Fibrosis in Fontan physiology

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More than 50 years ago, Elster, Braunwald, and Wood¹ first evaluated a biomarker for use in adult heart failure, demonstrating an association of elevated levels of C-reactive protein with increasing severity of clinical symptoms associated with clinical heart failure. Since then, hundreds of candidate biomarkers have been studied. Few, however, satisfy the 3 criteria outlined by Morrow and de Lemos² in 2007: “Can the clinician measure it? Does it add new information? Does it help the clinician to manage patients?” A variety of factors affect the release of molecular markers into the serum of patients that can be subsequently measured and associated with clinical conditions. These include markers of inflammation (eg, C-reactive protein and interleukins), oxidative stress (eg, oxidized low-density lipoprotein), neurohormones (eg, endothelin), myocyte injury (eg, creatinine kinase and troponins), myocyte stress (eg, B-type natriuretic peptide), and extracellular matrix (ECM) remodeling (eg, collagen propeptides).³ The ECM remodeling class reported on by Sugimoto and colleagues⁴ in this issue of the *Journal* associated procollagen III amino terminal peptide (PIIP) as a marker of tissue fibrosis in patients with Fontan circulations.

Fibrosis is an evolutionarily conserved process that facilitates host defense and wound healing. Deregulated fibrosis, however, is invariably associated with loss of organ function. Many therefore view fibrosis as an imbalance between ECM production and degradation. Collagen is the most abundant component of the ECM in the heart and includes 5 isoforms (types I, III, IV, V, and VI.) Among these, collagens of types IV and V are components of the basement membrane, whereas collagens of types I and III are the main constituents of the ECM. A number of different cell types in the heart are responsible for collagen synthesis, although all cardiac collagen types are produced by fibroblasts. Degradation of collagen is mediated by both intracellular and extracellular pathways, with the latter pathways balanced by the activities of matrix metalloproteinase (MMPs) and their tissue inhibitors.⁵ Growth signals from tissue growth factors and angiotensin II induce the production of PIIP, one of the most frequently and extensively

The amino-terminal peptide domain of procollagen is cleaved and released into plasma.

Central Message

The Fontan procedure helps to reduce fibrogenesis, and persistently increased fibrogenesis is associated with ventricular diastolic dysfunction.

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studied markers of tissue fibrogenesis. PIIP is cleaved during conversion from type III procollagen to type III collagen in the fibroblasts and subsequently released into the bloodstream (Figure 1). In adult heart failure, PIIP levels have long been known to increase in patients with heart failure, with circulating levels of PIIP an independent predictor of mortality.⁶ The response of the heart burdened by congenital heart disease is unique, especially in single-ventricle physiology with volume overload and relative cyanosis. The results of these insults and the heart's response with hypertrophy and remodeling are complex. Compensatory mechanisms that preserve cardiac function in the short term have side effects, one of which is cardiac fibrosis.⁷

In this issue of the *Journal*, Sugimoto and colleagues⁴ explore the hypothesis that volume overload and cyanosis observed in single-ventricle circulation are associated with increased ventricular fibrogenesis during the staged Fontan procedure. Sugimoto and colleagues⁴ are to be congratulated on a rigorous, thoughtful, well-written, and innovative study of patients with single-ventricle circulation. This article is important because it injects mechanism into otherwise largely descriptive approaches. Sugimoto and colleagues⁴ suggest that the Fontan procedure helps to reduce fibrogenesis, and they also suggest that persistently increased fibrogenesis in the Fontan ventricle is associated with ventricular diastolic dysfunction. To test their hypothesis, they measured serum PIIP as a marker of tissue fibrogenesis. The study population consisted of 172 patients younger than 10 years with single-ventricle circulation (59 after a Blalock-Taussig shunt, 60 after a bidirectional Glenn shunt, and 53 after a Fontan procedure) undergoing

FIGURE 1. Structure of collagen. Procollagen is composed of 2 $\alpha 1$ chains and 1 $\alpha 2$ chain intertwined into a triple helix. Propeptide domains at the carboxy-terminal and amino-terminal ends are cleaved and released into the plasma. (From Fan D, Takawale A, Lee J, Kassiri Z. Cardiac fibroblasts, fibrosis, and extracellular matrix remodeling in heart disease. *Fibrogenesis Tissue Repair*. 2012;5:15.)

catheterization and a comparison group of 149 children without known cardiac disease but with asthma, epilepsy, or infection. Sugimoto and colleagues⁴ successfully demonstrated a statistically significant correlation between PIIIP levels and single-ventricle status, preoperative volume load, preoperative cyanosis, postoperative ventricular diastolic stiffening, and renin-angiotensin-aldosterone system activation. In summary, Sugimoto and colleagues⁴ suggest that serum PIIIP provides important diagnostic information on myocardial fibrosis in patients with single-ventricle circulation and raise the possibility that ventricular fibrogenesis may be a potential therapeutic target in this population. This is provocative and important to consider.

One important aspect that this study does not fully elucidate is a correlation between PIIIP levels and tissue pathology. Collagen synthesis or degradation, as measured in serum biomarkers, does not wholly predict collagen deposition and fibrogenesis. When evaluated histopathologically, the spatial distribution of cardiac fibrosis may have important electromechanical effects that are not predicted by total amounts of fibrosis.⁸ This study is thought provoking, however, and deserves attention for both its content and its mechanistic approach. With mechanism, rational therapies can be designed and may help in the care of these challenging patients.

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