

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Ejection Fraction Pros and Cons

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ABSTRACT

Ejection fraction (EF) reflects both cardiac function and remodeling, and is widely recognized as a valuable diagnostic and prognostic tool. Its use in a variety of settings, ranging from heart failure and myocardial infarction to valvular heart disease, has made it a cornerstone of modern cardiology, pervading guidelines and practice. However, the development of the test was in another era, with younger patients and a lower prevalence of heart failure with preserved EF. The performance expectations of EF in the current era are also demanding—in relation to detection of subclinical LV dysfunction, and especially relating to recognition of changes in LV function on sequential testing—for example in patients taking cardiotoxic drugs. This review discusses whether the impressive evidence base for EF justifies its ongoing use in the context of newer markers of LV function, and the sophisticated questions posed by modern cardiology.

(J Am Coll Cardiol 2018;72:2360–79) © 2018 by the American College of Cardiology Foundation.

Before the development of left ventricular (LV) imaging, the assessment of cardiac function was limited to the measurement of pressure and flow. The development of left ventriculography and indicator dilution techniques in the early 1960s enabled estimation of LV volumes, and ejection fraction (EF) as stroke volume indexed to end-diastolic volume (1,2). The resulting measurement of cardiac function is now a keystone of modern cardiology, pervading guidelines and practice. This review discusses whether this evidence base justifies its ongoing use in the context of newer markers of LV function, and the more sophisticated questions posed by modern cardiology.

summary of the status of the circulation. A low EF may be due to low stroke volume or increased LV diastolic volume. LVEF is mainly affected by preload, afterload, and contractility, and absolute LV volumes reflect these factors differently: end-systolic volume (ESV) is mainly affected by afterload and contractility, and end-diastolic volume (EDV) by preload and contractility.

In heart failure (HF) with reduced EF (HFrEF) and ischemic heart disease, both systolic and diastolic ventricular volumes may be increased, so although stroke volume is preserved, LVEF is reduced. Indeed, LVEF is as much a marker of LV remodeling as it is of systolic function (3). LV remodeling in athletes means that a normal stroke volume originating from an enlarged ventricle leads to the calculation of an impaired LVEF at rest (Figure 1). Conversely, in a small heart with a normal EF (4) (Figure 2), stroke volume may be low, insufficient to generate a significant gradient across a stenotic aortic valve, even though this lesion is responsible for HF symptoms, or possibly inadequate for an appropriate cardiac output. Thus, in some situations, for example in

BASIC PHYSIOLOGY

EF AND VOLUMES. In general, left ventricular ejection fraction (LVEF) is more useful than stroke volume as a marker of LV function, because it takes into account the Frank-Starling relationship. However, although EF measurement is useful in many instances, it does not always provide an appropriate



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Manuscript received May 21, 2018; revised manuscript received August 6, 2018, accepted August 9, 2018.

valvular heart disease and HF with preserved EF (HFpEF), stroke volume is an important descriptor of cardiac function, independent of EF.

The limitations of LVEF as a marker of LV function are apparent, not only in HFpEF, but also in preclinical HF. In these situations, LV dysfunction, which may be prognostically important, may be identified by markers of deformation when LVEF is normal. The role of 2-dimensional (2D) echocardiography in the definition of stage B HF (SBHF) was more useful in an era when a greater proportion of asymptomatic LV dysfunction was due to post-infarction scar with impaired EF, scar, thinning, and regional wall motion abnormalities, as opposed to diffuse myocardial disease (5). However, it is less useful in the current era when hypertension and metabolic diseases are important causes (6). Impairment of myocardial deformation in the absence of reduced LVEF is a common scenario that should be described as sub-clinical LV dysfunction (Figure 3).

As an ejection phase index, the role of EF as a marker of LV function is influenced by ventricular loading (especially afterload). In severe mitral regurgitation (MR), the LV dP/dt may be estimated from the rate of velocity rise of the mitral regurgitant jet (7). A number of load independent indices have been developed, but these correlate only modestly with EF. In fact, the prospect of a load-independent marker of LV function remains elusive, and although often neglected, performance and recording of blood pressure whenever LVEF is obtained is a simple but important means of being able to compensate for load effects.

When EF is used as a marker of myocardial function, it is important to remember that this is an endocardial measurement. In the setting of LV hypertrophy, myocardial function might be better represented by midwall shortening rather than endocardial function. Thus, EF as a marker of LV function is influenced by geometry (8).

PHYSIOLOGICAL SIGNALS MISSED BY EF. Delayed contraction is a sensitive marker of LV dysfunction (9), and quantification of LVEF is a simplification which does not account for the speed of contraction. An alternative that takes into account the speed of contraction is velocity of circumferential fiber shortening (10), as well as more modern and sophisticated markers such as strain rate.

A second aspect of timing relates to intraventricular synchrony. Features of disturbed LV activation in left bundle branch block can be identified by 2D echocardiography (2DE), but require high temporal resolution and sampling throughout the RR interval, rather than the end-systolic and end-diastolic frames

used for measurement of EF (11). The assessment of mechanical dyssynchrony in selection of patients with wide QRS for cardiac resynchronization therapy remains controversial. Nonetheless, contractile dispersion among the ventricular segments seems to be a prognostically important marker that reflects the likelihood of arrhythmia (Figure 4), perhaps due to myocardial fibrosis (12).

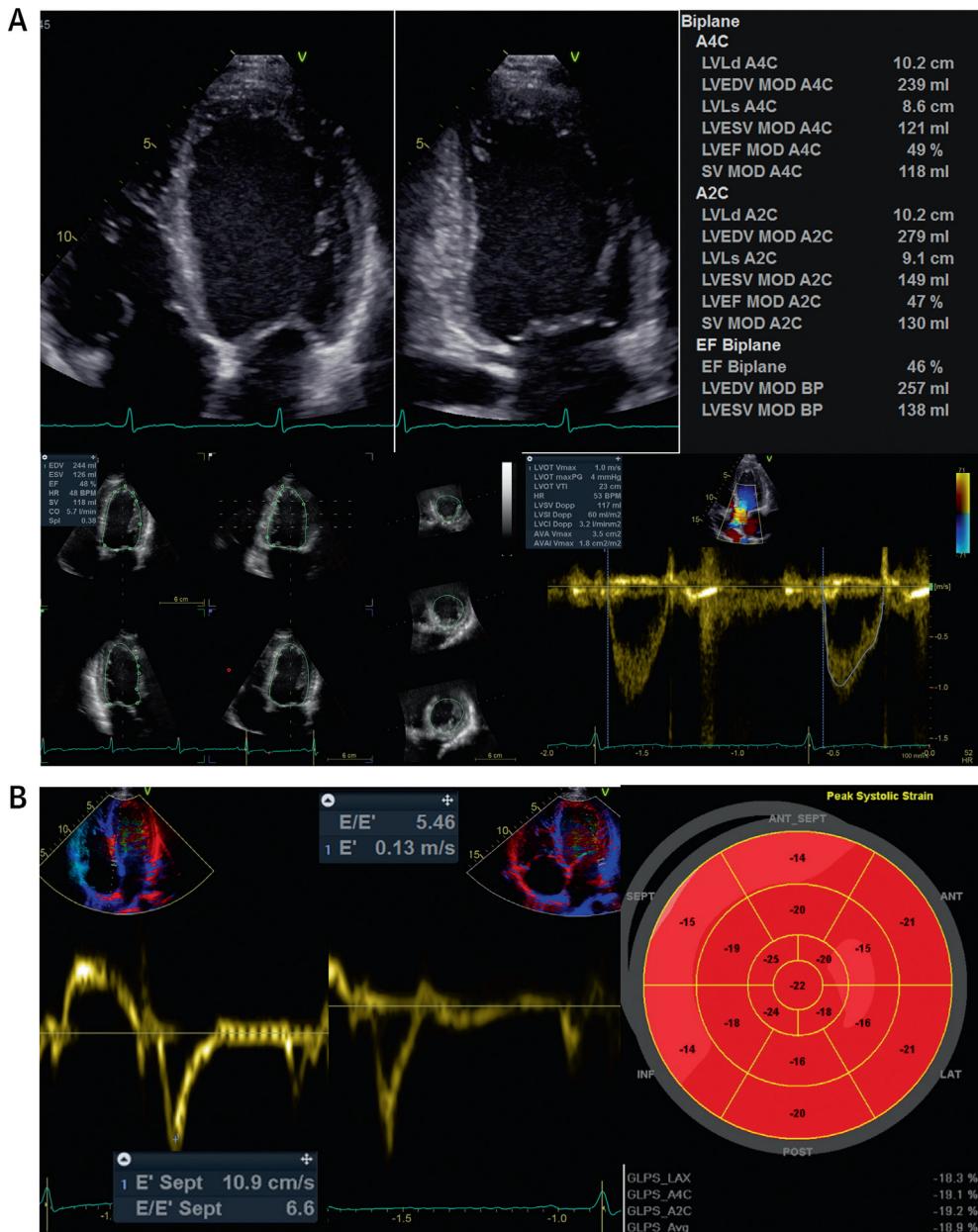
Changes in LV volumes between end-diastole to end-systole also do not account for the complexity of myocardial mechanics related to systole. Twist and untwist are important contributors to systole and diastole respectively (13). Although these markers have not yet been incorporated into clinical measurement, this reflects the technical challenges of obtaining images at sufficient temporal resolution, as well as being able to measure the distance over which torsion develops, and both of these barriers may be scaled by technical developments, such as faster single-beat 3-dimensional (3D) capabilities.

NEW PARAMETERS. A variety of new parameters have become available for the assessment of LV function. Most prominent are indices of myocardial deformation such as strain and strain rate, which have been proposed as an adjunctive parameter to LVEF (14). The clinical adoption of this modality has been slow, initially inhibited by variations between vendors, which have now been reduced to the level of less widely appreciated vendor variations of EF and other measurements (15). Myocardial strain rate has a linear relationship with LV dP/dt, and is among the most feasible clinical markers of contractility (16).

A recently published clinical validation of an elliptical LV model explains the inconsistency of the association of global longitudinal strain (GLS), and global circumferential strain with EF, through the roles of wall thickness and short-axis diameter (17). Global circumferential strain is much more closely associated with EF than is GLS. More importantly, increased LV wall thickness or reduced LV diameter contribute to preserved EF in the face of reductions in especially longitudinal, but also circumferential shortening. Thus, patients with myocardial dysfunction, but a small LV cavity and LV hypertrophy have a preserved EF in the face of impaired GLS. This is an important observation because it indicates a benefit of GLS, irrespective of the technique of EF estimation.

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional
2DE = 2-dimensional echocardiography
3D = 3-dimensional
3DE = 3-dimensional echocardiography
AR = aortic regurgitation
AS = aortic stenosis
CI = confidence interval
CMR = cardiac magnetic resonance
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
GLS = global longitudinal strain
HF = heart failure
HFmrEF = heart failure with midrange ejection fraction
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with recovered ejection fraction
ICD = implantable cardioverter-defibrillator
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
MI = myocardial infarction
MR = mitral regurgitation
RV = right ventricle/ventricular
SBHF = stage B heart failure

FIGURE 1 Assessment of the Athlete's Heart

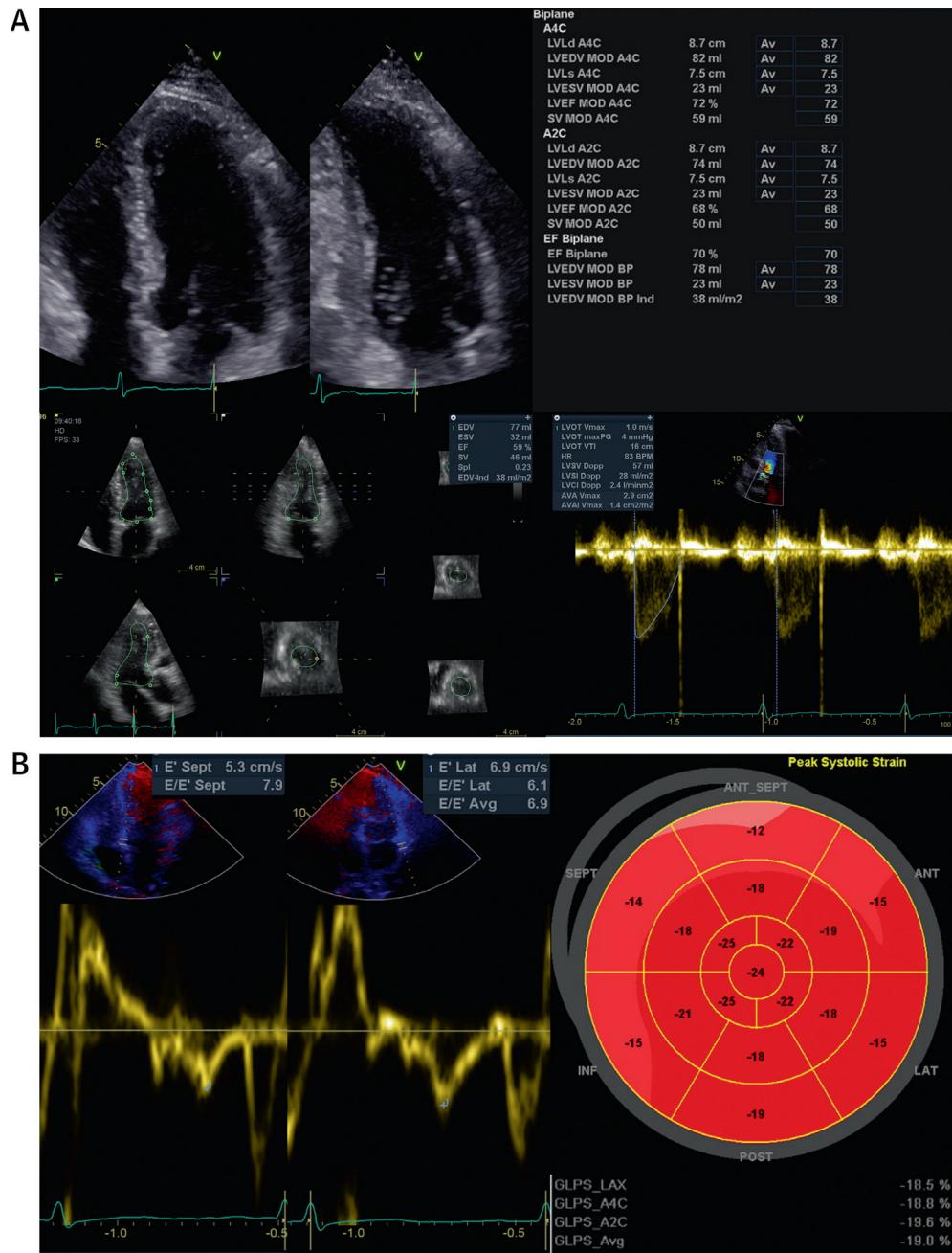
This athlete showed severe LV enlargement with mild dysfunction on the basis of 2DE (LV end-diastolic 143 ml/m^2 , LV end-systolic 77 ml/m^2 , stroke volume 119 ml, EF 0.46) and 3DE (LV end-diastolic 136 ml/m^2 , LV end-systolic 70 ml/m^2 , stroke volume 118 ml, EF 0.48) (A). Stroke volume is validated with pulsed-wave Doppler (117 ml) (A). Medial and lateral tissue velocity (mean 12 cm/s) and global longitudinal strain (19%) are consistent with normal myocardial function (B). 2DE = 2-dimensional echocardiography; 3DE = 3-dimensional echocardiography; EF = ejection fraction; LV = left ventricular.

TECHNICAL CONSIDERATIONS OF LV IMAGING

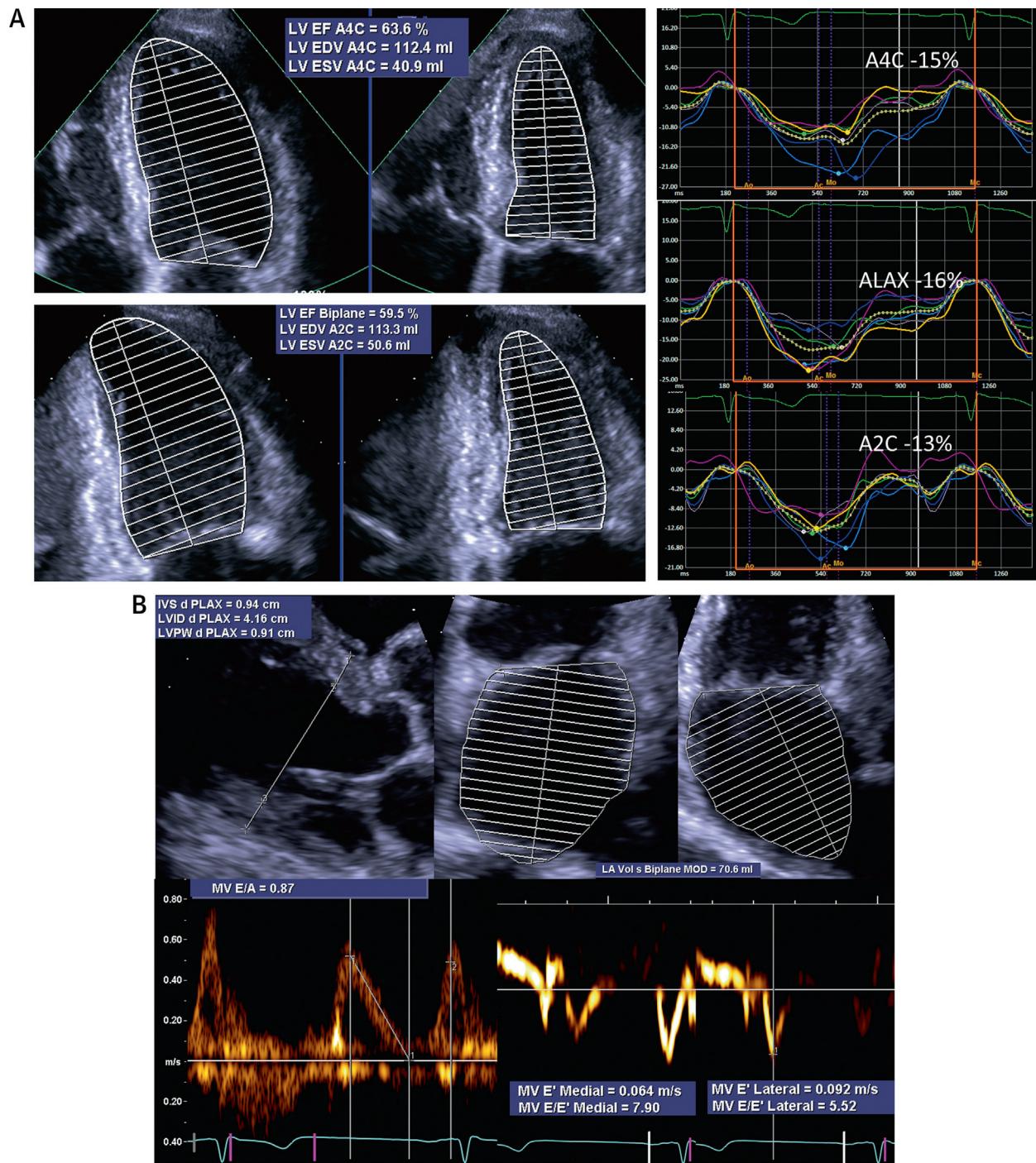
IMAGING METHODOLOGY. Clinical decision-making based on EF usually neglects how this has been

obtained. Even in the modern era, the randomized trials of implantable cardioverter-defibrillators (ICDs) that led to information about the levels of EF associated with benefit did not have a standardized approach to EF measurement (18,19).

FIGURE 2 Assessment of Ventricular Function in a Small Heart

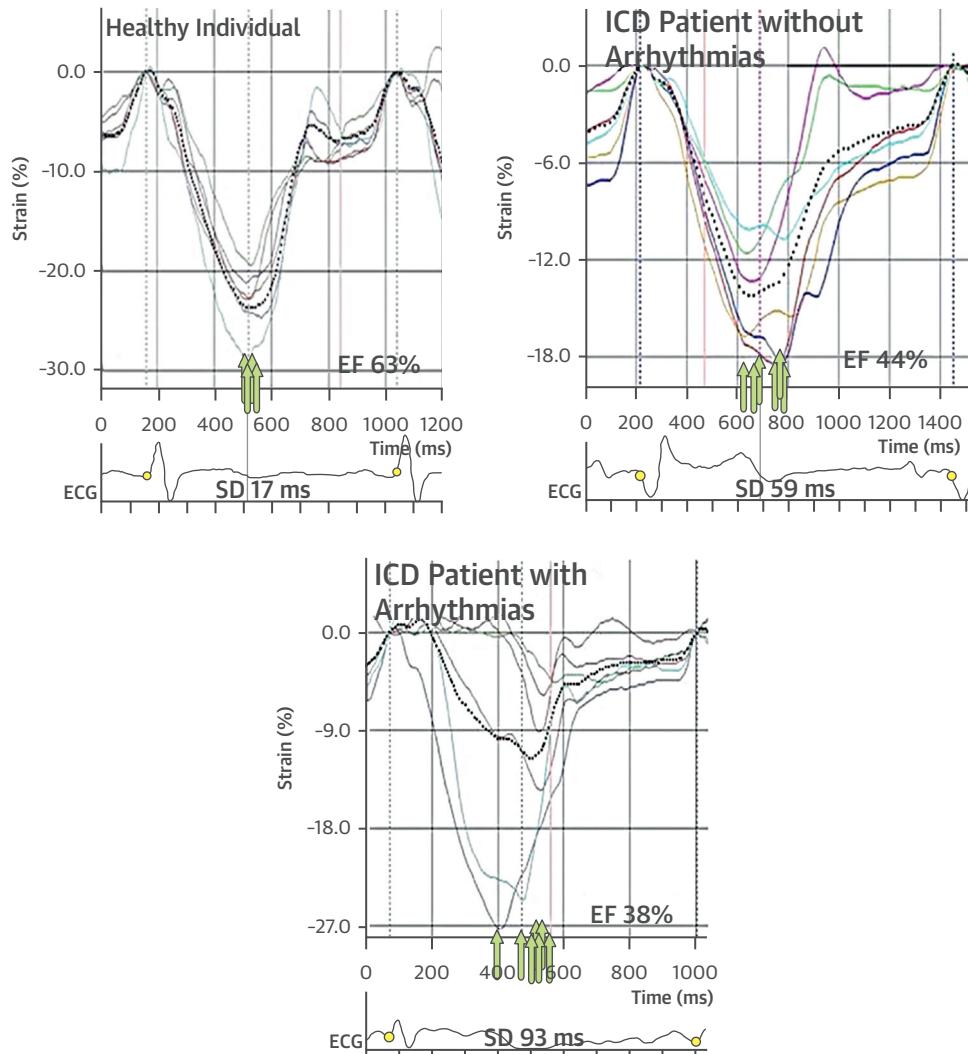


Cardiac assessment in this elderly female showed: (A) LV at the lower limits of normal size (LV end-diastolic 38 ml/m², LV end-systolic 12 ml/m², stroke volume 55 ml, EF 0.70) and 3DE (LV end-diastolic 39 ml/m², LV end-systolic 16 ml/m², stroke volume 46 ml, EF 0.59). Stroke volume by 2DE is validated with pulsed-wave Doppler (57 ml). Although the small heart and low stroke volume prompt concern about heart failure with preserved EF, medial and lateral tissue velocity (mean 6 cm/s) and GLS (19%) (B) are consistent with normal myocardial function. In this setting, a normal hemodynamic response to stress would confirm the noncardiac source of these symptoms. GLS = global longitudinal strain; other abbreviations as in Figure 1.

FIGURE 3 Subclinical LV Dysfunction

This asymptomatic, but inactive, elderly patient with type 2 diabetes mellitus (T2DM) shows normal LV size and ejection fraction (0.59%), but impaired GLS (15%) (**A**). The presence of myocardial disease is supported by LA enlargement (38 ml/m²), and mild concentric remodeling (LV mass 121 g, relative wall thickness 0.44), despite normal diastolic function and tissue Doppler (**B**). This pattern of impaired GLS without diastolic dysfunction accounts for a subgroup of T2DM patients with LV dysfunction (81). LA = left atrial; other abbreviations as in Figures 1 and 2.

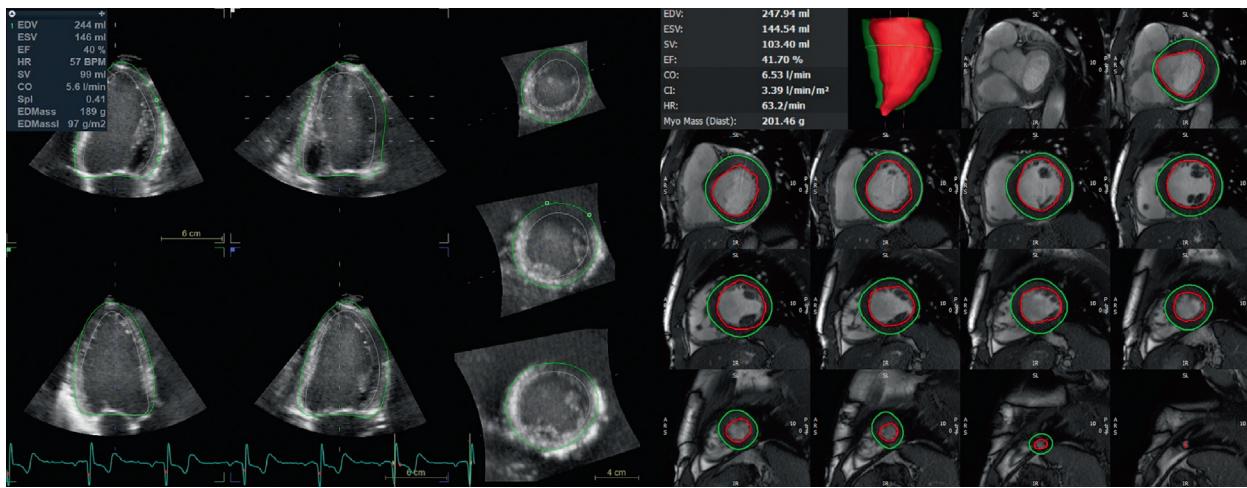
FIGURE 4 Contractile Dispersion



The time to peak LV deformation in all myocardial segments provides a measure of contractile dispersion. This is predictive of arrhythmias. Reproduced with permission from Haugaa et al. (12). ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; SD = standard deviation; other abbreviations as in Figure 1.

The excellent contrast resolution of cardiac magnetic resonance (CMR) has made this the reference standard among noninvasive modalities (Figure 5). Indeed, the low test-retest variation of CMR has led to the proposal that this test be selected in order to minimize the required recruitment in follow-up studies of LV remodeling (20). Computed tomography measurement of EF is also accurate, and has been validated against CMR (21), but has the disadvantage of involving the use of contrast and radiation exposure. Nuclear medicine measurement of EF started in

the era of gated blood pool scans but is probably most widely obtained with gated single-photon emission computed tomography. The acquisition of multiple cardiac cycles with this technique has permitted its use for the assessment of LV synchrony (22). However, although the technique is truly 3D, the acquisition of these data at low temporal resolution may lead to undersampling, meaning that end-diastolic and end-systolic frames may not provide the true maximum and minimum LV volumes, and therefore underestimate EF. Echocardiography remains the

FIGURE 5 LV Volume and EF Calculation With CMR and 3DE

An endurance athlete with acute LV dysfunction. Both 3DE and CMR demonstrate a dilated left ventricle (LV end-diastolic volume = 250 ml) and reduced EF (approximately 0.40). Unlike 3DE, in which endocardial and epicardial borders are traced in 3D space, volume calculations with CMR derive from tracing borders in "stacks" of short-axis slices. Contrast and spatial resolution are excellent, but some variability may arise from the selection of the basal LV slice and potential inclusion of LA volume. (Figure kindly provided by Andre LaGerche, MBBS, PhD). CMR = cardiac magnetic resonance; other abbreviations as in [Figures 1 and 3](#).

source of the majority of EF measurements. However, it is important that the exact methodology is described: clinical reports are often unclear as to whether this is estimated qualitatively, measured using the 2D Simpson's rule, or quantified with 3D echocardiography (3DE). The calculation of EF using the Teichholz formula from a single-plane M-mode image has been superseded by other techniques, and should no longer be used.

Probably the least appropriate means of making a selection of imaging modality for EF measurement is to use the same one in every case. Different imaging modalities have different strengths with respect to spatial temporal and contrast resolution as well as repeatability sensitivity to minor change ([Table 1](#)). In general, contrast and spatial resolution of the highest with CMR, temporal resolution highest with echocardiography, especially 2D and tissue Doppler. Truly

3D such as CMR and 3DE show the least test-retest variation, because the same cut-plane does not need to be replicated at each time point. Subtle changes of LV systolic function may be better identified using GLS than EF.

The limitations of EF can be classified as physiological, technical, and clinical ([Table 2](#)). A fundamental problem with all of the techniques which image the ventricle in 1 or 2 dimensions is that geometric assumptions are required to measure EF. This is mainly a problem when the ventricle has a non-geometric shape, most commonly in patients with ischemic heart disease. In the current era of 3D imaging, the geometric influences in calculation of EF should no longer be a problem. However, whereas irregular geometry can be addressed by 3D imaging, image quality of 3DE remains a potential problem, and suboptimal spatial resolution leads to trabeculae being incorporated in the myocardial tracing, hence underestimating LV volumes ([Figure 6](#)), albeit to a much lesser degree than with 2DE ([23](#)). Moreover, temporal irregularities (for example provoked by bundle branch block) continue to cause ambiguity.

NORMAL RANGES AND RELIABILITY. The accuracy of a test pertains to its accurate measurement of what it truly represents. The challenge with EF is the definition of what such a reference standard should be; because the parameter itself is an artificial construct, there is no physiological measurement that

TABLE 1 Selecting the Right Tool for the Job: Imaging Characteristics of Various Tests

	Technique	Application
High spatial resolution	CMR	LV hypertrophy, infiltration
High temporal resolution	Tissue Doppler, strain	LV synchrony
High contrast resolution	CMR, contrast echo	LV volumes
High repeatability	CMR, 3DE	Sequential follow-up
Sensitivity to minor change	Strain	Subclinical cardiomyopathy

3DE = 3-dimensional echocardiography; CMR = cardiac magnetic resonance; LV = left ventricular.

replicates it. Inevitably, therefore, this becomes a comparison with an alternative noninvasive measure of either LV excursion or timing. Validity is a surrogate for accuracy when there is no reference standard; for example, 2 means of measuring EF may be compared with other data that are content- or criterion-related (e.g., prognostic data). In other circumstances, precision (or reproducibility) is a more important metric, with the implication that the consistency of the finding is more important to the user than the concordance with another measure.

All imaging modalities can provide an EF measurement, and normal ranges of EF are different among different modalities (Table 3). Within each modality, “normal” EF varies according to age and sex. The definition of a “normal” EF by echocardiography does not necessarily mean that this is an appropriate cutpoint in all scenarios. In severe MR, an EF <0.60 denotes abnormal LV function aortic stenosis (AS) (24), and the 0.50 cutpoint used in the Valvular Heart Disease guidelines as a to guide intervention in AS (24), not only is abnormal by the current guidelines (25), but misses patients with an EF of 0.50 to 0.60, who are also at increased risk.

Inconsistencies in the tracing of the LV cavity are an important source of lack of uniformity in the measurement of LV volumes and EF. The guidelines for echocardiography are that the LV is segmented from the cavity at the junction of the compacted myocardium (i.e., trabeculae and papillary muscles are included in the cavity) (25). There is no standardized approach to this question with CMR (26), but the resulting variation has a greater effect on measured LV volumes and mass than EF.

The nomenclature of LV function parameters may also be a source of ambiguity. In this review, absolute levels of EF are expressed as a decimal proportion of 1 (e.g., 0.50), allowing percentage to be used to express relative change in EF. Likewise, although shortening is conventionally expressed as a negative deformation, description of measurements that are greater or less than a threshold becomes unnecessarily complex. GLS is therefore expressed without negative sign in this review.

SEQUENTIAL TESTING. Repeated testing of LV function may be useful in the assessment of patients at risk of developing HF (e.g., taking cardiotoxic chemotherapy) (27), in patients with EF <0.35 after myocardial infarction (to determine whether there is a therapeutic response that would influence ICD decision-making) (28), before starting HF therapy (29) and in valvular heart disease (especially regurgitant lesions) (30).

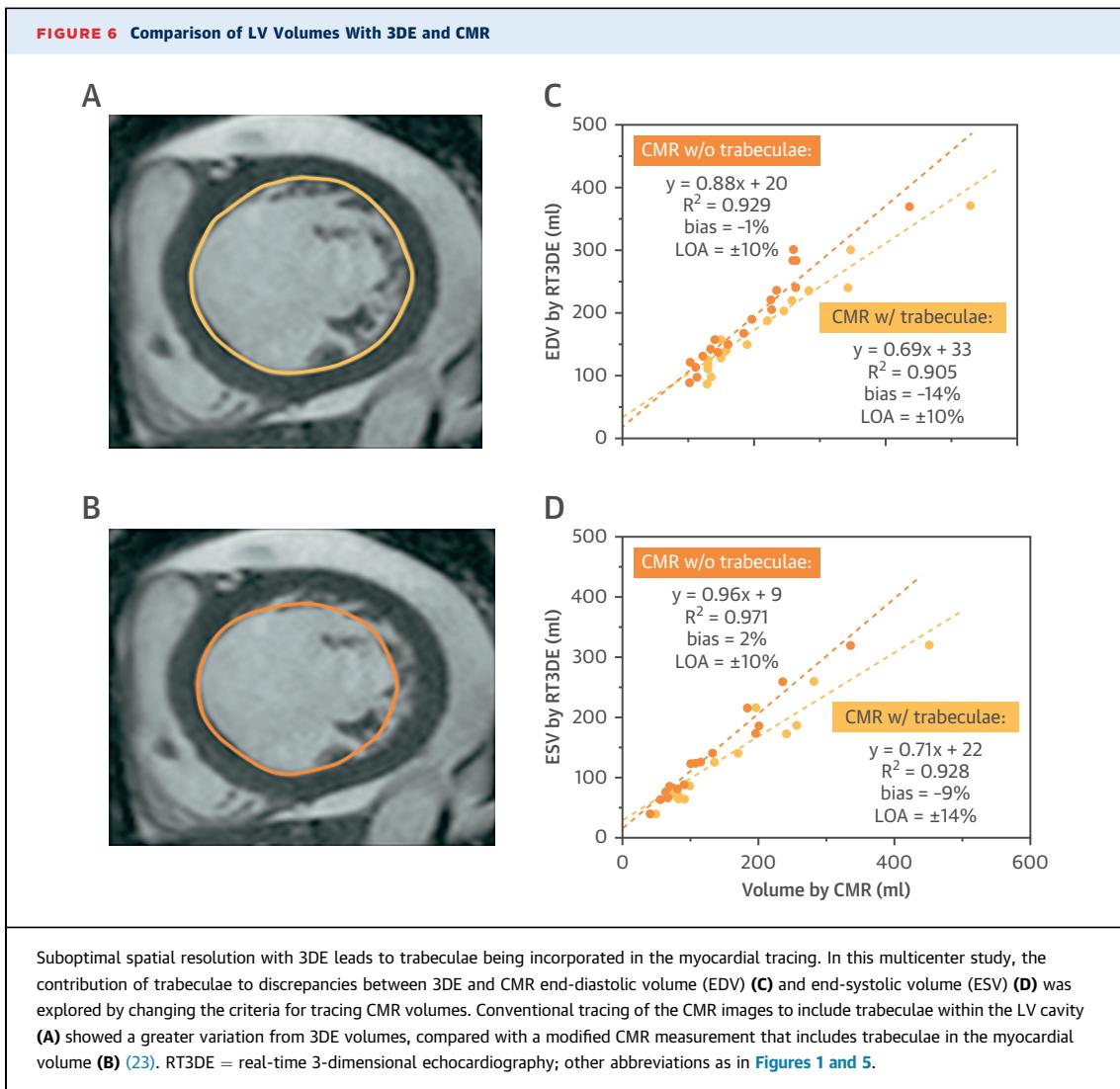
TABLE 2 Limitations of EF as a Marker of LV Function

	Circumstances of Inaccuracy	Potential Solution
Physiological limitations	Load dependent Difficult at high and low HR Mitral regurgitation (Unloading, typical fall of EF after MV repair) Small LV (LVH and small cavity leads to overestimation)	Pressure volume loops High frame-rate imaging Pre-ejection markers Consider another marker (e.g., GLS)
Technical considerations	Image quality Geometry dependent LBBB (regional systole and diastole are not simultaneous) Irregular RR intervals (e.g., AF) LV hypertrophy Hyperdynamic areas remote to myocardial infarction lead to lead to a higher EF than might be expected for a given infarct size	LV opacification 3D imaging, geometry-independent techniques No ready solution Single-beat imaging Mid-myocardial shortening Use of a sum of regional function (e.g., wall motion score index)
Clinical considerations	Prognosis—close to EF 0.50 Subclinical LVD	Consider another marker (e.g., GLS)

3D = 3-dimensional; AF = atrial fibrillation; EF = ejection fraction; GLS = global longitudinal strain; HR = heart rate; LBBB = left bundle branch block; LV = left ventricular; LVD = left ventricular dysfunction; LVH = left ventricular hypertrophy; MV = mitral valve.

Serial assessment of EF and volumes can offer useful prognostic information in patients on therapy, even when the LVEF is >0.40. In a meta-analysis of 69,766 patients in 30 randomized controlled trials of >500 patients of 25 drug or device therapies, Kramer et al. (31) showed that the risk of death was correlated with drug/device effects on LVEF ($r = -0.51$; $p < 0.001$), EDV ($r = 0.44$; $p = 0.002$), and ESV ($r = 0.48$; $p = 0.002$), and that the likelihood of neutral or favorable effects in the mortality randomized trials increased with mean increases in LVEF and with mean decreases in EDV and ESV in the remodeling trials. The use of sequential echocardiograms to quantify hemodynamics in the follow-up of HF is based on the same principle that underpins the use of ambulatory testing of pulmonary artery pressure, that hemodynamic changes are the prelude to worsening symptoms (32). Of course, although ambulatory imaging devices have been developed, the information provided by imaging is episodic, which introduces challenges regarding calibration and test-retest variability.

Showing that an intervention has an effect independent of the variation of sequential measurements of LV volumes and EF can be very challenging (33). This problem is primarily about feasibility, because in addition to changes in LV function, differences between sequential measures may be caused by differences in acquisition (including equipment and technicians), test-retest variation (which is



particularly problematic using 2D imaging because of differences between cut-planes), regression to the mean, and other sources of biological variation, including changes in LV loading conditions, beat-to-beat variation caused by respirophasic changes, and other causes (including atrial fibrillation and frequent extrasystoles). Reliability can be measured as measurement variation (inter- and intraobserver), test-retest variation (subject/instrument variables) or as measure as standard deviation or coefficient of variation (continuous), % agreement, or kappa (categorical). Reliability may be optimized by standardization (e.g., end-expiratory measurement, avoidance of post-extrasystolic beats, and averaging of selected RR intervals in atrial fibrillation), training and repetition, or quantitation. For echocardiography, the total

variability (measured as coefficient of variation) is 0.15, and test-retest variability (including biological variability) accounted for the majority (0.12), with equal contribution from interobserver and intraobserver variability. The smallest ΔEF detected with 95% confidence was 0.11 (34). The lower test-retest variation with 3DE than 2DE (35) supports the use of the former for sequential follow-up. In an LV remodeling study in which CMR EF changed from 0.48 ± 0.12 to 0.51 ± 0.12 ($p < 0.01$), the correlation between change in EF by CMR and 3DE exceeded that with 2DE ($r = 0.58$ vs. -0.03 ; $p < 0.01$) (36).

WHAT EF HIDES. A major limitation of EF is that it is sometimes a source of disproportionate focus, to the exclusion of other features. Although the assessment of LV function is a part of most cardiac imaging

TABLE 3 Weighted Lower Limits of Normal in Recent Reports of Normal LV Function

	Advantage	Disadvantage	Men	Women
2D echo	Accessible, inexpensive, quick, easy, online	Dependent on image quality, may be controlled with contrast LV opacification but this is underused. Foreshortening common High interobserver and intraobserver variability Requires geometric assumptions	0.52	0.54
3D echo	Overcomes concern about foreshortening, test-retest variation, and geometric assumptions	Very dependent on image quality	0.50	0.53
CMR	High contrast resolution; excellent discrimination of LV wall and cavity	Access, cost. Lack of other hemodynamic information provided by echo—e.g., diastolic evaluation. Multibeat protocols are susceptible to RR variation.	0.57	0.59
Gated SPECT Radionuclide ventriculography	High feasibility of gathering EF data contemporaneously with myocardial perfusion scans	Radiation exposure, lack of other hemodynamic information provided by echo. Low temporal resolution may lead to undersampling.	0.52 0.46	0.55 0.46
Computed tomography	High feasibility of gathering EF data contemporaneously with coronary imaging	Radiation exposure, lack of other hemodynamic information provided by echo. Low temporal resolution may lead to undersampling.	0.47	0.53

Normal ranges adapted from Wood et al. (82).

2D = 2-dimensional; EF = ejection fraction; SPECT = single-photon emission computed tomography; other abbreviations in Tables 1 and 2.

examinations, additional details about EF as well as non-EF markers are extremely important.

Clinical decisions made on the basis of EF need to be contextualized by the hemodynamic setting. It is hard to make a judgement about ventricular function when the EF is mildly impaired and the systolic blood pressure is 220 mm Hg, or the heart rate is 150 beats/min in atrial fibrillation. LV function evaluation should also include assessment of ventricular volumes: at an EDV of 60 ml, an EF of 0.55 provides a stroke volume of only 33 ml, providing a cardiac output of 2.3 l/min at a heart rate of 70 beats/min. LV volumes are best provided by 3D techniques that do not rely on geometric assumptions: either CMR or 3DE. Likewise, LV hypertrophy, shape, synchrony, and filling pressure are prognostically important LV parameters that risk being neglected with too much focus on EF (Table 4).

In circumstances in which the EF is challenging to measure with echocardiography, other systolic indices are potentially important (25). These include dP/dt, the myocardial performance index, and GLS. One very simple step for quality control that is often neglected is to cross correlate the/volume obtained from volumetric Doppler calculations with that derived from the difference between systolic and diastolic LV volume measurements (Figures 1 to 3).

A focus on EF also risks the exclusion of a number of cardiac function parameters that provide useful physiological and prognostic information, including right ventricular (RV) size and function, quantification of atrial size, and diastolic filling patterns.

APPROPRIATE USE. LV imaging for the assessment of volumes and EF is considered appropriate in many acute and chronic settings, including in patients presenting with HF and cardiomyopathy (Table 5), as well as with myocardial infarction and valvular heart disease (37). Surveillance (repeated assessment in the absence of symptoms) is the most problematic application from an appropriate use standpoint. Testing is appropriate with multiple different modalities, although echocardiography is the most widely used.

Much of the appropriate use published reports are written from the standpoint of avoiding unnecessary testing, but the performance of echocardiography has

TABLE 4 Where EF Is Not Enough: Use of Other Markers of Cardiac Function

Functional Marker	Echo Modality	Other Modality
Left ventricular		
Systolic mechanics	Tissue velocity and 2D strain	CMR
Diastolic dysfunction	Tissue velocity, LA size	CMR
Hemodynamics	Doppler	RHC
Viability & ischemia	2D strain, MCE, stress	CMR, PET
LV synchrony	Tissue velocity and 2D strain	—
LV mass	3D	CMR
Myocardial characterization	2D strain	CMR
Non-LV		
RV size and function	Tissue velocity and 2D strain	CMR
Left atrial size	2D and 3D echo	CMR
Mitral regurgitation	Doppler, 3D	CMR

Diabetes mellitus, systolic blood pressure, and renal impairment are all potential effect modifiers of both EF and other cardiac function variables on outcome.

LA = left atrial; MCE = myocardial contrast echocardiography; PET = positron emission tomography; RHC = right heart catheterization; RV = right ventricular; other abbreviations as in Tables 1 to 3.

TABLE 5 Appropriate Use of Imaging in HF and Cardiomyopathy

HF	
Initial evaluation of suspected HF (HFpEF or HFrEF)	A (9)
Re-evaluation of HF after change in clinical status without precipitant	A (8)
Re-evaluation of HF after change in clinical status without precipitant	U (4)
Re-evaluation to guide therapy	A (9)
Routine surveillance (<1 yr) with no clinical change	I (2)
Routine surveillance (≥1 yr) with no clinical change	U (6)
Cardiomyopathy	
Initial evaluation of suspected cardiomyopathy	A (9)
Re-evaluation to guide therapy	A (9)
Routine surveillance (<1 yr) with no clinical change	I (2)
Routine surveillance (≥1 yr) with no clinical change	U (5)
Screening structure and function in first-degree relatives of a patient with a potentially inherited cardiomyopathy	A (9)
Baseline and serial evaluation in patients undergoing cardiotoxic chemotherapy	A (9)

In addition to a continuous score from least appropriate (I) to most appropriate (9), the indications are categorized as appropriate (A), uncertain (U), and inappropriate (I) (now described as rarely appropriate) (37).

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

been associated with better HF outcomes in 2 studies. Senni et al. (38) reported that 137 of 216 patients (63%) in the Rochester Epidemiology Project satisfied the Framingham criteria for congestive heart failure and underwent echo within 3 weeks of the diagnosis had a more favorable survival and wider use of angiotensin-converting enzyme inhibitors than those who did not. Similarly, in 799 consecutive patients admitted for a first episode of HF, Tribouilloy et al. (39) showed that the early performance of echocardiography was associated with a lower relative risk of death, even after using propensity scores to reduce baseline differences between echo and no-echo groups. These outcome differences seem most likely to be driven by the therapeutic responses to reduced EF. Indeed, echocardiography has been shown to change management, especially in patients with preserved EF (40).

QUALITY CONTROL. EF is so important to decision making that steps should be taken to ensure the reliability of this parameter. When EF is obtained from echocardiography, segmentation of the LV cavity may be compromised by suboptimal image quality, and LV opacification with contrast should be considered (41). Indeed, the frequency of LV opacification may be considered as a quality marker; many echo laboratories use contrast in <5% of cases, and the optimal use is perhaps in the 10% to 15% range. In addition to improving the usability of echocardiography in technically difficult studies, LV opacification also has the benefit of producing LV volumes that are closer to those obtained with CMR. In part, this

relates to ensuring that the LV trabeculae are included within the LV cavity. In a comparison of 2DE and 3DE with and without contrast, the use of contrast improved the accuracy and reliability of 2DE, almost to the level achieved with 3DE (42).

The reliability of EF, based on comparison with a reference standard for an expert group, should be defined in any imaging laboratory. The use of an intramural process to enhance the accuracy and reliability of measurements has been described from multiple laboratories (43).

RIGHT VENTRICULAR EF. The nongeometric structure of the RV makes it a notoriously difficult chamber to quantify without 3D techniques. Although the use of fractional area change is reported in the guidelines as an acceptable marker of global RV function, this measurement is highly susceptible to off-axis imaging, and reliability can be challenging. Alternative RV quantitative parameters include RV longitudinal function including RV s', tricuspid annular plane displacement, and RV free-wall strain (44). However, improvements in 3DE image quality have made the measurements of RV volumes feasible. Nonetheless, the preferred qualitative approach for RVEF is CMR.

STRESS EF. The assessment of LV function during stress may be performed with multiple imaging modalities, most commonly echocardiography and nuclear ventriculography, although stress CMR is also feasible. Apart from the evaluation of inducible ischemia, stress echo is used for the investigation of symptoms despite nonsevere valve disease, or if resting function is normal, but there are concerns about asymptomatic LV dysfunction (45). Although loss of contractile reserve has been associated with unfavorable outcome in both aortic regurgitation (AR) and MR, tracing out LV volumes after stress is technically very demanding. Thus, although exercise capacity and the pulmonary artery systolic pressure response are effective predictors of outcome, the role of echocardiographic EF is more controversial (46). Likewise, although failure to augment EF is a feature of subclinical dysfunction, the use of stress testing has been superseded by the performance of myocardial strain.

CLINICAL

EF IN HF. The asymptomatic stages of HF are categorized into stage A (risk factors such as hypertension and diabetes) and SBHF (subclinical LV dysfunction, including reduced EF, LV hypertrophy, and valvular regurgitation). Each stage has important implications

TABLE 6 Multicenter Studies That Have Defined Criteria for EF for the Guidance of Management in HF					
Study, Year	Intervention	n	Technique	Core Lab	Entry Criteria
SOLVD, 1991	Enalapril	2,569	Echo, RNV, LVgram	Yes	EF ≤0.35
Hydralazine nitrate, 1991	Enalapril vs. hydralazine nitrate	804	Echo, RNV	Yes	EF <0.45, LVEDD >27 mm/m ² BSA
CIBIS, 1994	Bisoprolol	641	RNV, LVgram	No	EF <0.40
US Carvedilol, 1996	Carvedilol	1,094	Echo	Yes	EF ≤0.35
MERIT-HF, 1999, 2000	Metoprolol XL	3,991	Unspecified	No	EF ≤0.40
CIBIS II, 1999	Bisoprolol	2,647	Echo, RNV, LVgram	No	EF ≤0.35
CAPRICORN, 2001	Carvedilol	1,959	Echo, RNV, LVgram	No	EF ≤0.40, WMSI ≤1.3
Carvedilol, 2001	Carvedilol	2,289	Unspecified	No	EF <0.25
BEST, 2001	Bucindolol	2,708	RNV	No	EF <0.35
MIRACLE-ICD, 2003	CRT/ICD	369	Echo	Yes	EF ≤0.35
COMET, 2003	Carvedilol vs. metoprolol	1,511	Echo, RNV	No	EF <0.35
CHARM, 2003	Candesartan	2,548	Unspecified	No	EF ≤0.40
SCD-HeFT, 2005	ICD	3,521	Unspecified	No	EF <0.35
CARE-HF, 2005	CRT	813	Echo	Yes	EF ≤0.35, LVEDD >30 mm/m height

BEST = Beta-Blocker Evaluation Survival Trial; BSA = body surface area; CAPRICORN = Carvedilol Post-Infarct Survival Control in LV Dysfunction; CARE-HF = Cardiac Resynchronization in Heart Failure trial; CHARM = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CIBIS = Cardiac Insufficiency Bisoprolol Study; COMET = Carvedilol or Metoprolol European Trial; CRT = cardiac resynchronization therapy; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LVEDD = LV end-diastolic dimension; LVgram = contrast ventriculography; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; MIRACLE-ICD = Multicenter InSync ICD Randomized Clinical Evaluation trial; RNV = radionuclide ventriculography; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial; SOLVD = Studies of Left Ventricular Dysfunction trial; WMSI = wall motion score index.

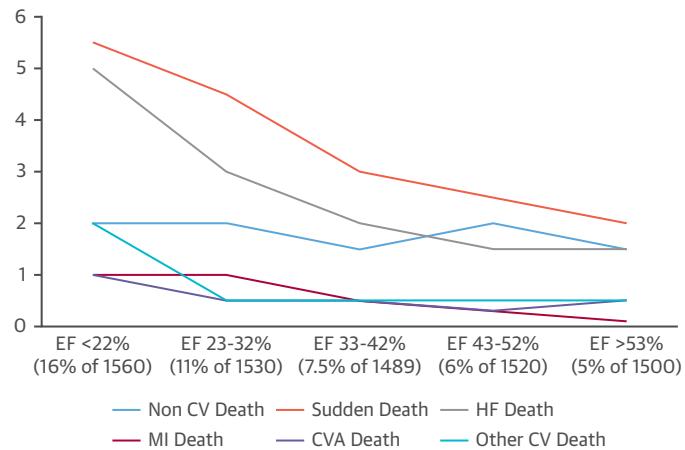
for medical therapy (5). In the current era, EF is often not reduced in the preclinical phase, and there may be some benefit in considering other contractile markers, such as GLS.

The classification of patients with symptomatic HF into HFrEF and HFpEF also has important therapeutic implications. Because well-being, quality of life, and functional capacity are poorly correlated with EF, the use of imaging to assess LV function is unavoidable. The prognostic benefit from blockade of the renin-angiotensin-aldosterone system and beta-adrenoceptors has been shown at EF <0.40, although the lack of core laboratories and use of various modalities in the original studies all argue against too literal an interpretation of this cutoff (Table 6). Conversely, there appears to be a second population of HF (HFpEF) with near normal EF (keeping in mind that “normal” varies by modality, sex, and race). Preserved EF has variously been designated as EF >0.40 and >0.50, but fundamentally, EF is a marker of this group rather than an explanation of its pathophysiology and HF patients with EF >0.40 to 0.50 do not have normal systolic function.

An intermediate group called HF with mid-range EF (HFmrEF) has been a focus of attention in the current HF guidelines (47). In both HFpEF and HFmrEF, the diagnosis requires, not only symptoms or signs and an abnormal EF, but also elevated natriuretic peptides with of LV hypertrophy and LA enlargement or diastolic dysfunction. It is difficult to

perceive these patients as belonging to a unique phenotype. The 95% confidence intervals (CIs) of repeated measures of EF are >0.10, so it is inevitable that a substantial number of patients move into and out of this group on subsequent echocardiograms, without implying any change of underlying pathology. In addition, a number of patients, particularly with ischemic heart disease, improve from being in the HFrEF category into the HFmrEF group.

The process of understanding the temporal trajectory of EF is also important in the definition of another category—HF with recovered EF (HFrecEF), a specific entity that has been well-characterized over the last 5 years (48). Over one-half of the patients with a history of HF, but EF >0.50, have HFrecEF. These relatively low-risk patients may be misinterpreted from a single echocardiogram as having HFpEF, so the lack of information regarding the trajectory of EF is an important limitation of current HFpEF criteria, which contributes to the heterogeneity of this population. However, HFrecEF patients are much less likely to die or require ventricular assist devices or transplantation over the following decade, and also less likely to require hospitalization than either the HFrEF or HFpEF groups (48). Although HFrecEF has a more favorable prognosis than other categories of HF, it does not constitute a benign entity, having evidence of persistent neurohormonal activation, oxidative stress, and cardiomyocyte injury, and it warrants ongoing cardioprotective therapy. Nonetheless, this is clearly a heterogeneous

FIGURE 7 Mortality Rate and Cause in Different Categories of LVD

These data, redrawn from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) study (49) emphasize the inverse relationship between mortality and EF, especially sudden death and death due to HF. CV = cardiovascular; CVA = cerebrovascular accident; EF = ejection fraction; HF = heart failure; LFLG = low-flow low gradient; LVD = left ventricular dysfunction; MI = myocardial infarction.

group, and among them are individuals who have had a transient myocardial injury with remission of the causative pathology. The persistence of the underlying pathology is ambiguous in this setting. It may have resolved (e.g., tachycardia-related cardiomyopathy), or it may have improved, leaving a component of subclinical LV dysfunction (e.g., myocarditis or Takotsubo cardiomyopathy). The relative insensitivity of EF to minor changes makes the distinction of these entities difficult, and further work is needed to differentiate patients with true myocardial recovery.

EF has been shown to have prognostic significance across a wide spectrum, particularly with EF <0.40 (49). Unfortunately, however, when the EF exceeds 0.40, different levels of EF are not associated with differences in outcome (Figure 7). By contrast, impairment of GLS provides prognostic information across the spectrum of LV function (50), and provides the greatest incremental information when the EF is relatively preserved and regional wall motion scores are normal (51). In that experience, EF <0.35 and GLS <12% were analogous (51). Nonetheless, GLS maintains its prognostic value in HFrEF (52); in patients with EF <0.22, GLS <5.9% substratified a particularly high-risk group. The categorization of HFrEF, HFmrEF, and HFpEF was recently compared with mildly (GLS >12.6%), moderately (GLS 8.1% to 12.5%), and severely (GLS <8.0%) reduced strain in a

series of 4,172 consecutive acute HF patients (average GLS 10.8%, mean LVEF 0.40). Reduced GLS provided better gradation of risk assessment (5-year mortality of 49%, 38%, and 34% in severely, moderately, and mildly reduced GLS, respectively; $p < 0.001$) than the classification of HFrEF, HFmrEF, and HFpEF (5-year mortality 41%, 38%, and 39%, respectively; $p = 0.03$). In multivariable models adjusting for demographics (age, sex), clinical history (risk factors, known heart disease), medication (beta-adrenoceptor, mineralocorticoid, and renin-angiotensin antagonism), moderate (hazard ratio: 1.31 [95% CI: 1.13 to 1.53] relative to mild GLS) and severe GLS (hazard ratio: 1.61; 95% CI: 1.36 to 1.91)—but not EF categories—were associated with mortality (53).

EF IN CORONARY ARTERY DISEASE. The assessment of LV function after myocardial infarction (MI) is complicated by compensatory hyperkinesis in the noninfarct territory and by the geometric assumptions inherent in 2D imaging in the irregularly shaped LV following MI. The impact of these problems may be limited by the use of wall-motion scoring (54) and 3D imaging. Nonetheless, the prognostic value of EF—initially with contrast ventriculography and radionuclide imaging, and then with echocardiography—has been known for over 40 years (55). However, although mortality risk is greatest in the initial period after MI in patients with severe LV dysfunction, the implantation of defibrillators (ICDs) early after MI has shown no impact on overall mortality, because reduction of sudden cardiac death was balanced by nonarrhythmic death (56).

The problem with early measurement of EF is that residual viable myocardium is common, and the resolution of myocardial stunning leads to spontaneous improvement of LV dysfunction. This process is likely responsible for the improvement of LVEF in over 50% of post-MI patients (57). Thus, the time course of improvement of LV dysfunction may be an important clue in optimizing the timing of ICD implantation. An important measurement of this was made in 100 patients with LVEF 0.31 ± 0.06 after MI, 10% of whom had life-threatening arrhythmias over the next couple of months. Sequential echocardiograms at 5 days, and 1 and 3 months showed the main improvement in LVEF was at 1 month (at which stage 55% no longer had an indication for ICD insertion due to an LVEF >0.35), but the mean EF change between 1 and 3 months was only 2% (58).

EF AND ARRHYTHMIAS. In addition to the thresholds for medical therapy of HF mentioned above, EF <0.35 is significantly associated with malignant ventricular

arrhythmias in sudden cardiac death, and consequently been used for decision making about implantable defibrillators (28). The strongest evidence in favor of this was obtained in ischemic cardiomyopathy. However the value of this cutoff in nonischemic cardiomyopathy has been debated, with a recent large study showing no benefit from ICD implantation in nonischemic patients with EF <0.35 (59). Although the individual risk of death is greater in patients with worse LV dysfunction, total numbers of nonsevere LV dysfunction are greater, and therefore, these account for an important proportion of deaths. Because <50% of patients experiencing sudden cardiac death have EF <0.30 to 0.35, and one-half of ICD implants with EF <0.30 do not derive survival benefit, the use of EF seems an inexact approach to the selection of primary prevention ICDs in nonischemic LV dysfunction (60). Alternative and perhaps superior testing strategies include the quantification of LV fibrosis using CMR (61), and its analog, mechanical dispersion at strain imaging (12).

EF IN VALVULAR HEART DISEASE. Extensive evidence supports the use of EF in patients with regurgitant valve lesions, although here, too, there are limitations that newer imaging modalities may address.

AORTIC STENOSIS. Patients with critical AS with high wall stress may have impaired EF due to afterload mismatch, and are likely to recover EF following aortic valve replacement (62). For this reason, although reduced EF may be a contributor to perioperative risk, it should not preclude intervention. LVEF has prognostic value in patients presenting with AS, and this has been used as a rationale for valve replacement in asymptomatic AS (24). In patients with reduced EF, a low stroke volume may lead to a paradoxically low gradient, and the distinction between pseudosevere and severe AS may be facilitated bydobutamine echocardiography. Failure to demonstrate contractile reserve (improved stroke volume) in the setting is associated with a poor prognosis.

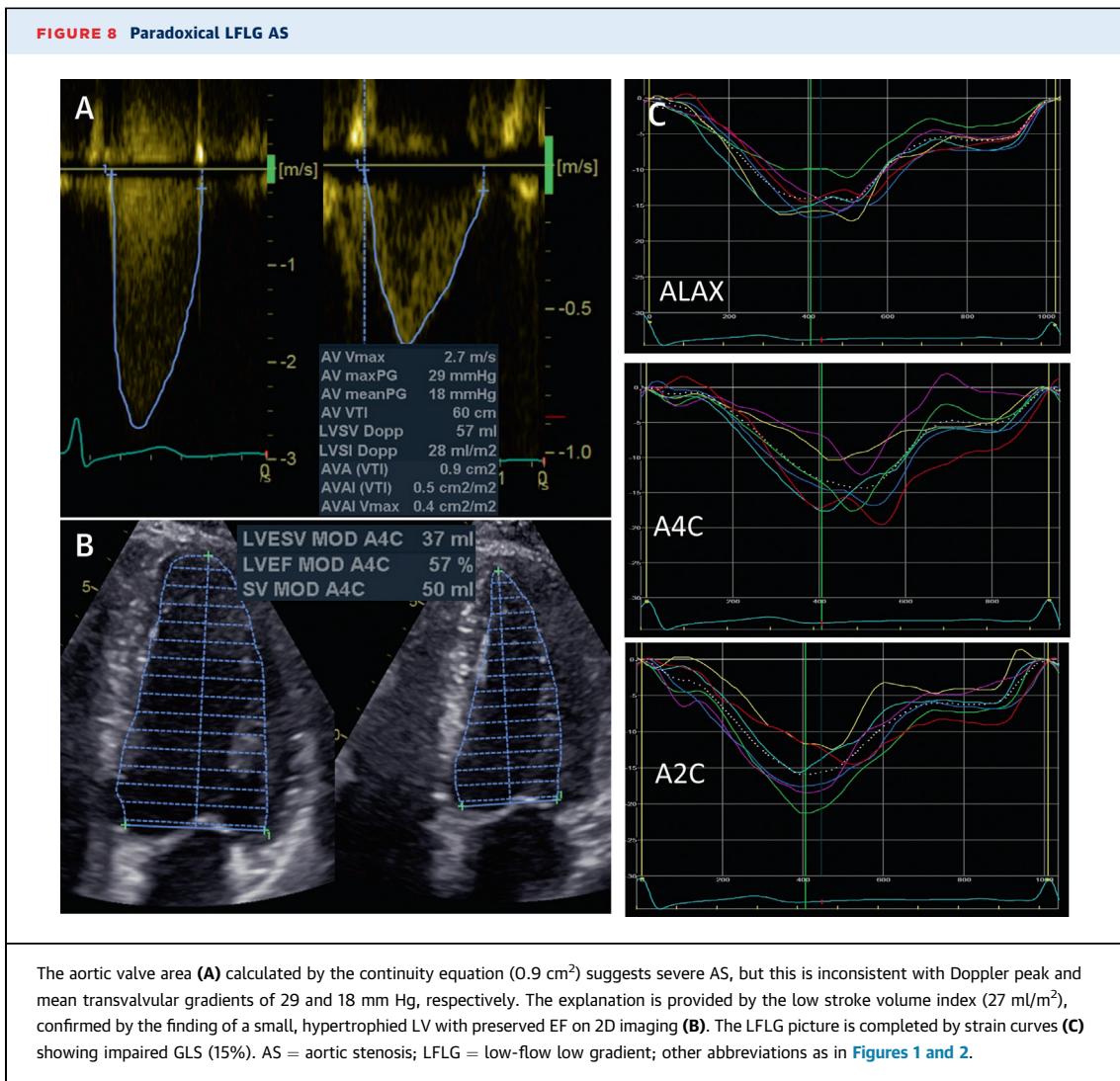
With the aging of the population, AS is increasingly seen as a syndrome that includes hypertension and arterial dysfunction, which have effects on the LV independently and incremental to AS. The novel phenotype of paradoxical low-flow low-gradient AS is characterized by a small, often hypertrophied ventricle, typically associated with HFrEF. As in HFrEF, EF is not a good marker of LV function, and alternative parameters may be needed. GLS is attractive for this purpose (Figure 8), although loading conditions, LV geometry, dyssynchrony, and

segmental impairment may all be potential confounders. A basal longitudinal strain <13% is predictive of the need for aortic valve replacement in asymptomatic patients over 2 years of follow-up (63), and other observational data have proposed increased risk with GLS <16% (64).

AORTIC REGURGITATION. Regurgitant severity, LV end-systolic dimension >55 mm, and LVEF 0.50 are the usual markers that underpin surgical decision making in AR (65). The volume load associated with AR eventually leads to LV decompensation and impaired EF. Before this, however, the consequences of LV dysfunction are hidden by compensatory mechanisms, and LV dysfunction precedes symptom onset in >25% of patients (66). Hence, reduced EF is associated with impaired prognosis in the AR patient, even if they are asymptomatic (65).

Lack of contractile reserve measured by exercise EF, LV volumes, or deformation parameters is a technically difficult, but potentially useful, marker of subclinical LV dysfunction that becomes apparent after exercise. However, as in other settings of subclinical dysfunction, the presence of normal EF does not necessarily signify normal myocardial function. GLS has been shown to provide independent and incremental value to resting parameters, but resting and exercise RV function were incremental to it as well (67). The presence of GLS <18% in asymptomatic medically treated AR has been associated with disease progression, evidenced by symptom onset, >15% increase in LV ESV index, and >10% EF reduction (68).

MITRAL REGURGITATION. Surgical decisions in asymptomatic MR are based on LV geometry and function. Because of LV unloading due to the regurgitant volume, the presence of EF <0.60 is considered abnormal (24). LV dysfunction may be identified from loss of contractile reserve. The risk of post-operative LV dysfunction is least with LVEF >0.64 and LVESD <37 mm (69), but the areas under the receiver-operating characteristic curves are <0.70, suggesting that discrimination is not ideal. Lack of contractile reserve measured by exercise EF, LV volumes, or deformation parameters is a technically difficult, but potentially useful, marker of subclinical LV dysfunction that becomes apparent after exercise. Resting GLS is able to identify patients who are likely to demonstrate LV dysfunction in follow-up, and several studies have associated GLS <18% to 20% as a predictor of post-operative LV dysfunction (70–72) and therefore a potential contributor to decision making regarding surgical timing (Figure 9).



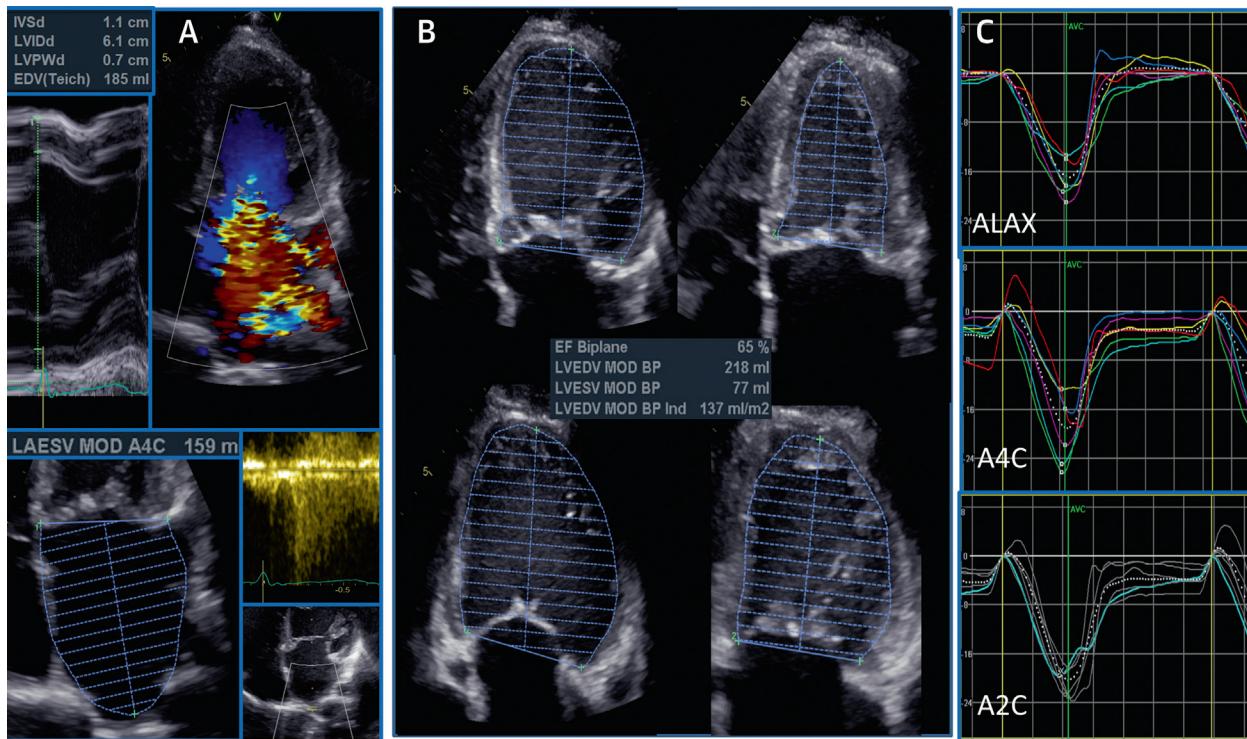
POPULATION HEALTH

POPULATION HEALTH STUDIES. Cardiovascular disease remains a major disease burden, not only in the developed world, but increasingly, in the developing world. The population-level samples can provide evidence about the distribution of health determinants, preclinical and clinical disease, as well as health outcomes, which can contribute to specific interventional trials as well as policies. In addition to surveys, questionnaires, biological samples, and physical measures, imaging of cardiac function has been an important component of many of these studies, including MESA (Multi-Ethnic Study of Atherosclerosis) (echocardiography and CMR) (73) and UK Biobank (CMR) (74). In addition to the usual concerns about safety, cost, and radiation exposure, these

protocols involve thousands or hundreds of thousands of patients, so they often have time constraints, and medication and contrast agents are not feasible. These studies are often focused rather than complete exams, and our typical protocols involve detailed evaluation of the LV (LV mass, EF, GLS, and diastolic function), LA, and RV.

The avoidance of “reader drift” requires standardization of data acquisition and frequent training of technicians and readers. CMR is attractive in this sense, because it provides a more automated protocol and lower variability. As discussed in the preceding text, the lower variation of CMR implies that the effect sizes of risk factors can be detected with tighter CIs, and more marginal effects can be identified than with less accurate or reliable methodologies. However, CMR is costly, and scanner access can be

FIGURE 9 EF in MR



This asymptomatic patient has severe mitral regurgitation (MR) arising from anterior leaflet pathology, with flow reversal into the pulmonary veins and LA and LV enlargement (A). LV volumes are increased (B) but the preserved biplane EF (0.65) is confirmed by LV strain curves (C) showing preserved GLS. Abbreviations as in Figures 1 to 3.

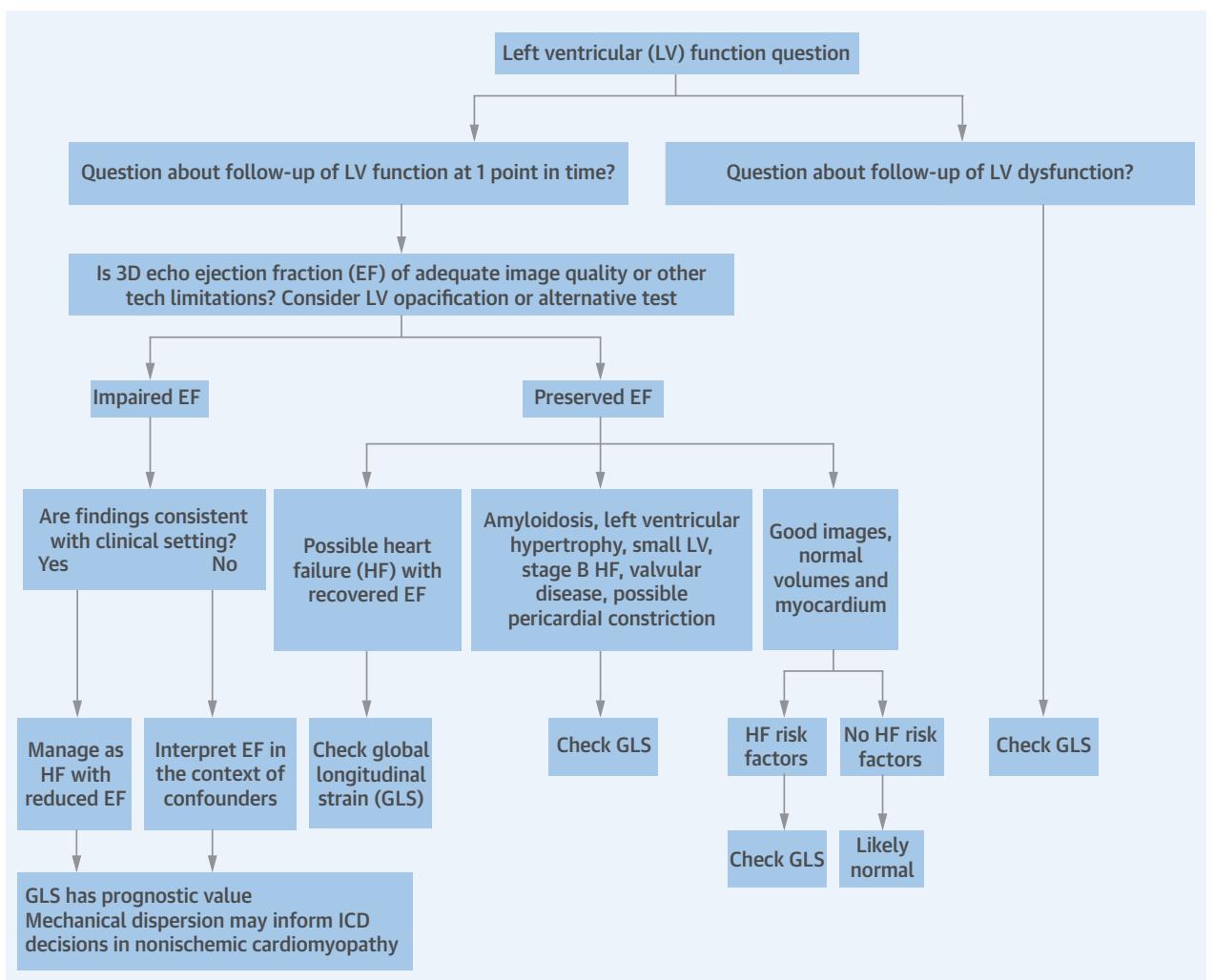
problematic for community-based populations in socioeconomically depressed and rural areas.

HF SCREENING. The progression of HF prevalence is relentless; in the United States, it is expected that there will be more than 8 million people with HF by 2030 (75). Apart from the human cost of this chronic disease, the financial burden is also extreme, with costs growing to \$70 billion in the next decade. In this context, efforts to detect and prevent HF in the population would therefore seem to be a prudent step. Because patients with an LVEF <0.50 have a 12-fold increase of HF risk (76), and even patients with a mid-range EF (0.40 to 0.50) have a 3-fold increase of incident HF (77), the identification of SBHF might be a means of identifying patients at risk. Although it might be argued that, in the absence of an effective therapy for HFrEF, the appropriate therapeutic response is unclear, the use of a natriuretic-based screening protocol has been associated with a reduction of incident HF (78). The challenge, of course, comes from the adoption of population data to individuals, especially using a technique with wide CIs

such as 2DE. More critical to test selection, however, is the nature of the question. EF will identify fully evolved, but undetected, disease leading to HFrEF. However, it is not useful for either the detection of the earlier stage of HFrEF before EF has fallen, or the preclinical phase of HFrEF. Population-based studies have shown that the classical features of SBHF (such as reduced EF and LV hypertrophy) do not capture all of the patients with subclinical LV dysfunction, and not only is diastolic dysfunction predictive of the development of HF (79), but so also is impaired myocardial deformation (80).

WHAT IS THE FUTURE FOR EF?

There can be few parameters in the whole of medicine that have had such a ubiquitous role in the characterization and management of disease as EF in cardiology. Despite its limitations, it is hard to anticipate a situation in which EF would no longer be used for the detection of LV systolic dysfunction and the consequent prognostic implications of this condition.

CENTRAL ILLUSTRATION Proposed Decision Process About When to Trust and Distrust Ejection Fraction

Marwick, T.H. *J Am Coll Cardiol.* 2018;72(19):2360-79.

There is broad value in gathering global longitudinal strain (GLS) in every case, but the enclosed scenarios summarize where this measurement is most useful. 3D = 3-dimensional; EF = ejection fraction; HF = heart failure; ICD = implantable cardioverter-defibrillator; LV = left ventricular; MI = myocardial infarction.

Advances are continuing in the main alternative methodologies; new CMR protocols are shorter, potentially reducing cost, whereas improvements in 3DE have enabled many echo acquisitions to be performed using a single beat, thereby removing the need for breath-holding and potential stitch artifacts. Moreover, in the age of machine learning, automation is already being seen in the process of tracing the endocardium. Nonetheless, caution is necessary concerning the use of semiautomatic algorithms to calculate volumes and EF, regardless whether from 2D or 3D data. Manual correction is important,

although it has been made difficult by the presentation of only thumb-sized LV images with most software. Other improvements can be expected that might ensure that appropriate 2D image planes are selected, or cross-correlation with other measurements (e.g., Doppler).

Nonetheless, disease phenotypes have changed from the era when EF was developed, and we now have an expectation of identifying disease at an early stage. In many situations, the information provided by EF is inadequate; this is especially the case in the assessment of HFP EF and the recognition of SBHF,

but is also pertinent to amyloidosis, hypertrophic cardiomyopathy, and the recognition of LV impairment in various valvular heart diseases, including regurgitant lesions and AS. There is a risk that classification by EF will be a barrier to deeper phenotyping of these illnesses—which is essential to develop targeted treatment strategies. Thus, the best way forward seems to be to retain EF because of its historical role and evidence base, but to accept that in a number of circumstances, EF alone is insufficient

(**Central Illustration**). New and more sensitive markers of LV dysfunction, especially GLS, should be used when EF appears to be normal, or when particular diagnoses are sought where EF is unsuitable.

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KEY WORDS ejection fraction, heart failure, myocardial infarction, strain, valvular heart disease