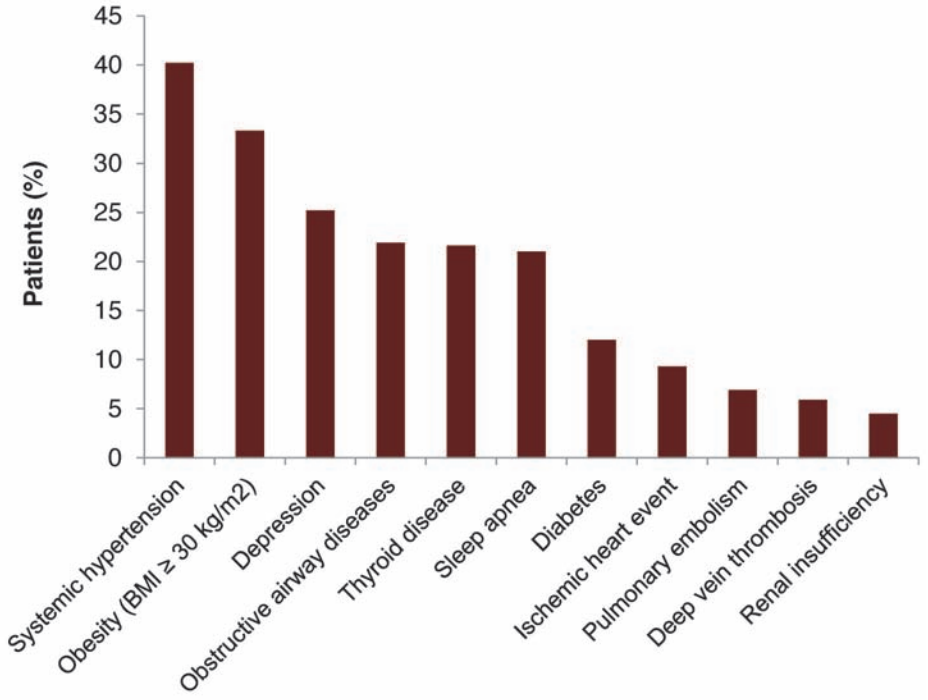

Figure 2: Comorbid conditions in patients diagnosed with PAH [2].

PHYSICIAN CONTRIBUTIONS TO DELAYED DIAGNOSIS

We also need to be ready for patients when they do come to our attention. Patients with PAH carry diagnoses that are common in the US population: systemic hypertension, obesity, and diabetes (Figure 2). As an example, the percentage of individuals with body mass indices (BMI) >30 kg/m^2 in the US was 35.7% in 2011 according to the Centers for Disease Control and Prevention.[14] In the REVEAL Registry, the percentage of patients with a BMI >30 kg/m^2 was 33.3%.[2] Patients with PAH can consequently look like an average clinic patient at rest but greater than 85% of them will describe dyspnea with exertion.[2] The differential diagnosis of chronic dyspnea (dyspnea lasting more than 1 month) is broad, and a large proportion of patients presenting with this finding are ultimately diagnosed with obstructive airway diseases (Figure 3).[15,16] Given the commonality of asthma and chronic obstructive pulmonary disease (COPD) in the general population, it is not unexpected that these diagnoses predominate. A Canadian Family Medicine investigation reported that 31.8 % of people less than 45 years of age were given the diagnosis of asthma in the evaluation of chronic dyspnea.[15] Young people are vulnerable when it comes to identifying PAH. In adult patients enrolled in the REVEAL Registry the youngest subset, those <36 years of age at symptom onset, had the highest likelihood of delay in PAH recognition with an adjusted odds ratio of 3.07 (95% confidence interval 2.03-4.66).[7] The misdiagnosis of PAH as obstructive airway diseases is known.[17] The presence of dyspnea and obstruction does not exclude the diagnosis of PAH, as abnormal spirometry can be found in patients

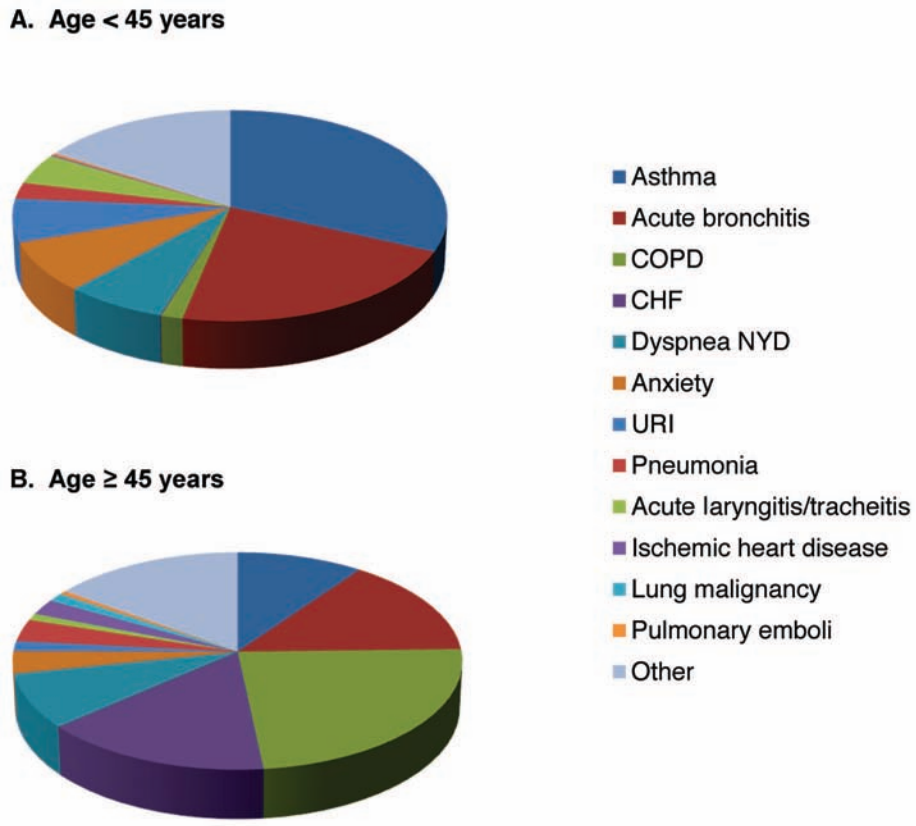

Figure 3: Differential diagnosis of dyspnea by age [15]. Reproduced with permission from the Canadian Family Medicine Association.

with pulmonary vascular diseases.[18,19] An added complexity is that obstructive airway diseases are documented as comorbid conditions in PAH patients. Whether these are correct diagnoses or misdiagnoses is unknown, but in the REVEAL Registry 22% of patients carried the diagnosis of obstructive airway diseases. These patients were more likely to have >2 years of PAH-attributable symptoms before their disease was recognized.[2,7] There are truly rare manifestations of PAH that mimic chronic conditions. Extrinsic compression of the airways or left coronary artery by enlarged pulmonary arteries have been known to masquerade as treatment-resistant asthma or angina respectively.[20,21] Failure of therapy to provide clinical improvement of dyspnea may not indicate the presence of similar extraordinary conditions, but it should stimulate consideration of an alternative diagnosis. PAH ranks lower on the scale of differential diagnoses of chronic dyspnea, yet it is a component of the diagnostic algorithm.[22] The disorder should be a consideration especially when the classic symptoms of PAH are present, risk factors for the disease have been identified, or treatment failure of an alternative diagnosis has become apparent.

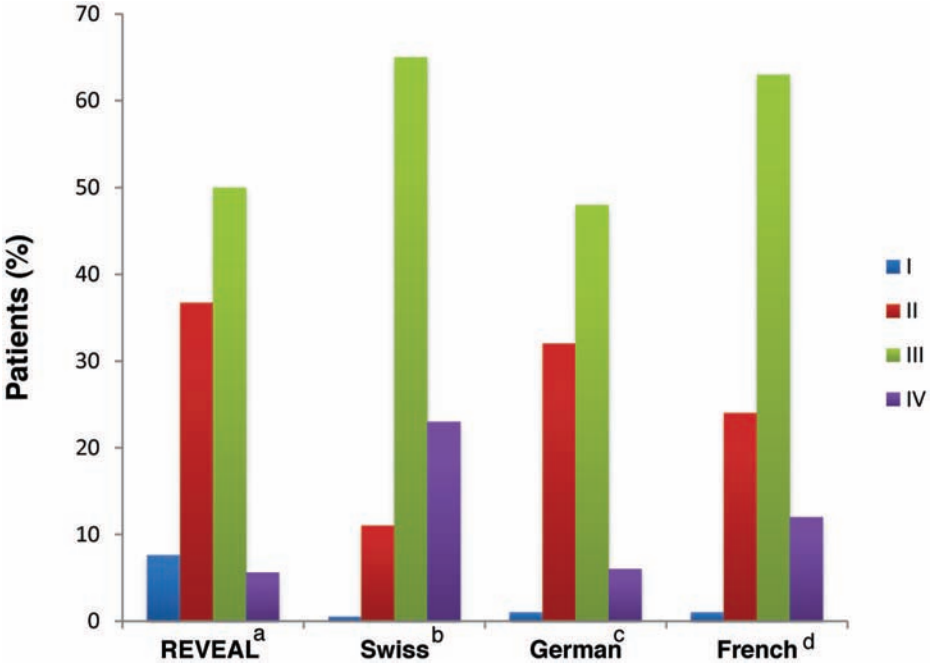

Figure 4: Functional classification of PAH patients at diagnosis.

Without an adequate explanation for their symptoms, patients frequently become stuck in the quagmire of "unexplained dyspnea." In a cohort of German patients, 54% consulted 3 or more physicians before a final diagnosis of PAH was rendered.[3] When a diagnosis was arrived upon successfully, the majority of patients were not identified during the earliest stages of functional impairment but rather after they had progressed to functional class III status; 6% to 12% were not identified until functional class IV symptoms were present and the risk of death was high (Figure 4).[1,2] The statistics are similar for those patients who are known to carry diagnoses that are risk factors for developing PAH, such as those with collagen vascular diseases.[2] These patients are the greatest contributors to the subgroup of associated PAH and they are known to have one of the most concerning trajectories in regard to survival.[23] In heritable PAH where the diagnosis has already been established in a family member, there are reports of a year of symptoms preceding the diagnosis of a first-degree relative.[24] The persistence of these diagnostic delays in idiopathic patients and especially in patients with obvious risk factors for PAH raises the question of who is missing the diagnosis. The

answer seems to be that all specialties contribute to the problem. In the REVEAL Registry, patients with the greatest time to diagnosis were first seen by cardiologists, pulmonologists, internists, and rheumatologist alike.[7]

When a diagnostic evaluation for PAH is pursued, the correct diagnosis is not always inevitable. The PAH field is constantly challenged by the lack of an easily performed diagnostic test that might facilitate earlier diagnosis, such as those available in other rare conditions like cystic fibrosis. We rely on the measurement of hemodynamics by right heart catheterization (RHC) as the definitive diagnostic assessment, yet correct interpretation of the measurements is not without difficulty as demonstrated by the persistent confusion over the basic differentiation between pulmonary hypertension and pulmonary arterial hypertension.[25] All of these complexities persist even in the setting of multiple published algorithms for the diagnostic evaluation of PAH.[26,27] Even before the performance of an RHC there can be reliance on noninvasive imaging. The 2D echocardiogram maintains its status as an invaluable tool accessible to all practitioners.[26] The stereotypical changes in the right ventricular structure and function seen in a patient already experiencing obvious symptoms should lead to a high enough suspicion of PAH that a comprehensive diagnostic workup, including a confirmatory RHC, be performed by a knowledgeable physician. The availability of 2D echocardiography makes missing the diagnosis of PAH even more disappointing. There are increasingly more intricate noninvasive ways of evaluating the heart and pulmonary vasculature.[28-30] These methods hold promise that identification of PAH will eventually occur at the earliest point of structural and functional abnormalities. As the sophistication of research in the field of PAH moves forward, though, it may be that reaching backward with simplicity is equally important. No method of evaluating for PAH will occur if the diagnosis has not been contemplated.

CONCLUSION

Patients with PAH are often symptomatic for years prior to receiving an accurate diagnosis and there are patient- and physician-related contributions to these delays. Substantial advances in the understanding and treatment of PAH have occurred, but the simplest step of considering the diagnosis in the first place continues to be one of the biggest hurdles.

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