Heart failure (HF) is a leading cause of cardiovascular morbidity and mortality worldwide. In the developed countries, ≈1% to 2% of the adult population has HF, and the prevalence rises to ≥10% in individuals >70 years of age.1 HF results in >1 million hospitalizations annually, with 5-year mortality rates as high as ≈50%.2,3 Unfortunately, the burden of HF is only expected to grow further with an aging population and an ever expanding pool of surviving patients with coronary artery disease. HF is considered to be a clinical diagnosis based primarily on the patient’s symptoms and clinical examination findings.4

Aside from brain natriuretic peptide, which is relatively useful in the diagnosis of heart failure, especially HF with reduced ejection fraction (HFrEF), laboratory investigations traditionally do not form part of establishing the diagnosis of HF. However, clinical diagnosis of HF is often challenging because the symptoms and signs of HF are either too nonspecific or too infrequent, resulting in an overall diagnostic accuracy of less than even 25% for most of the clinical features.5 Consequently, demonstration of any structural or functional abnormality of the heart provides important corroborating evidence for the diagnosis of HF.

Abstract: Echocardiography, given its safety, easy availability, and the ability to permit a comprehensive assessment of cardiac structure and function, is an indispensable tool in the evaluation and management of patients with heart failure (HF). From initial phenotyping and risk stratification to providing vital data for guiding therapeutic decision-making and monitoring, echocardiography plays a pivotal role in the care of HF patients. The recent advent of multiparametric approaches for myocardial deformation imaging has provided valuable insights in the pathogenesis of HF, elucidating distinct patterns of myocardial dysfunction and events that are associated with progression from subclinical stage to overt HF. At the same time, miniaturization of echocardiography has further expanded clinical application of echocardiography, with the use of pocket cardiac ultrasound as an adjunct to physical examination demonstrated to improve diagnostic accuracy and risk stratification. Furthermore, ongoing advances in the field of big data analytics promise to create an exciting opportunity to operationalize precision medicine as the new approach to healthcare delivery that aims to individualize patient care by integrating data extracted from clinical, laboratory, echocardiographic, and genetic assessments. The present review summarizes the recent advances in the field of echocardiography, with emphasis on their role in HF phenotyping, risk stratification, and optimizing clinical outcomes. (Circ Res. 2016;119:357-374. DOI: 10.1161/CIRCRESAHA.116.309128.)

Key Words: deformation imaging ■ echocardiography ■ ejection fraction ■ heart failure ■ informatics ■ mechanics ■ phenotyping
evidence supporting the diagnosis of HF. Echocardiography is the most commonly used modality for this purpose because of its ease of application, noninvasive nature, safety, and ability to provide a vast amount of information about cardiac structure and function. Additionally, echocardiography also plays an important role in guiding therapeutic decision-making and in monitoring response to therapy. Over the past 3 decades, numerous advancements have occurred in the field of echocardiography that have helped improve our understanding of the morpho-functional aberrations occurring in HF. This review summarizes the recent advances in echocardiography as applicable to the evaluation and management of HF.

**Classification of Heart Failure**

To facilitate clinical management, several attempts have been made to divide HF patients into categories that unify them according to their dominant clinical presentations. Thus, HF has often been described as low output failure or high output failure; forward failure or backward failure; systolic HF or diastolic HF; HFrEF or HFpEF with preserved ejection fraction (HFpEF); and so on. More recently, HF has also been classified according to alterations in the mechanical function of the left ventricle (LV; Table 1).

The classification of HF into systolic or diastolic HF appeared to be intuitive, categorizing patients based on the primary pathogenic abnormality, that is, impairment of cardiac contractility or impairment of filling. However, this description has now been abandoned with the recognition that these 2 entities are not mutually exclusive and have considerable overlap. Significant LV diastolic dysfunction is a ubiquitous occurrence in patients with systolic HF, whereas systolic dysfunction is known to occur in most patients with so-called diastolic HF. Moreover, several cardiac and extracardiac abnormalities contribute to the clinical syndrome of the so-called diastolic HF. LV diastolic dysfunction, although important, is just one of the aspects of the clinical presentation. Given these limitations, the newer classification of HF based on LV ejection fraction (EF) has gained wider recognition in the clinical literature and is now universally accepted. HFpEF, which accounts for almost half of all cases with HF, is diagnosed when a patient with clinical features of HF has relatively preserved LVEF and has some evidence of LV diastolic dysfunction. Although there has been controversy regarding the cut off for defining preserved LVEF, the recent guidelines consider LVEF ≥50% as preserved, whereas HF with LVEF 41% to 49% is termed as HFpEF with borderline EF. When LVEF is ≤40%, it is termed as HFrEF.

The classification of HF into HFrEF or HFpEF stems from the observations that these 2 entities represent distinct patient populations. Patients with HFpEF are generally older and more often women and have a higher prevalence of hypertension, atrial fibrillation, and other comorbidities than patients with HFrEF. Noncardiac deaths are more frequent in HFpEF than in HFrEF, and none of the therapies shown to improve survival in patients with HFrEF has been shown to be beneficial in HFpEF. However, despite these clear distinctions, debate exists whether these 2 entities are really 2 separate entities or merely represent 2 different stages in the overall continuum of HF.

**HF Pathogenesis and Phenotyping: Role of Echocardiography**

In the mid-19th century, Ludwig and Marey made the first steps in physiological assessment of cardiac function using a recording equipment. Since then, our understanding of changes in cardiac pressure, volume, and flow during the cardiac cycle have seen a remarkable advancement. These efforts resulted largely in the conception of 3 main models of cardiac functions, the hydraulic input–output model, the ventricular hemodynamic (compression) pump model, and the ventricular muscular pump model (Table 2). These models provided mechanistic insights into cardiac pump function at a macroscopic level and described it as composed of a contraction phase and a relaxation phase. The origin of these phases, however, lies in the contractile shortening and deformation of the cardiac myocyte, which is the microscopic mechanical unit of the heart. The interconnection of myocytes produces a special 3-dimensional (3D) structure of the heart that is composed of 2 oppositely directed helices—endocardial helix and epicardial helix. The contraction of the myocytes in this special conformation creates simultaneous deformation in different directions. The resultant shortening in the longitudinal and circumferential directions as well as thickening in the radial directions and the release of these forces during relaxation result in the overall grossly...
can exist subclinically. Further progression of either systolic LV myocardial fibrosis and abnormalities of LV diastolic dysfunction, a prerequisite for HFrEF, LV hypertrophy (LVH), and cation of HF; Figure College of Cardiology/American Heart Association classification of HF; Figure 1). In this sense, LV systolic dysfunction, a prerequisite for HFrEF, LV hypertrophy (LVH), and LV myocardial fibrosis and abnormalities of LV diastolic dysfunction occurring as a part of the pathophysiology of HfPEF, can exist subclinically. Further progression of either systolic or diastolic dysfunction and the additive effect of several other cardiac and extracardiac comorbidities can lead later in the course of the disease to overt symptoms with the development of HfPEF or HFrEF corresponding to class C or D in the American College of Cardiology/American Heart Association classification of HF.

<table>
<thead>
<tr>
<th>Phenotypic Classification of HF</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic HF or diastolic HF</td>
<td>Conforms to the dominant pathophysiological abnormality May help in selection of appropriate therapies Has prognostic connotations also</td>
<td>These 2 entities are not mutually exclusive No information about the underlying mechanism responsible for these abnormalities</td>
</tr>
<tr>
<td>HfPEF or HFrEF</td>
<td>Identifies 2 distinct groups of patients who have distinct clinical presentations, pattern of LV remodeling, response to therapy, and overall clinical outcomes</td>
<td>It is not known whether HfPEF and HFrEF are 2 different entities or just 2 different stages in the spectrum of HF Does not explain the origin of significant LV diastolic dysfunction in HfPEF No mechanistic explanation for what transforms HfPEF into HFrEF.</td>
</tr>
<tr>
<td>HF with predominant longitudinal dysfunction, circumferential dysfunction, or both (transmural dysfunction)</td>
<td>Provides a classification that conforms to the patterns of aberrant myocardial mechanics. Explains the mechanism of dominant systolic or diastolic dysfunction in different patients. Has the potential to identify patients with similar presentations, prognosis, and response to therapeutic interventions Supported by myocardial layer-specific changes at cellular level</td>
<td>Cannot distinguish between patients in whom isolated subendocardial dysfunction will remain the dominant abnormality and those in whom it will progress to transmural dysfunction</td>
</tr>
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</table>

HF indicates heart failure; HfPEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and LV, left ventricular.

It is important here to note that although dysfunction of myocardial cells is the basic mechanism of HF, the presence of a dysfunctional myocardium is not enough for the clinical presentation of HF to develop and can be associated with a subclinical stage of the disease (stage A and B in American College of Cardiology/American Heart Association classification of HF; Figure 1). In this sense, LV systolic dysfunction, a prerequisite for HFrEF, LV hypertrophy (LVH), and LV myocardial fibrosis and abnormalities of LV diastolic dysfunction occurring as a part of the pathophysiology of HfPEF, can exist subclinically. Further progression of either systolic or diastolic dysfunction and the additive effect of several other cardiac and extracardiac comorbidities can lead later in the course of the disease to overt symptoms with the development of HfPEF or HFrEF corresponding to class C or D in the American College of Cardiology/American Heart Association classification of HF.

**Table 1.** Relative Advantages and Disadvantages of Different Phenotypic Classification Schemes for Heart Failure

<table>
<thead>
<tr>
<th>Hydrodynamic Input–Output System</th>
<th>Hemodynamic Compression Model</th>
<th>Muscular Pump Model</th>
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<tbody>
<tr>
<td>CO=SV×HR</td>
<td>LVEDV/LVESV/LV mass/EF</td>
<td>Global and segmental displacement and velocity (longitudinal, radial, circumferential)</td>
</tr>
<tr>
<td>PCWP and LVEDP</td>
<td>LVFP/left atrial size</td>
<td>Global and segmental strain, strain rate (longitudinal, radial, circumferential)</td>
</tr>
<tr>
<td>PAR</td>
<td>Doppler assessment of LVFP (E/A, E'/e', IVRT, pulmonary venous velocities, etc) Percentage of untwist during IVRT and early diastolic untwist rate</td>
<td>Global and segmental rotation, twist and torsion, torsional rate</td>
</tr>
</tbody>
</table>

A indicates late diastolic mitral inflow velocity; CO, cardiac output; E, early diastolic mitral inflow velocity; e', mitral annular early diastolic tissue velocity; EF, ejection fraction; HR, heart rate; IVRT, isovolumic relaxation time; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVFP, left ventricular filling pressure; PAR, peripheral arterial resistance; PCWP, pulmonary capillary wedge pressure; and SV, stroke volume.
Table 3. Echocardiographic Variables Used for Assessment of Left Ventricular Geometry and Function in Patients With Heart Failure

<table>
<thead>
<tr>
<th>Category</th>
<th>Modality</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric</td>
<td>2D or M-mode</td>
<td>End-diastolic thickness of interventricular septum and posterior wall</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative wall thickness</td>
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<tr>
<td></td>
<td></td>
<td>LV end-diastolic dimension, end-systolic dimension</td>
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<tr>
<td></td>
<td></td>
<td>Fractional shortening</td>
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<tr>
<td></td>
<td></td>
<td>LV end-diastolic volume, end-systolic volume, stroke volume</td>
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<td></td>
<td>LV ejection fraction</td>
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<td></td>
<td></td>
<td>LV mass index</td>
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<td></td>
<td></td>
<td>Left atrial anteroposterior dimension</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td>2D</td>
<td>Segmental wall motion analysis, wall motion score index</td>
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<tr>
<td></td>
<td></td>
<td>Left atrial volume</td>
</tr>
<tr>
<td></td>
<td>3D</td>
<td>LV volumes, LV ejection fraction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LV mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LA volume</td>
</tr>
<tr>
<td>Pulsed-wave or</td>
<td></td>
<td>Mitral inflow E velocity, A velocity, E/A ratio</td>
</tr>
<tr>
<td>continuous-wave</td>
<td></td>
<td>Deceleration time of mitral E wave</td>
</tr>
<tr>
<td>Doppler</td>
<td></td>
<td>Pulmonary vein flow pattern (systolic/diastolic velocity ratio; deceleration time of diastolic wave; mitral inflow A duration−pulmonary vein A reversal duration)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isovolumic relaxation time</td>
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<td></td>
<td></td>
<td>Myocardial performance index</td>
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<tr>
<td></td>
<td></td>
<td>Velocity of propagation (Vp)</td>
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<tr>
<td></td>
<td></td>
<td>LVOT-VTI for calculation of LV stroke volume and cardiac output</td>
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<tr>
<td></td>
<td></td>
<td>Estimation of PASP from Doppler assessment of TR signal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Estimation of pulmonary vascular resistance (PVR; ≈TR velocity/RVOT-VTI)</td>
</tr>
<tr>
<td>Color Doppler</td>
<td></td>
<td>Mitral inflow propagation velocity</td>
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<tr>
<td>Tissue Doppler</td>
<td></td>
<td>Mitral annular E′ velocity, E′/A′ ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isovolumic relaxation time / TV_{i,e}</td>
</tr>
<tr>
<td>Deformational</td>
<td>Tissue Doppler and STE</td>
<td>Velocity and displacement</td>
</tr>
<tr>
<td></td>
<td>(2D or 3D)*</td>
<td>Global longitudinal strain and strain rate, global radial strain and strain rate, global circumferential strain and strain rate</td>
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<tr>
<td></td>
<td></td>
<td>Time to peak velocity and deformation (for assessment of dyssynchrony)</td>
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</table>

(Continued)

**Quantitative Approaches for Assessing LVEF**

Echocardiography is the most commonly used modality for assessment of LVEF. Although there are several M-mode and 2-dimensional (2D) methods for estimation of LV volumes and EF, biplane Simpson’s method is the recommended method. However, all 2D echocardiographic methods used for this purpose involve several geometric assumptions and are also susceptible to off-axis imaging. For these reasons, 2D echocardiography has significant test–retest variability and frequently understimates the true volumes. The use of ultrasound contrast for LV cavity opacification minimizes these errors by facilitating proper image acquisition and by enhancing endocardial border recognition. The application of automated methods for image analysis can also potentially alleviate the variability in the estimation of LVEF. However, 3D echocardiography is currently the most accurate echocardiographic method for estimation of LV volumes and EF. It demonstrates good precision and correlation with cardiac magnetic resonance imaging (MRI). Real-time acquisition of volumetric data in 3D echocardiography alleviates the need for geometric assumptions. However, current 3D technology has its own inherent limitations, including low spatial and temporal resolution.

**Assessment of LV Mass and Geometry**

In patients with HFrEF, LV myocardium generally responds by increasing the radial thickness of the muscle fibers, which is accompanied by increased deposition of extracellular collagen. This results in an increase in the LV wall thickness and overall muscle mass, termed as concentric LVH (Figure 2). In some cases, however, the absolute LV mass is not significantly increased but the wall thickness is increased. This is known as concentric remodeling. The distinction between these 2 entities is important because concentric LVH is associated with much worse prognosis as compared with concentric remodeling. Rarely, in 7% to 9% patients, there may be eccentric LVH, which is characterized by an increase in LV mass without a proportionate increase in LV wall thickness. The LV geometry is normal in the remaining 30% of the patients. In contrast, the patients with HFrEF have an elongation of cardiac myocytes with no increase in the width. There is also...
myocyte necrosis and degradation of extracellular collagen because of the increased activity of matrix metalloproteinase and other similar enzymes.9,16,17 As a result, there is eccentric LV remodeling with an increase in LV cavity size without any increase in LV wall thickness, or there may even be LV wall thinning. In addition, as LV dilates, it tends to assume a more spherical shape because a spherical geometry allows it to accommodate greater volume for the same length of the myocardium. However, increased sphericity of the LV seems to be a maladaptive process because it increases wall stress, leads to greater LV remodeling, and is associated with poor clinical outcomes.22–26

Echocardiographic measurement of LV mass estimation is performed using area–length method or truncated ellipsoid method. Using any of these 2D methods, the normal LV mass is defined as $\leq 88$ g/m$^2$ in women and $\leq 102$ g/m$^2$ in men.11 Relative wall thickness is calculated as $(2 \times$ posterior wall thickness)/($\text{LV internal diameter at end-diastole}$). When the relative wall thickness is >0.42, it indicates concentric remodeling, whereas a value $\leq 0.42$ is suggestive of eccentric remodeling11 (Figure 2).

In patients with eccentric remodeling, LV sphericity can be assessed by measuring sphericity index, which is calculated by dividing LV length by LV diameter in the apical 4-chamber view. A value of $\leq 1.5$ is considered to be abnormal.23 Some investigators have used a reverse formula (ie, LV diameter divided by LV length) for calculating sphericity index. In this case, a value $\geq 0.7$ is considered to be abnormal.24,25

**Myocardial Deformation Imaging**

In a normal heart, the right ventricle is a pure volume pump in both systole and diastole with 15 mm Hg pressure variation such that blood enters at $\approx 5$ to 10 mm Hg and leaves the right ventricle (RV) at a pressure of 15 to 25 mm Hg. The LV, on the other hand, is a combined volume and pressure pump in systole and a volume (suction) pump in diastole. LV ejection is associated with a unique pattern of 3D deformation during the cardiac cycle, which is characterized by longitudinal and circumferential shortening and radial thickening as well as shearing in the circumferential–radial, longitudinal–radial, and circumferential–longitudinal planes. The circumferential–longitudinal shear deformation is identified as LV rotational mechanics (LV twist). This complex, multidimensional deformation becomes possible because of the
obliquely arranged double-helical orientation of LV myocardial architecture. Endocardial fibers, which are aligned more parallel to the long axis of the LV, are associated primarily with the longitudinal mechanics, whereas epicardial fibers are responsible primarily for the circumferential mechanics. Radial deformation represents the sum of subendocardial and subepicardial deformations in the radial direction. Both subendocardial and subepicardial fibers contribute to LV rotational mechanics.

Rotation and twist are unique properties of the LV contractile behavior and are pivotal in maintaining its normal systolic and diastolic functions. During the isovolumic contraction phase, as depolarization wavefront spreads from the endocardium toward epicardium, the subendocardial fibers are activated first. Activation of the subendocardial fibers results in rotation of LV base in counterclockwise direction (when viewed from apex) and of apex in clockwise direction. The electrically unstimulated subepicardial fibers are passively stretched at this stage. This early systolic stretch of the subepicardial fibers serves an important function because it leads to stretching of titin molecules within the myocytes. Stretching of titin molecules invokes the so-called stretch activation response, which is a unique length-sensing mechanism that adjusts the force and timing of the myocyte contraction according to the magnitude of the stretch. This allows the development of strong contractile force, despite fixed cavity volume, and primes the ventricle for subsequent forceful ejection. As the electric activation then spreads to the epicardial layers, the subepicardial fibers also get activated and, given their larger radius of arc, become the dominant force. As a result, the direction of LV rotation is quickly reversed, and the LV base now rotates clockwise and the apex rotates in counterclockwise direction. The rotation of LV base and apex in opposite directions results in twisting of the LV, which greatly augments the ejection performance of the ventricle and is responsible for translating a mere 15% to 20% shortening at myocyte level to >55% reduction in the volume at the LV level. Furthermore, the LV twist also serves to interlink the systolic and diastolic functions of the LV. The deformation of the myocardial matrix during systole results in storage of the mechanical energy, which facilitates rapid untwist and recoil during early diastole, generating diastolic suction required for early rapid filling of the ventricle. The LV untwist at macroscopic level, thus, helps amplify the elastic recoil occurring at microscopic level because of rapid uncoupling of actin myosin cross-bridges and restoration of titin molecules to their original shape.

Myocardial deformation imaging permits assessment of all the above components of LV contractile function. Using deformation imaging, displacement, velocity, strain, strain rate, and rotation parameters (LV torsion, torsional rate, and early diastolic untwist rate and percentage of untwist) can be calculated and used to assess myocardial function. Strain is the percentage change in the length of a myocardial segment relative to its resting length, whereas strain rate is the rate of such deformation (unit 1/s or s⁻¹). Although both strain and strain rate are affected by loading conditions (strain much more than strain rate), they provide useful information about myocardial contractile behavior. Echocardiographic deformation imaging was first introduced as a postprocessing feature of tissue Doppler imaging with velocity data converted to strain and strain rate. However, being a Doppler-based technique, it is heavily dependent on the angle of insonation, which is the major limitation of this technique. Because of this limitation, only longitudinal deformation can be quantified and even that becomes challenging when LV is dilated and distorted.

Speckle-tracking echocardiography (STE) was introduced later as a gray scale–based technique for myocardial deformation imaging and has completely revolutionized this field. STE depends on the anisotropic acoustic properties of the myocardium, which is caused by the presence of myocardial patterns of constructive–destructive interferences that are seen in the image as granular noise of bright and dark dots or the so-called speckle noise. These speckles are stable acoustic markers in the gray-scale cardiac ultrasound images that can be tracked both in 2D and 3D images to generate myocardial deformation curves in different directions.28-30

Despite the great advantages that STE offers over tissue Doppler imaging, it too has several limitations (Table 4). 2D-STE is dependent on imaging quality; suffers inaccuracies because of through plane motion; tracking quality is usually inferior in distal compared with proximal speckles; and too high or too low frame rates are associated with poorer tracking. 3D-STE avoids the problem of through-plane motion,31 but lower temporal resolution, greater susceptibility to gray-scale image quality, and the need for greater expertise are some of the challenges that remain. Velocity vector imaging is yet another gray scale–based technique for assessment of myocardial deformation. However, compared with conventional STE, velocity vector imaging initially appeared to have greater measurement variability and less robust agreement with MRI-derived myocardial deformation indices.32 Standardization efforts are currently underway for reducing variability in STE- and velocity vector imaging–based measurements.

Role of Deformation Imaging in HF Phenotyping

Normal LVEF is not synonymous with normal LV systolic function. LVEF, being a global measure, is able to detect LV systolic dysfunction only when fair degree of myocardial contractile dysfunction has already set in. Moreover, as mentioned earlier, LV myocardial wall has multilayered architecture with different myocardial layers behaving as interlinked, yet distinct functional units. Thus, impairment of contractile function of one layer may get compensated by the augmentation of the function of other layers, thereby maintaining LVEF within the normal range. Recognition of these fundamental concepts is one of the reasons why the earlier classification of HF into systolic and diastolic HF has now been abandoned in favor of less ambiguous classification into HFrEF and HFrEF. However, even this nomenclature only describes the overall outcome of the myocardial functional abnormalities (ie, preserved EF or reduced EF) but does not provide insights into actual myocardial mechanics.

Recent studies focusing on myocardial mechanics have demonstrated specific patterns of abnormal LV myocardial mechanics in different subsets of HF patients. Such patterns
patients with isolated subendocardial dysfunction, such as those with several aortic stenosis.34

However, although the LV ejection performance is relatively preserved, LV diastolic function can be significantly compromised at this stage.35 As the period of early myocardial relaxation is the most energy-demanding phase of the cardiac cycle,36 even mild impairment of subendocardial function may lead to progressive slowing of the LV relaxation. This process is further compounded by gradual fibrosis of LV myocardium with the progression of the disease, which results in progressive loss of cardiac muscle resilience and worsening of LV diastolic function. These patients, therefore, typically present as HFrEF.

HF With Transmural Dysfunction (Longitudinal and Circumferential Dysfunction)

Transmural involvement of the LV myocardium can occur either because of gradual extension of the disease process from the subendocardial or subepicardial regions or because of simultaneous involvement of all the layers, classically seen in acute myocardial infarction. As a result, there is simultaneous impairment of the LV longitudinal and circumferential mechanics, leading to a fall in LVEF. In addition, the loss of support from the circumferential fibers results in dilatation of the LV.36,37 These patients typically present as HFrEF.

HF With Predominant Circumferential Dysfunction

Certain cardiac pathologies, such as pericardial diseases, tend to involve the subepicardial layers. The involvement of subepicardial layers leads to impairment of circumferential and twist mechanics of the LV, but the ejection performance of the LV remains relatively preserved because of relative sparing of longitudinal mechanics from the subendocardial layer that attempts to compensate for the loss of subepicardial contraction.37 However, as normal LV twist is central to suction behavior of the LV, diastolic function ensues. These
patients also present as HFPeEF. Although most of the cases with predominant circumferential fiber dysfunction are of pericardial origin and present as HFPeEF, subepicardial affection occurs also in patients with myocarditis as suggested by delayed gadolinium-enhanced MRI. However, patients with myocarditis usually present with HFrEF rather than HFPeEF. It has been clarified that viral myocarditis may not be just isolated subepicardial affection, rather transmural dysfunction occurs because of chronic microvascular spasm that leads to diffuse ischemia (ie, HF with transmural dysfunction in myocarditis may exist, even though delayed gadolinium enhancement suggests presence of only subepicardial fibrosis).38

It is evident from the above description that both the echocardiographic classifications, based either on LV geometry and global function or on myocardial mechanics, describe HF in complementary, even though different, perspectives (Figures 1 and 3). However, the layer-specific classification has the advantage that it provides mechanistic explanation for the different phenotypic expressions of HF and, therefore, promises to identify cohorts of patients with similar clinical presentations, prognosis, and response to therapeutic interventions. It also explains why patients with HFPeEF may have lower cardiovascular mortality than those with HFrEF, even though overall morbidity is not different. Furthermore, such layer-specific classification is also supported by the parallel changes at the molecular level, as discussed subsequently.

**Figure 3.** Myocardial mechanical dysfunction in heart failure. Subendocardial dysfunction attenuates left ventricular (LV) longitudinal function; this may be compensated by hypernormal or relatively preserved mechanical function in other directions. Progressive insult with transmural affection causes exhaustion of the compensatory mechanisms and development of dilated myocardial chambers and reduction of ejection fraction (EF). In the rare occasion of subepicardial dysfunction, for example in pericardial disease, longitudinal function may remain relatively preserved, whereas myocardial functions in circumferential direction are more affected (reduced circumferential shortening and torsion).

**Figure 4.** Speckle-tracking echocardiography–derived mechanics in patients with heart failure. A, An example of a patient with heart failure with preserved ejection fraction because of left ventricular hypertrophy caused by long-standing hypertension. GLS is blunted, whereas GCS and left ventricular torsion are exaggerated, thus, the preserved ejection fraction. Left ventricular untwist is delayed. B, An example of a patient with heart failure with reduced ejection fraction because of dilated cardiomyopathy. GLS is seen to be severely decreased compared with heart failure with preserved ejection fraction. In addition, mechanics in all other directions are also blunted, including reduced GCS, GRS, left ventricular torsion, and untwist rate, signifying the exhaustion of the compensatory mechanisms and the reduction of ejection fraction. 2C indicates 2-chamber; 3C, 3-chamber; 4C, 4 chamber; GCS, global circumferential strain; GLS, global longitudinal strain; and GRS, global radial strain.
**Exercise Response of Myocardial Mechanics**

Many patients who present with exertional dyspnea and are suspected to be having HFpEF may not have any apparent evidence of LV diastolic function during echocardiography performed at rest. Subtle abnormalities of myocardial mechanics (eg, reduced longitudinal strain, impaired LV twist/un twist) are usually, but not always, present. In such patients, exercise can help unmask significant dysfunction of LV myocardial mechanics. LV untwist is markedly compromised, and longitudinal strain is also reduced immediately after exercise. Importantly, these abnormalities of myocardial mechanics are invariably accompanied by evidence of markedly increased LV filling pressure (LVFP) at exercise, providing explanation for the patient’s symptoms.

**Myocardial Mechanics and Molecular Mechanisms of HF**

Myocardial deformation imaging also serves as a tool to study the molecular mechanisms behind HF. Studies using different deformation variables have shown an association between myocardial dysfunction and genetic expression and stimulation of beta adrenergic receptors. The HF patients have a significant reduction in \( \beta \)-receptor density in the subendocardial layers, which is restored by treatment with \( \beta \)-blockers, resulting in an improvement in LV long-axis function. Similarly, significant associations between segmental strain, global LV systolic and diastolic function, and the mRNA and protein expression of sarcoplasmic reticulum calcium ATPase (SERCA2a), and phosphorylated phospholamban in end-stage dilated cardiomyopathy have also been shown.

In contrast to systolic dysfunction, the mechanisms behind origin of diastolic dysfunction are more complex and range from abnormalities at the level of thick and thin filaments, myosin-binding protein C, linkage protein titin, calcium signaling and calcium uptake proteins to changes in extracellular matrix and how the changes in myocardial mechanical properties interact with loading conditions. Extracel lular matrix abnormalities are generally similar between HFpEF and HFpEF; however, myocytes are stiffer in patients with HFpEF. Notably, in patients with risk factor and conditions that lead to alteration in myocardial stiffness, abnormalities of myocardial deformation become apparent much before overt cardiac dysfunction occurs. For example, the association between early myocardial dysfunction and abnormal interstitial depositions of collagen and amyloid material has been elucidated in several animal models of HFpEF. Similarly, in a rat model of chronic hypertension, it was recently noticed that progressive disruption of T-tubule and defects in calcium cycling started at an early stage and were associated with progressive subclinical reductions in systolic and diastolic myocardial mechanics. These changes preceded the occurrence of clinical symptoms and development of cardiac fibrosis, which was associated with the fall in LVEF.

**STE for Measurement of Myocardial Work**

Myocardial work is a load-independent measure of myocardial contractility and has traditionally required invasive pressure–volume studies for its estimation. Although the product of LV stroke volume and mean arterial pressure has been used as a noninvasive surrogate for LV stroke work, it only provides rough global estimate. Recently, STE has been found to be useful for noninvasive estimation of global and regional myocardial work. By combining STE-derived segmental strain curves with brachial blood pressure, regional myocardial work was calculated, which correlated well with the invasively derived estimates. The ability to measure myocardial work noninvasively is an important advancement and may help provide important insights into mechanisms of LV remodeling and dysfunction. STE has also been used for estimation of wasted work in patients with intraventricular conduction defect. Wasted work specifically has been shown to be an important predictor of response to cardiac resynchronization therapy (CRT). However, these newer applications of STE are currently in experimental stage only.

**Echocardiographic Approaches for Quantifying Myocardial Fibrosis**

The reflectivity of myocardial tissue to ultrasound depends on the tissue characteristics of the myocardium, with increasing amount of collagen increasing the reflectivity. Thus, the amplitude of ultrasound backscatter can be used as a surrogate for myocardial fibrosis. This technique is known as integrated backscatter (IBS) analysis and is based on gray-scale imaging. For assessment of myocardial fibrosis, calibrated IBS is used, in which pericardial reflectivity is used as a reference for myocardial tissue signals. Calibrated IBS has been used to assess the extent and the distribution of myocardial fibrosis in various disease conditions. An alternate approach is to assess cyclic variation in IBS, which reflects the cros s over of actin and myosin within the myocardial structures, resulting in changes in myocardial reflectivity.

It, thus, measures myocardial contractile function, rather than myocardial fibrosis. Unfortunately, both forms of IBS analysis have major technical limitations that restrict their use to research arena only.

**Echocardiographic Parameters for Management and Risk Stratification**

Cardiac structural and functional changes during the initial stages of HF serve as important compensatory mechanisms. However, as the disease process advances, these changes often prove to be maladaptive. Echocardiographic characterization of these structural and functional changes, therefore, provides a framework for key management decisions and impacts overall prognosis and outcomes. A combination of geometric, hemodynamic, as well as deformational parameters can be used for this purpose (Table 3 and Figure 5).

**Global LV Systolic Function and Geometry**

A baseline low or progressively decreasing LVEF is predictive of HF occurrence and adverse clinical outcomes, including all-cause mortality, as well as cardiac and HF-related mortalities. Being a powerful predictor of sudden cardiac death in HFpEF, LVEF is currently the most important criterion for deciding about the need for implantable cardioverter defibrillator in
these patients, with a cut off value of EF ≤35% recommended for the primary prevention of sudden cardiac death. LVEF ≤35% is also the cut off value recommended for CRT in patients who have wide QRS complexes on ECG. Such cut-off values, however, were derived primarily from studies that had included patients with severely depressed LVEF, leaving out those with HFpEF or those with only mildly impaired LVEF. Recently, a multivariate model identified a group of patients at risk for developing sudden cardiac death similar to that in HFrEF. However, the value of implantable cardioverter defibrillator implantation in patients with HFpEF to prevent sudden cardiac death is not yet known, but the recent findings question the appropriateness of using a simple cut off value of LVEF ≤35% as an indication for implantable cardioverter defibrillator implantation.

It is important to note that despite the well-established predictive ability of LVEF, it should not be used in isolation from other measures of risk. For instance, in the Candesartan in Heart failure—Assessment of Mortality and Morbidity (CHARM) program of 7599 symptomatic HF patients, even though LVEF <45% was among the 3 most powerful predictor of all-cause mortality and cardiovascular death and HF-related hospitalizations, LVEF itself was a poor predictor of risk in those with EF >45%, suggesting a complex interplay of risk that is beyond the predictive ability of LVEF alone. In these patients, various comorbidities are often present that significantly contribute to the increased CV risk, independent of LVEF. The CHARM program, the mortality risk in diabetic patients with LVEF 40% was equivalent to that of a nondiabetic patient with an LVEF of 25%. Similarly, chronic kidney disease also contributes to poor prognosis in HF, with one pooled analysis suggesting a doubling in the 10-year mortality risk in patients with both depressed LVEF and chronic kidney disease. Apart from LVEF, the presence of LVH, overall LV mass, type of LV remodeling and LV shape (ie, sphericity), and so on are also predictive of morbidity and mortality in HF, as described earlier.

LV Diastolic Dysfunction and LVFP

Changes of LV relaxation, untwist, suction, stiffness, distensibility, and atrioventricular, and ventriculo-arterial coupling can affect the clinical and hemodynamic status in patients with HF. Unlike in patients with HFrEF, these changes are the dominant pathological abnormalities in those with HFpEF. This usually results in ineffective left atrial (LA) emptying, impaired LV filling with increased LVFP, and blunted cardiac responses to exercise, all leading eventually to increased pulmonary pressures, pulmonary congestion, and development of symptoms.

Figure 5. Echocardiographic modalities for evaluation and risk stratification of heart failure patients. 3D indicates 3-dimensional; EF, ejection fraction; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; and PASP, pulmonary artery systolic pressure.
LV relaxation and LVFP can be assessed by echocardiography using a combination of parameters, including the ratio of early diastolic to late diastolic mitral inflow velocities (E/A), deceleration time of E wave, mitral annular early diastolic tissue velocity (e’), ratio of mitral E/e’, pulmonary venous velocities, tricuspid regurgitation velocity, and so on. It is worth noting that although e’ was suggested to be a load-independent measure of LV relaxation, it is also affected by blood pressure, systolic function, and LV minimal pressure. In general, in a patient with preserved systolic function, blunting of mitral annular e’ is usually indicative of the presence of abnormal relaxation and diastolic dysfunction. Pulmonary venous velocities have also been suggested as a load-independent measure of LVFP. An increased pulmonary venous atrial contraction (PV−A) velocity and duration and reversed S/D ratio (<1.0) are indicative of elevated LVFP. These measures can also be used to assess chamber compliance and response of diastolic function and filling pressures to exercise, known now as diastolic stress testing.

It must be remembered, however, that diastolic dysfunction represents an altered interaction between elastic stiffness and myocardial relaxation. Conventional indices such as E/A, DT and e’ are the result, rather the cause, of this interplay and cannot independently quantify relaxation or stiffness. Thus, for the purpose of LV diastolic function assessment, no single variable has proven to be sufficiently accurate, and therefore, algorithm-based decision trees composed of several parameters are recommended. The most recent American Society of Echocardiography guidelines for the use of echocardiography in the assessment of LV diastolic function have identified the following 4 variables to be the most useful for this purpose—mitral E/A ratio, average E/e’, LA volume index, and peak tricuspid regurgitation velocity. By combining these variables, LV diastolic function and LVFP can be estimated in most patients with structural myocardial disease with or without reduced LVEF.

In patients with HF, restrictive mitral filling pattern has been consistently demonstrated to be an independent predictor of adverse clinical outcomes. Similarly, an elevated E/e’ has also been shown to be an independent prognosticator in HF, both in HFrEF and HFrEF. However, recently, the accuracy of mitral E/e’ in the assessment of LVFP in patients with HF has been questioned, especially in patients with HFrEF. It was shown that in patients with unexplained dyspnea, E/e’ ratio neither accurately estimated LVFP nor identified patients with elevated LVFP, highlighting again that in this group of patients, pathophysiological associations are multivariate and cannot be explained using single variables.

**LA Dilatation and Dysfunction**

LA enlargement is reported in most patients with HFrEF and in nearly 50% to 66% patients with HFrEF. The presence of LA enlargement is an adverse prognostic marker and is associated with increased risk of atrial fibrillation, HF hospitalizations, stroke, and overall cardiovascular mortality. Echocardiography is the most commonly used modality for LA volume estimation, and the biplane area–length method is the recommended method for this purpose. Although 3D echocardiography has been demonstrated to be more accurate and more reproducible, the lack of a standardized methodology limits its routine use.

In addition to LA dilatation, LA dysfunction is also common in patients with HF, both HFrEF and HFrEF. Furthermore, LA contractility during stress is blunted in HFrEF, which may contribute to the transition from the subclinical state to a symptomatic stage of HFrEF. During echocardiography, LA contractile function is traditionally quantified by measuring phasic LA volumes, but STE offers a much simpler alternative. STE-based LA strain measurement has been shown to have incremental value over LA volumes for predicting clinical outcomes in patients with HF.

**Pulmonary Hypertension and RV Dysfunction**

Pulmonary hypertension with or without secondary RV systolic dysfunction is widely prevalent in patients with HF, both HFrEF and HFrEF. Although the estimation of pulmonary artery systolic pressure by echocardiography has its limitations, the presence of elevated pulmonary artery systolic pressure in patients with HF is an adverse prognostic marker. The presence of RV systolic dysfunction also has prognostic implications in HF, independent of pulmonary hypertension. Several echocardiographic parameters are available for quantifying RV systolic function, including tricuspid annular plane systolic excursion (M-mode), fractional area change (2D), tricuspid annular systolic velocity (tissue Doppler imaging), and RV free wall strain (STE). Although RVEF estimation by 3D echocardiography has been validated against cardiac MRI, it is technically challenging and not yet ready for routine use.

**LV Deformation Parameters**

LV deformation parameters are able to provide prognostic information in both HFrEF and HFrEF. For example, in the HFrEF population, as in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, reduction of global longitudinal strain (GLS) was shown to be the most important echocardiographic predictor of cardiovascular death or HF. Similarly in the PARAMOUNT (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction) trial, GLS was significantly impaired in patients with HFrEF as compared with normal controls or the patients with hypertensive heart disease. Global circumferential strain and LVEF were preserved, suggesting that preserved global circumferential strain was a compensatory mechanism. GLS was also found to be a predictor of poor outcome, unlike LVEF or EuroSCORE (European System for Cardiac Operative Risk Evaluation), in patients with advanced aortic stenosis. The blunting of GLS in HFrEF is related to both systolic and diastolic dysfunction, suggesting a coupling between diastolic and longitudinal systolic function in these patients.

In HFrEF, GLS adds prognostic value to LVEF and other measures of LV systolic function. A recent study involving 1065 HFrEF patients admitted to an HF clinic found GLS to be an independent predictor of all-cause mortality, especially in male patients without atrial fibrillation. Similarly, in the VALIANT (Valsartan in Acute Myocardial Infarction) trial, both reduced GLS and global circumferential strain were independently associated with all-cause mortality and combined
death or HF hospitalization. Reduced longitudinal strain rate added significant incremental value in the prediction of all-cause mortality when added to LVEF and clinical variables. Furthermore, increased standard deviation of LV segmental time to peak velocity and to strain rate had an increased risk of all-cause mortality or HF hospitalization. In patients with HFrEF secondary to coronary artery disease, strain imaging has also been used for predicting the transmural extent of infarct. The likelihood of segmental and global functional recovery, and HF-related clinical outcomes.

LV Dyssynchrony

Nearly one third of all patients with HFrEF have ventricular dyssynchrony as evidenced by wide QRS complex on ECG. The presence of ventricular dyssynchrony in these patients is an adverse prognostic marker, and its correction with the help of CRT has been shown to improve morbidity and mortality in them. However, nearly 30% patients undergoing CRT do not show clinical benefit. Several echocardiographic parameters have been developed to assess mechanical dyssynchrony and, thus, to predict response to CRT, but none has been shown to be consistently helpful to justify routine application. However, a few recent studies have shown that STE-based radial strain measurement can be helpful in identifying appropriate site for LV lead placement and may help minimize chances of nonresponse. CRT is likely to result in the greatest benefit when LV lead is implanted adjacent to the most delayed (determined by time to peak radial strain) but nonscarred (segmental radial strain >10%) LV myocardial segment. In addition, in patients requiring CRT, an increase in GLS after implantation, in addition to the standard echocardiographic measurements, has been shown to predict responders and all-cause mortality at 1-year follow-up.

Although LV dyssynchrony is reported even in patients with HFP EF, CRT has not been shown to result in any benefit when LVEF is >35% and, therefore, not recommended in these patients. Instead, some studies have suggested that HFP EF patients often have interatrial dyssynchrony, which may contribute to their symptoms. The therapeutic significance of this finding is not yet defined.

Functional Mitral Regurgitation

LV remodeling seen in patients with reduced LVEF is also associated with the development of functional mitral regurgitation (MR). Echocardiography permits a comprehensive assessment of the severity of MR, mechanism of MR and mitral valve and LV geometry. Tenting height, tenting area, posterior leaflet angle, mitral annulus diameter, interpapillary muscle distance can all be calculated easily. 3D echocardiography is far superior to 2D echocardiography for assessment of mitral valve geometry and seems to be more accurate for estimation of MR severity. Although the severity of functional MR generally correlates with the degree of LV dilatation and dysfunction, significant functional MR can also occur with relatively milder LV systolic dysfunction when it is secondary to an inferior or posterior wall myocardial infarction. Nonetheless, the presence of any degree of functional MR is an adverse prognostic marker, with a graded relationship between the severity of MR and the risk of adverse clinical outcomes.

Recent Technological Innovations

Miniaturization and Remote Echocardiography

Recent studies have already demonstrated high diagnostic yield of the hand-held and pocket echocardiographic equipment when used by experienced echocardiographers. The incremental value of point-of-care echocardiography seems to be greatest for the diagnosis of LV systolic dysfunction. Moreover, the demonstration of LVH in a patient presenting with dyspnea can be an important corroborative finding. In addition to the initial diagnostic assessment, bedside echocardiography is also greatly helpful in serial hemodynamic assessment of the patients with HF and obviates the need for invasive monitoring.

The integration of portable echocardiography with clinical evaluation has now become feasible even in remote outpatient settings. Long-distance remote telerobotic ultrasound over a local nondedicated Internet connection is an advancement in the field of telemedicine. Such an application can be rapidly learned by sonographers for cost-effective resource utilization and is promising to give an online helping hand that can expand the ability of sonographers and physicians to reach HF patients. A recent randomized study explored the use of long-distance telerobotic ultrasound to establish a safe and efficient eHealth solution for communication and examination to improve the quality of life in HF enrollees. A substantial reduction in the time to delivery of care in the remote consultation arm was noted in HF patients randomized to long-distance telerobotic cardiac ultrasound examination. Although such strategies can enable patients to have easier access to echocardiography and specialist consultations in remote places, the cost-effectiveness and overall impact of such interventions on long-term population-based outcomes remain to be tested.

New Software and Computational Approaches

Blood Flow Visualization

Blood flow through the cardiovascular system is not uniformly laminar. Rather, the moving blood stream breaks down into spiral streams or vortices at several points within the cardiovascular system. In the context of global or regional LV systolic dysfunction, abnormality of the flow pattern within the LV is associated with progressive remodeling of the ventricle, worsening of HF symptoms, and an increased risk of intracardiac clot formation. Additionally, the breakdown of normal vortical flow pattern in the LV also adversely influences its diastolic function and increases the risk of LA dilatation/dysfunction. In patients with hypertrophic cardiomyopathy, abnormal flow vortices may contribute to the development of systolic anterior motion of the mitral leaflet and the LV outflow tract obstruction. Velocity-encoded cardiac MRI, color Doppler echocardiography, and echocardiographic contrast particle imaging velocimetry are currently the most commonly used modalities for in vivo visualization of the intracardiac flow. Although still in the experimental stage, application of these techniques to HF patients may help in better mapping of the ongoing mechanical aberrations, improve prognostic assessments, and may also have a role in guiding therapeutic decision-making. For example, assessment of the intracardiac flow dynamics may be useful in predicting response to CRT and guiding device optimization.
Furthermore, because these flow abnormalities appear much earlier in the course of the disease, analysis of intracardiac flow patterns may help in early diagnosis of HF, even before the onset of symptoms.\(^\text{142}\)

**Phenomapping and Machine Learning Approaches**

Despite the breakthroughs in the understanding of HF pathogenesis, the classifications and characterization of the disease still depend on limited measures that harbor inaccuracies and can lead to potential overlapping diagnoses and misclassification, which not uncommonly lead to confusion in therapies. Improved taxonomical classifications are, thus, needed for better phenotypic characterization of the disease. Phenotyping of any disease is the identification of disease subtypes on the basis of molecular, clinical, and biological measurements. The amount of information that can be derived from cardiac imaging, like echocardiography, is huge, especially in the new era where characterization of myocardial mechanics is possible by STE. The use of the full potential of such amount of data alone or in combination with other clinical and biological variables in enriching disease phenotyping is not yet fully explored. Recent efforts aiming at characterization of different HF phenotypes using unbiased cluster analysis approaches have shown the feasibility of integrating echocardiographic, clinical, and laboratory data in an effective new classification for diagnosis of patients with HFrEF.\(^\text{156}\) Such findings may help define homogeneous patient subclasses and can be of prognostic and therapeutic value. We have also recently shown that data derived from new echocardiographic methods, such as STE, can be sufficient if used in its full potential in the diagnosis and classification of different grades of diastolic dysfunction. For example, Figure 6 shows a heat map developed in our laboratory for unbiased cluster analysis using only speckle tracking–derived measures of volume and strain for the phenotypic characterization of LV diastolic function in patients with HF. In that heat map, one can appreciate that STE variables help cluster patients into 3 different groups. A post hoc analysis of such data revealed that these patients can be classified as mild, moderate, and severe diastolic dysfunction. Importantly, improving the phenotypic classifications by incorporation of STE data has the advantage of being fit for developing automatic methods of assessment by leveraging machine-learning approaches.\(^\text{157}\) Automated approaches using machine learning algorithms can reduce inter- and intraobserver variability in interpretation\(^\text{13}\) and may be helpful in increasing diagnostic throughput and efficiency of cardiac ultrasound in the face of the growing burden of cardiovascular disease in the community and the existing workforce-shortage in the field.\(^\text{158-160}\)

**Conclusions**

Echocardiography has the unmatched ability to combine safety and ease of application with the depth of diagnostic and prognostic information it provides in patients with HF. For this reason, it is the most widely used modality for the evaluation and management of these patients. Additionally, the recent addition of myocardial deformation imaging has greatly aided our understanding of the pathogenesis of HF and...
the mechanisms of LV dysfunction and remodeling. At the same time, ongoing technological advancements in the form of big data analytics and miniaturization and digitalization of echocardiography promise to further expand the role of echocardiography as the diagnostic modality of choice in various forms of HF and in various clinical settings.

Disclosures

None.

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Unexplained Dyspnea: Lack of Accuracy in Estimating Left Ventricular Ejection Fraction


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_Circ Res._ 2016;119:357-374  
doi: 10.1161/CIRCRESAHA.116.309128

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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