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EDITORIAL COMMENT

Toward Early Diagnosis of Pulmonary Hypertension

Lessons From Oz*

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Elevated blood pressure in the pulmonary circulation is the sine qua non of pulmonary hypertension (PH). In the minority of PH patients with pulmonary arterial hypertension (PAH), pathogenicity is due to interplay between molecular and genetic factors that promote a unique plexogenic arteriopathy. However, PH far more commonly occurs in relation to left ventricular dysfunction, primary mitral valvular abnormalities, obstructive and fibrotic lung diseases, sleep-disordered breathing, or other highly prevalent cardiopulmonary disorders (1). It is well-established that in these patients, hypertrophic, fibrotic, and occlusive vascular remodeling of distal pulmonary arterioles occurs and often persists despite optimal medical therapy that targets the underlying cause of PH (2). Because of the detrimental effect of increased afterload on right ventricular (RV) morphology and performance and the importance of RV failure to clinical outcome, it follows that PH is a reproducible risk factor for elevated morbidity and mortality across the medical spectrum (3,4).

Clarifying the totality of clinical risk in PH has emerged as a contemporary priority for 2 reasons (5). First, it is well-recognized that the original definition of PH (standardized in 1973), which stipulated a mean pulmonary artery pressure (mPAP) of ≥25 mm Hg measured by right heart catheterization (RHC), was established arbitrarily in the absence of robust normative or outcome data (6). Second, PH patients are often diagnosed in clinical practice when hemodynamic abnormalities are already moderate or severe, despite mounting evidence that earlier recognition of PH is likely important for optimizing management, including risk factor modification for most patients and drug therapy selection in the case of PAH (7,8).

To this end, determining the hemodynamic risk profile in PH was identified as a principal unmet need at the 2013 World Pulmonary Hypertension Symposium (9). In response to that call-to-action, large RHC population studies emerged with findings that were consistent with historical data from healthy control subjects and previous observations in smaller studies that suggested the mPAP upper limit of normal was <25 mm Hg (10). For example, in the Veterans Affairs study of 21,727 individual RHCs in which mPAP was modeled as a continuous variable, the hazard for mortality began at 19 mm Hg, and mPAP of 19 to 24 mm Hg was associated with a 22% increase in the adjusted mortality risk (11). These findings were affirmed in a large sex-balanced referral cohort at Vanderbilt University (N = 4,343); however, findings from this study also observed progression of mPAP over time in some patients (12). These collective data helped to mark a conceptual shift in PH, emphasizing reconsideration of the hemodynamic criteria for diagnosis and the development of a better strategy for early detection as a path forward toward disease prevention.

Although RHC is required for definitive PH diagnosis and risk stratification, transthoracic echocardiography is often viewed as a screening test because it

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is highly accessible and noninvasive. There are a number of limitations to using echocardiography for diagnosing and/or characterizing PH in individual patients: mPAP or other hemodynamic variables important in PH (pulmonary vascular resistance and others) are not measured; RV systolic pressure must be estimated (eRVSP) from the tricuspid valve regurgitant velocity (TRV); and PH has been reported in nearly one-half of patients in whom a TRV was not detected (13). Nonetheless, echocardiography is scalable, and thus, more practical compared with RHC for detecting clinically significant, albeit mild, PH in populations, as demonstrated in a recent meta-analysis (14).

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In this issue of the *Journal*, Strange et al. assembled a remarkable database of approximately 157,800 individual patient echocardiograms over a 20-year period from an Australian national cohort (15). The data were linked to hard clinical endpoints, and the population size permitted an analysis of eRVSP risk not contingent on pre-specified values, which, in turn, provided novel information on the association between mortality and mildly elevated PA pressure when measured noninvasively. The investigators specifically showed that adjusted risk for all-cause and cardiovascular-associated mortality increased significantly by 41% and 35%, respectively, beginning at an eRVSP of approximately 30 mm Hg (corresponding to mPAP of ~20 mm Hg [14]). Directionally similar findings for the adjusted hazard for all-cause mortality were observed even after accounting for the confounding influence of age or the presence and/or absence of echocardiographically defined left heart disease. Furthermore, mild PH was common and observed in 29% of patients, which provided contemporary insight into the epidemiology and extent of this clinical problem.

Although these findings crystalize the relevance of subtly elevated PA pressure and show the potential usefulness of screening for mild PH using echocardiography, this study also begins to address a key and controversial issue: is adverse outcome associated with mild PH simply a reflection of patient comorbidity, or could this degree of afterload be sufficient to cause structural and functional changes to the RV? The investigators noted a graded increase in the prevalence of right atrial dilation, RV dilation, and RV dysfunction (qualitative) across increasing eRVSP quintiles, beginning with 30 mm Hg. Compared with eRVSP <30 mm Hg, the number of patients with abnormalities in any of these right heart parameters was nearly 2-fold greater for patients with eRVSPs of 30 to 39.9 mm Hg. Overall, these findings imply that mild PH adversely affects RV function.

Notwithstanding this progress, detailed assessment of RV function in patients with mild PH was lacking in this study. For example, future efforts studying tricuspid annular plane systolic excursion and RV–pulmonary artery coupling would provide much needed information to strengthen the assertion that mild PH impairs RV function, as well as characterizing RV pathophysiology more broadly in this subgroup. Nonetheless, findings from the current work should divert attention away from comorbid disease as the sole determinant of adverse outcome in mild PH, as proposed by some, toward a contemporary approach in which the potential ramifications of mild PH on RV pathophysiology are considered more seriously.

Strange et al. provide compelling evidence from a large national database in Australia on the continuum of risk relative to PA pressure when measured noninvasively. They observed that mild PH, defined by an eRVSP of approximately 30 mm Hg, was common and associated with substantial clinical hazard. This study opens a path toward diagnosing PH earlier in the community, emphasizes the need to understand better RV function in mild PH, and moves the field one step closer to an era of preventative medicine. Completing clinical studies that inform practitioners on the trajectory of patients with mild PH suggested by echocardiography, particularly recommendations on specialty referral and effective risk modification strategies, is a natural next phase in this exciting time for pulmonary vascular medicine.

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