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EDITORIAL COMMENT

Stress Echocardiography

Diastole to the Rescue*

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Assessment of myocardial ischemia by echocardiography rests on the detection of systolic wall motion abnormalities, namely, reduced wall thickening. Traditionally, this assessment is performed visually and is therefore subjective and variable (1). Tissue Doppler and strain echocardiography that allow quantitation of regional myocardial mechanics recently have been shown to be accurate in detection of coronary artery disease (CAD) (2–4). Although there has been a focus on assessment of systolic abnormalities, ischemia also affects diastole. Several processes mediating relaxation at the subcellular level are energy dependent. Myocardial contraction is prompted by cytosolic calcium binding troponin C, resulting in disinhibition of troponin I and actin–myosin cross-bridge formation. Two important mechanisms in reversing these interactions resulting in

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myocardial relaxation are the interaction of adenosine triphosphate with the myosin head causing actin–myosin dissociation and a weak cross-bridge binding state, and the removal of cytosolic calcium by sarcoplasmic reticulum calcium adenosine triphosphatase. Regional energetic depletion that occurs with ischemia impacts both of these processes and can impair myocardial relaxation (5). However, diastolic mechanics have been generally ignored because they are challenging to evaluate visually. Moreover, techniques that could reliably quantify diastolic mechanics were generally lacking.

Despite these limitations, an increasing body of literature has been generated over several years showing the existence of diastolic abnormalities during ischemia (6). Although many of the techniques used did not actually assess regional myocardial mechanics, they did confirm the presence of regionally heterogeneous relaxation in the presence of ischemia (7,8). The introduction of tissue Doppler echocardiography (TDE) and strain echocardiography offered new options for quantifying regional diastolic mechanics (9,10). Akin to global systolic dysfunction, we showed that regional diastolic dysfunction could exist in the absence of global diastolic dysfunction and that a certain critical mass of regional diastolic dysfunction resulted in global diastolic dysfunction (11,12). We further developed on these observations in a clinical study when we reported altered diastolic strain rates in the setting of ischemia at rest (13). Notably, diastolic strain rates seemed more specific and a combination of diastolic and systolic mechanics provided the highest accuracy for prediction of CAD. Lastly, Pislaru et al. (14) showed that despite a similar reduction in systolic strain rates and strain, diastolic strain rates and strain could discriminate between an infarcted and viable, stunned myocardium. Thus, there is increasing evidence that ischemia induces regional diastolic mechanical abnormalities that are recognizable using novel imaging techniques such as strain echocardiography, and these altered diastolic patterns could be potentially applied to quantify and improve detection of CAD by echocardiography.

Most published data concerning diastolic mechanics in CAD have focused on resting abnormalities. However, an important potential application of this new knowledge would be in stress echocardiography. We showed that time to onset of regional relaxation was delayed in segments with inducible wall motion abnormality during dobutamine stress (15). In an experimental model we showed that this time to regional relaxation was related to regional perfusion and was able to distinguish ischemic from control segments.

To date, similar data were not available with regard to exercise stress. Exercise is physiological and therefore a preferred method for stress testing. However, efficient implementation of stress echocardiography is limited because of the rapid return of the heart rate to baseline, leaving only seconds to obtain the necessary stress images for wall motion interpretation. Images collected in this hurried fashion are often suboptimal in quality because of excessive translational motion and the challenge of locating the best echo window in a limited period of time. The paper in this issue of the *Journal* by Ishii et al. (16) addresses this deficiency by examining diastolic strain in the setting of exercise stress. This study is unique in many ways. It uses diastolic strain rather than strain rate, strain was determined by speckle tracking rather than Doppler-based techniques, the study cohort is large, and it specifically addresses the issue of timing of changes with relation to the stress.

Although most studies examining diastolic mechanics have focused on diastolic strain rates, there are data showing that diastolic strain may be equally informative in CAD. Diastolic strain rates, especially early diastolic, pertain mostly to early relaxation mechanics associated with early

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rapid filling. Early diastolic strain rates are sensitive markers of myocardial pathology and are altered pre-clinically in a variety of pathologies including ischemia and cardiomyopathies (17–20). However, they are more challenging to measure. Diastolic strain, on the other hand, pertains more to regional myocardial stiffness. Diastolic strain is also a more robust signal and therefore is easier to measure.

A major limitation of current TDE and Doppler-derived strain echocardiography is that peak amplitudes of velocity and strain variables are influenced by the angle of the incident ultrasound beam with the myocardial wall (21). This affects reliability, especially when the operator is unable to align the myocardial wall parallel to the ultrasound beam, which could occur more often than not in the post-exercise situation. Image acquisition is often duplicated because TDE images are collected in addition to standard B-mode images. These issues make stress application of TDE-based strain challenging and time consuming thereby reducing its wider applicability. Ishii et al. (16) overcame many of these limitations by using 2-dimensional speckle-tracking techniques.

Speckle-tracking methods, in contrast to Doppler-based methods, are not influenced by the angle of the incident beam (22,23). Speckle-derived strain has other advantages in stress echocardiography. The B-mode images can be collected in a standard fashion, thus saving time and avoiding duplication of image acquisition. As Ishii et al. (16) show, it is also feasible to estimate strain in orthogonal directions (transverse strain). However, existing validation data suggest that these strain measurements are much less reliable (24).

There has always been a question regarding the reliability of speckle-derived strain in stress echocardiography given its low frame rates compared with TDE-derived strain. However, speckle-derived strain was recently validated in an experimental study using dobutamine stress (25). In this study, correlation between sonomicrometry and speckle-derived strain was best for longitudinal strain and least for radial strain.

The major and paradigm-shifting observation in the article by Ishii et al. (16) relates to the timing of diastolic versus systolic changes. They show that changes in diastolic strain last longer than changes in systolic strain. In patients with significant coronary artery stenosis, systolic wall motion abnormalities were noted in 80% of the patients immediately after exercise, but only in 8% of patients at 5 min and in no patients at 10 min after exercise. The authors used a diastolic index (DI) to quantify diastolic relaxation (ratio of the difference between systolic and diastolic strain normalized to systolic strain). The DI decreased significantly (abnormal response) in 191 territories at 5 min and 162 territories at 10 min after exercise. Unfortunately, the authors do not relate these territory numbers back to patient numbers, so a direct comparison with the prevalence of systolic abnormalities is challenging. These results with diastolic abnormalities after stress recapitulate the results from a previous publication (26).

These data from a large clinical cohort bring diastolic stress testing closer to clinical use. However, the significance of this article needs to be tempered by certain factors that may affect its overall interpretation. The results are skewed by the severity of illness in the study cohort. Over 70% had significant coronary stenosis and over one-third had multiple vessel disease. Nearly 60% had significant ST-segment depression, and 12 patients needed sublingual nitroglycerin for persistent chest pain. Systolic wall motion abnormalities were noted in 80% of the patients. This group had a significantly larger burden of disease than is typically seen at our institution. Application of diastolic stress imaging in a healthier group would obviously alter test accuracy.

Exclusion of patients for uninterpretable diastolic signal occurred in 3% of patients. We suspect these rates of exclusion would be significantly higher in other populations. Likewise, as the authors point out, image quality would impact test reliability and so would the presence of other conditions that may influence diastolic properties such as hypertension and cardiomyopathy. This latter issue leads us to suggest that additional examination of diastolic mechanics may be needed before a clear picture emerges on how best to use diastolic stress echocardiography to detect coronary artery disease. One issue that remains unresolved is whether diastolic strain is superior to diastolic strain rates. Strain rates are more dynamic and can more effectively be separated early from late diastolic abnormalities. One could argue that energetic deficiencies should selectively affect early and myocardial stiffness affect late diastolic properties. Therefore, stress-induced ischemia may be better detected by evaluating early rather than late diastolic abnormalities. Diastolic strain, on the other hand, may not be as effective in separating the 2 phases. At this time there are not enough data to derive any reliable conclusions on the differences between diastolic strain rates and strain.

The authors do not fully utilize the 16- or 17-segment model. Major vascular territories are represented by single segments. A clear justification for this strategy is not offered.

Diastole is highly influenced by heart rate, and an in-depth examination of the influence of tachycardia on diastolic strain was not performed or discussed. Although diastolic strain is likely less influenced by tachycardia than strain rates, the authors do not comment on where one would measure early strain in the setting of tachycardia. Also, would the diastolic strain rate ratio have similar implications regardless of heart rate? Given that diastolic abnormalities persist late in recovery, by which time we presume the heart rate is considerably lower, our consternation about heart rate may not be relevant.

Notwithstanding these comments, the article by Ishii et al. (16) amplifies the drum roll for incorporation of diastolic phase mechanics in the assessment of stress echocardiography.

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Key Words: 2D speckle tracking echocardiography ■ post-ischemic delayed relaxation ■ diastolic stunning ■ exercise stress test ■ effort angina.