Sympathetic drive stimulating diastolic dysfunction?

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Diastolic heart failure accounts for half of the heart failure population and its pathophysiology remains an area of active research. The renin angiotensin and aldosterone axis has been the focus of clinical trials to treat patients with heart failure with preserved ejection fraction, however with limited yield in terms of clinical success. Sympathetic activity has been considered a plausible cause for the molecular changes that lead to diastolic dysfunction. Based on this understanding the study by Gimelli et al uses MIBG to evaluate for association between diastolic dysfunction and sympathetic denervation. The results of this study set the stage for a follow up study for evaluation of sympathetic denervation in isolated diastolic dysfunction

Key Words: Atherosclerosis • echocardiography • endothelial dysfunction • heart failure

Abbreviations			
AR	Adrenergic receptor	MEK/ERK	Mitogen/extracellular signal-regulated kinase
EF	Ejection fraction	MIBG	^{123}I-metaiodobenzylguanidine
HF	Heart failure	MMP	Matrix metalloproteinase
HFpEF	Heart failure with preserved ejection fraction	RAAS	Renin-angiotensin aldosterone system
HFrEF	Heart failure with reduced ejection fraction	SR	Sarcoplasmic reticulum

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Heart failure (HF) afflicts over 500,000 people in the United States. Approximately half of these heart failure patients are broadly categorized as having HF with reduced ejection fraction (HFrEF), and the remaining patients are considered to have heart failure with preserved ejection fraction (HFpEF) or diastolic HF.[1] HFpEF patients are noted to have an ejection fraction (EF) >50%, and those between 40% and 50% are considered intermediate. As with HFrEF, HFpEF portends a poor prognosis with both increased morbidity and mortality.

Diastolic dysfunction as a consequence of structural abnormality may involve an infiltrative process, hypertrophy, or fibrosis. Diastolic heart failure related to impaired relaxation of myocytes may be due to hypoxia, ischemia, or abnormal myocyte calcium handling. Variation in intracellular ionized calcium levels mediates the contraction and relaxation of cardiac muscle.

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During the generation of the action potential, the sarcoplasmic reticulum (SR) releases calcium from its stores. Calcium binds to troponin to generate systolic contraction. Diastole requires the active removal of calcium via ATPase back into the SR. Abnormal calcium handling, which can be due to (i) increased influx of calcium, (ii) decreased efflux, or (iii) decreased reuptake of calcium by the SR, leads to impaired relaxation. During ischemia, there is increased intracellular calcium which impairs diastolic function.

Common accompaniments of diastolic dysfunction, including obesity, hypertension, metabolic syndrome, and ischemic injury, can all lead to increased activity of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II, via the angiotensin type 1 receptor, is involved in regulating processes including inflammation and apoptosis. The association of diastolic dysfunction to collagen type I and type III over-expression is well noted in patients with HFpEF.[2] The collagen content of the extracellular matrix is determined by the production of collagen, *and* its breakdown by matrix metalloproteinase (MMP1). Angiotensin II has been shown to decrease MMP1 expression in fibroblasts with increased collagen type 1 production.[3] Angiotensin II causes pressure-independent myofibrosis, hypertrophy, and impaired myocardial relaxation.[4] Under ischemic conditions, increased circulating levels of angiotensin II have been associated with worsening diastolic function [5]

Aldosterone is increased in animal models with pressure overload states. Aldosterone stimulates mineralocorticoid receptors, phosphokinase C, and reactive oxygen species-dependent activation of the mitogen/extracellular signal-regulated kinase MEK/ERK pathway.[6] This leads to increased activity and expression of MMP which are implicated in myocardial remodeling and collagen deposition.[7,8] Nuclear Factor-kappa B (NF-kB) activation by aldosterone mediates cardiac fibrosis through a pro-inflammatory state.[8] Antagonism of mineralocorticoid receptors has been seen in experimental studies to reduce cardiac collagen and elastin density, thereby preventing cardiac and arterial fibrosis.[9,10]

Beyond these hormonal abnormalities, there is a compelling body of evidence supporting the role of the sympathetic nervous system in diastolic heart failure. Patients with diastolic heart failure have reduced exercise capacity, reduced cardiac output reserve, decreased chronotropic competence, reduced coronary vasodilator reserve, and delay in heart rate recovery after exercise.[11]

Epinephrine and norepinephrine act on the cardiovascular system by binding to alpha and beta adrenergic receptors (AR). Three beta receptor subtypes are present on the myocytes. Beta 1 and beta 2 AR stimulations lead to increased chronotropic and inotropic response; however, beta 3 receptor stimulation produces a negative inotropic response. Patients with systolic heart failure have sustained sympathetic hyperactivity explained by multiple factors including increased central sympathetic outflow, altered renin-angiotensin aldosterone axis, and decreased neuronal reuptake of norepinephrine. Chronically elevated stimulation of the ß AR system leads to ß AR desensitization in the myocardium of HFrEF patients due to downregulation of ß1 AR with reduced receptor density and functional desensitization via uncoupling from G proteins.[12,13] G protein receptor-coupled receptor kinase (GRK2) regulates signaling of the ß AR in the myocardium. Its upregulation in heart failure in cardiomyocytes leads to reduction in adrenergic and inotropic reserve.[14,15] In comparison, it is possible that patients with isolated diastolic dysfunction may not experience chronic neurohormonal activation the same way as HFrEF patients.[16] They may manifest similarly but with more intermittent spikes in neuroendocrine activity. For example, hypertension is a very common cause for diastolic dysfunction. Intermittent severe spikes in blood pressure may produce severe spikes in neurohormonal activation. Grassi et al demonstrated with peripheral sympathetic nerve microneurography that the hypertensive baroreflex in hypertensive patients is attenuated in the presence of sympathetic over-activity, and this is observed in patients with diastolic dysfunction.[17] This impairment of the baroceptor reflex by elevated sympathetic activity interferes with blood pressure control and may facilitate further spikes in sympathetic activation, thereby acting as one of the mediators of diastolic dysfunction in heart failure subjects.

In the present study, the authors used the norepinephrine analog, iodine-123-metaiodobenzylguanidine (MIBG), to explore the relationship of cardiac sympathetic neuronal activity to the presence of diastolic left ventricular dysfunction, measured by peak left ventricular filling rate.[18] Reduced MIBG uptake into presynaptic sympathetic nerve terminals, as measured by a reduced MIBG heart-to-mediastinum ratio, reflects reduced beta AR density in heart failure patients. It also is strongly correlated with heart failure progression and cardiac death in heart failure patients with left ventricular dysfunction. Limited data are currently available concerning the prognostic implications of a reduced MIBG heart-to-mediastinum ratio in heart failure patients with preserved systolic function. The study by Gimelli et al reports a relationship between diastolic left ventricular dysfunction and cardiac sympathetic nerve activity as assessed by the IMIBG heart-to-mediastinum ratio. Interestingly, the authors found an independent relationship of the left ventricular innervation/perfusion ratio to peak left ventricular filling rate. They interpret this as a particular relationship of sympathetically

denervated myocardium located in regions of preserved perfusion. Impaired presynaptic neuronal reuptake of catecholamines has been described after ischemic myocardial injury, with the area of sympathetic denervation exceeding the size of the area of the myocardium that remains under-perfused.[19] Although intensity and temporal variability in sympathetic nerve activity likely contribute to the differences between HFrEF (with intense, chronic sympathetic over-activity) and HFpEF (with less intense or more intermittent spikes in sympathetic nerve activity), the present findings from Gimelli et al raise an additional explanation.[20] The presence of denervated, perfused myocardium may itself predispose to diastolic heart failure.

Why is the role of sympathetic nervous system activation particularly important in HFpEF? In contrast to the success of medical therapies in the treatment of HFrEF, effective treatments for HFpEF have remained elusive. On the basis of the RAAS involvement previously documented in diastolic dysfunction, a number of trials using angiotensin receptor blockers were initiated without any demonstrated benefit in patients with HFpEF.[21] Aldosterone receptor blocker treatment, trialed in the Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonisT (TOPCAT) study, resulted in an overall neutral trial result, albeit the results generated debate as there was geographic variation noted in post hoc analysis of the results. Increased renal sympathetic nerve activity leads to central sympathetic stimulation and increased systemic sympathetic discharge. Catheter-based renal denervation, for treatment of hypertension, has been shown to reduce sympathetic activation as measured by reduced whole body and renal norepinephrine spillover.[22] Renal denervation has been shown to cause regression in left ventricular hypertrophy, improved ejection fraction and diastolic dysfunction.[23] This has translated into the ongoing DenervatIon of the renAl Sympathetic nerves in hearT failure with nOrmal Lv Ejection fraction (DIASTOLE) randomized clinical trial. (Clinical Trial Identifier: NCT 01583881). To date, these negative, inconclusive, and uncompleted studies of therapies for patients with HFpEF underscore the need to better understand the pathophysiology of the sympathetic nervous system in diastolic dysfunction, and to explore new approaches to sympathetic nervous system modification in HFpEF patients.

In the present study, the authors have shown that innervation/perfusion mismatch is significantly associated with diastolic left ventricular dysfunction. They studied 72 patients with mild to overt diastolic dysfunction. Mean left ventricular ejection fraction in the group with mild diastolic dysfunction was 45% ± 16%, whereas in the overt diastolic dysfunction group it was lower at 29% ± 13%. Seventy-three percent of the patients had experienced a prior coronary event. They noted a similar correlation between sympathetic denervation and diastolic dysfunction in patients with mild as well as overt diastolic dysfunction. The independent prediction of diastolic dysfunction by a sympathetic innervation/perfusion ratio in this population of patients, many of whom had a prior myocardial infarction, raises the question whether peri-infarction injury to sympathetic nerves surrounding the infarct set up a residual border zone of diastolic dysfunction (and potential ventricular arrhythmia). Whether this mechanism of innervation/perfusion mismatch also applies in the absence of prior myocardial infarction, for example, in patients with fibrosis from left ventricular hypertrophy alone, requires assessment of HFpEF in a pure population of patients with left ventricular ejection fraction $\geq$50% with no prior myocardial infarction. As the authors note, definitive study of the relationship of sympathetic nerve activity to pure diastolic left ventricular dysfunction will also require studies in patients in whom myocardial ischemia from coronary artery disease has been excluded. In addition, a more definitive examination of the relationship between diastolic left ventricular dysfunction and cardiac sympathetic innervation might be obtained using invasive measurement of left ventricular diastolic pressure.

Regardless of these limitations, the present study lends support to the theory of increased sympathetic activity contributing to the development of diastolic dysfunction. The next steps should include a study designed to elaborate on the association of sympathetic denervation and isolated diastolic dysfunction (HFpEF) with left ventricular ejection fraction $\geq$50%. The present study is a step toward better understanding of the underlying mechanisms of heart failure with preserved left ventricular function, supporting new pathways for therapeutic targets in HFpEF.

Disclosure

The authors have indicated that they have no financial conflict of interest.

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