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EDITORIAL COMMENT

Strain Echocardiography

The New Gold Standard for Imaging Ventricular Function?*

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Much has changed since the pioneering work by Feigenbaum and Dodge to develop strategies to estimate left ventricular (LV) ejection fraction (LVEF) by using echocardiography (1). In the decades that passed since then, use of echocardiographic estimation of LVEF has become an everyday part of our lives in cardiology, particularly for establishing diagnosis and monitoring long-term care of patients with heart failure (HF). In such patients, LVEF estimation is embedded in clinical practice guidelines for determining treatment options; for example, patients with HF and reduced EF (HFrEF) are treated very differently from patients with HF with preserved EF (HFpEF). These differences in treatment are predicated on the clinical trials of therapies for each form of HF, which prominently included LVEF as part of their key inclusion criteria. Estimation of LVEF is therefore of incalculable importance to everyday clinical practice.

Despite the obvious importance of estimation of LVEF, it is now well-accepted that it comes with substantial caveats. Beyond the obvious interobserver variability of LVEF estimation (which may be, troublingly, as high as ± 14%) (2), numerous issues undermine use of LVEF. First, to the extent that LVEF is an expression of a fraction of how much blood is ejected (stroke volume) from the total end-diastolic volume, there can be dramatic differences in cardiac structure and function without much difference in LVEF, provided the relationship between the 2 is preserved. Furthermore, EF may be exquisitely sensitive to loading conditions in the left ventricle, something not easily or routinely measured by echocardiography. In addition, it is now recognized that myocardial contraction is far more complex than a single layer of muscle squeezing in a uniform direction: the left ventricle consists of muscular helices surrounding a midventricular circumferential layer of muscle fibers squeezing with myocardial torsion from apex to base, this contraction may not be entirely homogeneous, particularly in the context of structural heart disease (3). Finally, misunderstanding about what LVEF really is has led to deleterious consequences: although it is often assumed that LVEF estimation informs ventricular contractility, this is incorrect. Myocyte contractile function at the cellular level may not be necessarily impaired in HFrEF (4), and efforts to increase contractile function over the long term in patients with "reduced LVEF" have been either futile or even detrimental in HF syndromes unless remodeling and other derangements such as neurohormonal activation are also affected (5).

Because of the issues that undermine LVEF estimation, enthusiasm grew to understand more clearly how the left ventricle contracts by analyzing differences in myocardial deformation. The growing use of strain imaging has attempted to address this question.

In echocardiography, myocardial "strain" is synonymous with "deformation"; strain imaging was

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developed to give a more objective assessment of regional myocardial function. At its most basic, strain imaging (which is now widely available in echocardiography laboratories worldwide) assesses lengthening, shortening, or thickening of the heart muscle in various dimensions (longitudinal, circumferential, and radial, primarily). Beyond the degree of myocardial deformation that may occur during contraction, the velocity (or strain "rate") of such deformation may also be quantified. Thus, strain imaging incorporates complex geometric aspects of LV contraction in a more comprehensive manner than simple LVEF estimation.

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Clinically, because strain imaging incorporates several aspects of the complex nature of myocardial contraction, use of this imaging technique has been shown to have advantages over LVEF assessment in certain circumstances (6). For example, because it is sensitive to beat to beat perturbation in myocardial performance, strain has been found to afford unique information compared with LVEF for detecting and quantifying myocardial ischemia and may be useful for myocardial viability prediction in patients with coronary artery disease. Strain imaging may be useful to detect subclinical abnormalities in LV systolic function among patients undergoing cardiotoxic cancer chemotherapy, thereby identifying patients with normal LV function who may be expected to have a future decrease in LVEF (7). In valve disease, strain may become abnormal before symptom onset or drop in LVEF. Finally, in patients with cardiomyopathies, strain has been found to be particularly enticing. For example, in patients with HFrEF, strain imaging may be useful to assess adequacy of cardiac resynchronization therapy and/or guide its adjustment. Although it adds relatively less diagnostic or prognostic in the context of reduced LVEF, among those patients with preserved ventricular function, strain imaging has several potential advantages over LVEF estimation for detection of subclinical myocardial dysfunction and to predict prognosis (6). For example, in patients with hypertrophic cardiomyopathy, despite preservation of LVEF, substantial reduction in strain or strain rate may be present. In patients with HFpEF, a similar picture emerges; although the assumption exists that patients with HF and normal LVEF have abnormalities in diastolic relaxation, studies of strain imaging in such patients indicate significantly lower longitudinal and circumferential strain (8). This finding suggests that impaired systolic function may contribute to the syndrome that is HFpEF, despite what would be considered normal ventricular contraction when using estimation of LVEF alone.

Besides these possible clinical advantages, myocardial deformation assessment by strain imaging may also inform understanding of why LVEF estimation may be inaccurate in certain circumstances. In this issue of the *Journal,* Stokke et al. (9) provide a mathematical analysis examining LVEF, global longitudinal strain, global circumferential strain, LV wall thickness, and LV short-axis diameter in 100 patients. Of these patients, 20 had coronary artery disease, 20 had chest pain without coronary obstruction, 20 had dilated cardiomyopathy, 20 had hypertrophic cardiomyopathy, and 20 were normal control subjects; most had a normal LVEF. The principal findings of the work by Stokke et al. (9) included the important finding that circumferential strain contributed more than twice as much to LVEF as longitudinal strain; for every 1% of circumferential strain, there was an estimated 1.8% increase in LVEF, whereas a 1% rise in longitudinal strain was accompanied by a smaller 0.8% increase in EF. Additionally, Stokke et al. (9) confirm the long-held assumption that LVEF could be preserved despite loss of stroke volume provided that end-diastolic volume was lost in proportion: increased wall thickness or smaller LV diameter could result in a "preserved" EF despite significant reduced strain in longitudinal or circumferential direction.

Besides confirming the compensatory nature of ventricular hypertrophy and remodeling in subclinical LV dysfunction, on a clinical level, the results of Stokke et al. (9) reveal interactions among different forms of strain and how they compensate for early LV dysfunction: longitudinal fibers are typically oriented in the subendocardium and thus more vulnerable to wall stress in patients with HF, in contrast to the midwall circumferential fibers, which are not as greatly affected. Given its relatively greater contribution to LVEF, increased circumferential strain can therefore maintain stroke volume, despite significant loss of subendocardial strain. Stokke et al. (9) rightfully conclude that strain imaging probably better reflects systolic function in patients with a preserved estimated LVEF.

Although the results are modestly incremental and the study was performed in a relatively small number of subjects, the findings of Stokke et al. (9) are illustrative. First, they convince us a normal LVEF does not prove normal systolic function, and reliance on LVEF may mask reduced systolic shortening if not specifically looked for; other confounding factors such as volume and thickness also need to be accounted for. Second, the results help to explain the

value of strain imaging over LVEF in certain patients and provide clarity about how strain may facilitate better care in certain patient types. Besides allowing for detection of earlier disease in patients with coronary artery disease or valvular abnormalities or in patients undergoing cancer chemotherapy, strain imaging may help to untangle the conundrum that is HFpEF: given the repeated futility in therapeutic trials for HFpEF predicated on the use of LVEF to include trial participants, it begs the question whether an LVEF standard could be abandoned for such patients, as some investigators have argued (10).

Despite the advantages of strain imaging over LVEF, it is necessary to concede that strain imaging has several important limitations that would make it impossible to envision strain replacing the current standard means for assessing LV function. First, whether strain is affected by normative aging, sex, race, and frequent comorbidities in patients with heart disease it is not completely established; indeed, recent data convincingly suggest that end-diastolic volume may affect strain results (11), a finding arguing for the need to consider strain in the context of such volumes. Furthermore, although a unique value of strain imaging may exist for the diagnosis of certain forms of cardiomyopathy (including amyloidosis or hypertrophic cardiomyopathy), it is necessary to concede that the knowledge base in this area requires greater study. Finally, vast numbers of research studies and HF treatment trials have used LVEF as a key inclusion criterion, and LVEF is broadly incorporated in clinical practice guidelines internationally. Taken together, although strain is emerging as the more optimal marker for LV systolic function, there seems to be no way to replace LVEF at this time, no matter how inaccurate it may be. Interventional studies showing outcome benefits on the basis of deformation imaging may be needed to dethrone EF completely as the current arbiter of "heart failure."

Moving forward, as experience with strain grows, we would argue (as do Stokke et al. [9]) that the best approach may very well be to index LVEF with these important geometric parameters to give the most balanced assessment of ventricular performance possible while the knowledge base grows for this important imaging modality. Incorporation of strain assessment should become routine in clinical trials of cardiovascular medicine, particularly in studies of HF therapies. Only with a better understanding of this newer means of LV functional assessment can we know for sure whether it will move the needle forward for better recognition and treatment of our patients with heart muscle disease.

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