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EDITORIAL COMMENT

Magnetic Resonance Assessment of Pulmonary Artery Compliance

A Promising Diagnostic and Prognostic Tool in Pulmonary Hypertension?*

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Pulmonary hypertension, whether caused by idiopathic pulmonary arterial hypertension or as a complication of an increasingly recognized number of primary disease states, is associated with significant mortality and morbidity (1,2). Diagnosing pulmonary hypertension, however, may be challenging (3). Symptoms can be nonspecific and may be attributed to the underlying disease, and unlike blood pressure monitoring in the systemic arterial tree, there is no simple, inexpensive test for evaluating the pulmonary arteries. The widely available biomarker brain natriuretic peptide (BNP) is not specific for pulmonary hypertension. Resting echocardiography is limited by technical expertise in measurement of the tricuspid regurgitant jet, patient factors such as body habitus, and cost. Moreover, it may not be sensitive enough to detect mild pulmonary hypertension or exercise-induced pulmonary hypertension. Right heart catheterization is usually needed for a definitive diagnosis, but it is invasive and provides an assessment of resting and, at most, exercise pulmonary vascular resistance, only one of several factors that contribute to right ventricular overload. Thus, for many reasons, patients are frequently diagnosed and treatment is initiated only after the development of moderate or worse symptoms and significant hemodynamic abnormalities. Although there are no data about the natural history or treatment of mild and exercise-associated pulmonary hypertension, early treatment potentially could slow or prevent the progression of the disease. A widely available, noninvasive method of assessing the pulmonary arteries to identify early disease would be a significant advance.

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Systemic arterial vascular stiffness has been intensively studied and is a known independent risk factor for cardiac events. The pathophysiology and clinical consequences of increasing arterial stiffness have recently been reviewed (4). The cushion and conduit functions of the peripheral arterial system are finely tuned so that pulsatile blood flow becomes constant in organ capillaries, and reflected pressure waves augment diastolic blood flow and myocardial oxygen delivery. With aging, structural changes in the large arteries result in dilation and stiffening. The cushioning function is compromised, resulting in increasing pulse pressure. Systolic blood pressure increases and reflected waves now return earlier in systole, thereby increasing afterload. Flow that remains pulsatile at the level of the capillaries may cause microvascular injury and end-organ damage. Although there are no coronary arteries to perfuse at the junction of the right ventricle and the pulmonary artery, the physiology of ventricular-arterial coupling is otherwise similar in the pulmonary circulation as are microvascular lesions in the lungs and other organs when the system becomes dysregulated.

Hemodynamic assessment of the patient with pulmonary hypertension relies on pressures measured during right heart catheterization and the calculated pulmonary vascular resistance. Pathologic changes in the post-capillary resistance vessels of pulmonary arteries increase right ventricular afterload until patients present with symptoms of and eventually die of right-sided heart failure.

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Resistance, however, is only one component of afterload, capacitance and impedance being the others. Furthermore, resistance calculations assume a constant blood flow, whereas compliance capacitance and impedance are more useful to describe pulsatile flow. Measures of pulmonary artery stiffness better reflect these latter components that could contribute to worsening right heart failure and pulmonary microvascular disease by the same mechanisms that affect the left heart and systemic circulation. Several studies have begun to measure and explore the clinical relevance of pulmonary artery stiffness in pulmonary hypertension.

In this issue of *iJACC*, Sanz et al. (5) report on patients with known or suspected pulmonary hypertension studied with same-day right heart catheterization and cardiac magnetic resonance (CMR) to characterize pulmonary artery stiffness. Of 94 patients included in the analysis, 75 had pulmonary hypertension with a mean pulmonary artery pressure of 43 mm Hg and a mean cardiac index of 3.2 l/min/m^2. Thirteen had normal hemodynamics, and 6 had exercise-induced pulmonary hypertension only. In comparison to normal subjects, every measure of arterial stiffness (pulsatility, compliance, capacitance, distensibility, elastic modulus, and stiffness index) was significantly worse in patients with pulmonary hypertension. In patients with exercise-induced pulmonary hypertension, compliance and capacitance were significantly worse than in normal subjects. Statistically significant correlations were shown between mean pulmonary artery pressure and pulmonary vascular resistance versus all measures of arterial stiffness with the exception of the stiffness index, β.

The work by Sanz et al. (5) complements and extends other investigations about the significance of pulmonary artery stiffness. Three recent studies that have found that increased pulmonary artery stiffness is associated with increased mortality (6–8). Rodes-Cabau et al. (6) showed intravascular ultrasound measurement of decreased pulsatility in distal pulmonary arteries of 20 patients was associated with a higher 12-month mortality. Another study showed that pulmonary arteriolar capacitance measured during right heart catheterization in 104 patients was a better predictor of mortality than 6-min walk distance, cardiac index, right atrial pressure, pulmonary vascular resistance, and National Institutes of Health 4-year predicted survival equation (7). In another study of 70 patients and 16 control subjects followed up over 48 months, CMR measured changes in relative cross-sectional area of the proximal vessel was a better marker of death than 6-min walk distance, pulmonary vascular resistance, or right atrial pressure (8).

The study by Sanz et al. (5) adds to these by providing same-day invasive hemodynamic data and CMR imaging and by showing the graded relationship between severity of hemodynamic findings and severity of changes in pulmonary artery stiffness. The study further reinforces the possible pathophysiologic importance of pulmonary artery stiffness and raises a new possibility: that the assessment of pulmonary artery stiffness could lead to early diagnosis of pulmonary hypertension.

It seems then that conventional assessment of the pulmonary vascular system and right heart with echocardiography and right heart catheterization are not telling the whole story. Worsening pulmonary arterial stiffness may be among the first pathophysiologic manifestations of pulmonary hypertension before pressure or resistance begins to increase. In a large cohort of patients with variable degrees of pulmonary hypertension, Sanz et al. (5) show a curvilinear relationship between measures of pulmonary artery stiffness and systolic pulmonary artery pressure. Pulmonary artery stiffness was markedly increased in patients with even mild increases in pulmonary artery pressure. Pulmonary artery stiffness was markedly abnormal but quite similar over a range of elevated pulmonary artery pressures. Furthermore, although hemodynamics in patients with exercise-induced pulmonary hypertension were not significantly different than those for controls, stiffness was significantly worse. Lankhaar et al. (9) reported findings in a smaller cohort of patients for whom longitudinal data were available showing a similar relationship between capacitance and pulmonary vascular resistance. The product of capacitance and resistance was constant over time, supporting the notion of progression along the curve with stiffness worsening before resistance increasing. Pulmonary artery stiffness may contribute to the disconnect between the severity of hemodynamic abnormalities and treatment response to vasodilator drugs (1).

A compelling clinical application of pulmonary artery stiffness assessed by CMR could be the early detection of pulmonary hypertension among patients at elevated risk for the disease. Further study is required to examine the natural history of exercise-induced and mild pulmonary hypertension, but it seems likely that patients with advanced pulmonary hypertension at some time may have had early disease characterized by mildly abnormal hemodynamic alterations (10). It also is reasonable to

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hypothesize that treatment at an early stage of the disease, before the development of significant hemodynamic compromise, could alter the natural history and disease progression leading to an improvement in morbidity and mortality.

The main limitations of the study by Sanz et al. (5) are the small number of patients with exercise-induced hypertension, a particularly important group in which there are insufficient data regarding prognosis and treatment. In addition, although noninvasive and not requiring exercise, CMR is still an expensive and technically challenging test. Its routine clinical application in the assessment of pulmonary hypertension is therefore premature.

The study by Sanz et al. (5) represents a significant contribution to the growing body of literature showing the importance of pulmonary artery stiffness in pulmonary hypertension. Larger prospective trials that assess whether increased pulmonary artery stiffness as detected by CMR, particularly in exercise-induced pulmonary hypertension, predicts development of resting pulmonary hypertension will be necessary. If validated, it could provide an important tool in both research and clinical practice.

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