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Myocardial Fibrosis as a Potential Maladaptive Feature of Right Ventricle Remodeling in Pulmonary Hypertension

The ability of the right ventricle (RV) to adapt to increased pulmonary pressures is the main determinant of clinical outcomes in patients with pulmonary hypertension (PH). The RV and the pulmonary vasculature behave as a single interrelated cardiopulmonary unit, and an improved understanding of the nature and range of RV responses to increased afterload is needed. Some RV responses to elevated pulmonary pressures are clearly adaptive, whereas others are thought to be maladaptive. Early recognition of features of maladaptive change may enable timely interventions to prevent deterioration of RV function (1).

Myofibroblast activation is a cellular response to increased RV afterload, which leads to myocardial fibrosis and an altered extracellular matrix. Precisely where RV fibrosis falls on the continuum of adaptive to maladaptive RV change is a topic of ongoing debate (2). Histologic studies support RV fibrosis as a consistent feature of PH; however, these studies have mostly examined myocardial biopsies and explants from patients with end-stage PH. Noninvasive imaging methods that indirectly assess fibrosis enable examination of patients in earlier stages of the disease course and offer insights into physiologic consequences of RV changes. Most previous magnetic resonance imaging (MRI) studies in PH have measured late gadolinium enhancement as a surrogate of fibrosis (3). Recently, T1 mapping with myocardial extracellular volume (ECV) assessment has emerged as a more useful technique for assessing diffuse interstitial fibrosis and for following changes in the extent of fibrosis over time (4, 5).

In this issue of the *Journal,* Jankowich and colleagues (pp. 776–779) use myocardial ECV assessment in patients with PH to investigate the relationship between diffuse interstitial fibrosis in the RV free wall and pulmonary artery (PA) stiffness, as measured by PA pulse wave velocity and PA relative area change (6). The authors found a strong positive correlation between RV ECV and PA pulse wave velocity (0.73; $P = 0.001$) and a strong negative correlation between RV ECV and PA relative area change (-0.69; $P = 0.003$), supporting a relationship between RV fibrosis and PA stiffness in this cohort. Univariable linear regression models demonstrated significant associations between RV ECV and these surrogates of PA stiffness, and associations remained significant after adjustment for biological variables and MRI metrics of RV function in bivariable models. No significant relationships existed between RV ECV and measures of RV function, such as RV ejection fraction (RVEF), in this cohort.

The authors should be commended for their use of a new, and perhaps more sensitive, MRI technique to investigate a relatively unexplored issue: the nature and clinical significance of RV fibrosis in PH. Their study offers unique insight into a cohort of patients with early disease and relatively preserved RV function, with a mean RVEF of 46% (SD, 12%). In addition, this is one of only a few MRI studies that have examined changes in the RV free wall, rather than limiting observations to the septum and ventricular insertion points. Given previously reported associations between measures of PA stiffness and poor clinical outcomes in PH, the authors suggest that RV fibrosis may be an early marker of deleterious RV remodeling, observed in this cohort before deterioration in any functional metric, such as RVEF.

Although it is provocative to speculate that RV fibrosis may be an early maladaptive response to PA stiffness, Jankowich's study has several limitations that should lead to cautious interpretation of its results. As a cross-sectional study, these results do not give any hints to temporality. That is, these findings do not support a conclusion that PA stiffness causes, or even necessarily precedes, RV fibrosis. Several additional issues limit the generalizability of the results. This is a rather small cohort ($n = 16$) with a sex distribution atypical for PH cohorts (94% male). Further, the cohort comprises patients across multiple different World Symposium on Pulmonary Hypertension (WSPH) classifications of PH, with the majority of patients classified as group 2 ($n = 6$) and group 3 ($n = 6$). Different WSPH groups are known to have different pathobiologic features, and variations in pathophysiology are therefore to be expected. Indeed, there is evidence that even within the group I classification of PH, patterns of fibrosis differ across disease subtypes. Hsu and colleagues found that patients with scleroderma-related pulmonary arterial hypertension have significantly more fibrosis on endomyocardial biopsies of the RV

Originally Published in Press as DOI: 10.1164/rccm.201906-1154ED on June 19, 2019

septum than patients with idiopathic pulmonary arterial hypertension, although increased fibrosis did not seem to explain RV diastolic dysfunction, which was quite similar in these two groups of patients (7).

PA stiffness occurs early in the development of PH, causes an increase in pulsatile afterload that affect RV remodeling, and is associated with poor outcomes (8–10). However, whether RV fibrosis is a consequence of PA stiffness, and whether RV fibrosis represents maladaptive RV remodeling remain unclear. Although determinants of RV fibrosis are largely unexplored, a recent preclinical study demonstrated that galectin 3 was an important driver of RV fibrosis through the expansion of PDGFRα (platelet-derived growth factor receptor α)/vimentin-expressing cardiac fibroblasts. Curiously, interventions that successfully targeted fibrosis failed, however, to improve RV function, suggesting a potential disconnect between fibrosis and RV dysfunction in this animal model (11). Future studies should prospectively examine temporal relationships among RV fibrosis, metrics of RV function, and clinical outcomes in homogeneous cohorts consisting of patients belonging to a single WSPH group. It would be particularly interesting to use serial ECV assessments to study the extent to which RV fibrosis is reversible with PH therapies and interventional or surgical procedures that unload the RV.

The ability to reliably assess the extent of RV fibrosis noninvasively with novel imaging techniques raises new questions and invites a host of investigative possibilities. The particular circumstances under which RV fibrosis develops and progresses, and the clinical consequences of such progression, are now amenable to longitudinal study. With further study, we may come to recognize RV fibrosis as a maladaptive clinical feature of disease progression that should prompt escalation or tailoring of specific PH therapies. The study by Jankowich and colleagues marks an important initial step in the overall investigation into the clinical relevance of RV fibrosis in PH. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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The MISSION Act: Challenges to Sleep Medicine and Other Specialties in the Veterans Health Administration

On June 6, 2018, President Trump signed into law the Maintaining Internal Systems and Strengthening Integrated Outside Networks (MISSION) Act, directing the Veterans Health Administration (VA) to give veterans greater access to non-VA community care to address long wait times for appointments within the VA (1). The MISSION Act program replaces the community care provided previously to veterans through Fee Basis agreements between VA facilities and local private providers and the Choice program that used third-party administrators to contract with outside providers. Under the MISSION Act, many more veterans are eligible for non-VA care. Among other criteria, veterans needing specialty care are now eligible for community care when their average drive time to the VA is greater than 60 minutes or their wait time for a VA appointment is greater than 28 days. The MISSION Act was officially launched on June 6, 2019. Its implementation is likely to increase the transformation of the VA healthcare system to a make-buy model of care delivery (2).

Originally Published in Press as DOI: 10.1164/rccm.201906-1278ED on July 16, 2019