Stage B Heart Failure Is it More Common Than We Think?*

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The American College of Cardiology/American Heart Association endorse a scheme embracing the progressive nature of heart failure (HF), which exists as a continuum from asymptomatic, at-risk individuals to those with progressively more symptomatic disease (1). Patients with HF risk factors such as diabetes mellitus (DM), hypertension, coronary artery disease, metabolic syndrome, and obesity without morphological evidence of left ventricular (LV) remodeling or low ejection fraction (EF) are classified as having stage A HF (SAHF). Because LV hypertrophy (LVH) and reduced LVEF are associated with even greater risk of incident HF, asymptomatic patients with these structural changes are categorized as having stage B HF (SBHF). HF is also linked with deterioration in cardiac systolic and diastolic function, which may develop independently of structural remodeling or depressed EF; to date, these functional changes have not been incorporated into the HF staging system (1).

In this issue of the Journal, Kosmala et al. (2) introduced a new concept in which novel systolic and diastolic ventricular function parameters measured by echocardiography can enhance SBHF identification. They hypothesized that these sensitive measures of LV function would have a similar association with exercise capacity as does the current standard identifying stage B (LVH) in patients with normal EF and apparent SAHF. Asymptomatic patients (N = 510) with DM, hypertension, or obesity underwent cardiopulmonary treadmill exercise testing and comprehensive echocardiography, including tissue Doppler and strain imaging. The researchers defined SBHF by structural remodeling (based on LVH) as in the current guidelines and then added depressed longitudinal strain or elevated E/e’ as additional markers. Using this scheme, SBHF was observed in 243 patients, with the remaining 267 patients defined as having SAHF. Notably, about one-half (n = 120) of those classified with SBHF did not have significant LVH. Exercise capacity, assessed by peak oxygen consumption (VO2) and peak metabolic equivalents achieved, decreased progressively as the number of abnormal components increased in individual patients. Although patients with SBHF, defined by elevated E/e’ or low strain, were not as severely limited as those with LVH, they were significantly more limited than patients with SAHF, and each individual functional component was independently associated with exercise capacity in multivariable analysis. The researchers concluded that novel echocardiography-based LV functional measures improved the recognition of SBHF beyond what LVH identifies alone (2). These data hold important implications, both for HF staging and for the design of future trials. Before pondering these implications further, it is worth reflecting on the novel echocardiographic indexes examined in this study.

**STRAIN IMAGING**

The most commonly used measure of systolic function in clinical practice, LVEF, is not a robust index of myocardial or chamber contractility because of its load dependence and sensitivity to chamber size (3). For example, when a patient has concentric remodeling, as in LVH, HF with preserved ejection fraction
(HFPpEF), and hypertrophic cardiomyopathy, the LV chamber volume shrinks, and thus EF tends to be maintained even as LV systolic function diminishes (3).

Strain imaging measures the extent of tissue deformation as a percentage of the baseline (4,5) and can be measured in the longitudinal, circumferential, radial, and transverse directions. Contraction along the longitudinal direction from the apex is the earliest and simplest marker of myocardial dysfunction. It is reduced in almost all, if not all, forms of myocardial disease, even during early asymptomatic stages. Tissue velocity and strain reductions occur commonly in HFPpEF, and reduced longitudinal strain has been associated with higher levels of N-terminal pro-B-type natriuretic peptide (BNP) (6,7). A meta-analysis of global longitudinal strain and LVEF demonstrated superior prognostic value for strain compared with EF for predicting adverse outcomes in HFPpEF, aortic stenosis, and amyloidosis (8). Accordingly, some raise the question: Should LVEF be replaced by global longitudinal strain (9)? One can make a compelling argument that strain imaging should be performed routinely in all patients with normal EF, especially when they have a risk factor or are symptomatic.

E/e’ (MITRAL FLOW AND ANNULUS EARLY DIASTOLIC VELOCITY RATIO)

Transmitral E measures the early diastolic velocity of blood flowing into the LV, which is pre-load dependent and increases with higher filling pressure. The denominator, e’, represents the early diastolic velocity of mitral annular motion, which is related to the extent of LV relaxation. In patients with prolonged relaxation, e’ is relatively pre-load independent. Because myocardial relaxation is impaired in most patients with cardiac disease, as well as with aging, DM, and hypertension, e’ velocity is often reduced in these conditions. Because the E/e’ numerator varies directly with pre-load and the denominator inversely with relaxation, their quotient provides a valuable noninvasive marker of filling pressures at rest and with exercise (10). In people with HFPpEF, E/e’ is often elevated, and Kosmala et al. (2) now showed that even among people at risk for HFPpEF, an increased E/e’ identified patients with limited exercise capacity.

CLINICAL IMPLICATIONS

More than one-half of people with HF have preserved EF and, in SBHF, the data from Kosmala et al. confirmed and extended on what has recently been observed in patients with stage C HF. Individuals with HFPpEF have reduced systolic and diastolic tissue motion, impaired cardiac output reserve, and chronotropic incompetence (6,7,11,12). Intriguingly, in the asymptomatic patients with SBHF studied, there was also more severe chronotropic incompetence as more abnormalities in LV strain, LVH, and E/e’ were observed (2). Indeed, evidence of progressively lower peak VO2 with increasing numbers of abnormalities is strikingly similar to previous data from our group comparing older-aged healthy volunteers to asymptomatic hypertensives (with SBHF) with patients with HFPpEF, who have progressively more cardiovascular limitations and worse exercise capacity (13). In light of prior research, the findings from the current study strongly support the researchers’ conclusion that abnormal strain and E/e’ should be added to the current scheme by which we define SBHF (2).

What might be the implications if this new definition of SBHF is accepted? First, the pool of patients with SBHF will grow substantially—indeed, it doubled in the current study beyond use of LVH alone. This creates a larger cohort of patients in whom strategies can be tested to prevent HF. It is notable that Kosmala et al. observed that strain, E/e’, and LVH were each individually more predictive of exercise capacity than BNP, suggesting that these novel echocardiography parameters could be used as entry criteria for future trials.

Finally, the current data questioned whether these patients are truly “asymptomatic.” When caregivers ask about dyspnea, patients consider it in light of their daily routine, which may be limited if they are sedentary. The fact that striking reductions in peak VO2 were observed in patients with abnormal strain and E/e’ suggests that these patients may not be as asymptomatic as they (or we) think they are.

Appropriate use of strain and E/e’ in clinical practice requires standardization of echocardiography instruments and techniques. Confirmatory data from larger trials employing strain and diastolic function parameters will be important moving forward. Maybe the time has come to routinely apply these sensitive systolic and diastolic echocardiography parameters in our approach to patients with and at risk for HF. Kosmala et al.’s investigation urges us to do so sooner rather than later.

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