Diabetic Heart Disease: Insights from Cardiac Mechanics

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LEFT VENTRICULAR MECHANICS

The left ventricle undergoes complex deformations with contraction and relaxation that involve shortening, thickening, twisting, and torsion during systole in order to eject blood efficiently. The process is reversed with lengthening, dilation, and untwisting of the left ventricle in early diastole that generate the intracavity pressure gradient (diastolic suction) that facilitates early diastolic left ventricular (LV) filling. These processes reflect the LV myocardial architecture, which can roughly be divided into three layers. The myofibers in the subendocardium are arranged in a right-handed helical geometry that is almost longitudinally oriented. The myofibers transition to a circumferential orientation in the midwall and then attain a left-handed helical geometry in the subepicardium.[1–3] The extracellular matrix contributes to maintenance of LV geometry, myocardial function, and stiffness. LV deformation abnormalities can precede other indicators of LV dysfunction and can provide prognostic information.

Cardiac remodeling in response to physiologic or pathologic alterations occurs at the molecular level significantly before measureable abnormalities in the standard performance metrics (e.g., LV ejection fraction [LVEF]) can be detected and quantified. Echocardiographic assessment of cardiac performance has become progressively more sophisticated and as such can now identify and quantify abnormalities of cardiac performance before the onset of overt clinical disease. The recent introduction of tissue deformation imaging has greatly enhanced the ability of echocardiography to differentiate physiologic from pathologic LV hypertrophy[3] and to identify subclinical cardiac performance abnormalities, potentially allowing earlier therapeutic interventions.[4]

LV deformation can be quantified using a number of techniques: Doppler tissue imaging, magnetic resonance imaging (MRI), and speckle-tracking echocardiography (STE). The last is based on the principle that a characteristic speckle pattern that is spatially and temporally invariate can be tracked over time and used to measure regional wall motion in order to quantify systolic and diastolic LV deformation. Generally, strain ($\varepsilon = \Delta L/L_0$, where ΔL is the change in the separation between two imaged myocardial points [speckles] and L_0 is the initial separation distance) and strain rate ($d\varepsilon/dt$) are calculated. LV twist and torsion can also be measured. Measuring these parameters requires obtaining images in multiple planes by two-dimensional (2D) echocardiography in order to characterize LV deformations in a comprehensive manner. MRI and three-dimensional echocardiography may simplify image acquisition. The performance of each of the myocardial layers is reflected in its relevant strain measurement. Longitudinal strain predominantly reflects the performance of the subendocardium, circumferential strain measurements reflect midwall performance, and subepicardial contraction is represented by radial strain measurements.[2,4] Regional strain varies significantly, even in normal individuals. However, there appears to be no standard approach regarding the number of planes imaged in any study, despite the findings of disease-related variability in abnormalities in speckle-tracking echocardiographic measurements. Global and regional longitudinal strain and strain rates obtained from the apical views are reported to be most reproducible, while those measurements obtained from other views are less so. The reproducibility of longitudinal strain measurements obtained from the apical views is enhanced not only by the higher axial resolution achieved by imaging parallel to the ultrasound beam but also by the apical displacement of the left ventricle that generally parallels the ultrasound beam. In contrast, circumferential and radial strain measurements performed in the short-axis view suffer from the variable angles of the displacement vectors with the ultrasound beam, the lower azimuthal resolution, and motion of the left ventricle outside of the imaging plane.[2] Cheng *et al.*[5] reported excellent interobserver and intraobserver reproducibility of 2D speckle-tracking echocardiographic measurements of global longitudinal and circumferential strain and only slightly lower correlation coefficients for transverse and radial strain in a small sample of patients from a large community-based study. However, strain rate measurements are subject to greater variability due to artifacts induced by obtaining the first derivative of strain. In addition to the image acquisition protocol and the quality of the images obtained, measurements of LV mechanics depend on the manufacturer of the ultrasound machine and the algorithms used by the offline workstation to perform the semiautomated LV wall edge detection and speckle-tracking.[6] These algorithms are manufacturer specific and proprietary, a problem that will have to be addressed before wide implementation of the technique.[7,8]

CHANGES IN LEFT VENTRICULAR MECHANICS IN PATIENTS WITH DIABETES MELLITUS

Diabetes mellitus (DM) can induce myocardial metabolic, structural, and ultrastructural changes that result in cardiac remodeling affecting all four chambers[9,10] and is manifest by reduced performance, especially of the left ventricle, independent of its frequently associated comorbidities of hypertension, hyperlipidemia, and atherosclerotic coronary artery disease. Diabetic cardiomyopathy (CM) was first described by Rubler *et al.*[11] and is defined as myocardial dysfunction occurring in the absence of coronary artery disease, hypertension, or valvular heart disease. LV diastolic dysfunction is reported to occur in ≥30% of those with type 2 DM, can be detected early after its onset (<2 years), and is a frequent precursor to the development of heart failure.[12,13]

Multiple mechanisms have been implicated in the pathogenesis of diabetic CM.[14] Chronic hyperglycemia and hyperlipidemia induce cardiac structural remodeling and dysfunction involving all of the myocardial layers by a number of interrelated pathways. Cardiomyocyte injury and necroptosis result from the combined toxic effects of increased oxidative stress because of the production of reactive oxygen species, the formation of advanced glycation end products, the

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induction of inflammatory cytokines by upregulation of nuclear factor–κB, the production of toxic fatty acid metabolites (e.g., ceramide), and abnormalities of calcium homeostasis. The myocardial injury is amplified by the development of a microangiopathy. The DM-induced oxidative stress is also associated with depletion of cluster of differentiation 34–positive endothelial progenitor cells, responsible for maintenance of microvascular integrity. The depletion of these cells is independently associated with reduced LV global circumferential strain.[15] Abnormal calcium transport results from upregulation of the hexosamine pathway and lipotoxic mitochondrial injury and affects not only cardiomyocyte energy production and use but also myocardial contraction and relaxation. Myocardial stiffness is increased by at least two mechanisms in addition to derangements in calcium handling: First, interstitial fibrosis and alterations in extracellular matrix result from toxic fatty acid metabolites combined with increased intracellular angiotensin II levels. Second, advanced glycation end products increase myocardial collagen-elastin cross linkage. Both of these contribute to increased myocardial stiffness. Hypertrophy of the remaining myocytes is induced by cardiac angiotensin II. However, despite the compensatory hypertrophy resulting in increased wall thicknesses (especially in women), reduced cardiac myocyte function combined with increased interstitial fibrosis results in reduced systolic and diastolic LV performance.[16] These abnormalities are amplified by microvascular and macrovascular coronary artery disease, hypertension, obesity, autonomic dysfunction, and aging on cardiac anatomy and physiology. In fact, many of the abnormalities found in diabetic CM are analogous to those found in the aging left ventricle. Age-related cardiac remodeling is characterized by increased wall thicknesses and decreased LV volumes. Myocyte loss and hypertrophy of those remaining myocytes, combined with an increase in collagen content, lipid accumulation, amyloid deposition, and abnormal calcium handling, alter the physical properties and performance of the left ventricle.

Hypertension, a frequent comorbidity of DM and a cause of LV hypertrophy and remodeling, alters LV strain measurements. Celic *et al.*,[17] in a study using 2D and three-dimensional STE, reported that peak longitudinal, circumferential, and radial strains all were decreased in patients with untreated and uncontrolled hypertension compared with normal subjects. However, the LV strain values in patients with well-controlled hypertension were closer to those of the normal cohort. In contrast, peak systolic twist and torsion were increased in the former groups. A potential explanation for these observations was provided by Kang *et al.*[18] They reported that decreased longitudinal strain and increased torsion in patients with hypertension were correlated with the serum level of tissue inhibitor of matrix metalloproteinase–1, a biomarker of collagen turnover and myocardial fibrosis. Because the LV subendocardial region is most sensitive to ischemia and fibrosis, and because increased extracellular fibrosis would lead to myocardial stiffening, these findings are consistent with the known effects of remodeling not only in patients with hypertension but also those with DM and coronary atherosclerosis. Thus, it is not surprising that coexistent hypertension and coronary artery disease amplify the deleterious effects of DM on the left ventricle.

Controversy exists as to whether LV diastolic dysfunction is the earliest manifestation of preclinical diabetic CM, preceding a decline in systolic performance. Early studies using 2D Doppler echocardiography and Doppler tissue imaging reported abnormal indices of LV diastolic function, often in the setting of normal systolic performance.[19] However, clinical diastolic performance measures may be more sensitive indicators of abnormal LV filling and annular motion than those used to assess systolic performance. Systolic deformation alterations and LV remodeling can occur before a significant decrease in the LVEF is detectable even by rigorous semiautomatic calculations using biplane transthoracic images. This is especially so in clinical echocardiography laboratories, where LVEF is often estimated by visual inspection. Measurements of LV strain and strain rate have been used to uncover subtle abnormalities of LV systolic performance that precede a detectable decline in LVEF and can presage the development of significant clinical disease (e.g., anthracycline-induced cardiotoxicity).[20]

Ernande *et al.*,[21–24] in a series of recent publications, have used both STE-derived and MRI-derived measurements of LV strains to advance our understanding of the effects of type 2 DM on LV mechanics and to provide important insights into the mechanisms underpinning the development of diabetic CM. They reported that global and regional longitudinal and radial strains measured by STE, and midwall fractional shortening, were reduced in asymptomatic middle-aged patients with type 2 DM compared with controls despite comparable values for other indices of systolic LV performance.[21] However, they did observe significantly lower values for diastolic function and a slight, but significant, increase in LV sphericity in those with DM. Reduced longitudinal strain was associated with DM and gender; only DM was correlated with radial strain alteration. In a second publication,[22] they reported that although diastolic dysfunction is commonly observed in type 2 DM, it is affected by a number of confounders, whereas systolic strain alterations are associated only with gender and DM. Importantly, they found that isolated systolic alteration occurred in 28% of patients with DM with normal diastolic function and in 35% with diastolic dysfunction.[22] Thus, reduction in systolic strain in early diabetic CM is not invariably coupled to diastolic dysfunction, and it may precede echocardiographic metrics of abnormal diastolic performance. In a third article, they reported that the MRI technique of cine displacement encoding with stimulated echoes was able to quantify decreased longitudinal, radial, and circumferential systolic strains in type 2 DM with a high degree of reproducibility.[23] As in the previous reports, the alterations in strains correlated with the presence of DM.

Their most recent report, published in this issue of *JASE*,[24] compares the differences in LV remodeling after 3 years of follow-up in patients with asymptomatic type II DM with altered global longitudinal strain ($|\varepsilon_L| < 18\%$) with results in a cohort with normal longitudinal strain ($|\varepsilon_L| \geq 18\%$). The cohorts were well matched with regard to clinical and biologic characteristics, and except for the higher percentage of patients in the altered-strain group who were receiving angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, but they were well matched with regard to their other medications. Despite general comparability of echocardiographic measurements between the groups, the altered-strain cohort demonstrated small, but significant, increased mean relative LV wall thickness and end-systolic volume and a slight reduction in LVEF. Also, the mitral valve deceleration time was mildly prolonged in both groups, despite normal values for other measurements of diastolic function. An interesting finding was a small but significant decline in ε_L in the cohort with normal ε_L at 3 years. After controlling for a number of confounding variables, ε_L was independently associated with relative LV wall thickness but not gender. After 3 years, no significant changes in LV volumes were reported in those patients with altered ε_L. However, a slight increase in end-diastolic volume was observed in the female patients. In contrast, significant decreases in LV volumes were observed in patients with normal ε_L. No change in relative wall thickness occurred in either group. Reduced LV systolic longitudinal strain and gender were the only predictors of