Commentary: Myocardial relaxation matters

Paige E. Brlecic, MD, and Todd K. Rosengart, MD

Despite the performance of anatomically complete revascularization, recovery of myocardial function and regression of symptomatology following coronary artery bypass grafting (CABG) is often incomplete. This impaired recovery is often found to be related to diastolic dysfunction in the setting of significant recovery of systolic function and improvements in ejection fraction. Diastolic dysfunction after CABG associated with poor ventricular compliance as well as elevated left ventricular end-diastolic and pulmonary vascular pressures has been associated with adverse outcomes, including major adverse cardiac events and mortality, and thus remains a challenge to the efficacy of CABG.1-4

The etiology of diastolic dysfunction following anatomically complete revascularization remains unclear, but it has been associated with the development of fibrosis and functional impairment of chronically ischemic myocardium.5,6 The extent of such diastolic dysfunction after reperfusion remained poorly characterized.

In the current issue of the Journal, Aggarwal and colleagues7 provide exploratory mechanistic insight on the pathophysiology of diastolic dysfunction following CABG. Using magnetic resonance imaging in a healthy juvenile porcine myocardial ischemia model, the authors are able to demonstrate persistent diastolic dysfunction 4 weeks after CABG. The authors are able to further demonstrate in this model that CABG only partially reverses inflammation that may have contributed to the conversion of cardiac fibroblasts to collagen-producing myofibroblasts that induce myocardial “stiffening.”

Further molecular studies demonstrated that expression of the mitochondrial biogenesis regulator PGC1α was increased and the proinflammatory transcription factor nuclear factor kappa B (NFκB) and other downstream inflammatory mediators such as tumor necrosis factor-alpha were partially decreased to baseline levels after CABG.7 Given previous evidence that NFκB binds and represses PGC1α expression in cardiomyocytes, the downregulation of NFκB and/or upregulation of PGC1α could decrease inflammation and fibrogenic catalysts and/or enhance myocardial energetics and restore calcium dynamics in such a way as to further improve diastolic relaxation after CABG.8-10 This reporting offers an intriguing link between inflammation, mitochondrial dysfunction, and metabolic/calcium flux disturbances that could prove to be ideal secondary treatment avenues to enhance the results of CABG.

The current work further suggests mitigation of NFκB-mediated inflammation and/or enhancement of PGC1α expression as specific potential targets for adjuvant molecular interventions in the setting of CABG. Increasing mitochondrial biogenesis, restoring energy homeostasis, and reducing oxidative stress with such an intervention could enhance diastolic recovery following CABG. The extent to which these would need to be preemptive to chronic ischemia, as opposed to adjunctive to CABG, however, is unclear. Were the latter scenario proven to be the case, however, the authors’ previous work using epicardial stem cell patches as an adjunct to CABG could represent means to reduce oxidative stress and inflammatory response and thereby inhibit the conversion of fibroblasts into myofibroblasts and improve diastolic dysfunction.11 PGC1α gene
therapy could alternatively be readily delivered therapy via direct myocardial injection of an adenoviral vector during CABG. More broadly, these findings suggest a potential array of molecular and biological interventions as an important adjunct to CABG and other functional cardiomyopathies.

References