

Methods used for the assessment of LV systolic function: common currency or tower of Babel?

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ABSTRACT

The last decade has produced a proliferation of techniques for the assessment of left ventricular systolic function, and there now seems to be more choice than seems rational for the questions that we need answers to. In some instances, simple estimation is all that is required—the risk stratification process is inexact, as emphasised by the variety of modalities used to characterise ejection fraction (EF) in studies that validated the efficacy of treatments selected on the basis of EF. Nonetheless, while technical advances often cause disruption and confusion, it would be wrong to dismiss them as lacking benefit. The purpose of this review is to try to provide rational grounds for selecting both test modality and physiological parameter in various specific clinical situations.

The assessment of global left ventricular (LV) systolic function is a cornerstone of risk evaluation and management in most cardiac diseases. The simplest and most widely used parameter for this purpose has been ejection fraction and regional wall motion analysis, initially from x-ray contrast ventriculography, then nuclear ventriculography and echocardiography. Over the last 10–15 years, this choice has been supplemented by new technologies including CT and cardiac magnetic resonance (CMR), as well as the movement from two dimensional (2D) to three dimensional (3D) imaging. Finally, over the last decade, new parameters such as strain imaging have become available. In short, all modalities used to image the heart—ultrasound, scintigraphy, x-ray contrast (with and without CT) and CMR can provide this assessment. Rather than categorise the techniques by modality, we should categorise them on the basis of assessing global and regional function, whether they are quantitative versus qualitative, and the clinical setting under which they are used.

INDICATIONS FOR SYSTOLIC FUNCTION EVALUATION

The most common indications for LV systolic function evaluation are listed in table 1.

The diagnosis and evaluation of heart failure is probably the most common indication for echocardiography. Two studies have shown that heart failure patients who undergo echocardiography have a better outcome than those that do not.^{1 2} Although a variety of biases may account for these observations, it seems plausible that performing an imaging study identifies individuals with heart failure and reduced ejection fraction who can then be initiated on therapies that are known to have a favourable impact on survival.

A second (but related) indication for echocardiographic evaluation of systolic function relates to individuals where LV dysfunction is an important component of risk evaluation for decision-making. In these settings, cut-offs of LV function are surrogates for the assessment of risk and cut points have to be acknowledged as arbitrary, although the need for them is understandable from the standpoint of decision-making. However, table 2 illustrates how the methodologies and cut-offs used in studies that have defined these ejection fraction criteria for the guidance of management are highly variable, with few studies using core laboratories.^{3–18} Recognition of an ejection fraction of <35% is important in decision-making regarding device therapy, either with implantable defibrillators or cardiac resynchronisation therapy (CRT).^{19 20} Figure 1A emphasises how difficult this is to perform accurately with techniques that require tracing of the LV cavity and contrasts this with the automated measurement of global strain (figure 1B). Similar to the ejection fraction criteria for intervention in regurgitant valve lesions,²¹ it seems reasonable to conclude that these numbers should be considered to be guides rather than thresholds.

A third group relates to asymptomatic subjects at risk for heart failure, in whom the detection of reduced ejection fraction or subtle structural heart disease reclassifies the patient from stage A to stage B of heart failure, with resulting management implications.²² A specific group of these patients are those who have previously been administered cardiotoxic chemotherapy, but it also includes individuals with gene-positive cardiomyopathies, amyloidosis or other infiltrative conditions who are expected to have a subclinical phase to their cardiomyopathy (figure 2).

The fourth common indication relates to the evaluation of regional systolic dysfunction in patients with chest pain or suspected ischaemic heart disease. There is a strong association of wall motion abnormalities with ischaemic heart disease and Framingham risk score,²³ although other conditions such as sarcoidosis and myocarditis may result in regional changes. The calculation of strain appears to be a reliable and reproducible means of quantifying regional function at both echocardiography and CMR (figure 3).

Finally, although the temporal analysis of LV contraction carries prognostic information, the clinical application of this remains uncertain. There are very strong prognostic reasons to undertake CRT in patients with heart failure symptoms, systolic dysfunction and left bundle branch block, irrespective of the measurement of mechanical synchrony, and there are reasonable grounds to doubt the reliability

Table 1 Indications for left ventricular (LV) evaluation and potential modalities

Indication	Modality
Ejection fraction? HF	2DE screening Patients near cut-offs undergo CMR, 3DE or contrast
Risk evaluation	
Electrical therapy	3D, contrast
Preclinical HF	Strain
Regional function	WM analysis, strain
Regional timing	Uncertain clinical value

CMR, cardiac magnetic resonance; 2DE, two dimensional echocardiography; 3DE, three dimensional echocardiography; HF, heart failure; WM, wall motion.

of some of the literature on prediction of CRT response.²⁴ Nonetheless, it has to be acknowledged that the LV needs to be dyssynchronous in order to be resynchronised, and a reliable method to measure this may some day have value. Paradoxically, measurement of synchrony may come into clinical use in the selection of patients for implantable defibrillators rather than cardiac resynchronisation, as measurements of dispersion of mechanical activation may be of value in understanding the risk of arrhythmia.²⁵

METHODOLOGY AND LIMITATIONS OF EJECTION FRACTION

The simplicity of EF as the ratio between stroke volume and end-diastolic volume hides a heterogeneity in its calculation. Of the commonly performed techniques, only radionuclide ventriculography (which is count-based) and strain imaging (which is based on calculation of average deformation) avoid tracing LV borders. While these methods are therefore less dependent on definition of the border (which is a positive aspect in terms of test-retest variation), they are still dependent on image quality—for example, attenuation can cause inaccuracy with the nuclear technique. Although their results clearly have a stable ‘exchange rate’ with other measures of global function, they are not the same and should not be mixed. For the remaining methods, border tracing is an important source of heterogeneity and

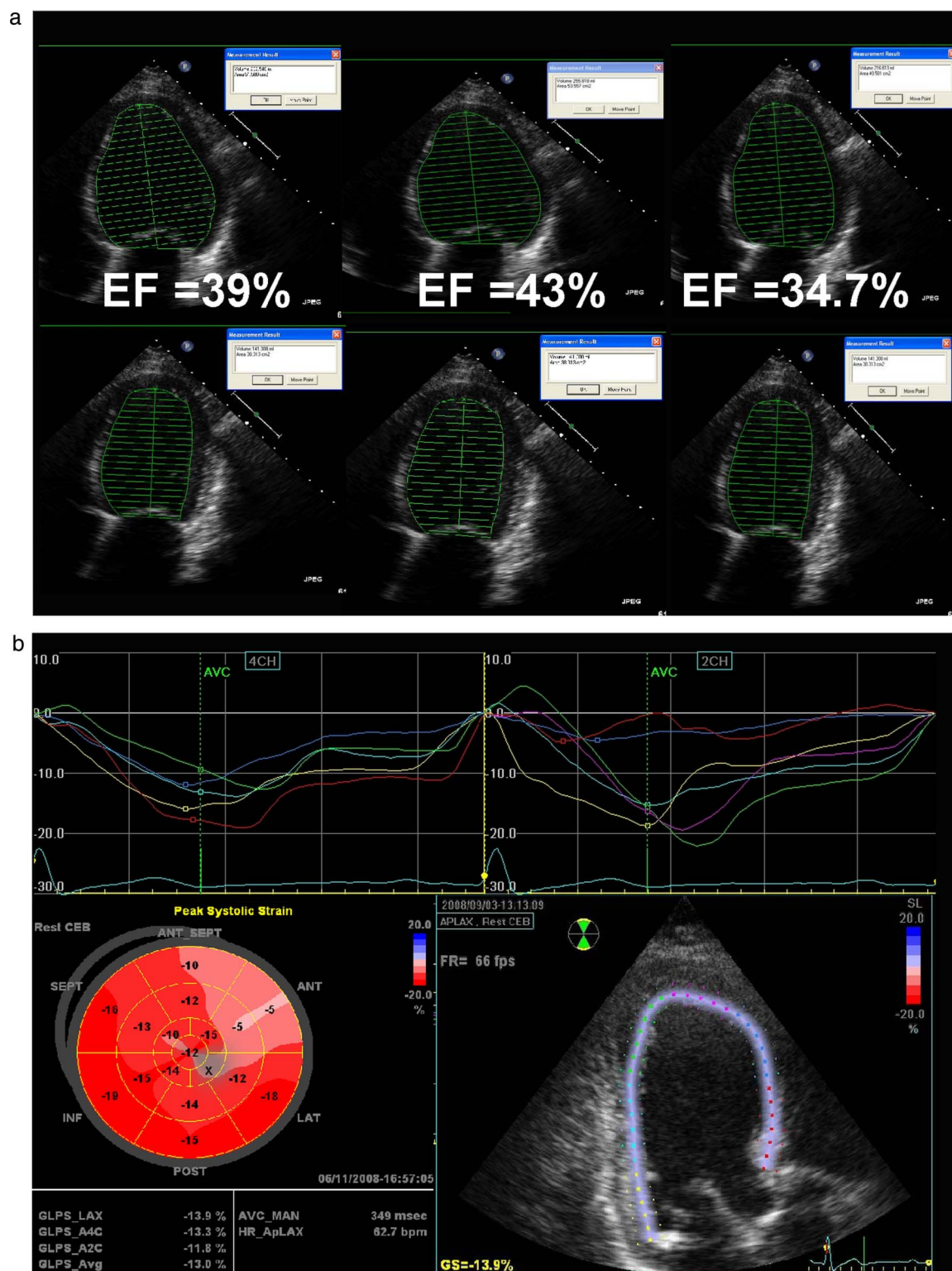
segmentation of myocardium from LV cavity is dependent on the contrast resolution of the underlying method. The implication is that the LV volumes that underpin calculation of EF are potential sources of variation between methods, especially when the use of contrast or analogous non-contrast changes (contrast echocardiography, x-ray ventriculography, CT, CMR) and spatial resolution provide differences in visualisation of the trabeculae.²⁶ These techniques should not be mixed with non-contrast techniques and probably not with each other. Finally, methods that are truly 3D are independent of geometric assumptions, but it should be recognised that even 3D imaging is a broad category that encompasses methods which generate a 3D construct of the LV (3D echocardiography and some CMR approaches), to approaches that offer a limited number of views to create a model of the LV (figure 4). In patients with regional variations in function, differences between 2D and 3D methods pose particular problems in ensuring the same planes are replicated, and 2D methods pose problems for sequential follow-up within individuals rather than populations (figure 5). In general, techniques should not be mixed, and cannot be expected to offer homogeneous results for even as simple as EF. Although EF has been widely used for decades as the ‘common currency’ of ventricular imaging and has a central role in many guidelines,^{19 20} this evidence base for a number of interventions has been created with a variety of methods (table 3).

EF has a number of important limitations (table 4). Some of these, such as the calculation of ejection fraction using a variety of geometric assumptions, as well as the error introduced by tangential tomographic planes, generally pose a greater problem to the evaluation of LV volumes than EF, as the errors seem to cancel in the evaluation of ejection fraction. Ejection fraction is load dependent, meaning that it cannot be interpreted as a reflection of contractility in the absence of knowledge about afterload and preload. The classical approach to understanding contractility is the performance of a pressure-volume loop, which may be facilitated by more accurate volumetric imaging. Alternatively, some pre-ejection markers are independent of afterload,²⁷ but they are noisy and require high temporal resolution. Perhaps the best way to integrate the role of loading in the evaluation of LV function is to ensure that the measurement of blood pressure (as an analogue of central pressure) and to a

Table 2 Multicentre studies that have defined ejection fraction criteria for the guidance of management in heart failure

Study	Intervention	n	Technique	Core lab	Entry criteria
SOLVD (1991) ³	Enalapril	2569	Echo, RNV, LVgram	Yes	EF≤35%
Hydralazine-nitrate (1991) ⁴	Enalapril vs hydralazine-nitrate	804	Echo, RNV	Yes	EF<45%, LVEDD >27 mm/m ² BSA
CIBIS (1994) ⁵	Bisoprolol	641	RNV, LVgram	No	EF<40%
US Carvedilol (1996) ⁶	Carvedilol	1094	Echo	Yes	EF≤35%
MERIT-HF, 1999 (2000) ^{7 8}	Metoprolol XL	3991	Unspecified	No	EF≤40%
CIBIS II (1999) ⁹	Bisoprolol	2647	Echo, RNV, LVgram	No	EF≤35%
Capricorn (2001) ¹⁰	Carvedilol	1959	Echo, RNV, LVgram	No	EF≤40%, WMSI≤1.3
Carvedilol (2001) ¹¹	Carvedilol	2289	Unspecified	No	EF <25%
BEST (2001) ¹²	Bucindolol	2708	RNV	No	EF<35%
MIRACLE-ICD (2003) ¹³	CRT/ICD	369	Echo	Yes	EF≤35%
COMET (2003) ¹⁴	Carvedilol vs metoprolol	1511	Echo, RNV	No	EF<35%
CHARM (2003) ^{15 16}	Candesartan	2548	Unspecified	No	EF≤40%
SCD-HeFT (2005) ¹⁷	ICD	3521	Unspecified	No	EF<35%
CARE-HF (2005) ¹⁸	CRT	813	Echo	Yes	EF≤35%, LVEDD >30 mm/m height

BSA, body surface area; CRT, cardiac resynchronisation therapy; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic dimension; LVgram, contrast ventriculography; RNV, radionuclide ventriculography; WMSI, wall motion score index.



lesser extent, inferior vena cava characteristics, should be included in imaging studies that could be used clinically to surmise contractility.

Third, ejection fraction is influenced by heart rate. The increased stroke volume associated with bradycardia may lead to overestimation of the true ejection fraction, and conversely in

tachycardia the reduced stroke volume may lead to underestimation of the actual function. There is no technique that corrects for this, so heart-rate needs to be kept in mind in the application of EF data. Atrial fibrillation represents a special problem not only due to tachycardia, but because LV filling may alter from beat-to-beat depending on the R-R interval. This is a

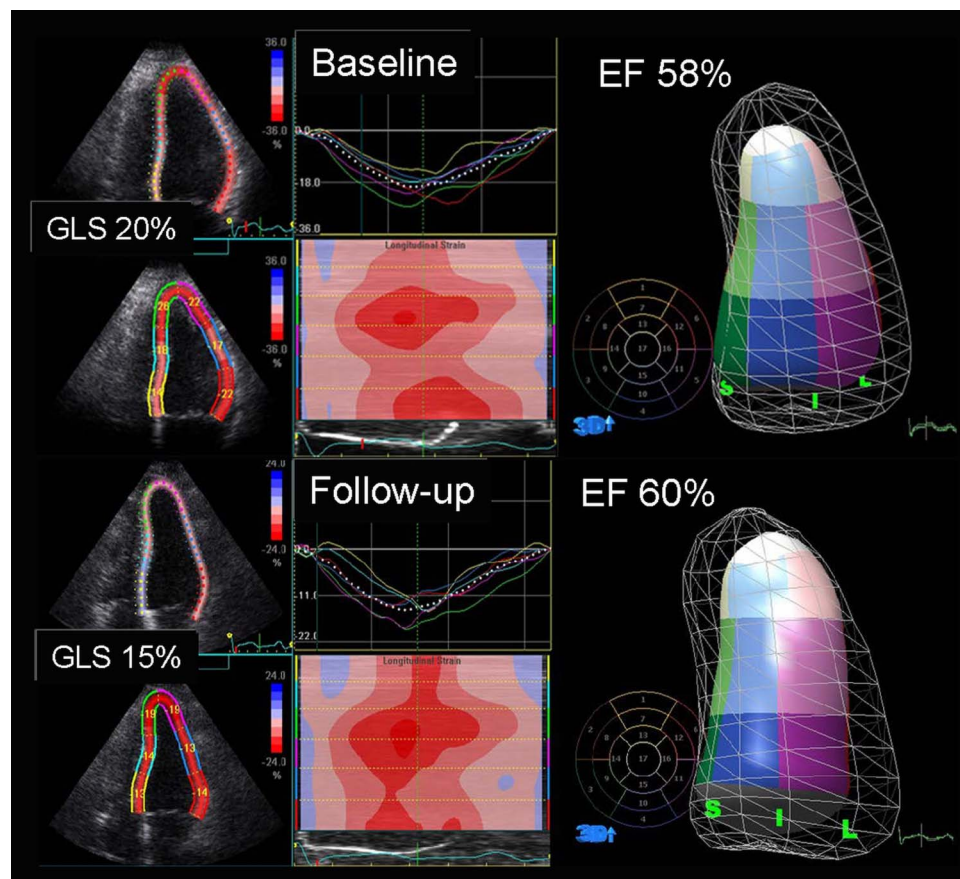


Figure 2 Sequential follow-up of a chemotherapy patient showing stability of EF but a reduction of global longitudinal strain.

particular problem if the image is constructed from multiple beats (eg, nuclear ventriculography and commonly used CMR methods), although arrhythmia rejection algorithms may allow averaging in these situations. The development of a new, single-beat approach to 3D echocardiography appears to have overcome this limitation for this technique,²⁸ potentially allowing averaging of multiple beats.

Ejection fraction is essentially a measurement of endocardial strain, and in some contexts such as LV hypertrophy, which is a function in the mid-myocardium, this may not correspond well with the real interest of the clinician.²⁹ Finally, EF functions best as a marker of gross LV dysfunction, but may be insufficiently sensitive to identify mild degrees of systolic dysfunction, perhaps evidenced by the inability to identify a gradation of risk in patients with EF >45%.³⁰ In contrast, the use of global longitudinal strain offers the greatest increment in predictive power in patients with EF >35%, and without wall motion abnormality (WMA).³¹ Finally, the wide use of EF suggests that not all assessment is performed at the same level of expertise—indicating that more formal quality control, automation and quantitation may be desirable.³²

TECHNOLOGIES FOR ASSESSMENT OF LV SYSTOLIC FUNCTION

Although the various imaging techniques are often classified on the basis of the technology that underlies the generation of their images,³³ an alternative approach to selection of the appropriate modality could be based upon fundamental considerations that characterise the strengths and weaknesses of imaging (table 4). These include spatial, temporal and contrast resolution, 3D

acquisition and display, repeatability, and intraobserver and interobserver variation.³⁴

Echocardiography, CMR imaging and cardiac CT have a spatial resolution of between a millimetre and a few millimetres.³³ In contrast, nuclear cardiology techniques have a lower spatial resolution of up to 1.0 cm. These considerations are relatively unimportant with respect to the assessment of global function, although problems may arise in relation to evaluation of the small, female heart.³⁵ They may be pertinent with respect to the measurement of wall thickness (eg, amyloidosis, hypertrophy) or thinning (eg, myocardial infarction) and recognition of regional wall motion disturbances, especially if these are small. Techniques with lower spatial resolution are inherently less suited to the generation of exact information regarding regional wall motion disturbances, wall thickness and dimension.

The highest temporal resolution is available using echocardiographic techniques. Generally, this component of imaging is considered important when assessing the rate of contraction or the presence and degree of LV dyssynchrony. In patients with a stable cardiac cycle, in whom it can be assumed that tissue follows a predictable trajectory between sampling points, interpolation may be used to improve the apparent temporal resolution of the technique, for example, using a Fourier transform. This underlies the assessment of LV synchrony with techniques of low temporal resolution such as 3D echocardiography and single photon emission computed tomography (SPECT). Another aspect of temporal resolution that is often neglected is the importance of measuring and averaging a large number of cardiac cycles in patients with stable cardiac rhythm. Failure to

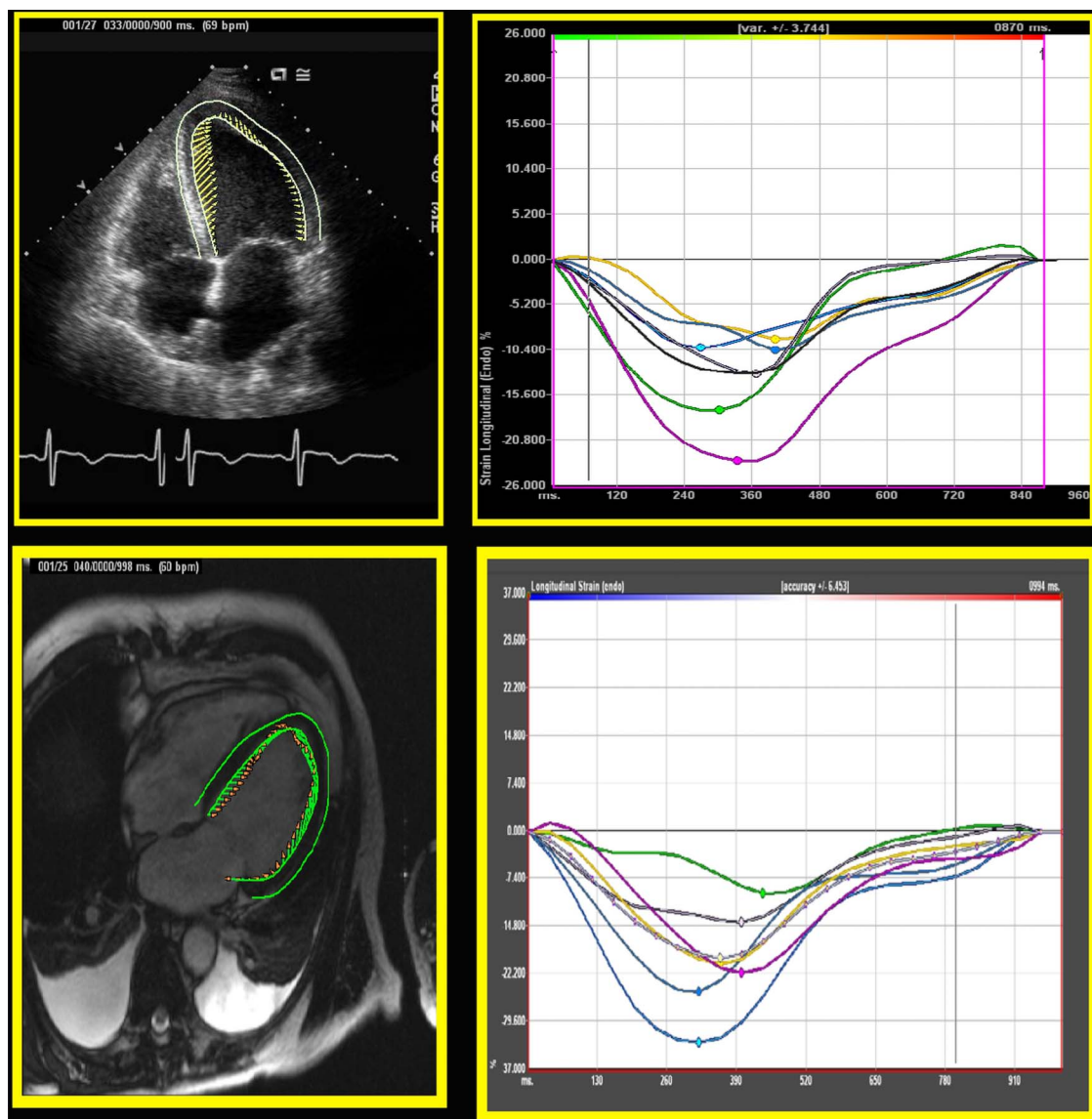


Figure 3 Quantification of regional functional impairment with strain using feature-tracking of echocardiographic and cardiac magnetic resonance (CMR) images.

do so is one of the weaknesses of echocardiography, which then exposes measurements to the risk of sampling error based on individual cardiac cycles. In the future, it is possible that signal averaging using nuclear and magnetic resonance techniques will make them the test of choice for the assessment of LV synchrony.³⁶

Contrast resolution is the ability to accurately segment the LV wall from the blood pool. The best contrast resolution is obtainable using MRI. Contrast techniques such as contrast echocardiography or ventriculography improve the contrast resolution of the underlying technique. These considerations are vital in the accurate measurement of LV dimensions and volumes. From the standpoint of contrast resolution, as well as tissue characterisation, MRI is the optimal tool.

3D imaging is available with echocardiography, MRI and CT. The main attraction of 3D imaging is to avoid geometric assumptions when calculations of LV volumes are being obtained, and to avoid errors created by cutting a 3D structure in two dimensions. In a generic sense,³⁷ 3D imaging using any technique is superior to 2D imaging for the purpose of calculating volumes and to a lesser extent ejection fraction. The latter is

true because the errors in volume calculations tend to cancel out when expressed in a ratio to obtain ejection fraction.

Repeatability, precision or test/retest variation relates to the ability to obtain the same measurement on multiple tests when there has been no interval change of function.³⁸ This parameter is often neglected but is extremely important in patient follow-up—clearly a technique with a high degree of test/retest variation is unfavourable for follow-up applications. This is particularly a problem with 2D imaging, because of the previously mentioned variations in cut planes from episode to episode of imaging (figure 3). 3D techniques are generally more repeatable, as are techniques which are independent of volumetric considerations such as global strain. Intraobserver and interobserver variability is often related to image quality. While techniques with limited intraobserver and interobserver variability may still be used with appropriate training, less variable methods have the potential attraction of operating at a high level of quality in less expert hands.

Combining these fundamental aspects of imaging technologies with the situations where LV imaging is required can provide some clues as to the most appropriate imaging choices. First, situations where accurate sequential follow-up is needed are most favoured

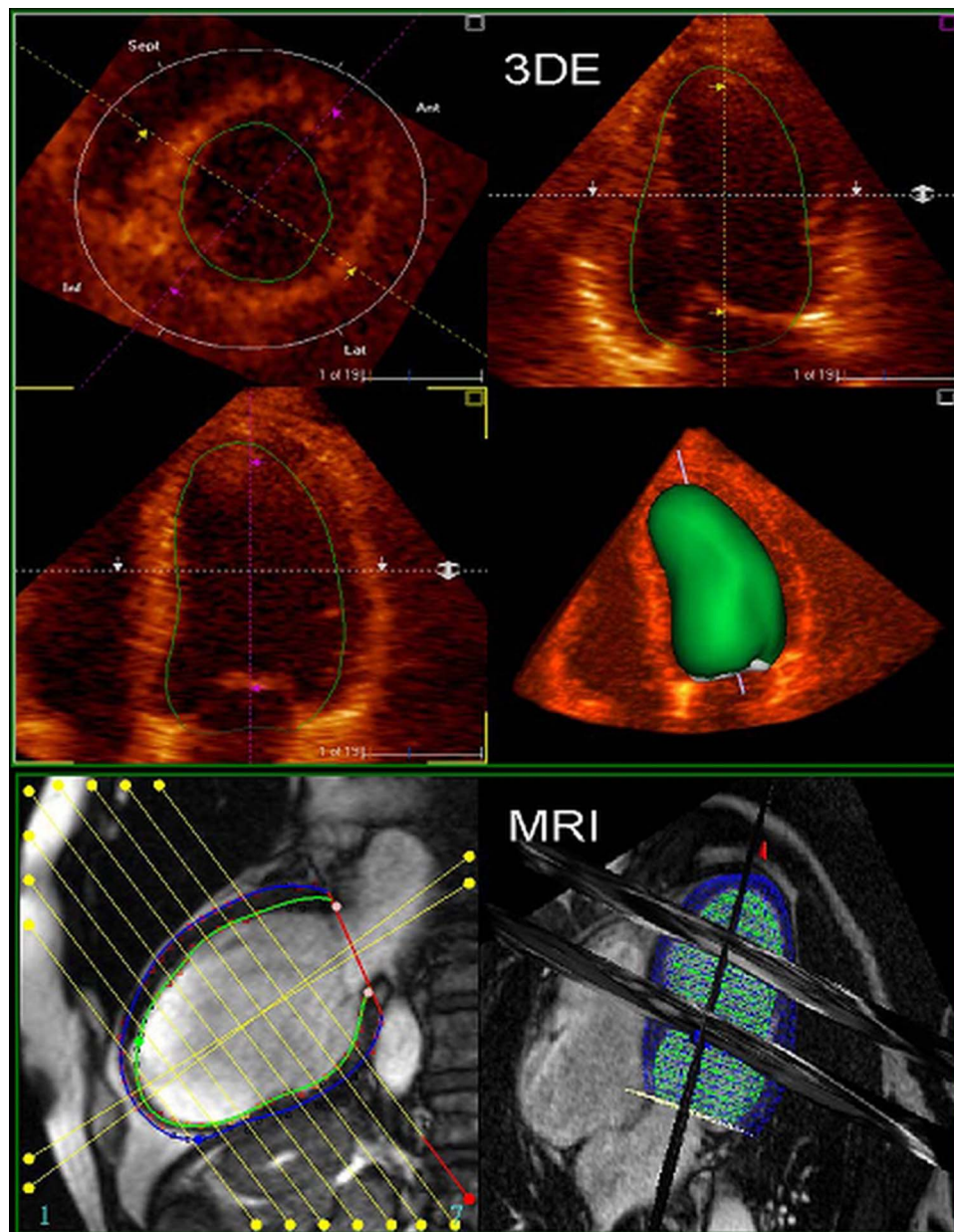


Figure 4 Different approaches to 3-dimensional (3D) imaging. In this cardiac magnetic resonance (CMR) technique (above), traditional short axis slices are integrated with longitudinal slices to create a 3D model of the left ventricular (LV). In the 3DE method, observer interaction with automated tracking of the walls is used to inform segmentation in the entire 3D dataset.

using 3D imaging, for example, MRI with 3D echocardiography being a good alternative. While nuclear ventriculography has been used for this purpose, it may be less sensitive to minor change.³⁹ Subtle disturbances of systolic function may not be apparent on ejection fraction. In these situations, such as the follow-up of patients on cytotoxic chemotherapy, strain techniques could become the test of choice. Decisions requiring an accurate calculation of LV volumes, or ejection fraction should be performed using an inherently 3D technique such as MRI or 3D echo. Such circumstances might include decisions for device therapy in heart failure,⁴⁰ or when quantitative methods are used to facilitate surgical decision-making in patients with valvular heart disease.⁴¹ Assessment of regional wall motion is best performed using a high resolution technique, such as echocardiography or MRI. Contrast should be used with echocardiography whenever indicated by the failure to visualise >2 segments⁴²—the benefit of contrast in the absence of sub-optimal imaging is unproven and may be detrimental.

CONCLUSIONS

Despite its limitations, ejection fraction has become part of the lingua franca of cardiology. The evidence base for modern cardiology is so heavily based on this simple measurement that it is unlikely to disappear. The ubiquitous presence of heart failure, and its association with frailty, mandates an inexpensive, widely available test that is able to provide haemodynamic assessment—so echocardiography is likely to remain as the workhorse of LV functional assessment.

However, while the simple estimation of global function using ejection fraction is quick and sufficient for screening, it also provides suboptimal data in many situations. Subtle disturbances may need to be sought with more sophisticated and sensitive parameters such as strain. When ejection fraction is reduced, and a pivotal decision (such as device implantation or surgery) is to be based on the measurement, more accurate assessment can be obtained using either MRI or

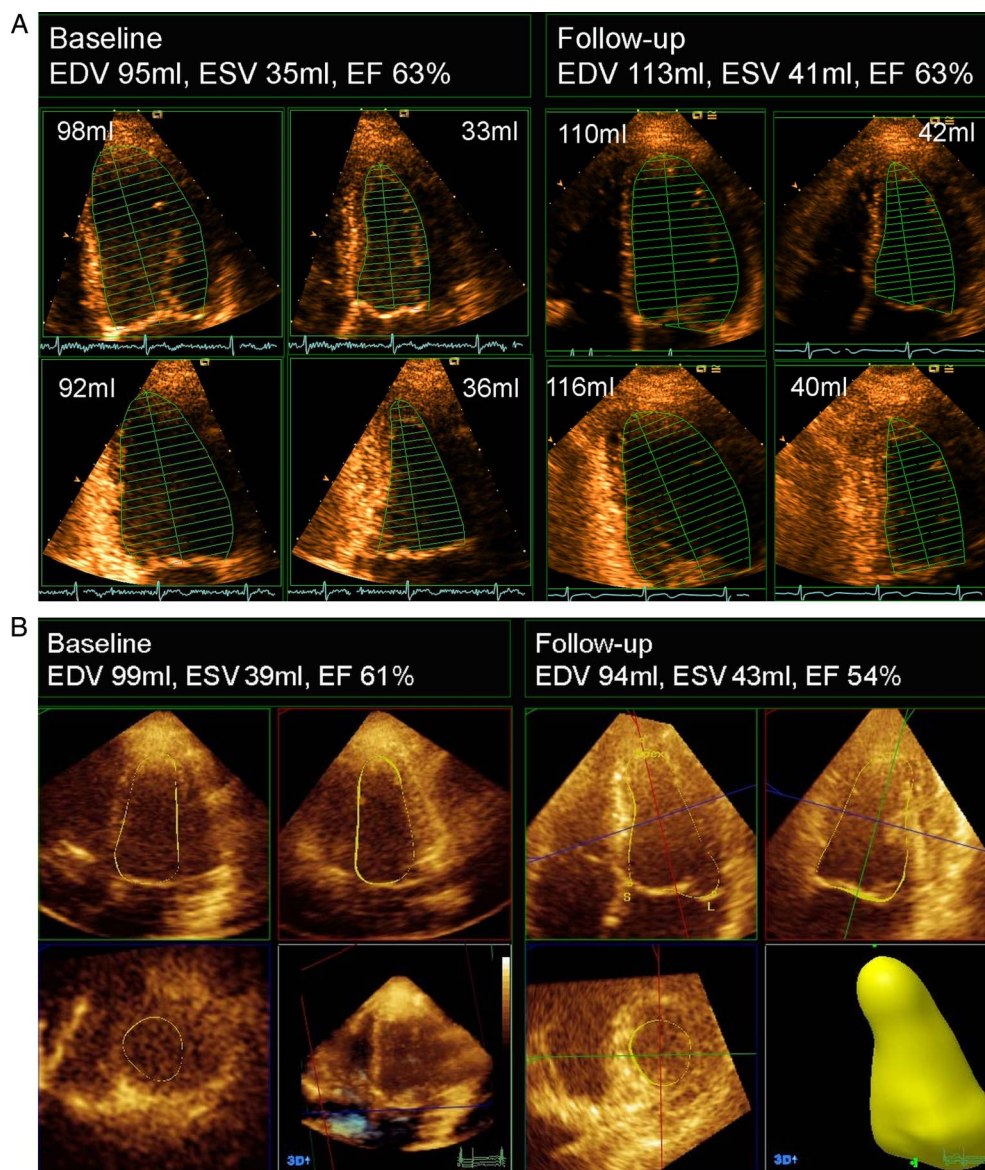


Figure 5 Variation between techniques for sequential left ventricular (LV) assessment. In this patient, 2-dimensional imaging suggests increasing LV volumes with a stable EF (A), but 3-dimensional (confirmed by cardiac magnetic resonance) documents a falling EF (B), end-diastolic volume (EDV) and end-systolic volume (ESV).

Table 3 Limitations of ejection fraction

Problem	Circumstances of inaccuracy	Potential solution
Geometry dependence	LBBB, extensive wall motion abnormality, off-axis imaging	3D imaging, geometry-independent techniques
Load dependence	Extremes of afterload, mitral regurgitation	Pressure volume loops, pre-ejection markers
High and low HR	Heart block, tachycardias (especially atrial fibrillation)	None
Marker of endocardial shortening	LV hypertrophy	Mid-myocardial shortening
Insensitivity to minor change	Prognostic value close to EF 50%	Non-EF techniques for assessing subclinical dysfunction
Expertise	Wide use of EF	Quantitation

3D, 3-dimensional; LBBB, left bundle branch block; LV, left ventricular.

echocardiography with 3D imaging or echocardiographic contrast. When volumes are required, as in the assessment of valvular disease, 3D techniques should become mandatory. Finally follow-up studies should require a 3D strategy or geometry independent techniques such as the assessment of global strain.

For regional function, visual assessment is sufficient in many circumstances. If there is a desire to follow sequentially, or to

Table 4 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, 3D echo	Sequential follow-up
Sensitivity to minor change	Strain	Subclinical cardiomyopathy

CMR, cardiac magnetic resonance; 3D, 3-dimensional; LV, Left ventricular.

improve sensitivity, for example, in the assessment of myocardial viability response to dobutamine, quantitative strain should be considered.

Finally, the selection of imaging techniques is sometimes driven by the measurement of comorbid conditions. Patients with valvular disease are probably still best studied with echocardiography. Where the aetiology of heart failure is sought (eg, infiltrative disorders such as amyloidosis), the selection of CMR provides the potential of tissue characterisation. Patients requiring perfusion imaging can have gross ejection fraction disturbances identified using SPECT.

Competing interests None.

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