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Noninvasive Cardiac Imaging and the Prediction of Heart Failure Progression in Preclinical Stage A/B Subjects

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ABSTRACT

Heart failure (HF) continues to grow as a cause of morbidity and mortality in our community and presents a significant public health problem, predominantly in individuals ≥65 years of age. Early intervention in asymptomatic HF subjects (Stage A/B) at risk of progression to symptomatic HF (Stage C/D) may provide an opportunity to halt this epidemic. The ability of cardiac imaging to assess cardiac structure and function permits early identification of those at increased risk of developing symptomatic HF. Systolic, diastolic, and structural left ventricular parameters each predict symptomatic HF, but no single parameter has sufficient sensitivity for screening to identify individuals with Stage A/B HF who are at increased risk of disease progression. Transthoracic echocardiography (TTE) has the advantage over other imaging modalities in being able to measure systolic, diastolic, and structural left ventricular parameters, and it identified at least 1 abnormal parameter in >50% of individuals with Stage A/B HF ≥65 years of age. Moreover, identification of at least 1 abnormality according to TTE in individuals with Stage A/B HF ≥65 years of age had 72% to 82% sensitivity for detection of those who subsequently developed symptomatic HF. Therefore, a case can be made for cardiac imaging by using TTE for community-dwelling populations with Stage A/B HF ≥65 years of age to identify those with increased risk of symptomatic HF who can be offered preventative therapies. Further studies are required to determine the best strategy for identifying the risk of symptomatic HF in younger individuals. (J Am Coll Cardiol Img 2017;10:1504–19)

Heart failure (HF) is a major cause of premature morbidity and mortality, with approximately 50% of people with symptomatic HF dying within 5 years of diagnosis (1). On the basis of data from the 2011 to 2014 National Health and Nutrition Examination Survey, an estimated 6.5 million Americans ≥20 years of age have HF, with a projected increase to >8 million people ≥18 years of age with HF in 2030 (2,3). In 2012, the total annual cost for HF was estimated to be $30.7 billion and is projected to increase to $69.7 billion in 2030. Great potential, therefore, exists for reductions in premature morbidity and mortality and for cost savings through more effective prevention of HF by the improved identification of individuals at increased HF risk and the prescription of preventative therapies.

HF is a progressive condition. The American College of Cardiology Foundation/American Heart Association describe 4 stages of HF: Stages A and B, which are asymptomatic (**Figure 1**), and Stages C and D, which are symptomatic. At age 45 to 95 years, lifetime risks for HF are 30% to 42% in white male subjects, 20% to 29% in black male subjects, 32% to 39% in white female subjects, and 24% to 46% in black female subjects; these risks are higher for those with higher blood pressure and body mass index at all ages (3). In addition to the risk factors that define Stage A HF, the predominant risk factor is age. In the Framingham Heart Study (1980 to 2003), the annual rates per 1,000 person-years of new HF events for white male subjects were 9.2 for those 65 to 74 years of age, 22.3 for those 75 to 84 years of age, and 43.0 for those ≥85 years of age; for white female subjects in

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the same age groups, these rates were 4.7, 14.8, and 30.7, respectively. Thus, any strategy for HF prevention may need to be aimed at older individuals (≥60 years of age) at greatest risk.

HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood (1). HF may result from disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels, or metabolic abnormalities; however, most patients with HF have symptoms due to impaired left ventricular (LV) structure or function. Although many cardiac imaging modalities detect systolic and diastolic dysfunction and structural abnormalities that predict HF progression in subjects with preclinical Stage A/B HF, the lower cost and widespread availability of transthoracic echocardiography (TTE) makes this modality the most useful for this purpose. This state-of-the-art paper summarizes the mechanisms of systolic and diastolic dysfunction and structural abnormalities detected by using cardiac imaging and reviews the utility of cardiac imaging for the prediction of HF progression in subjects with preclinical Stage A/B HF. This paper highlights the need for further understanding of the prognostic utility of many commonly used imaging parameters in daily practice and an evaluation of their use in an HF prevention strategy.

MECHANISMS OF SYSTOLIC AND DIASTOLIC DYSFUNCTION AND STRUCTURAL ABNORMALITIES

Systolic, diastolic, and structural abnormalities frequently co-exist (4–6), and the mechanisms of these abnormalities overlap (**Table 1**). These mechanisms result from changes induced by an initial insult, such as ischemia, pressure or volume overload, or inflammation (7,8), and they may result in HF with either preserved (HFpEF) or reduced (HFrEF) ejection fraction. Early post-infarct rat models demonstrated dilatation of both infarcted and noninfarcted segments that initially maintains cardiac output but leads to a decline in left ventricular ejection fraction (LVEF) (9). Pressure and volume overload induce an increase in myocyte diameter and length, respectively, that normalize wall stress (10) and produce concentric and eccentric hypertrophy, respectively (**Figure 2**).

Alterations in extracellular matrix and calcium homeostasis affect both systolic and diastolic function. Collagen synthesis contributes to replacement fibrosis (scar) and reactive fibrosis and contributes to both increased myocardial stiffness and contractile dysfunction (11). Hypertensive rats with subendocardial fibrosis exhibited evidence of both impaired global longitudinal strain (GLS) and diastolic stiffness (12). Hypophosphorylation of titin contributes to myocyte stiffness in animal models (13). These impairments in myocardial relaxation and stiffness are reflected in diastolic parameters of mitral inflow and tissue Doppler indices (**Figure 3**) but also in the consequence of increased LV filling pressures with left atrial dilatation, increased tricuspid regurgitant velocity, and higher LV end-diastolic volumes. Diastolic dysfunction occurs in both HFpEF and HFrEF (4).

Driving these changes are concurrent neurohumoral influences. Hyperadrenergic signaling contributes to myocyte apoptosis and increased matrix metalloproteinase activity, which degrades the extracellular matrix causing LV dilatation (10). Conversely, excess inhibition of matrix metalloproteinase promotes fibrosis (8). Activation of the renin-angiotensin-aldosterone system promotes myocyte hypertrophy, apoptosis, and interstitial fibrosis (10).

Although best characterized in patients with HF, these same mechanisms (**Table 1**) contribute in varying degrees to the systolic and diastolic dysfunction and structural abnormalities of asymptomatic individuals. However, while the diastolic dysfunction of HFpEF (14) and HF (15) in diabetes is associated with fibrosis, the diastolic dysfunction of diabetes, obesity, or aging without HF is not associated with increased myocardial fibrosis (16–18). By contrast, patients with hypertension with diastolic dysfunction may have increased myocardial fibrosis (19).

The division of TTE parameters into those reflecting systolic and diastolic function and structural alterations are an attempt to simplify the complex mechanisms of cardiac dysfunction that lead to the development of HF. Indeed, it has also become customary to subdivide patients with HF into those with HFrEF and HFpEF depending on predominantly systolic and diastolic abnormalities, respectively. General thresholds for abnormality are presented in guidelines, but the impact of sex and age also need to be accounted for (**Table 2**). Many TTE parameters, separately and in combination, predict incident HF in

ABBREVIATIONS AND ACRONYMS

ALVDD = asymptomatic left ventricular diastolic dysfunction

ALVSD = asymptomatic left ventricular systolic dysfunction

BNP = B-type natriuretic peptide

CAC = coronary artery calcium

CMR = cardiac magnetic resonance

GLS = global longitudinal strain

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HHE = handheld echocardiography

LV = left ventricular

LVD = left ventricular dysfunction

LVEDD = left ventricular end-diastolic dimension

LVEF = left ventricular ejection fraction

LVH = left ventricular hypertrophy

TDI = tissue Doppler imaging

TTE = transthoracic echocardiography