Mechanical Stretch and Endothelial to Mesenchymal Transition
– Importance of Integrin β1–
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There is marked interest in understanding the mechanisms of heart failure (HF)-induced cardiac fibrosis in order to develop new HF therapies. It is well known that dysynchronous ventricular contraction (ie, mechanical dyssynchrony) is frequently observed in patients with HF because of electrical activation delay (ie, electrical dyssynchrony). HF with mechanical dyssynchrony decreases myocyte and myofilament functions, calcium handling and β-adrenergic responsiveness, among other factors. Cardiac fibrosis, which may be responsible for cardiac contractile dysfunction, is also observed in patients with dyssynchronous HF. Recently, several clinical studies showed that a pacemaker-based treatment termed cardiac resynchronization therapy could reduce cardiac fibrosis. However, the mechanism of dysynchronous HF-induced cardiac fibrosis is still uncertain.

In this issue of the Journal, Mai et al present their results of an interesting study on the mechanism of the development of cardiac fibrosis in dysynchronous HF induced by right ventricular pacing, which induces late-contracting and high-wall stretch in left ventricular lateral walls. They clearly demonstrate that dysynchronous HF caused by right ventricular pacing increased endomisial fibrosis (EndMT) activity and the expressions of collagen 1A2, integrin β1, and transforming growth factor-β (TGF-β), leading to the aggravation of cardiac fibrosis in the left ventricular lateral wall. Moreover, right ventricular pacing increased angiotensin II and endothelin-1 levels in the left ventricular lateral wall. These authors also show that biventricular pacing (ie, resynchronization therapy) was effective in improving cardiac fibrosis and changing several of the factors just described in dys synchronous HF.

This study is of great interest for several reasons. Firstly, this study demonstrated that regional heterogeneity of mechanical stretch caused EndMT. In fact, several recent studies have demonstrated that EndMT arose in models of cardiac fibrosis, including hypertrophic cardiomyopathy, diabetes-induced cardiac fibrosis, uremic cardiomyopathy, and myocardial infarction. For example, Widyananto et al demonstrated that EndMT, which was identified with co-positive cells for endothelial (CD31) and mesenchymal (α-SMA and fibroblast-specific protein 1) markers, was observed in a mouse model of streptozotocin-induced diabetes mellitus. They also showed that EndMT could be induced in isolated endothelial cell cultures under high-glucose conditions. Therefore, the present study provides interesting insight into the contribution of EndMT in the induction of cardiac fibrosis in dysynchronous HF. Secondly, this study also provides interesting insight into the contribution of integrin β1 and TGF-β protein expressions to the induction of EndMT by regional heterogeneity of mechanical stretch. This study demonstrated that the mechanical stretch increased integrin β1 and TGF-β protein levels in the left ventricular lateral walls where late-contracting and high-wall stretch occurred, and induced EndMT. In addition, biventricular pacing improved the abnormal expressions of integrin β1 and TGF-β, leading to inhibition of EndMT. Moreover, an in vitro study using HUVEC demonstrated that cyclic stretch increased integrin β1 protein levels, leading to EndMT induction. The integrin β1siRNA inhibited EndMT, but TGF-β administration induced it, suggesting that integrin β1 increases TGF-β expression, which induces EndMT. It is known that epithelial to mesenchymal transition is induced by signaling pathways mediated by TGF-β, canonical Wnt signal, Notch, Hedgehog, and receptor tyrosine kinases. Those pathways are activated by various stimuli from the local microenvironment, including growth factors and cytokines, hypoxia, and contact with the surrounding extracellular matrix. Several studies have shown that TGF-β plays a major causal role in EndMT induction. For example, TGF-β induces myocardial fibrosis and diastolic dysfunction through fibroblast activation in a pressure-overload rat model, and the administration of TGF-β-neutralizing antibody prevents this process. Moreover, TGF-β induces EndMT in cultured endothelial cells. Therefore, the present study provides new insight into the possibility of a contribution by integrin β1 to the induction of TGF-β-induced EndMT in dys synchronous HF.

As with all important findings, this one raises a variety of questions. This study demonstrated that regional heterogeneity of mechanical stretch increased integrin β1 and TGF-β levels, but decreased bone morphogenetic protein 7 (BMP-7) protein levels in the left ventricular lateral walls where the late-contracting and high-wall stretch occurred, and induced EndMT.
This study also showed that mechanical stretch increased the expression of angiotensin II and endothelin-1 in dysynchronous HF. Moreover, biventricular pacing improved the abnormal expression of integrin β1, TGF-β, angiotensin II, and endothelin-1, and the decreased expression of BMP-7, leading to inhibition of EndMT. A previous study demonstrated that the endothelial expression of endothelin-1 and TGF-β causes high glucose-induced EndMT. In addition, losartan, an angiotensin II type 1 receptor blocker, inhibits EndMT in mitral valve endothelial cells by blocking the TGF-β-induced phosphorylation of ERK, suggesting the contribution of angiotensin II to TGF-β-induced EndMT. Moreover, Bhowmick et al. showed that integrin β1 signaling is needed to induce TGF-β-mediated p38MAPK activation and EMT progression. Taken together, these results suggest that integrin β1, angiotensin II, and endothelin-1 affect TGF-β signaling activation, leading to the induction of EndMT and progression of cardiac fibrosis in heart disease, which may present a target for pharmacological therapy to treat cardiac fibrosis in HF (Figure). However, it has been demonstrated that the systemic administration of recombinant human BMP-7 (rhBMP-7) inhibits both EndMT and the progression of cardiac fibrosis in a pressure-overload mouse model. In addition, rhBMP-7 inhibited TGF-β-induced EndMT in adult human coronary endothelial cells, whereas myocyte knockdown of TGF-β type 2 receptor resulted in upregulation of BMP-7 in a pressure-overload mouse model. Moreover, Aisagbonhi et al. demonstrated that canonical Wnt signaling differed from TGF-β signaling that participated in EndMT in myocardial infarction (Figure). Thus, the question still remains about the target for optimal pharmacological therapy to treat cardiac fibrosis in HF. Nevertheless, the present results by Mai et al. warrant further study on inhibition of the induction of cardiac fibrosis and ventricular contractile dysfunction in HF.

References