Current Heart Failure Reports
https://doi.org/10.1007/s11897-021-00530-1

IMAGING IN HEART FAILURE (J. SCHULZ-MENGER, SECTION EDITOR)

Echocardiographic Longitudinal Strain Analysis in Heart Failure: Real Usefulness for Clinical Management Beyond Diagnostic Value and Prognostic Correlations? A Comprehensive Review

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Accepted: 14 June 2021

Abstract

Heart failure (HF) is a highly prevalent clinical syndrome characterized by considerable phenotypic heterogeneity. The traditional classification based on left ventricular ejection fraction (LVEF) is widely accepted by the guidelines and represents the grounds for patient enrollment in clinical trials, even though it shows several limitations. Ejection fraction (EF) is affected by preload, afterload, and contractility, it being problematic to express LV function in several conditions, such as HF with preserved EF (HFpEF), valvular heart disease, and subclinical HF, and in athletes. Over the last two decades, developments in diagnostic techniques have provided useful tools to overcome EF limitations. Strain imaging analysis (particularly global longitudinal strain (GLS)) has emerged as a useful echocardiographic technique in patients with HF, as it is able to simultaneously supply information on both systolic and diastolic functions, depending on cardiac anatomy and physiology/pathophysiology. The use of GLS has proved helpful in terms of diagnostic performance and prognostic value in several HF studies. Universally accepted cutoff values and variability across vendors remain an area to be fully explored, hence limiting routine application of this technique in clinical practice. In the present review, the current role of GLS in the diagnosis and management of patients with HF will be discussed. We describe, by critical analysis of the *pros* and *cons*, various clinical settings in HF, and how the appropriate use and interpretation of GLS can provide important clues.

Keywords Heart failure · Echocardiography · Strain imaging · Diagnosis · Pathophysiology · Outcomes

[…] speckle tracking is probably the most important advance in ultrasonic imaging since color Doppler.

[…] Virtually every practicing clinical cardiologist is expected to be, and should be, an expert in the field of echocardiography. They may not be investigators or promoters of the latest advances, but they should be able to use the latest technology that is available to manage their individual patients.
Harvey Feigenbaum, 2012 [1]

Introduction

Heart failure (HF), a clinical syndrome defined by the concomitant presence of cardiac dysfunction and congestion, is a widespread condition (≥ 10% among people > 70 years of age) [2]. Actually, according to the European guidelines, patients with HF are classified in three groups based on left ventricular ejection fraction (LVEF): (1) heart failure with reduced ejection fraction (HFrEF) (i.e., LVEF < 40%), (2) heart failure with mid-range ejection fraction (HFmrEF) (i.e., LVEF in the range of 40–49%), and (3) heart failure with preserved ejection fraction (HFpEF) (i.e., LVEF ≥ 50%) [2]. This classification has been widely criticized due to the complex underlying pathophysiological mechanisms that explain HF as a continuous spectrum [3, 4]. Moreover, the

This article is part of the Topical Collection on *Imaging in Heart Failure*

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Published online: 16 August 2021

results of some clinical trials and studies, suggesting that neurohormonal therapies may continue to have a benefit for patients with only very mild reductions in LVEF, with a treatment threshold of around 55–60% [5–7], suggested that a change of the cutoff value (i.e., higher) used to define HFpEF in the guidelines would be advisable.

Prognostic Role of Echocardiography in Patients With HF: Areas of Light and Shade

Although several echocardiographic parameters have shown a prognostic role of "imaging" in HF, its value in terms of improved health outcomes or reduced cardiovascular events remains of a subjective nature; evidence is limited and poorly demonstrated [8]. Moreover, some imaging techniques seem to require excessive time before their use in clinical practice becomes widespread. On the other hand, traditional health outcome measurements, such as survival, inadequately characterize the full impact of imaging on medical decision-making and health status [9].

The Limitations of Ejection Fraction and the Need for Additional Echocardiographic Parameters

Ejection fraction (EF) measurement is widely adopted as a marker of LV function, though it is mainly affected by preload, afterload, and contractility. EF's limitations as a marker of LV function are apparent in several conditions (e.g., HFpEF). EF fails to detect early and subclinical physiological signs of LV dysfunction [10]. Moreover, EF measurement is also affected by reproducibility issues and technical limitations, such as image quality, dilated geometry, irregular R-R intervals, and left bundle branch block on ECG.

Although EF has been shown to have prognostic significance in patients with HF, when the EF exceeds 55–60%, different levels of EF are not associated with differences in outcome [5–7]. Furthermore, the role of EF and its ability as a stand-alone parameter to identify, in advanced HF, patients with end-stage disease acting as a watershed during the clinical decision-making have not been proven. Finally, EF appears unfit to comprehensively stratify the risk of sudden cardiac death in patients suitable for prophylactic implantable cardioverter-defibrillator (ICD) [11], especially in those with non-ischemic cardiomyopathy [12].

Since LV longitudinal shortening plays an important role in cardiac pump function, the simple measurement of mitral annular plane systolic excursion (MAPSE) has been suggested as a useful surrogate of systolic function [13]. However, MAPSE appears unreliable in the setting of a regional wall motion abnormality, especially affecting the basal segments, as in the case of post-infarction scar. Pulsed wave tissue Doppler imaging is another ultrasound method to quantify myocardial contraction (and relaxation) velocities [14]. But, a Doppler technique relies on the parallel alignment of the beam to the moving object examined. Moreover, it is unreliable in the presence of regional wall motion abnormalities involving LV basal segments.

Other functional parameters derived by echocardiography, such as dP/dT, myocardial performance index, and ventriculo-arterial coupling, although theoretically interesting, have many shortcomings and have failed to gain widespread clinical use [15].

Rationale (Based on Cardiac Anatomy and Physiology) for the Study of Longitudinal Function

Following considerable experience of the anatomy of dissected hearts, Torrent-Guasp hypothesized the architectural organization of the ventricular fibers as represented by a myocardial band. This ventricular myocardial band describes two spirals: a basal loop and an apical loop. In both loops, two segments can be distinguished, an ascending segment (AS) and a descending segment (DS). During the ejection phase, the contraction of the DS produces shortening of the ventricular longitudinal axis and counterclockwise rotation (viewed from the apex) of the ventricular base (torsion and twisting motion). Subsequent AS contraction causes lengthening of the ventricular longitudinal axis, obliging the ventricular base to perform an ascending clockwise rotation and diameter augmentation (untwisting) [16]. Though criticized by some cardiac pathologists [17, 18], this theory provides the anatomic and "mechanistic" explanation of the revised conception of the cardiac cycle and diastole proposed by Brutsaert et al. [19]. Accordingly, "diastole" is viewed as an active phase (due to fiber contraction and thus named systolic ventricular filling), whereas the true diastole is limited to the diastasis and the atrial contraction phase. Most importantly, Torrent-Guasp's theory provides the rationale for the use of strain imaging [20]. This should be regarded as a method able to provide information on both systolic and diastolic functions of all the cardiac chambers simultaneously ("all-in-one technique"), according to cardiac anatomy and physiology/pathophysiology (Fig. 1).

Strain Imaging: Technical Considerations

Strain is defined as the deformation of an object, normalized to its original shape [21]. In echocardiography, the term strain (deformation imaging) may be used to describe lengthening, shortening, or thickening. Nowadays, the main echocardiographic approach to strain analysis is speckle tracking. This is a post-processing computer algorithm that uses routine grayscale images of the myocardium. A region of interest on the myocardial wall containing blocks of pixels

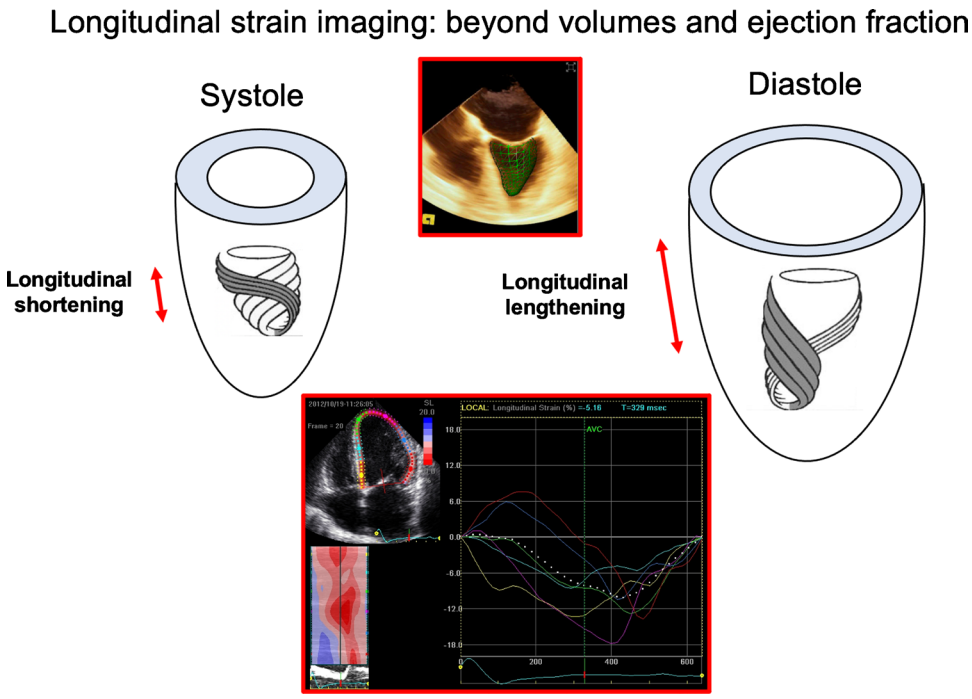

Fig. 1 Rationale for the use of longitudinal strain imaging

(and speckles) is mapped. The subsequent frames are analyzed by searching for the new location (i.e., movement) of speckles. The location shift of these acoustic markers provides information on myocardial deformation [22].

Methods

The authors approached the topic formulating the following research questions: (I) What is the role of global longitudinal strain (GLS) in the diagnosis of HF? (2) Has GLS a consistent additional diagnostic and prognostic value irrespective of other traditional echocardiographic indices? (3) Does the clinical application of GLS modify HF patient management in clinical practice? (4) Is GLS ready for routine clinical practice? A search through the web-based engine PubMed was therefore conducted in order to answer our research questions (Table 1). We critically reviewed the available data and proceeded to identify the *pros* and *cons* of the use of GLS in HF.

Strengths and Limitations of GLS: General Comments

It has been documented that, though angle independent and with some advantages over EF standard measurements, GLS, like EF, is also a load-dependent parameter [38]. Furthermore, the major constraint to its extensive clinical application is the inter-vendor reproducibility that results in considerable heterogeneity in the published literature [23] (Table 2). Recently, a joint task force has been set up comprising European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) members to standardize deformation imaging analysis among vendors [39–41].

GLS: Technical Issues and Potential Sources of Errors in Imaging Acquisition, Analysis, and Interpretation

Although GLS has been traditionally considered an easily obtainable data, not requiring particularly complex technical skills, thanks also to the semi-automated software programs/modules for strain analysis (often integral part of the equipment in modern ultrasound systems), there are some technical issues and challenges which would not allow an accurate quantification of GLS. These are summarized in Fig. 2.

Preclinical Dysfunction and Cardio-oncology

Although the clinical definition of HF implies the coexistence of signs and symptoms of congestion plus cardiac dysfunction, the American guidelines underline the importance of detecting the preclinical dysfunction which often precedes overt HF [44]. This is one of the goals of cardio-oncology [45]. It is critical to detect subclinical cardiac abnormalities, which may influence clinical decisions such as increased surveillance, indication for cardioprotection, shift, or halt in chemotherapy treatments [46]. The use of EF to assess LV function in this context has several limitations and poor sensitivity in detecting subtle and initial signs of

Table 1 Studies investigating the role of longitudinal strain in heart failure

Author	Study	HF category	Disease/etiology	Sample size (*n*)	Main results
Plana JC et al. [23]	Consensus ASE/EACVI	HFpEF HFmrEF HFrEF	Cancer therapeutics–related cardiac dysfunction	N/A	GLS relative percentage reductions > 15% (from baseline) are very likely to be abnormal
Čelutkienė J et al. [24]	Position statement ESC-HFA	HFpEF HFmrEF HFrEF	Acute heart failure (various etiologies)	N/A	GLS adds incremental predictive value regardless of EF
Park JJ et al. [25]	Prospective study	HFpEF HFmrEF HFrEF	Acute heart failure (various etiologies)	4172	GLS has greater prognostic value than LVEF
Sengeløv M et al. [26]	Retrospective study	HFrEF	Heart failure (various etiologies)	1065	GLS is an independent predictor of all-cause mortality especially in male patients without atrial fibrillation
Mele D et al. [27]	Prospective study	HFrEF	Chronic heart failure (miscellaneous etiology)	64	GLS increases both the number of responders and the magnitude of echocardiographic response to CRT
Park JH et al. [28]	Retrospective study	HFpEF HFmrEF HFrEF	Acute heart failure (miscellaneous etiology)	1824	RVGLS was significantly associated with all-cause mortality regardless of LVGLS; patients with decreased biventricular GLS showed the worst prognosis
van Kessel M et al. [29]	Retrospective study	RV heart failure	Pulmonary hypertension	57	RVGLS free wall ≥ 20% remained a significant predictor of all-cause mortality after adjusting for PH-specific treatment
Lisi M et al. [30]	Prospective study	HFrEF	Chronic heart failure (miscellaneous etiology)	27	RV free wall myocardial deformation correlates with the extent of RV myocardial fibrosis and functional capacity
Mingo-Santos S et al. [31]	Prospective study	HFpEF	Acute cellular rejection in heart transplantation	34	LV and RV free wall longitudinal strain may be able to identify a group of heart transplant patients who are unlikely to have acute cellular rejection
Cameli M et al. [32]	Prospective study	HFrEF	End-stage heart failure with LVAD	19	RV myocardial deformation can be used to evaluate RV function before LVAD implantation, to drive decisional strategy regarding the management of this type of patients, and after LVAD implant for the follow-up
Saba S et al. [33]	Prospective study	HFrEF	Chronic heart failure (miscellaneous etiology)	187	Strategy of echocardiographic guidance including GLS to LV lead placement is superior to a routine approach in CRT device
Khan FZ et al. [34]	Prospective study	HFrEF	Chronic heart failure (miscellaneous etiology)	220	Compared with standard CRT treatment, the use of speckle-tracking echocardiography to the target LV lead placement yields significantly improved response and clinical status and lower rates of combined death and heart failure–related hospitalization

Table 1 (continued)

Author	Study	HF category	Disease/etiology	Sample size (*n*)	Main results
Phelan D et al. [35]	Case–control study	HFpEF HFmrEF HFrEF	Chronic heart failure (cardiac amyloidosis)	55 vs 30 controls	A relative "apical sparing" pattern of GLS is a useful method to differentiate CA from other causes of LV hypertrophy
DeVore AD et al. [36]	Prospective study	HFpEF	Chronic heart failure (miscellaneous etiology)	187	Impaired LVGLS is common among patients with HFpEF indicating the presence of overt systolic dysfunction despite normal LV ejection fraction
Luszczak J et al. [37]	Prospective study	HFpEF	Moderate-severe aortic stenosis	82	MAPSE can still be used to assess LV systolic longitudinal function in case of suboptimal acoustic windows speckle-tracking echocardiography

GLS global longitudinal strain, *LVEF* left ventricular ejection fraction, *CRT* cardiac resynchronization therapy, *RV* right ventricular, *PH* pulmonary hypertension, *LVAD* left ventricular assist device, *CA* cardiac amyloidosis, *MAPSE* mitral annular plane systolic excursion

myocardial dysfunction. When a reduction in LVEF during chemotherapy is established, it may be too late for cardioprotective treatment [47]. Deformation imaging is able to promptly detect LV dysfunction secondary to cancer therapy [46–48]. A relative GLS percentage reduction of > 15% from baseline is considered abnormal and a marker of early LV dysfunction [49]. The results of GLS application in cardio-oncology are really promising; the authors of the Consensus Document for imaging evaluation of patients with cancer consequently stated that "echocardiographic laboratories following patients with cancer should strive to incorporate strain assessment in their echocardiography laboratory protocols" [23]. This is the first example of incorporation of strain imaging in a guideline document and its application in "routine" clinical practice. However, concerning the usefulness of GLS in patients with cancer, it has to be considered that, despite the undoubted diagnostic performance of GLS for the detection of early and subtle myocardial dysfunction, its direct impact on medical treatments and decisions still remains limited. Promising results have been provided for a strain-oriented strategy for guiding cardioprotection initiation in patients with cancer [50], though results of large multi-center randomized trials on this topic are awaited [51]. At the present time, the decision to start medical treatment with ACE inhibitors and beta-blockers is mainly driven by EF (i.e., relative reduction > 10% to an absolute value below 50%) [46].

Overt Heart Failure

The role of GLS has been investigated in both chronic and acute heart failures of different etiologies [24, 52].

In a large study involving 4172 consecutive patients with acute heart failure classified as LVEF (HFrEF, HFmrEF, and HFpEF) with GLS values mildly reduced (GLS > 12.6%), moderately reduced (GLS 8.1%/ − 12.5%), or severely reduced (GLS ≤ 8.0%), strain, but not EF, was a predictor of 5-year all-cause mortality [25]. Another study analyzing the echocardiographic examinations of 1065 patients with HFrEF admitted to a heart failure clinic showed similar findings; GLS was again an independent predictor of all-cause mortality, especially in male patients without atrial fibrillation (AF). Furthermore, GLS was a better prognosticator compared with other standard echocardiographic parameters (i.e., LVEF, LV mass, tricuspid annular plane systolic excursion (TAPSE), mitral E and A velocity, E/e′ ratio) [26]. GLS is recommended by the EACVI for the evaluation of cardiac performance in all patients with acute HF, indicating mild and severe dysfunctions if reduced by ≤ 16% and ≤ 10%, respectively [24, 52].

Given the inadequate characterization of clinical phenotypes provided by the classification of patients with HF based merely on EF [2], we should acknowledge some

Table 2 Reference values for GLS according to the available literature

Cardiac chamber	Normal values (mean + SD or absolute value)	References	Already accepted by the guidelines or consensus documents (yes/no)
Left ventricle (LV) GLS	Vendor 1: from − 22.1 ± 2.4 to − 20.3 ± 1.9 Vendor 2: from − 19.9 ± 2.5 to − 16.7 ± 2.1 Vendor 3: from − 21.4 ± 1.7 to − 17.8 ± 2.8 (depending on age groups)	Plana JC et al. [23] ASE/EACVI consensus statement (2014)	Yes
	> − 16.0%	Pieske B et al. [42] HFA-PEFF diagnostic algorithm (2020)	Yes
Left atrium (LA) PALS	31.1 ± 2.6 (age 20–40) 27.7 ± 1.5 (age 40–60) 22.7 ± 2.0 (age > 60)	Sugimoto T et al. [43] EACVI Norre Study (2018)	No
Right ventricle (RV) GLS	-24.5 ± 3.8	Morris DA et al *European Heart Journal – Cardiovascular Imaging* 2017	No
RV free wall LS	− 29.0 ± 4.5* (abnormality threshold < − 20%)	Lang RM et al Chamber Quantification by Echocardiography in Adults ASE/EACVI 2015	Yes
Right atrium (RA) PALS	49.0 ± 13	Padeletti M et al Reference Values of Right Atrial Longitudinal Strain Imaging by Two-Dimensional Speckle Tracking-Echocardiography (2011)	No

*Values may vary depending on the vendor and software version

methodological limitations of the studies investigating the role of GLS in HF. The different HF etiologies were largely unspecified in a number of studies [25, 26]. Taking into account the role of loading conditions (e.g., in patients with greater than moderate valvular regurgitation), especially in the acute HF setting, these could be potential confounders in the association between strain and the primary outcome [38]. Another important issue regarding the use of GLS in HF is the lack of really universally accepted and standardized reference values. Moreover, only the upper normal limit is usually specified, while the thresholds for moderate or severe impairment are usually considerably less well defined (Table 2). The cutoff values of left ventricular global longitudinal strain (LVGLS) presented in the international scientific societies' recommendations (e.g., ≤ 16% and ≤ 10%) mainly refer to patients with cardiomyopathy, and in the absence of data deriving from a relevant number of large randomized controlled trials [24, 52]. Furthermore, the authors of the recommendations specify that these values still require validation in acute settings and are not applicable to patients with systolic HF being treated with inotropic agents or mechanical circulatory support [24]. In this clinical scenario, other classic and relatively simple echocardiographic measurements (e.g., stroke volume and cardiac output and their changes with fluid challenge or leg raising, LV filling pressures estimated with E/A and E/e′ ratio, inferior vena cava diameter, TAPSE, right ventricular (RV) fractional area change, pulmonary artery systolic pressure (PASP), B-lines on lung ultrasound) [53–55] or derived indices (e.g., ventricular and arterial elastances) [56] may provide precious information on hemodynamics, thus helping clinicians in the medical management of critically ill patients. Do we really need strain imaging in this context?

Arrhythmias and Cardiac Implantable Electronic Devices

Strain echocardiography may be able to improve ventricular arrhythmia risk prediction after myocardial infarction and in non-ischemic dilated cardiomyopathy [57, 58]. Additionally, since there are no defined echocardiographic criteria for the selection of candidates for cardiac resynchronization therapy (CRT), strain imaging may help to increase the number of responders via a more precisely guided and optimized lead position [27].

A clinical issue is the risk of sudden cardiac death in patients with LVEF > 35% or 40% for whom (according to the guidelines) there is usually no indication for the implantation of cardiac devices (ICD or CRT) [2, 44]. GLS should be an independent predictor of malignant arrhythmias in

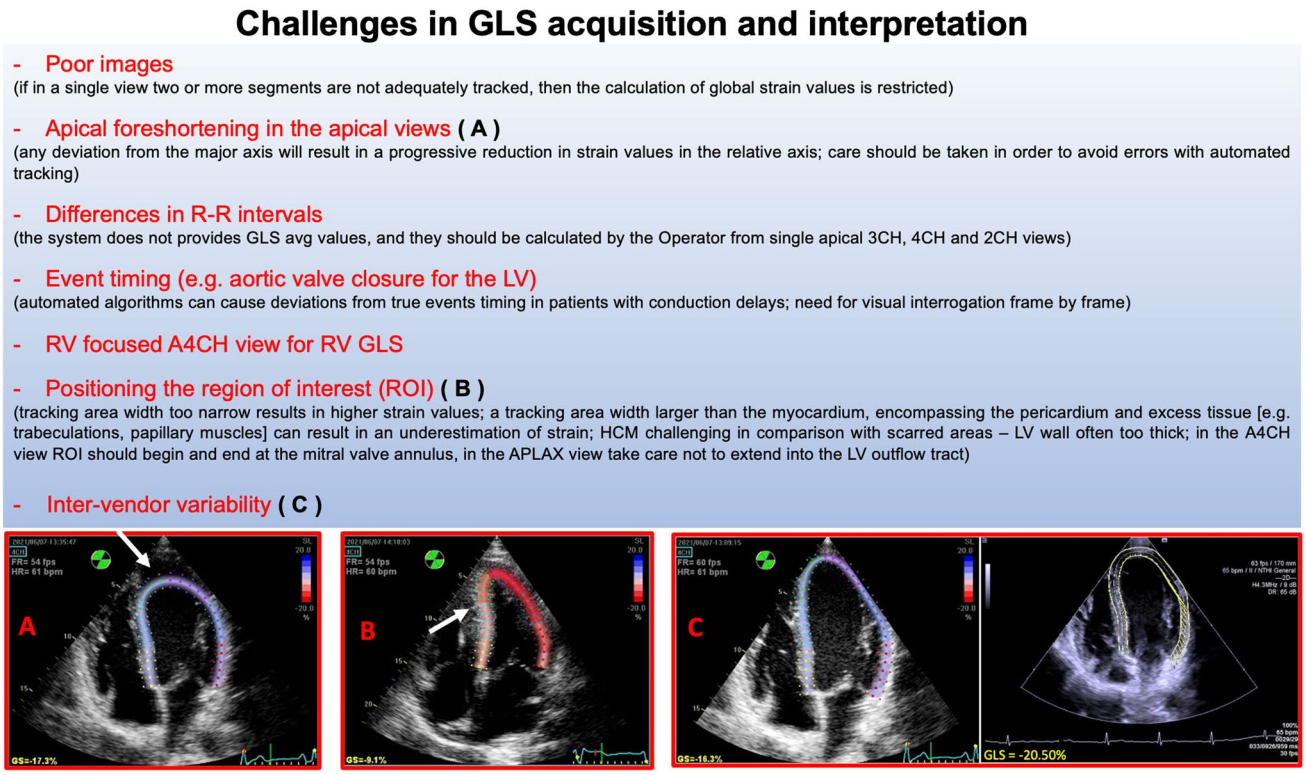

Fig. 2 Reliability of GLS according to some technical issues. (**A**) A 27-year-old male (A4CH view); the apical segments are excluded from tracking (white arrow). However, the software "catches" some signal resulting in a false tracking and subsequent unreliable strain value. (**B**) A 72-year-old male patient with TTR amyloidosis (wild type). The interventricular septum is too thick to be included into the ROI (white arrow). (**C**) A 27-year-old male; there is significant inter-vendor variability (−16.3% vs −20.5%); examinations performed on the same day (within 15 min, at rest). This could be of clinical relevance when strain values are below the normal range and a preclinical disease should be excluded

patients after myocardial infarction and with a LVEF above the threshold for an ICD implantation; in this context, GLS could identify patients at risk of ventricular arrhythmias, despite a LVEF > 35% [59]. It is largely unknown whether GLS has the same diagnostic and predictive power in patients with non-ischemic cardiomyopathy. This is a clinical need since it has been shown that in patients with dilated cardiomyopathy and LVEF ≥ 40%, the presence of late gadolinium enhancement on cardiac magnetic resonance imaging is strongly predictive of the composite endpoint of sudden cardiac death and aborted sudden cardiac death (HR 35.9) and has marked predictive value beyond that of LVEF alone in patients with LVEF 40 to 50% [60]. Patients with HFmrEF may also have conduction disturbances. Patients with left bundle branch block (LBBB)-induced cardiomyopathy may exhibit various degrees of LV dysfunction [61]. In this setting, early CRT should be beneficial, but patient selection is crucial. In patients with LBBB, GLS was significantly associated with a composite endpoint of cardiovascular mortality and hospitalization for HF, thus providing better risk stratification than LVEF [62]. As previously stated, GLS may also help in positioning the LV lead in optimal position, in order to potentially reduce the percentage of non-responders [27, 33, 34].

Right Ventricular Dysfunction, Cardiac Transplantation, and Ventricular Assist Devices

Park et al. [28] showed that in patients ($n = 1824$) with acute HF, right ventricular global longitudinal strain (RVGLS) was significantly associated with all-cause mortality regardless of LVGLS, and the predictive power of RVGLS was more prominent in the absence of pulmonary hypertension. RV function plays a pivotal role in patients with HF. Even though RV dysfunction is usually associated with LV failure, isolated RV dysfunction can occur in the context of primary lung disease/circulatory disorder, congenital heart disease, cardiomyopathy, and cardiac surgery [63]. Computing RV systolic function by TAPSE has several limitations in these conditions. Its decrease after cardiac surgery is consistently a well-known phenomenon, supporting the hypothesis of geometrical rather than functional changes in the right ventricle [64]. Furthermore, when RV dysfunction occurs in patients with pulmonary hypertension, there are often discordant

Table 3 The main applications of longitudinal strain imaging in heart failure with strengths and weaknesses

HF category	Disease	Diagnostic utility	Additional prognostic value	Impact on clinical management
HFrEF	Advanced HF (patients with CIED + GDMT)	😐	☹	☹
	Advanced HF (LVAD or HTx candidates)	😐	😐	☹
	Cardiac toxicity induced by cancer treatments	☺	☺	😐
	Patients with LBBB (CRT-P/CRT-D candidates)	☺	😐	😐*
HFmrEF	Patients with potential risk of SCD despite LVEF >35% (ICD potential)	😐**	😐	☹**
HFpEF	LVH (e.g. differential diagnosis CA/HCM)	☺***	☺	☺***
	Atrial fibrillation	☹	☹	☹
	Valvular heart diseases	😐	😐	☹****

CIED cardiac implantable electronic devices, *GDMT* guideline-directed medical therapy, *LVAD* left ventricular assist device, *HTx* heart transplantation, *LBBB* left bundle branch block, *CRT* cardiac resynchronization therapy (*P* pacemaker, *D* defibrillator), *SCD* sudden cardiac death, *LVEF* left ventricular ejection fraction, *ICD* implantable cardioverter-defibrillator, *LVH* left ventricular hypertrophy, *CA* cardiac amyloidosis, *HCM* hypertrophic cardiomyopathy

*The impact of left ventricular lead positioning guided by strain echocardiography in the real world should be confirmed. Many other factors may potentially influence the following results: (1) The delay between cardiac walls might be related to cardiac fibrosis/scar, and only the presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) may reveal it, potentially avoiding a useless procedure, and (2) the anatomy of the coronary sinus and its branches plays a pivotal role for the final result of the CRT procedure

**Although deformation imaging and its derived measurements (e.g., mechanical dispersion) may improve risk prediction in both ischemic and non-ischemic patients, there is no sufficient evidence to support a different and more aggressive management in these patients. A multi-parametric approach based on the results of other imaging tests (e.g., presence and extension of LGE on CMR), clinical history, genetic tests (e.g., in patients with laminopathies), and ECG and clinical monitoring

***The differential diagnosis between CA and HCM should also impact medical treatments

****A more aggressive treatment (i.e., early surgery or percutaneous interventions) guided by strain echocardiography is not supported by guidelines

(i.e., pseudo-normalized) TAPSE values [29]. This false enhancement could be related to the rocking motion of the failing right ventricle [65]. RV free wall longitudinal strain evaluated by speckle-tracking technique correlates with the extent of RV myocardial fibrosis in patients with end-stage heart failure, while TAPSE shows a poor correlation [30].

Patients with advanced HF may require heart transplantation (HTx) or mechanical circulation support, particularly with left ventricular assist devices (LVADs); echocardiography may help to identify those individuals who will benefit from HTx or LVAD [66]. In patients undergoing HTx, it has been found that the combination of a reduced LVGLS and free wall RVLS identifies patients at major risk of acute transplant reject [31]. Furthermore, since the LVADs' main effect is the unloading of the left ventricle and, at the same time, a potential increase in RV loading, the success of this therapy strictly depends on RV function. It was noticed that patients with higher RVGLS before implant often reveal an improvement in RV function after LVAD therapy [32].

A point of concern is the lack of GLS reference values for the right ventricle. In a recent review, Pastore et al. [67] reported RVGLS cutoff values in HFrEF (based on five different studies involving 999 patients overall) ranging from ≤ 12.1 to ≤ 19%. Should we accept such a large difference for a diagnostic test?

HFpEF and Cardiomyopathies

HFpEF represents a challenge for clinicians. The HFpEF category emphasizes once more the need for a reappraisal of the definition of HF, possibly based on morphological, functional, and clinical phenotypes [3]. The role of GLS in HFpEF has been extensively investigated.

The available data indicate the use of GLS in HFpEF, and the European Society of Cardiology's Heart Failure Association (HFA) recommendations included this parameter in the diagnostic algorithm for HFpEF [42]. Left ventricular hypertrophy (LVH) is an echocardiographic feature frequently observed in patients with HFpEF [2]. Athletes and hypertensive patients aside, LVH is a hallmark of several inherited or acquired heart diseases. In this context, strain imaging has been shown to be useful in terms of differential diagnosis and prognostic stratification. GLS regional patterns are an easily recognizable and accurate method

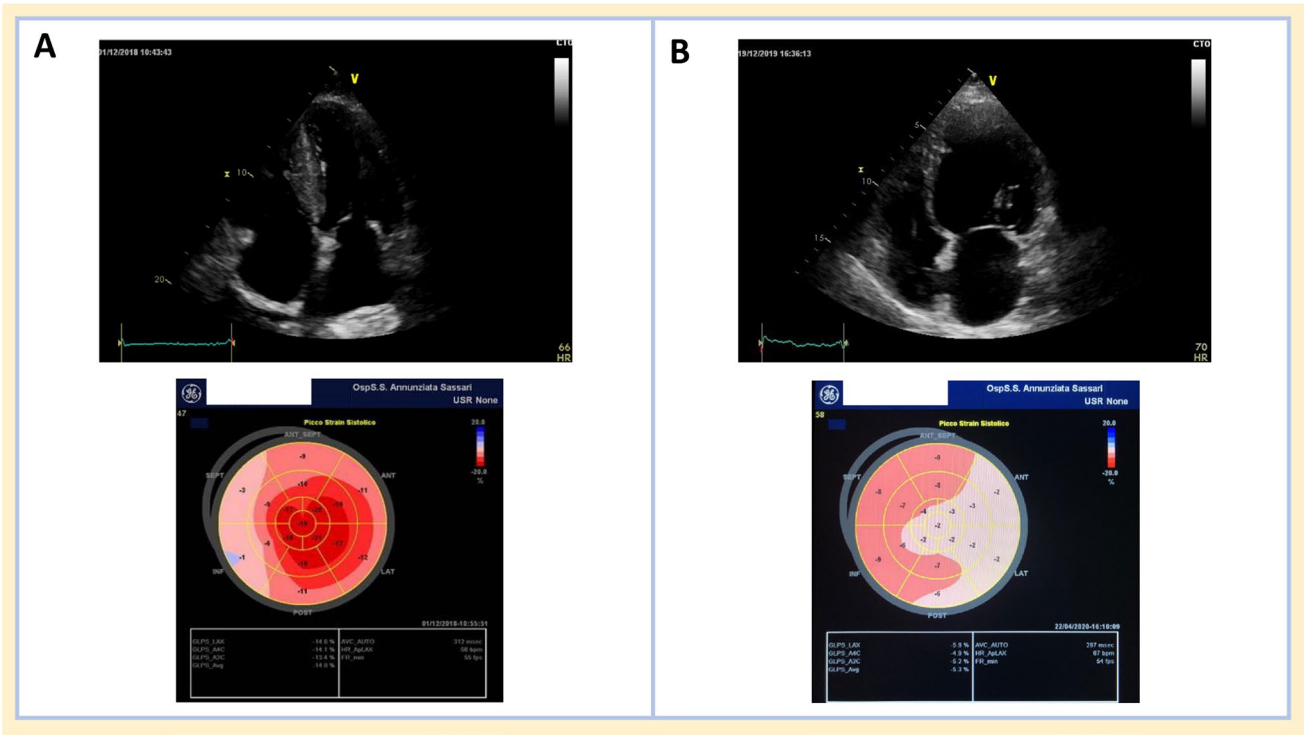

Fig. 3 Two *real-world* clinical examples (Heart Failure Clinic, Sassari University Hospital) showing the pros and cons of the use of GLS in HF. Left panel (pros) **A**: a 75-year-old man with clinical and laboratory features suggesting amyloidosis. Abdominal fat pad biopsy negative. Thanks to the detection of typical echocardiographic features (i.e., "apical sparing"), the diagnosis was not ruled out and the patient underwent further tests confirming it. Right panel (cons) **B**: a 59-year-old female with HFrEF diagnosed more than 10 years earlier. CRT-D implanted in 2009. Already on the waiting list for cardiac transplantation. INTERMACS levels IV–V. LVEF 21%. Does GLS (Avg − 5.3%) really impact clinical management of patient at this late stage of the disease (e.g., modulation of pharmacological treatments, prevention of significant fluid retention, re-hospitalization, etc.)?

of differentiating cardiac amyloidosis from other causes of LVH, particularly sarcomeric hypertrophic cardiomyopathy (HCM) [35, 68]. Patients with cardiac amyloidosis usually exhibit a typical GLS pattern characterized by the relative "LV apical sparing" compared with the reduced longitudinal strain of the basal segments. This is not the case in HCM, characterized by regional variations (e.g., GLS reduced within the septum in the classic asymmetric forms) or by a base-to-apex decreasing gradient of GLS values, thus reflecting a better function of the basal LV segments compared to apex (especially in the apical forms) [35, 68]. The use of GLS should be promising also in other conditions characterized by protein misfolding and reproducing the pattern of cardiac amyloidosis [69]. Patients with Alzheimer's disease have been shown to have (often subclinical) cardiac involvement, with mild ECG and echocardiographic abnormalities, suggesting an infiltrative amyloid-like disorder [69]. LVEF can be normal in hypertrophic hearts, although a small LV cavity can only eject a small stroke volume. In HCM with normal LVEF, longitudinal ventricular shortening is frequently depressed, and a reduction of GLS to 15% is associated with myocardial fibrosis [70]. In this HCM setting, GLS carries a huge prognostic impact on outcome, constituting the strongest independent predictor of severe events (ventricular arrhythmia, HF, transplantation, all-cause death) [71]. A recent systematic review of more than 3000 patients with HCM confirmed these data which suggest an association of abnormal GLS with adverse composite cardiac outcomes and ventricular arrhythmias [72]. Although GLS seems to be a better echocardiographic index and prognosticator compared with LVEF in patients with HFpEF, the available data is not always sound. Thus, despite its recent inclusion by the European Society of Cardiology's HFA in the so-called HFA-PEFF score for the diagnosis of HFpEF, LVGLS is only a minor criterion. Furthermore, the cutoff value of < 16% seems somehow arbitrary even taking into account the reference studies considered in the document [42]. Another important question is the real usefulness of GLS in the clinical management of patients with preserved ejection fraction and HF symptoms. In this regard, we should underline the difference between the European and American guidelines for the diagnosis and management of HF [2, 44]. While the former consider HF diagnosis only in the presence of cardiac dysfunction plus symptoms

of congestion, the latter distinguish four stages (A to D) where stage B indicates an established structural heart disease but without signs or symptoms of HF [2, 44]. Most of the studies investigating the role of GLS in HFpEF were conducted in patients without overt symptoms. This again underlines the role of GLS as an early, prognostic marker of disease, although its impact in clinically established and overt pathological states is much less evidence based. In patients enrolled in the RELAX trial, there was no linear association of LVGLS with the Minnesota Living with Heart Failure Questionnaire scores (6-min walk distance, peak oxygen consumption, or expiratory minute ventilation/carbon dioxide excretion slope) [36]. Another important issue is the real additive value of GLS in comparison with other traditional echocardiographic parameters in HFpEF. In patients with LVH, EF fails to be a reliable parameter to assess LV systolic function. But do we really need GLS? During the 1990s, attention was given to the impaired midwall fractional shortening (MFS) that precedes EF alteration in hypertensive patients in the presence of LV concentric geometry and LVH [73, 74]. Furthermore, the prognostic value of GLS in arterial hypertension is still under debate, since currently only left ventricular mass index seems to consider incremental prognostic value in addition to established risk factors [75]. Another useful (although neglected) echocardiographic index in patients with LVH and possibly HFpEF is MAPSE [13]. In patients with aortic stenosis (AS), MAPSE is reduced even in the presence of normal LVEF [13]. It is lower in patients with symptomatic compared with asymptomatic severe AS and may be of use in predicting the onset of symptoms [13]. Moreover, a close inverse correlation was found between interstitial fibrosis and mitral ring displacement [76]. MAPSE seems to be non-inferior to GLS in detecting early longitudinal LV dysfunction in AS [37]. We discussed the usefulness of GLS in differentiating diverse phenotypes in patients with pathological LVH [35]. However, we should take regional variability into account in longitudinal strain across vendors [77, 78].

Left Atrium

LV diastolic dysfunction and left atrial (LA) structural and functional remodeling are both traditional hallmarks of HFpEF [2, 79]. Although volume is the echocardiographic parameter chosen for LA assessment guidelines and is used as a diagnostic marker for HFpEF [42], data have convincingly shown that functional parameters perform better than volume in terms of early diagnosis and prognostic impact [80, 81]. Strain should be a tool to investigate LA dynamics during exercise. A recent study conducted with HF patients (both HFrEF and HFpEF) showed that an impaired LA strain response is a trigger for right ventricular pulmonary circulation uncoupling and exercise ventilation inefficiency [82].

In the context of HF and its classification based on EF, the question is whether the LA characteristics differ between the three categories of HFrEF, HFmrEF, and HFpEF. According to the existing literature, patients with HFmrEF show larger sizes and a worse phasic function compared with those with HFpEF [83]. The study of LA function, traditionally considered one of the strengths of deformation imaging, deserves more reflection. In fact, the study of LA function is also feasible with volumetric methods [84, 85]. Furthermore, despite the recent publication of normal reference values for atrial strain [43], we should again acknowledge some potential limitations. First of all is the feasibility of strain measurements in all patients; atrial walls are usually very thin, and echo dropouts may interfere with correct tracking by the software, thus rendering the strain measurements not feasible or at least less accurate and possibly unreliable.

Gaps in Evidence and Future Perspectives

The following is a short list of selected issues that deserve to be addressed in future clinical research:

1. Universally accepted and standardized (i.e., without differences across vendors) reference values for global longitudinal strain for all the four cardiac chambers, possibly including thresholds clearly defining normality, mild, moderate, and severe impairment
2. Real-world reproducibility data
3. Usefulness of preventive treatment strategies based on strain imaging in patients with subtle cardiac dysfunction without overt heart failure symptoms (e.g., cardio-oncology, LVH, valvular heart diseases)
4. Role of strain imaging in predicting outcomes in patients with HFmrEF (i.e., improvement of systolic function towards HFpEF or worsening towards HFrEF)
5. Real benefits in terms of patient outcomes deriving from the standard use of longitudinal strain once HF etiology has been established in patients with overt symptoms and advanced stages of the disease

Table 3 summarizes the main GLS applications in HF at the present time with strengths and weaknesses.

Conclusions

The assessment of myocardial deformation by speckle tracking is probably the most important advance in echocardiography of the last 20 years. This all-in-one technique is able

to provide significant information on all the four cardiac chambers. GLS is a powerful tool, able to detect cardiac dysfunction in the early stages before HF symptoms become evident. It is also able to distinguish different pathological phenotypes with potential implications in terms of disease management. Finally, GLS has been shown to be a good prognosticator in terms of adverse events in HF.

However, despite the amount of scientific literature produced over the last two decades (sometimes with the suspicion of "citation inflation") [86], GLS is far from being routinely implemented in clinical practice by cardiologists during their echocardiographic examinations as per the standard protocol. Universally accepted cutoff values and variability across vendors are issues yet to be fully achieved. Most importantly, we still need clinical trials to determine whether the use of GLS results in better outcomes in HF.

To conclude, the authors consider that the answer to the first two research questions raised (i.e., does GLS have a role in the diagnosis of HF? and does GLS provide additional diagnostic and prognostic value irrespective of other traditional echocardiographic indices?) is YES (Fig. 3A); however, the answer to the other two questions (i.e., does the clinical application of GLS modify the management of patients with overt and advanced HF in clinical practice? and is GLS ready for routine clinical practice?) at present is NO (Fig. 3B). GLS has been considered a toddler for too long; now, it really is time to grow up; otherwise, it will be regarded as a great failure in the field of echocardiology. On the other hand, we should also ask ourselves if we are not perhaps expecting too much from a diagnostic imaging modality. Are we? Like a carpenter in his woodwork, we use the tools we need for this "pathology-dependent" HF syndrome, refining our clinical judgment. The riddle of the HF syndrome will probably never be decoded by any single imaging modality, but will forever require a multidimensional, holistic approach.

Author Contribution GDS, MEC, and MG†: conceptualization; GDS, MEC, CS, RE, and SLM: literature search and data analysis; GDS, MC, CS, RE, SLM, and MG: manuscript drafting; GP and PN: manuscript critical revision as senior authors. All the authors were actively involved in all the stages of the project.

Data Availability Not applicable for this type of manuscript.

Code Availability Not applicable.

Declarations

Ethics Approval and Consent to Participate Not applicable (not required for this type of article).

Consent for Publication Not applicable for this type of manuscript.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

References

1. Feigenbaum H. Journal of the American Society of Echocardiography: 25 years old. J Am Soc Echocardiogr. 2012;25(1):1–2.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al; Authors/Task Force members; document reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18(8):891–975.
3. Triposkiadis F, Butler J, Abboud FM, Armstrong PW, Adamopoulos S, Atherton JJ, et al. The continuous heart failure spectrum: moving beyond an ejection fraction classification. Eur Heart J. 2019;40(26):2155–63.
4. Packer M. Heart failure with a mid-range ejection fraction: a disorder that a psychiatrist would love. JACC Heart Fail. 2017;5(11):805–7.
5. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al; TOPCAT Investigators. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J 2016;37(5):455–62.
6. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381(17):1609–1620.
7. Solomon SD, Vaduganathan M, Claggett BL, Packer M, Zile M, Swedberg K, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation. 2020;141:352–61.
8. Douglas PS, Taylor A, Bild D, Bonow R, Greenland P, Lauer M, et al. Outcomes research in cardiovascular imaging: report of a workshop sponsored by the National Heart, Lung, and Blood Institute. J Am Soc Echocardiogr. 2009;22(7):766–73.
9. Douglas PS, Cerqueira MD, Berman DS, Chinnaiyan K, Cohen MS, Lundbye JB, et al; ACC Cardiovascular Imaging Council. The future of cardiac imaging: report of a think tank convened by the American College of Cardiology. JACC Cardiovasc Imaging 2016;9(10):1211–1223.
10. Marwick TH. Ejection fraction pros and cons: JACC state-of-the-art review. J Am Coll Cardiol. 2018;72(19):2360–79.
11. Buxton AE. Should everyone with an ejection fraction less than or equal to 30% receive an implantable cardioverter-defibrillator? Not everyone with an ejection fraction < or = 30% should receive an implantable cardioverter-defibrillator. Circulation 2005;111(19):2537–49; discussion 2537–49.
12. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, et al; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375(13):1221–30.
13. Hu K, Liu D, Herrmann S, Niemann M, Gaudron PD, Voelker W, et al. Clinical implication of mitral annular plane systolic excursion for patients with cardiovascular disease. Eur Heart J Cardiovasc Imaging. 2013;14(3):205–12.
14. Galiuto L, Ignone G, DeMaria AN. Contraction and relaxation velocities of the normal left ventricle using pulsed-wave tissue Doppler echocardiography. Am J Cardiol. 1998;81(5):609–14.

15. Chen C, Rodriguez L, Levine RA, Weyman AE, Thomas JD. Noninvasive measurement of the time constant of left ventricular relaxation using the continuous-wave Doppler velocity profile of mitral regurgitation. Circulation. 1992;86(1):272–8.
16. Torrent-Guasp F, Kocica MJ, Corno A, Komeda M, Cox J, Flotats A, et al. Systolic ventricular filling. Eur J Cardiothorac Surg. 2004;25(3):376–86.
17. Anderson RH, Ho SY, Sanchez-Quintana D, Redmann K, Lunkenheimer PP. Heuristic problems in defining the three-dimensional arrangement of the ventricular myocytes. Anat Rec A Discov Mol Cell Evol Biol 2006;288(6):579–86.
18. MacIver DH, Stephenson RS, Jensen B, Agger P, Sánchez-Quintana D, Jarvis JC, et al. The end of the unique myocardial band: part I. Anatomical considerations Eur J Cardiothorac Surg. 2018;53(1):112–9.
19. Brutsaert DL, Sys SU, Gillebert TC. Diastolic failure: pathophysiology and therapeutic implications. J Am Coll Cardiol. 1993;22(1):318–25.
20. Mora V, Roldan I, Sauri Assumpcio, Fernandez-Galera R, Monteagudo M, Romero E, et al. Correspondence of myocardial strain with Torrent-Guasp's theory. Contributions of new echocardiographic parameters. Rev Argent Cardiol 2016;84:541–549.
21. D'hooge J, Heimdal A, Jamal F, Kukulski T, Bijnens B, Rademakers F, et al. Regional strain and strain rate measurements by cardiac ultrasound: principles, implementation and limitations. Eur J Echocardiogr 2000;1(3):154–70.
22. Gorcsan J 3rd, Tanaka H. Echocardiographic assessment of myocardial strain. J Am Coll Cardiol. 2011;58(14):1401–13.
23. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2014;27(9):911–39.
24. Čelutkienė J, Lainscak M, Anderson L, Gayat E, Grapsa J, Harjola VP, et al. Imaging in patients with suspected acute heart failure: timeline approach position statement on behalf of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2020;22(2):181–95.
25. Park JJ, Park JB, Park JH, Cho GY. Global longitudinal strain to predict mortality in patients with acute heart failure. J Am Coll Cardiol. 2018;71(18):1947–57.
26. Sengeløv M, Jørgensen PG, Jensen JS, Bruun NE, Olsen FJ, Fritz-Hansen T, et al. Global longitudinal strain is a superior predictor of all-cause mortality in heart failure with reduced ejection fraction. JACC Cardiovasc Imaging. 2015;8(12):1351–9.
27. Mele D, Nardozza M, Malagù M, Leonetti E, Fragale C, Rondinella A, et al. Left ventricular lead position guided by parametric strain echocardiography improves response to cardiac resynchronization therapy. J Am Soc Echocardiogr. 2017;30(10):1001–11.
28. Park JH, Park JJ, Park JB, Cho GY. Prognostic value of biventricular strain in risk stratifying in patients with acute heart failure. J Am Heart Assoc 2018;7(19):e009331.
29. van Kessel M, Seaton D, Chan J, Yamada A, Kermeen F, Hamilton-Craig C, et al. Prognostic value of right ventricular free wall strain in pulmonary hypertension patients with pseudo-normalized tricuspid annular plane systolic excursion values. Int J Cardiovasc Imaging. 2016;32(6):905–12.
30. Lisi M, Cameli M, Righini FM, Malandrino A, Tacchini D, Focardi M, et al. RV Longitudinal deformation correlates with myocardial fibrosis in patients with end-stage heart failure. JACC Cardiovasc Imaging. 2015;8(5):514–22.
31. Mingo-Santos S, Moñivas-Palomero V, Garcia-Lunar I, Mitroi CD, Goirigolzarri-Artaza J, Rivero B, et al. Usefulness of two-dimensional strain parameters to diagnose acute rejection after heart transplantation. J Am Soc Echocardiogr. 2015;28(10):1149–56.
32. Cameli M, Sparla S, Focardi M, Righini FM, Solari M, Alvino F, et al. Evaluation of right ventricular function in the management of patients referred for left ventricular assist device therapy. Transplant Proc. 2015;47(7):2166–8.
33. Saba S, Marek J, Schwartzman D, Jain S, Adelstein E, White P, et al. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region Trial. Circ Heart Fail. 2013;6(3):427–34.
34. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elsik M, et al. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. J Am Coll Cardiol. 2012;59:1509–18.
35. Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart. 2012;98(19):1442–8.
36. DeVore AD, McNulty S, Alenezi F, Ersboll M, Vader JM, Oh JK, et al. Impaired left ventricular global longitudinal strain in patients with heart failure with preserved ejection fraction: insights from the RELAX Trial. Eur J Heart Fail. 2017;19(7):893–900.
37. Luszczak J, Olszowska M, Drapisz S, Plazak W, Kaznica-Wiatr M, Karch I, et al. Assessment of left ventricle function in aortic stenosis: mitral annular plane systolic excursion is not inferior to speckle tracking echocardiography derived global longitudinal peak strain. Cardiovasc Ultrasound. 2013;11:45.
38. Grapsa J. Left ventricular ejection fraction and global longitudinal strain: prognostic when not load dependent? J Am Coll Cardiol. 2018;72(9):1065–6.
39. Thomas JD, Badano LP. EACVI-ASE-industry initiative to standardize deformation imaging: a brief update from the co-chairs. Eur Heart J Cardiovasc Imaging. 2013;14(11):1039–40.
40. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. J Am Soc Echocardiogr. 2015;28(2):183–93.
41. Ünlü S, Mirea O, Duchenne J, Pagourelias ED, Bézy S, Thomas JD, et al. Comparison of feasibility, accuracy, and reproducibility of layer-specific global longitudinal strain measurements among five different vendors: a report from the EACVI-ASE Strain Standardization Task Force. J Am Soc Echocardiogr. 2018;31(3):374-380.e1.
42. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail. 2020;22(3):391–412.
43. Sugimoto T, Robinet S, Dulgheru R, Bernard A, Ilardi F, Contu L, et al; NORRE Study. Echocardiographic reference ranges for normal left atrial function parameters: results from the EACVI NORRE Study. Eur Heart J Cardiovasc Imaging 2018;19(6):630–638.
44. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-239.
45. Lancellotti P, Suter TM, López-Fernández T, Galderisi M, Lyon AR, Van der Meer P, et al R. Cardio-oncology services: rationale, organization, and implementation. Eur Heart J 2019;40(22):1756–1763.

46. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al; ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016;37(36):2768–2801.
47. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55:213–20.
48. Santoro C, Arpino G, Esposito R, Lembo M, Paciolla I, Cardalesi C, et al. 2D and 3D strain for detection of subclinical anthracycline cardiotoxicity in breast cancer patients: a balance with feasibility. Eur Heart J Cardiovasc Imaging. 2017;18(8):930–6.
49. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol 2014;63(25 Pt A):2751–68.
50. Santoro C, Esposito R, Lembo M, Sorrentino R, De Santo I, Luciano F, et al. Strain-oriented strategy for guiding cardioprotection initiation of breast cancer patients experiencing cardiac dysfunction. Eur Heart J Cardiovasc Imaging. 2019;20(12):1345–52.
51. Negishi T, Thavendiranathan P, Negishi K, Marwick TH; SUCCOUR investigators. Rationale and design of the strain surveillance of chemotherapy for improving cardiovascular outcomes: the SUCCOUR Trial. JACC Cardiovasc Imaging 2018;11(8):1098–1105.
52. Lancellotti P, Price S, Edvardsen T, Cosyns B, Neskovic AN, Dulgheru R, et al. The use of echocardiography in acute cardiovascular care: recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. Eur Heart J Cardiovasc Imaging. 2014;16:119–46.
53. Roshdy A, Francisco N, Rendon A, Gillon S, Walker D. CRITICAL CARE ECHO ROUNDS: haemodynamic instability. Echo Res Pract. 2014;1(1):D1-8.
54. Price S, Platz E, Cullen L, Tavazzi G, Christ M, Cowie MR, et al; Acute Heart Failure Study Group of the European Society of Cardiology Acute Cardiovascular Care Association. Expert consensus document: echocardiography and lung ultrasonography for the assessment and management of acute heart failure. Nat Rev Cardiol 2017;14(7):427–440.
55. Lamia B, Ochagavia A, Monnet X, Chemla D, Richard C, Teboul JL. Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity. Intensive Care Med. 2007;33(7):1125–32.
56. Trambaiolo P, Bertini P, Borrelli N, Poli M, Romano S, Ferraiuolo G, et al. Evaluation of ventriculo-arterial coupling in ST elevation myocardial infarction with left ventricular dysfunction treated with levosimendan. Int J Cardiol. 2019;288:1–4.
57. Haugaa KH, Grenne BL, Eek CH, Ersbøll M, Valeur N, Svendsen JH, et al. Strain echocardiography improves risk prediction of ventricular arrhythmias after myocardial infarction. JACC Cardiovasc Imaging. 2013;6(8):841–50.
58. Haugaa KH, Goebel B, Dahlslett T, Meyer K, Jung C, Lauten A, et al. Risk assessment of ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy by strain echocardiography. J Am Soc Echocardiogr. 2012;25(6):667–73.
59. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. JACC Cardiovasc Imaging. 2018;11:260–74.
60. Halliday B, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaite M, et al. Association between mid-wall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. Circulation. 2017;135:2106–15.
61. Sanna GD, Merlo M, Moccia E, Fabris E, Masia SL, Finocchiaro G, et al. Left bundle branch block-induced cardiomyopathy: a diagnostic proposal for a poorly explored pathological entity. Int J Cardiol. 2020;299:199–205.
62. Hwang IC, Cho GY, Yoon YE, Park JJ. Association between global longitudinal strain and cardiovascular events in patients with left bundle branch block assessed using two-dimensional speckle-tracking echocardiography. J Am Soc Echocardiogr. 2018;31(1):52-63.e6.
63. Terrosu P. An unsolved conundrum: right ventricular dysfunction. J Cardiovasc Med (Hagerstown). 2017;18(Suppl 1):e44–9.
64. Tamborini G, Muratori M, Brusoni D, Celeste F, Maffessanti F, Caiani EG, et al. Is right ventricular systolic function reduced after cardiac surgery? A two- and three-dimensional echocardiographic study. Eur J Echocardiogr. 2009;10(5):630–4.
65. Giusca S, Dambrauskaite V, Scheurwegs C, D'hooge J, Claus P, Herbots L, et al. Deformation imaging describes right ventricular function better than longitudinal displacement of the tricuspid ring. Heart 2010;96(4):281–8.
66. Mandoli GE, Cameli M, Novo G, Agricola E, Righini FM, Santoro C, et al; Working Group of Echocardiography of the Italian Society of Cardiology. Right ventricular function after cardiac surgery: the diagnostic and prognostic role of echocardiography. Heart Fail Rev 2019;24(5):625–635.
67. Pastore MC, De Carli G, Mandoli GE, D'Ascenzi F, Focardi M, Contorni F, et al. The prognostic role of speckle tracking echocardiography in clinical practice: evidence and reference values from the literature. Heart Fail Rev. 2020. https://doi.org/10.1007/s10741-020-09945-9.
68. Rapezzi C, Fontana M. Relative left ventricular apical sparing of longitudinal strain in cardiac amyloidosis: is it just amyloid infiltration? JACC Cardiovasc Imaging. 2019;12(7 Pt 1):1174–6.
69. Sanna GD, Nusdeo G, Piras MR, Forteleoni A, Murru MR, Saba PS, et al. Cardiac abnormalities in Alzheimer disease: clinical relevance beyond pathophysiological rationale and instrumental findings? JACC Heart Fail. 2019;7(2):121–8.
70. Serri K, Reant P, Lafitte M, Berhouet M, Le Bouffos V, Roudaut R, et al. Global and regional myocardial function quantification by two-dimensional strain: application in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2006;47(6):1175–81.
71. Saito M, Okayama H, Yoshii T, Higashi H, Morioka H, Hiasa G, et al. Clinical significance of global two-dimensional strain as a surrogate parameter of myocardial fibrosis and cardiac events in patients with hypertrophic cardiomyopathy. Eur Heart J Cardiovasc Imaging. 2012;13(7):617–23.
72. Tower-Rader A, Mohananey D, To A, Lever HM, Popovic ZB, Desai MY. Prognostic value of global longitudinal strain in hypertrophic cardiomyopathy: a systematic review of existing literature. JACC Cardiovasc Imaging. 2019;12(10):1930–42.
73. de Simone G, Devereux RB, Roman MJ, Ganau A, Saba PS, Alderman MH, et al. Assessment of left ventricular function by the midwall fractional shortening/end-systolic stress relation in human hypertension. J Am Coll Cardiol. 1994;23(6):1444–51.
74. Lembo M, Santoro C, Sorrentino R, Canonico ME, Fazio V, Trimarco B, Tadic M, Galderisi M, Esposito R. Interrelation between midwall mechanics and longitudinal strain in newly diagnosed and never-treated hypertensive patients without clinically defined hypertrophy. J Hypertens. 2020;38(2):295–302.
75. Modin D, Biering-Sørensen SR, Mogelvang R, Landler N, Jensen JS, Biering-Sørensen T. Prognostic value of echocardiography in hypertensive versus nonhypertensive participants from the general population. Hypertension. 2018;71(4):742–51.
76. Herrmann S, Störk S, Niemann M, Lange V, Strotmann JM, Frantz S, et al. Low-gradient aortic valve stenosis myocardial fibrosis

and its influence on function and outcome. J Am Coll Cardiol. 2011;58(4):402–12.
77. Mirea O, Pagourelias ED, Duchenne J, Bogaert J, Thomas JD, Badano LP, et al. Variability and reproducibility of segmental longitudinal strain measurement: a report from the EACVI-ASE strain standardization task force. JACC Cardiovasc Imaging. 2018;11:15–24.
78. Sperry BW, Sato K, Phelan D, Grimm R, Desai MY, Hanna M, et al. Regional variability in longitudinal strain across vendors in patients with cardiomyopathy due to increased left ventricular wall thickness. Circ Cardiovasc Imaging 2019;12(8):e008973.
79. Freed BH, Daruwalla V, Cheng JY, Aguilar FG, Beussink L, Choi A, et al. Prognostic utility and clinical significance of cardiac mechanics in heart failure with preserved ejection fraction: importance of left atrial strain. Circ Cardiovasc Imaging 2016;9(3):https://doi.org/10.1161/CIRCIMAGING.115.003754 e003754.
80. Gupta DK, Shah AM, Giugliano RP, Ruff CT, Antman EM, Grip LT, et al; Effective aNticoaGulation with factor xA next GEneration in AF-Thrombolysis In Myocardial Infarction 48 Echocardiographic Study Investigators. Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48. Eur Heart J 2014;35(22):1457–65.
81. Mondillo S, Cameli M, Caputo ML, Lisi M, Palmerini E, Padeletti M, et al. Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. J Am Soc Echocardiogr. 2011;24(8):898–908.
82. Sugimoto T, Bandera F, Generati G, Alfonzetti E, Bussadori C, Guazzi M. Left atrial function dynamics during exercise in heart failure: pathophysiological implications on the right heart and exercise ventilation inefficiency. JACC Cardiovasc Imaging 2017;10(10 Pt B):1253–1264.
83. Al Saikhan L, Hughes AD, Chung WS, Alsharqi M, Nihoyannopoulos P. Left atrial function in heart failure with mid-range ejection fraction differs from that of heart failure with preserved ejection fraction: a 2D speckle-tracking echocardiographic study. Eur Heart J Cardiovasc Imaging. 2019;20(3):279–90.
84. Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol. 2014;63(6):493–505.
85. Badano LP, Miglioranza MH, Mihăilă S, Peluso D, Xhaxho J, Marra MP, et al. Left atrial volumes and function by three-dimensional echocardiography: reference values, accuracy, reproducibility, and comparison with two-dimensional echocardiographic measurements. Circ Cardiovasc Imaging 2016;9(7):e004229.
86. Sorrell VL. Citation inflation: when the adoption of a new technique becomes an avenue for publication. Echocardiography. 2016;33(9):1282–3.