Circulation: Cardiovascular Imaging

EDITORIAL

Stress Imaging in Heart Failure

Physiologic, Diagnostic, and Therapeutic Insights

See Article by Matsumoto et al

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When interviewing a patient with heart failure (HF), the medical student will ask the patient whether they are short of breath. The patient, resting comfortably in the examination room, will reply in earnest that they are not. The student will conclude from this encounter that HF is absent. After hearing the student's report, the seasoned clinician will then return to the room with the student and ask the patient how they feel when ascending a flight of stairs, or walking to the mailbox, or bathing, or eating breakfast. To the horror and dismay of the student, the patient will then confide that they are in fact extremely short of breath during these activities. After assuaging the student that their grade will not be jeopardized, the seasoned clinician will then (hopefully) take advantage of this learning opportunity to emphasize how important it is to evaluate symptoms that are elicited by stress rather than questioning about rest alone in the evaluation of HF.

The normal cardiovascular system copes with stressors so effectively that they rarely rise to the level of conscious thought. Thermal stress when ambient temperature changes, orthostatic stress when body position changes, and of course, exercise stress, where heightened oxygen requirements in skeletal muscle call for an increased delivery of blood flow. In order for the heart to pump more blood, there must first be greater venous return to the heart to augment ventricular preload. The inability of the heart to accommodate this increase in preload appropriately is a fundamental and defining characteristic of HF. Just as the student's medical history was enhanced by asking the patient about stress reserve, our functional assessments of the cardiovascular system are optimized by directly observing the heart during stress.[1–4] The question is how best to use stressors in clinical practice, and do these stress responses have clinical relevance?

In this issue of *Circulation: Cardiovascular Imaging*, Matsumoto et al[5] present intriguing new data that illustrate the potential added value for assessment of systolic and diastolic stress reserve in patients with HF with reduced ejection fraction (HFrEF). The authors prospectively examined 120 patients with HFrEF to evaluate systolic and diastolic functions by echocardiography at rest and during an acute increase in cardiac venous return induced by leg-positive pressure (LPP). Systolic and diastolic reserves were defined by changes in left ventricular (LV) stroke work index and E/e′ ratio during LPP, respectively. After this assessment, patients were followed to evaluate how these limitations in systolic and diastolic functions might be different between HFrEF patients with and without cardiovascular events, and how these functional reserve limitations related to outcomes.[5]

In patients without cardiovascular events, stroke work index increased by 18% during preload augmentation, with minimal changes in E/e′, indicating relatively

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preserved Frank–Starling cardiac reserve.[5] In contrast, stroke work index reserve was impaired, and E/e′ ratio substantially increased during LPP in HFrEF patients with cardiovascular events, indicating that these patients could not accommodate an increase in preload appropriately. Importantly, stroke work index and E/e′ measured at rest were completely ineffective to distinguish patients with and without events, but by assessing systolic and diastolic functions during LPP, the authors were able to demonstrate incremental prognostic value beyond conventional (resting) echocardiographic parameters.

The authors also performed assessments of right ventricular (RV) structure and function, as well as the geometric relationship between the LV and RV by echocardiography.[5] The latter was measured by the eccentricity index, which quantifies the magnitude of flattening of the interventricular septum.[6] An increase in the eccentricity index (the septum is flatter and less convex to the RV) indicates that there is more diastolic ventricular interaction (DVI). This term refers to the state where pressure and volume on one side of the heart reciprocally (volume) or additively (pressure) influence pressure and volume on the other side. DVI is frequently increased in patients with HF, tricuspid regurgitation, or pulmonary hypertension and plays an important role in determining central hemodynamics and cardiac reserve.[6–8] When venous to the heart is increased in the setting of enhanced DVI, there is an uncoupling of intracavitary pressure and volume. In the most common example, increased right heart overload causes the septum to bow from right to left, and intracavitary LV pressure increases even as LV volume is unchanged. This occurs because intracavitary pressure increases in this setting are mediated by external forces because of septal displacement on one side and the contact pressure exerted by the pericardium on the other. Thus, intracavitary LV pressure goes up as venous return is enhanced, but LV preload (chamber volume) does not.[6]

Matsumoto et al[5] found that LV eccentricity index did not change with LPP in patients without events, but in patients with events, the increase in venous return from LPP increased eccentricity index, suggesting that the observed impairment in Frank–Starling reserve was mediated, in part, by adverse DVI.[5] Together with impaired diastolic and systolic reserves, an increase in DVI with LPP was also found to be an independent predictor of adverse events. The authors conclude that diastolic, systolic, and DVI responses to LPP are important predictors of outcome in patients with HFrEF that are superior to assessments performed at rest alone.[5]

The authors are to be commended on this important contribution that demonstrates how a classical hemodynamic perturbation in HF (impaired Frank–Starling response to preload augmentation) can be used as a stress to help us identify patients at increased risk.[5] An important question is what caused this impairment. The authors suggest several possibilities, including impaired length–tension relationship, worsening mitral regurgitation, increased arterial afterload, or impaired RV or left atrial reserve.[5] Although their data are not adequate to prove causality, enhanced DVI may be a primary pathophysiological driver explaining their observation.[8]

The question is what caused DVI to be enhanced in patients with HFrEF and greater event rates in the current study?[5] It was not necessarily excessive RV dilatation because this was similar in patients with outcomes and those without. Although changes in inferior vena cava diameter did not differ between the groups, this is a rather crude estimate of central venous filling pressures, and one cannot exclude the possibility that RV filling pressure increased more in patients with events, similar to what is seen in patients with Kussmaul physiology.[9] Larger LV and left atrial volumes in patients with outcomes might have contributed to pericardial restraint and enhanced DVI by increasing total heart volume. Patients with events might also have displayed more severe elevation in pulmonary artery pressures, or worsening tricuspid regurgitation during stress, although neither of these possibilities were evaluated by the authors in this study.[5]

Although Matsumoto et al[5] enrolled patients with HFrEF in their study of the effects of LPP,[5] it is worth considering how these data might apply to HF with preserved ejection fraction (HFpEF), which will soon become the predominant form of HF in many parts of the world.[10] Diagnosis of HFpEF is often challenging because it can be difficult to estimate LV filling pressures noninvasively and because many patients with HFpEF display elevated filling pressures only during the stress of exercise.[1–4] Invasive hemodynamic exercise testing has emerged as the gold standard test to make (or refute) this diagnosis, and some data suggest that exercise echocardiography may also be useful.[1,4] Although volume loading is not as sensitive or specific of a stressor as exercise,[2] it is more feasible to obtain diagnostic quality echocardiographic imaging during volume loading. Passive leg raise has been evaluated as a stressor and does not enable adequate discrimination of HFpEF from controls.[4] However, as discussed by Matsumoto et al,[5] leg elevation alone does not provide a robust volume load, and further research is indicated to determine whether imaging during LPP can enhance diagnosis of HFpEF. It would also be interesting to evaluate whether preload stress echocardiography can identify patients more likely to respond poorly to interventions that are associated with RV volume loading, such as creation of an arteriovenous shunt for dialysis access or creation of an interatrial shunt device to reduce left atrial pressures.[11,12]

In addition to diagnostics and risk stratification, these data may have therapeutic implications. Theoretically, DVI can be targeted in 2 fundamental ways: by decreasing heart size or decreasing the external restraint on the heart that enforces competition between the 2 ventricles. As to the latter, we have recently demonstrated that resection of the anterior pericardium through a minimally invasive approach substantially mitigates the increase in LV filling pressures with volume loading, suggesting that direct interventions to reduce pericardial restraint through surgical modification could be a novel therapeutic approach targeting DVI in HFpEF.[13]

In patients with dilated hearts (like HFrEF), removal of external constraint could be a bad thing because it might promote even greater eccentric remodeling.[14] However, other interventions to reduce heart size could be effective in this cohort, such as diuretics to reduce volume overload, reduction in pulmonary artery pressures to decrease right heart volumes, or neurohormonal antagonists that may enable reverse remodeling in all 4 chambers.[15]

In summary, Matsumoto et al[5] have provided exciting new data identifying new ways to noninvasively use stress evaluation to better understand and treat patients with HF. Enhanced DVI limits recruitment of Frank–Starling reserve in patients with HF, and this contributes to adverse outcomes. What is needed now is further study to determine how we can apply preload reserve to other patient populations and how to optimally treat the enhanced DVI to improve outcome in people with HF, regardless of the ejection fraction.

ARTICLE INFORMATION

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Disclosures

None.

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