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Commentary: Calpains: Another piece of the cardiac fibrosis puzzle

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Myocardial fibrosis is a complex pathologic process that lies at the endpoint of a variety of cardiac diseases, ranging from coronary artery disease to hypertension to cardiomyopathies.¹ Cardiac fibrosis can be regional or diffuse in pattern and results in both diastolic and systolic dysfunction, as well as malignant arrhythmias.² Expanding our understanding of the molecular mechanisms that drive and perpetuate myocardial fibrosis is integral to the improvement of cardiac therapies.

In this issue of the *Journal*, Potz and colleagues³ report their findings on the effects of calpain inhibition (CI) on myocardial fibrosis in a porcine model of hypercholesterolemia and chronic myocardial ischemia. Calpains are a family of calcium-dependent, cysteine proteases that play a key role in myocardial fibrosis by activating transforming growth factor β and resultant collagen synthesis.⁴ The authors induced chronic myocardial ischemia in high cholesterol diet-fed Yorkshire pigs via placement of an ameroid constrictor on the left circumflex artery. Pigs were treated with either no drug, low-dose CI, or high-dose CI. Myocardial tissue from ischemic and nonischemic territories was analyzed. CI was found to decrease fibrosis as well as

Mark R. Helmers, MD (left), and Pavan Atluri, MD (right)

CENTRAL MESSAGE

For patients with ischemic heart disease and metabolic syndrome, calpain inhibition may be a valuable addition to the growing armamentarium of antifibrotic cardiovascular therapies.

Jak/STAT/MCP-1 signaling in the swine. CI was also shown to influence expression of focal adhesion proteins as well as cytoskeletal and structural proteins. Interestingly, the authors found variable modulation of transforming growth factor β and Jak/STAT/MCP-1 signaling in human ventricular fibroblast and rat fibroblasts, suggesting cell-type dependent effects of calpain signaling.

Although CI did not affect left ventricular hemodynamics or aortic pressures in the swine, the study did not involve any in vivo imaging. Although cardiovascular magnetic resonance imaging is expensive and limited in availability, late gadolinium enhancement and myocardial longitudinal relaxation time mapping enable accurate assessment and characterization of cardiac fibrosis.⁵ It is possible that cardiovascular magnetic resonance would have elucidated calpain-mediated ventricular remodeling in the swine.

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The authors should be commended for their contributions to our understanding of the pathogenesis of cardiac fibrosis and their growing body of work on calpain biology in the heart. This is an exciting time for antifibrotic cardiovascular therapies, with the development of novel approaches such as engineered T cells⁶ and long noncoding RNA targeting.⁷ And while clinical translation of previous promising preclinical antifibrotic cardiovascular therapies has been somewhat limited, it appears as though there is a role for combined therapeutic approaches.^{2,8} CI may well be another piece of the cardiac fibrosis puzzle.

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