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LV Diastolic Dysfunction and Prognosis

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To provide for tissue perfusion without pulmonary congestion, the left ventricle (LV) must eject an adequate stroke volume at arterial pressure (systolic function) and fill without requiring an abnormally increased left atrial pressure (diastolic function). Systolic and diastolic function must be adequate to meet the needs of the body both at rest and during stress (reserve capacity).

Normal LV diastolic function requires integration of left ventricular ejection, relaxation, and structure and is an active energy requiring process[1]. For example, LV diastolic function becomes markedly abnormal immediately following coronary ligation, before detectable changes in other measures of cardiac function, including wall motion or electrocardiographic S-T segment shifts[2]. LV diastolic function is impaired by all of the common pathological processes that affect LV function or produces LV hypertrophy or fibrosis, including: hypertension, diabetes, ischemia, myocarditis, toxins, and infiltrative cardiomyopathies. Thus, LV diastolic performance is a sensitive indicator of cardiovascular dysfunction.

Systolic function is conveniently (although not always accurately) measured as the ejection fraction (EF) Diastolic function has been more difficult to evaluate[1,3]. Traditionally, invasive measures of LV diastolic pressure-volume relations and the rate of LV pressure fall during isovolumetric relaxation have been used. However, these methods are not practical for routine clinical use and do not adequately evaluate all aspects of diastolic filling[3].

Approximately three decades ago, pulsed spectral Doppler was first used to quantitatively assess the velocity of blood flow from the left atrium into the LV. Since then, there have

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been many advances in the non-invasive assessment of LV diastolic function by echo-Doppler. One of the most important of these was the development of tissue Doppler (TDI), which was accomplished by adjusting the Doppler filter settings to focus on the low velocity, high amplitude signals produced by tissue motion. Ironically, these had previously been actively filtered out as “wall clutter” and thereby overlooked. TDI can measure the rate of mitral annular motion. The early diastolic annular velocity away from the apex is reduced and delayed in the presence of impaired relaxation. TDI can also be used to assess LV myocardial strain. Other more recent advances include color M-mode Doppler to measure flow propagation into the LV, and speckle tracking to assess twisting of the LV apex relative to the mitral annulus and untwisting in early diastole.

Comprehensive echocardiographic evaluation of the dynamics of LV filling utilizes Doppler measurements of mitral inflow and pulmonary venous flow, along with tissue Doppler evaluation of the early diastolic mitral annular velocities and measurements of left atrial size[4]. By combining these data utilizing written algorithms, specific patterns of LV filling can be discerned[4]. These patterns can define both normal diastolic function and the stages of diastolic dysfunction.

Echo-Doppler evaluation of diastolic function provides important prognostic information in a wide variety of patients. A normal filling pattern in community dwelling subjects indicates an excellent prognosis[1]. In contrast, an abnormal filling pattern and progressively greater abnormalities of left filling (impaired relaxation versus pseudonormalized and restricted filling patterns) indicate patients with progressively-increased risk of subsequent mortality. The stage of diastolic dysfunction correlates with the impairment of exercise capacity in patients without myocardial ischemia better than resting LVEF[5]. In patients with heart failure, the stage of diastolic dysfunction is a stronger predictor of mortality than EF[1].

A shortened early deceleration time indicates an increased LV operating stiffness. It is a hallmark of restrictive filling pattern and denotes poor prognosis in patients with myocardial infarction, dilated cardiomyopathy, heart transplantation, hypertrophic cardiomyopathy, and restrictive cardiomyopathy[4]. Both pseudonormalized and restricted filling patterns indicate a four-fold increase in the risk of death in patients with HF and coronary artery disease[6]. Similarly, an increased ratio of early mitral flow/early annulus velocity indicates poor prognosis in a variety of patients[4]. Recently, Mogelvang et al found that early diastolic annular velocity predicted mortality in a general population of patients, most of whom were free of apparent systolic and diastolic dysfunction by conventional echocardiographic methods[7].

However, there have been few data examining the utility of serial echo-Doppler assessments of LV filling, particularly in patients without significant systolic dysfunction. Kane et al recently reported on a randomly selected community cohort during 4 year follow-up[8]. They found that grade of systolic dysfunction worsened in 23% of subjects and was associated with older age. During 6.3 years of additional follow-up, those with worsened diastolic dysfunction had greater risk for heart failure, even after adjustment for age.

AlJaroudi et al in this issue of Circulation significantly extend these results by examining the impact of progression of LV diastolic dysfunction on mortality[9]. They examined 1,065 outpatients who had preserved LVEF on a baseline clinically indicated echocardiogram and who had a second clinically indicated echocardiogram 6–24 months later. Vital status was determined by use of public records. An abnormal LV diastolic filling pattern was highly prevalent at baseline (73%), although restricted LV filling pattern was present in just two patients. The investigators found that in these presumably relatively low risk patients (by virtue of their outpatient status and LVEF) subsequent mortality was substantial (13%). Thus, it appears that patients who have two clinically indicated echocardiograms within two years have a substantial risk of early death. Importantly, those with worsened LV filling patterns at follow-up had worse prognosis than those who had either no change or improvement in LV filling (21% vs. 12% mortality). Although many of those with worsened LV filling at follow-up also had developed reduced LVEF, the follow-up echo-Doppler LV filling patterns added significant, independent prognostic information beyond LVEF. Thus, progression of LV filling abnormalities in outpatients with preserved LV systolic function is a strong, independent predictor of all-cause mortality.

It is remarkable that serial evaluation of LV diastolic function could be such a powerful predictor of all-cause mortality, not just cardiovascular death. This is especially surprising given the recent report from the Framingham Study[10] that non-cardiac factors contribute significantly to the development of cardiac events, including heart failure, and others showing that once heart failure develops, non-cardiac co-morbidities contribute quite significantly to mortality[11]. It is likely that diastolic dysfunction and especially worsening diastolic dysfunction is a marker of increased risk. For example, hypertension, diabetes, ischemia, and reduced systolic function all are associated with diastolic dysfunction. In addition to being a marker of increased risk, diastolic dysfunction may also be a direct contributor to the adverse outcomes, perhaps by contributing to the progression of heart failure by limiting cardiac output reserve, accelerating neuroendocrine activation, increasing symptoms of breathlessness, and promoting physical inactivity, deconditioning, and frailty[12].

What might be some next steps in the further development of this important area? These impressive results of AlJaroudi et al and the earlier results of Kane et al were obtained by analyzing patterns of LV filling. These require some degree of expertise and time to interpret. Sometimes this must be done in the absence of one or more component variables, such as pulmonary vein flow which is the most technically demanding to acquire, or by reconciling apparent conflicts between component variables. Assignment of a specific pattern is not possible in all patients. This is demonstrated in the current study, in which approximately two-thirds of the patients had to be excluded from the analysis[9]. Some of these were because the patient lacked a valid U.S. Social Security number, had limited echocardiograms, or had not had diastolic function reported. However, as discussed by the authors, other patients who had to be excluded had common cardiology disorders, including severe valvular stenosis or regurgitation, prior mitral valve surgery, tachycardia, atrial fibrillation, or a poor acoustic window. In the Kane et al study, diastolic function grade could not be assigned in approximately 25% of subjects[9].The experience of these two important studies in this regard is not unique. A systematic analysis performed by

Aurigemma et al indicated that even with expert acquisition and interpretation, assignment of LV filling patterns is not possible in up to one-third of patients[13]. A metric that is feasible in all patients, is load-independent, yields a single continuously variable number, is quick, reliable, and automated would be desirable but has thus far been elusive.

In addition to the echo-Doppler techniques discussed above, there are other technologies that can provide, directly or indirectly, information regarding LV diastolic function. While currently less widely available, more resource intensive, and with lower temporal resolution than echo-Doppler, cardiac magnetic resonance imaging (CMR) provides very high quality images and reproducibility and has a relatively low rate of non-evaluability compared to echocardiography, in which high quality images cannot be obtained in many patients[14]. CMR techniques quantify velocity and vector of blood flow and tissue movement to provide diastolic strain rate, time dependent change in left ventricular and atrial volumes, untwisting, and flow propagation[15]. CMR can also characterize myocardial tissue, including subclinical fibrosis, and thus provide mechanistic insights into diastolic dysfunction[15]. A recently developed, novel method is 4D flow[16]. Like other CMR techniques, it may be complementary to Doppler-echocardiography[17]. The biomarker B-type natriuretic peptide (BNP) may also be useful. It is synthesized and released in response to LV stretch and correlates with the echo-Doppler grade of LV diastolic dysfunction[18]. Many studies have demonstrated its strong prognostic value, both as a single test and also as it changes over time. This widely available blood test is relatively inexpensive, simple, and fast compared to an echo-Doppler or CMR exam.

The results from AlJaroudi et al were obtained with measurements performed at rest. By assessing reserve capacity, stress testing can often detect important abnormalities that are not present or are more subtle at rest. Although technically challenging, diastolic function can be assessed during pharmacological stress or during immediate post-exercise and can provide valuable predictive information[19]. It is possible that doing so could provide, in a single exam and at an earlier stage, information that is similar in predictive power to that obtained by paired, follow-up resting echo-Doppler exams. Assessment of LV filling during exercise, though technically demanding, may be complementary with the other information provided by cardiopulmonary exercise testing, which assesses global cardiovascular reserve, is an independent predictor of mortality in a wide variety of populations, is semi-automated and reproducible, and has relatively modest cost[20].

In conclusion, normal LV diastolic function requires normal function and integration of left ventricular ejection, relaxation, and structure and is an active energy requiring process. Thus, diastolic performance is sensitive to nearly all of the common pathological processes that affect cardiovascular function. Comprehensive echo-Doppler/tissue Doppler evaluation of diastolic filling dynamics can sensitively detect abnormal LV filling dynamics. As demonstrated by AlJaroudi et al, echo-Doppler progression of diastolic dysfunction can detect LV dysfunction at an early stage and indicates increased risk for future events. This is a fertile area for continued important advances.

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