Hypertrophic cardiomyopathy (HCM) is a primary autosomal-dominant disorder of the myocardium caused by mutations in sarcomeric contractile proteins. Histopathologically, it is associated with myocardial hypertrophy, fiber disarray, increased loose connective tissue, and fibrosis, which are all thought to interfere with myocardial force generation and relaxation.1-3 There is tremendous heterogeneity in the phenotypic expression of HCM, which is generally unrelated to genotype. This is shown by the variability of the age of onset of clinical disease, degree and location of hypertrophy, and presence and site of intraventricular dynamic pressure gradients. Despite this heterogeneity, almost all patients with HCM have some degree of diastolic dysfunction. The presence of subtle changes in LV filling may even identify patients with preclinical disease without LV hypertrophy. Interventions such as medical therapy, septal alcohol ablation, and surgical myectomy improve symptoms by both reducing the left ventricular (LV) outflow tract gradients and improving diastolic function.

The origin of diastolic dysfunction in HCM is both multifactorial and complex, with changes at the molecular, myocardial tissue, and global LV levels. More than 400 mutations have been described in HCM, which result in the production of abnormal myocardial sarcomeric proteins that have altered contraction and relaxation characteristics. These include changes in the affinity between the various contractile proteins, in the sensitivity to Ca²⁺, and in the efficiency of energy use (from ATP) and its expenditure.3,4 These abnormalities may vary with the sarcomeric protein affected and the site and effect of the mutation. Myocardial ischemia also has been documented by reversible thallium perfusion defects, positron emission tomography, and abnormal lactate production. This may be due to small-vessel disease with decreased vasodilator capacity, myocardial bridging, decreased coronary perfusion pressure, obstruction to LV outflow, and myocardial supply demand mismatch. Morphological factors that influence the degree of diastolic dysfunction include the degree of ventricular hypertrophy, myocardial disarray, and interstitial fibrosis.4 These may be modulated by expression of growth factors and cytokines. Ventricular shape and geometry, including the presence of small LV systolic volumes and LV cavity obliteration, also may lead to reduced LV distensibility. Their effect on impaired diastolic filling is partially offset by the presence of increased elastic recoil. These changes may explain why dynamic diastolic pressure-volume curves measured during filling in patients with HCM often are considerably shallower than would be anticipated if one assumed high chamber stiffness.5

Evaluation of LV Filling Pressures by Doppler Echocardiography

Echo Doppler measures of diastolic dysfunction are accurate ways to assess both impaired relaxation and elevated filling pressures in a wide variety of diseases. This has been demonstrated in patients with coronary artery disease, congestive heart failure, valvular disease, and non-HCM cardiomyopathies. The integration of Doppler transmitral, pulmonary venous inflow, and tissue Doppler annular velocities has been used to accurately detect impaired relaxation and to quantify LV end-diastolic and mean left atrial (LA) pressures.6-9 This information has been useful in predicting patient outcomes and following the benefits of therapy.10

The importance of diastolic dysfunction in HCM has led to an extensive search for accurate, noninvasive methods of quantifying its severity.11 Given the complex interplay of factors causing diastolic dysfunction in HCM, it should not be surprising that despite initial false hope, no single noninvasive measure has been validated to be accurate. This was true for the use of transmitral Doppler E/A ratios, a marker for impaired relaxation, and mitral deceleration time, a useful way to quantify pulmonary capillary wedge pressure in patients with LV dysfunction. The challenges reflected in part the overwhelming effects of impaired LV relaxation in patients with HCM on the parameters reflecting elevation of filling pressures and the preload dependence of the variables. More recent reports by Nagueh et al11 suggested that the ratio of early transmitral to tissue Doppler annular velocities accurately quantified LV pressures in patients with HCM. In this issue of Circulation, Geske and coauthors12 report on 100 symptomatic patients with HCM who underwent measurement of transmitral Doppler flow velocities and mitral annular velocities simultaneously with (n=42) or within 48 hours of cardiac catheterization and direct LA pressure measurement. Although there were statistically significant correla-
tions between the Doppler-derived diastolic parameters and invasive measurements, the predictive accuracy of the ratio of mitral E to annular Ea in an individual patient was modest. These observations were the same regardless of whether measurements were taken from the medial or lateral annulus or LV pressure was used as the comparator. Although nonsimultaneous comparison with invasive hemodynamics was used in most patients, the results were quite similar in the subgroup in whom measurements were simultaneously acquired. The precise reason why the ratio of mitral to tissue Doppler measurements is less accurate in HCM is not clear. It likely reflects the complex nature of diastolic dysfunction in HCM. Other factors include the load dependence of mitral inflow measurements, inhomogeneity of relaxation, and abnormalities in myocardial longitudinal strain and twist that have recently been demonstrated.

Value of Echo Doppler Measurements of Diastolic Dysfunction
Whatever the reason, these findings again leave us without a single echo Doppler measurement that can accurately quantify diastolic dysfunction in a given patient with HCM. Despite this limitation, a number of studies have found clinical and prognostic correlates with echo Doppler–derived measurements. A high ratio of early diastolic mitral inflow velocity to mitral septal annular tissue velocity (E/e' ratio) predicted death, cardiac arrest, or ventricular tachycardia in children observed for 26 months. Other studies, including our own, have shown a relationship between E/e' and functional status, degree of hypertrophy, and LA enlargement, as well as the incidence of cardiovascular events. In addition, this ratio can be used to more accurately compare changes in therapeutic interventions in a given patient.10
Patients with HCM have a 5-fold-greater likelihood of developing atrial fibrillation than that of the general population, and atrial fibrillation will occur in about a third of patients during their lifetime. It is associated with a much higher risk of clinical deterioration and emboli-related death and disability.\textsubscript{14,17} The prevalence of atrial fibrillation increases progressively with age and LA size, which in turn is related to the degree of hypertrophy, severity of mitral regurgitation, and diastolic dysfunction. Moreover, LA volumetric remodeling predicts exercise capacity in nonobstructive HCM and may reflect chronic LV diastolic burden.\textsubscript{15,16} This simple noninvasive measure of LA size may provide a long-term indication of the effects of chronically elevated filling pressures in patients with HCM and should be performed routinely.

**Diastolic Function in HCM: Is There a Holy Grail?**

Despite the inability to find a single quantitative measure of filling pressures, echo Doppler studies remain the best measure of diastolic function and prognosis in HCM. Other noninvasive tools are limited by availability, cost, radiation exposure, or accuracy. Biomarker results, although interesting, also have limited clinical utility in a given patient. Should we give up our quest for the Holy Grail of an accurate noninvasive measure of diastolic function as an unobtainable goal? Other promising techniques require further evaluation. The assessment of myocardial muscle shortening (strain) and its rate (strain rate) is a new and developing tool in cardiac imaging. Strain rate imaging by tissue Doppler imaging calculates velocity differences between 2 adjacent points to generate a strain rate–time curve, which is then integrated to calculate strain. Validation of echo methods has been performed by comparative studies of magnetic resonance imaging tagging. Newer methods analyze 2-dimensional B-mode images by tissue tracking and allow direct measurement of regional tissue displacement, shortening (strain), and strain rate both longitudinally and circumferentially and can combine them into a 3-dimensional model. Such studies have shown reduced longitudinal strain and early diastolic strain rate.\textsubscript{18,19} Circumferential LV rotation also can be calculated. Our data\textsubscript{20,21} support the reduction of longitudinal strain shown previously; however, circumferential strain was increased. The diastolic measure longitudinal strain rate (SR) E was decreased by 23% and circumferential SR E was increased by 37%, reflecting the decreased longitudinal strain, systolic SR, and increase in their circumferential values in HCM. Both longitudinal and circumferential SR E/S ratio decreased significantly, indicating impaired relaxation (the Figure). Functional status (New York Heart Association class >1) was found to be related to decreased basal and mid longitudinal SR E. LV twist angle (maximal instantaneous basal-to-apical angle difference) was similar, but time to peak twist was decreased by 13%, and untwist time (peak to trough twist) was lengthened by 16%, also implying delayed relaxation (the Figure). Only time and more study will tell whether these techniques alone or in combination with others will allow us to achieve our goal of quantifying diastolic function or whether they will meet the same fate that Geske et al\textsuperscript{12} describe in this issue of *Circulation*.

**Disclosures**

None.

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