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Is Myocardial Fibrosis Impairing Right Heart Function?

Many articles describing results from pulmonary hypertension studies begin with a statement like this: "Severe pulmonary hypertension is terrible and patients die from right heart failure." For many years, this statement had become a mantra without much attention having been paid to the outcome of the pulmonary vascular diseases. Thankfully, this situation has changed. A recent workshop report sponsored by the American Thoracic society has moved right ventricular (RV) function and right heart failure into the limelight (1). One of the many unresolved questions that have been raised in this report is the following: Is myocardial fibrosis of functional importance in the setting of chronic pulmonary hypertension and right ventricular stress? The question is an important one and is exactly the subject of a collaborative multiinstitutional investigation published in this issue of the *Journal* by Crnkovic and colleagues (pp. 1550–1560) (2). If we can prevent the development of RV fibrosis and reverse established RV fibrosis, we perhaps might prevent RV failure. It is generally believed that fibrosis is bad, whether it is in the liver and kidney or in the context of interstitial lung diseases. Obviously, if we wish to prevent RV fibrosis, we need to understand the cellular and molecular mechanisms underlying tissue fibrosis. Teleological reasoning would have it that the injury that offsets the tissue homeostasis triggers a wound-healing program, and part of this program is fibrosis. Crnkovic and colleagues employ pulmonary artery banding in mice and the Sugen/hypoxia and monocrotaline rat models to stress the RV and generate RV fibrosis. The authors found that pirfenidone treatment of pulmonary artery-banded mice reduced the amount of fibrosis but did not restore RV function. Because the pro-fibrotic galectin-3 and elevation of circulating galectin-3 have been linked to the development of left heart failure and RV dysfunction (3–5), the authors focused their attention on galectin-3 to explain the (lack of) importance of RV fibrosis in RV failure.

The presented data appear at odds with a growing body of evidence linking fibrosis to poor function of the pressure-overloaded right heart. RV diastolic stiffness in pulmonary arterial hypertension is partially mediated by interstitial fibrosis (6) and is related to poor clinical outcomes (7). This mimics the clinical situation in left heart failure, where the pattern and extent of myocardial fibrosis is associated with reduced left ventricular ejection fraction and predicts adverse outcomes (8). In most clinical studies, myocardial fibrosis is quantified using late gadolinium enhancement, and histological proof of the validity of this concept is readily available (9). The list of drugs that concomitantly improve RV function and decrease fibrosis in experimental models is long and includes beta-adrenergic blockers (10), iloprost (11), p38 MAPK inhibition (12), pirfenidone (13), and nintedanib (14). In most of these studies, RV effects were partly mediated by a drug-induced decrease in pulmonary vascular resistance. But iloprost and p38 MAPK inhibition were tested in rats after pulmonary artery banding, isolating RV afterload from the pulmonary vasculature. In those studies, proof of a mechanistic link between fibrosis and RV dysfunction was to a certain degree circumstantial. RV fibrosis seems "guilty by association" to the development of RV failure. However, the lack of association between a drop in fibrosis and a change in RV function in the study by Crnkovic is similarly insufficient to completely dismiss fibrosis as a contributor to RV dysfunction. As such, the boldness of the title of the paper: "Therapy of right ventricular fibrosis does not ameliorate right ventricular dysfunction RV" may seem a bit of an overreach.

One simple explanation for Crnkovic's findings may be that an expected improvement in RV function was offset by adverse effects of pirfenidone unrelated to the drug's antifibrotic action. But on a deeper level, the difficulty of mechanistically linking fibrosis to function or dysfunction of the RV exemplifies a general problem in preclinical cardiac failure research: a reductionist attempt to explain RV dysfunction by one type of cellular response (hypertrophy, fibrosis, inflammation, capillary rarefaction, etc.) is unlikely to solve the puzzle. Under conditions of pressure overload, it is obvious that a certain degree of hypertrophy is necessary to increase contractility. Likewise, a certain response of the extracellular matrix is needed to provide a scaffold for the remodeling myocardium. The capillary network will need to adapt to the changing oxygen demand. The success of RV adaptation will depend on the "quality" of hypertrophy (contractile proteins), fibrosis (perivascular and diffuse type, linking of extracellular matrix proteins), inflammation (type of activity of immune cells), and endothelium (leakiness, facilitation of diffusion). Moreover, the overall quality of RV adaptation will depend on the exact matching of these different processes. As such, there is no "good" or "bad" hypertrophy, fibrosis, inflammation, or capillary rarefaction. Pirfenidone treatment in the studies by Crnkovic did not result in a repair of capillary rarefaction. As such, it is possible that the benefit of reduced fibrosis was negated by the persistence of myocardial ischemia. In contrast, fibrosis reduction during carvedilol treatment occurred alongside an improvement in capillary density and did result in RV functional improvement (10).

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It appears that the fibroblast phenotype identified by Crnkovic can be put into a larger concept of progressive fibrosis driven by an altered extracellular matrix and fibrogenic mesenchymal cells in a fibrotic niche (15). Another concept connects myocardial capillary endothelial cells and their mesenchymal transition to myocardial fibrosis, again emphasizing the importance of cell–cell interactions and cell phenotype switch in fibrogenesis (16). The experimental exploration pivots around galectin-3, a carbohydrate binding beta-galactoside that binds to fibronectin and tenascin; its expression is induced by tissue injury, and it has pleiotropic pro-inflammatory, pro-fibroblastic, and pro-angiogenic properties regulating cell proliferation, differentiation, and migration (17). Galactin-3 likely commands mechanisms of cardiac adaptation to stress; it has recently been named a "culprit protein" and thus made a therapeutic target (18). There has been an expert committee recommendation to include galectin-3 levels as a biomarker in the management of heart failure (19). Despite these impressive credentials in left heart failure, Crnkovic found no association between galactin-3 levels and clinical characteristics of patients with pulmonary arterial hypertension and observed no RV functional improvement after prevention of fibrosis by genetic deletion of galectin-3. The presented data seem to imply that RV fibrosis is unimportant to RV adaptation, but could also suggest that the importance and mechanisms of fibrosis in the RV are less dependent on galectin-3.

To summarize: the critical drivers of fibrosis are likely organ-specific, and in myocardial fibrosis, it continues to be prudent to consider cell–cell interactions, the role of inflammatory cells, capillary cells, and ischemia. Although the question: "Is myocardial fibrosis impairing RV function?" continues to warrant further investigations, we may still want to keep an eye on galectin-3 (20). ■

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