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Imaging (Q Truong, Section Editor)

Clinical Applications of Echo Strain Imaging: a Current Appraisal

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Abstract

Purpose of review This article reviews recent advances in echocardiographic strain imaging, particularly in its ability to prognosticate in cardiovascular outcomes and impact clinical decision making.
Recent findings Strain has been proposed as a sensitive tool in detecting early ventricular dysfunction. Left ventricular global longitudinal strain (LV-GLS) detects subtle changes in myocardial function, often not quantifiable by ejection fraction alone. Thus, LV-GLS provides the opportunity for early decision-making, and the implementation of more effective treatments, improving outcomes in a variety of diseases such as valvular heart diseases, cardio-oncology, ischemic heart disease, cardiomyopathies, heart transplantation, and pericardial diseases and cardiomyopathies.
Summary Strain is a promising tool for the early detection of myocardial dysfunction in patients with preserved left ventricular ejection fraction and can prognosticate long-term outcomes.

Introduction

Traditional echocardiographic assessment of myocardial motion relies on quantitative measurement of wall thickness and qualitative description of wall motion at various points throughout the cardiac cycle. However, these descriptions of wall motion thickening are limited because they fail to completely capture the complex

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three-dimensional motion of a myocardial region over the course of a cardiac cycle. Recent advances in echocardiography resolution and post-processing software now allow the tracking of specific myocardial regions throughout the cardiac cycle in a process known as strain imaging. In a growing body of evidence, strain imaging can detect subclinical dysfunction in a wide variety of cardiac pathologies. This review summarizes the most recent advances of echocardiographic strain imaging in clinical practice.

Myocardial strain imaging

Myocardial strain imaging can be assessed with tissue Doppler or with a process known as speckle tracking [1]. Doppler-derived strain is angle dependent and highly susceptible to artifact; thus, strain measured with speckled-tracking is preferred in clinical practice [2]. Speckle tracking is a process in which tissue markers are placed post-processing and tracked from frame-to-frame throughout the cardiac cycle. The degree of motion between speckles is then summed and integrated to produce a dimensionless index of change in a particular direction. While all of the cardiac chambers, and individual regions within that chamber, can be described in terms of longitudinal shortening, circumferential rotation, and myocardial radial thickening, left ventricular global longitudinal strain (LV-GLS) has emerged as a reproducible strain measurement that can provide a sensitive indicator of subclinical cardiovascular disease (Fig. 1a–c).

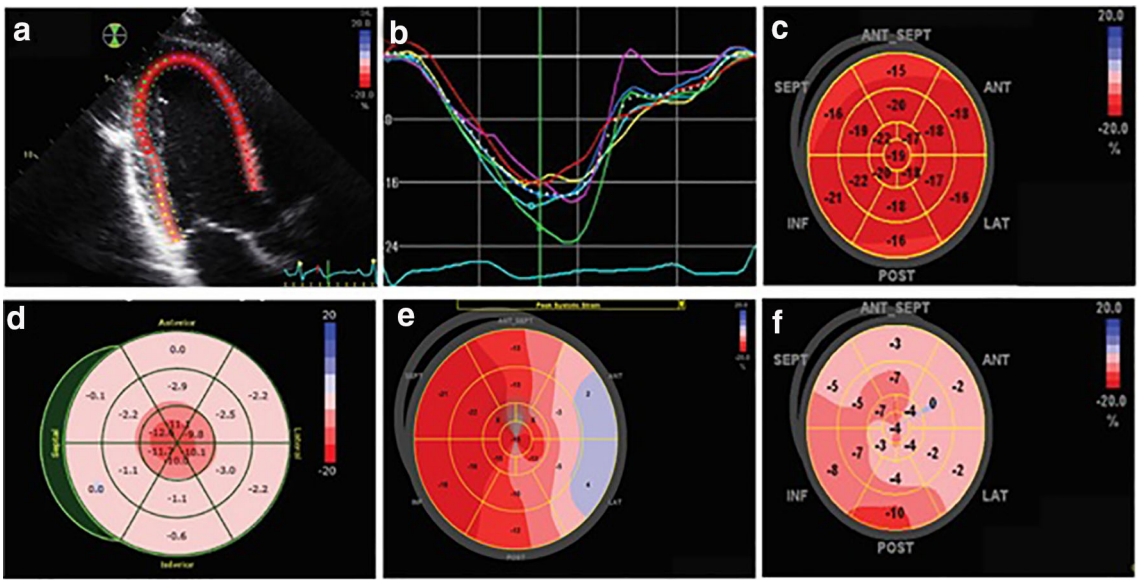

Fig. 1. Segmental longitudinal strain of patients with **a**–**c** normal and **d**–**f** abnormal strain pattern. **a** Image of the left ventricle through the apical long axis. The left ventricle is traced and speckles are placed throughout the myocardium. The movements of these speckles are tracked over the course of the cardiac cycle. **B** Longitudinal movement of speckles over the course of a cardiac cycle, with colors correlating to speckles on image in panel **a**. Each colored line shows the amount of strain of a particular left ventricular segment. **c** The segments are then integrated into a 17-segment model of the left ventricle, whose average is global strain. **d** Characteristic apical sparing pattern seen in the 17-segment model of patients with cardiac amyloid and **e** annulus reversus can be seen in pericardial constriction. **f** Example of diffusely abnormal strain, in this case, observed in a patient with hypertrophic cardiomyopathy.

LV-GLS is the averaged longitudinal (long-axis) motion of the individual segments of the left ventricle.

Normal values, intervendor variability, and reproducibility

A variety of post-processing software packages are offered in the market with strain measurements varying slightly among vendors [3]. Recognizing the critical need for standardization of strain imaging, the American Society Echocardiography (ASE) and the European Association of Cardiovascular Imaging developed, with the collaboration of technical representatives from all interested vendors, a consensus of standard definitions and nomenclature for the clinical parameters evaluated with speckle-tracking technology [4].

In a study of global longitudinal strain (GLS) measurements and its variability among seven different speckled-tracking software, the absolute normal value for LV-GLS ranges between − 18 and − 21.5% with an absolute difference between vendors up to 3.7% ($p < 0.001$) [5]. More negative values generally represent better cardiac function. Furthermore, interobserver variability ranged between 5.4 and 8.6%, and intraobserver variability from 4.9 to 7.3%, being comparable with other conventional echocardiographic parameters such as ejection fraction [5]. A meta-analysis of 24 studies with 2597 healthy patients reported a normal range of GLS between − 15.9 and − 22.1%, with heterogeneity depending on preload and afterload [2]. Current ASE guidelines suggest that a value better than − 20% with a standard deviation of ± 2% is highly likely to be normal, though variability still exists between labs and software vendors [6].

In the below sections, we will discuss the current state-of-the-art data and clinical applicability in various cardiac etiologies.

Cardio-oncology

Strain assessment following chemotherapy

Through a variety of mechanisms, many chemotherapeutic medications have cardiotoxic effects with a devastating prognosis [3]. With such agents, the goal of treatment is to protect the heart without reducing the efficacy of anticancer therapy. A major challenge in reducing cancer therapy–related cardiac dysfunction (CTRCD) is difficulty in detecting very early myocardial damage needing influence of oncologic treatment strategies [4]. Cancer therapy–related cardiac dysfunction (CTRCD) has been defined as a decrease in left ventricular ejection fraction (LVEF) of > 10% to a value < 53% confirmed by repeated cardiac imaging 2 to 3 weeks after baseline diagnostic. However, LVEF often fails to detect early subtle changes. Rather, reduced LVEF serves as a marker for advanced myocardial damage and is accompanied by a poor prognosis [5]. Several publications have showed that GLS is useful in detecting early dysfunction of left ventricle by chemotherapy [4]. A subclinical LV dysfunction is defined as a relative decrease in global longitudinal strain (GLS) by > 15% from the baseline confirmed by repeated cardiac imaging 2 to 3 weeks later, whereas a change of < 8% appears to be of less clinical significance [5].

Identifying patients at risk for developing cardiotoxicity is advantageous. It is known that the major clinical risk factors for chemotherapy-induced cardiotoxicity are preexisting hypertension, advanced age, diabetes mellitus, and smoking. LV-GLS provides significant incremental and independent risk stratification for CTRCD beyond traditional risk factors [6]. In patients with a baseline LVEF between 50 and 59%, abnormal GLS prior to initiation of chemotherapy identifies individuals at increased risk for cardiotoxicity [7]. Prior to the initiation of anthracyclines, a LV-GLS less than 17.5% is associated with a sixfold increase in cardiac events (heart failure and death) with subsequent therapy [8••].

Global longitudinal strain can also monitor cardiotoxicity during chemotherapy treatment. Changes in LV-GLS over the course of treatment allow prognostication of cardiac outcomes. In a study of women with breast cancer treated with epirubicin, LV-GLS was able to detect subtle early changes in LV systolic dysfunction before a decrease in LVEF parameters after the third cycle of treatment. GLS was the best independent and accurate predictor of cardiotoxicity [9]. In another study of 81 consecutive women prospectively treated with trastuzumab the strongest predictor of cardiotoxicity was a relative decrease in GLS > 11% at 6 months [6]. A recent systematic review that included over 1500 patients treated with anthracyclines found that reduction in LV-GLS between 10 and 15% during chemotherapy has a 65–86% sensitivity in detecting subsequent development of heart failure or reduced ejection fraction [4]. Likewise, an 11% relative reduction in LV-GLS during trastuzumab therapy was associated with a sensitivity of 65% and a specificity of 94% of detecting subsequent development of reduced ejection fraction [6]. While there is no consensus for management of decreasing LV-GLS during chemotherapy, preliminary data show that beta-blockers may prevent DCRTC in patients with abnormal LV-GLS at the initiation of cardiotoxic chemotherapy [6].

Regarding the use of strain after a completed chemotherapy treatment, there is no conclusive data in predicting events in the long term [10–12]. Although, chemotherapy can be associated with cardiotoxicity after several years, further long-term studies are needed to see if strain can help to identify these at-risk patients. In the interim, decreases in LV-GLS may help to promptly identify selective patients who would benefit from early heart failure therapies.

Strain assessment following radiotherapy

Patients who undergo high-dose chest radiation, frequently in the treatment of malignancies, are at risk of subsequently developing fibrotic changes in the radiation field years after treatment. Radiation heart disease can broadly manifest as coronary disease and valve disease, which is often best managed with cardiac surgery. However, patients with radiation heart disease often have surgical outcomes much worse than would be generally predicted based on traditional surgical risk factors alone [13]. Strain imaging is emerging as a modality that can help stratify cardiac surgery risk in patients with radiation heart disease. In a study of 163 patients with radiation heart disease who subsequently underwent cardiac surgery, low-risk patients with LV-GLS worse than – 14.5 had a 6-year mortality rate of 48% compared with 32% in patients

with normal LV-GLS [14]. Thus, strain imaging can help to re-classify risk in patients with radiation heart disease undergoing cardiac surgery.

Cardiac amyloidosis

Amyloidosis is a condition where misfolded proteins form an amorphous proteinaceous material in the extracellular space. Amyloid infiltration of the heart typically leads to ventricular hypertrophy, restrictive cardiomyopathy, and progressive heart failure. For poorly understood reasons, amyloid fibrils relatively spare the cardiac apex (Figure 1d) [15].Thus, the cardiac apex has relatively preserved longitudinal motion, compared with mid and basal segments, quantifiable by strain echocardiography. This impaired function is observed even when left ventricular ejection fraction is preserved [16]. This pattern of relatively preserved apical longitudinal strain is both sensitive and specific for cardiac amyloidosis. An apical relative regional strain ratio (RRSR) (RRSR = average apical longitudinal strain/(average basal longitudinal strain + average mid longitudinal strain)) of ≥ 1 has a sensitivity of 93% and a specificity of 82% for cardiac amyloidosis compared with control patients with undifferentiated left ventricular hypertrophy [17••]. Thus, given the relative availability of echocardiography, strain imaging is often the first clue in distinguishing cardiac amyloidosis from other cardiomyopathies in an undifferentiated patient. Indeed, given that cardiac amyloidosis with reduced ejection fraction has a survival on the magnitude of months, early diagnosis is quite important, particularly in an era of rapidly advance treatments for both light chain and transthyretin cardiac amyloid [18, 19].Longitudinal strain not only helps to diagnose cardiac amyloidosis, but also can provide incremental prognostic information as well. Log-transformed RRSR is independently associated with increased risk of mortality or cardiac transplantation in a combined cohort of light chain and transthyretin cardiac amyloid at 5 years with a HR (95% CI) of 2.45 (1.36–4.40) [15]. Specifically, apical sparing with a longitudinal RRSR of ≥ 1.19 is associated with increased mortality and heart transplantation 5 years on Kaplan-Meier's analysis ($p = 0.026$) [20]. In cardiac amyloidosis, abnormalities in longitudinal left ventricular strain often precedes left ventricular dysfunction and may be a better measure of contractile myocardial function than ejection fraction alone. Furthermore, even when corrected for heart failure covariates including NYHA status, serological biomarkers (TnT, logNT-proBNP), and ejection fraction, a LV-GLS better than − 11.8% was independently and incrementally associated with lower mortality in amyloidosis patients with a HR (95% CI) of 0.82 (0.76–0.87) [21].

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an often genetic disorder characterized by mutations in sarcomere-related genes that result in myofibril disarray and myocardial hypertrophy. Over time, this hypertrophy can lead to obstruction, heart failure, and arrhythmias. LV-GLS has been proposed as a risk modifier in the assessment of sudden cardiac death risk in HCM patients. In addition, LV-GLS can help to identify obstructive HCM who will most benefit from myectomy (Fig. 1f).

A recent systematic review of more than 3000 HCM patients with preserved ejection fraction found that abnormal LV-GLS is uniformly associated with increased ventricular arrhythmias, appropriate implantable cardiac defibrillator discharge, and death [22•]. Furthermore, LV-GLS may be more sensitive than cardiac MRI in identifying patients with myocardial fibrosis when compared with histopathology obtained during mycetomy [23]. Given that cardiac MRI with significant late gadolinium enhancement, representing myocardial scar burden, is sometimes used to identify patients at risk for sudden cardiac death (and thus benefit from implantable cardiac defibrillators), strain may have a future role in sudden cardiac death risk stratification, though further investigation is needed. When added to traditional ACC/AHA risk scores for sudden cardiac death in HCM patients, every percent worsening in LV-GLS was associated with an increased combined end point of cardiac death and appropriate internal defibrillator discharge with a HR (95% CI) of 1.11 (1.05–1.22) [24]. Currently, there is not an accepted threshold of abnormal LV-GLS in HCM patients, though published studies range between – 16 and – 10% [22•].

Left ventricular global longitudinal strain can also help to identify patients who will benefit from myectomy. As generalization, myectomy is primarily performed in HCM patients with left ventricular obstruction that results in symptoms such as angina, dyspnea, or syncope—refractory to medication therapy. In a study of over 1000 patients followed for approximately 10 years, obstructive HCM patients who did not undergo myectomy with a LV-GLS worse than – 14% had a 5-year event rate of a composite of cardiovascular death or ICD discharge of 13% compared with 6% in patients with LV-GLS better than – 14% with $p < 0.01$ on Kaplan-Meier's analysis [24]. These results would suggest that obstructive HCM patients with abnormal LV-GLS may benefit from early myectomy. While abnormal LV-GLS is uniformly associated with a worse prognosis in HCM patients and may help to identify patients who would benefit from HCM interventions such as ICD and myectomy, ultimately decision-making remains clinical owing to the lack of uniform analysis between studies analyzed.

Valvular heart disease

Aortic stenosis

In symptomatic patients with severe aortic stenosis (AS), the decision for aortic valve replacement is well informed by guidelines [25]. However, in patients with severe asymptomatic AS with preserved ejection fraction, the timing for valve replacement requires careful evaluation and close monitoring. Several studies have shown that LV-GLS can identify subclinical LV dysfunction to identify asymptomatic patients who would benefit from aortic valve replacement [26, 27]. In asymptomatic patients with preserved ejection fraction and an aortic valve area of < 1.3 cm^2, there is an incremental and progressive increase in the risk of all-cause mortality as LV-GLS becomes more abnormal, with markedly increased mortality on Kaplan-Meier's analysis when LV-GLS is worse than – 12.1% [28]. Also, strain offers prognostic value in the assessment of asymptomatic AS with preserved LVEF, beyond that of stress testing found that a LV-GLS worse than – 16.1% was associated with increased long-term mortality, even in patients with an exercise capacity above the 85th percentile of age-adjusted exercise capacity [29]. In this study, patients with LV-GLS better than – 17% who subsequently underwent aortic valve replacement had the best long-term survival [29]. In a

meta-analysis of 10 studies with 1067 asymptomatic patients with severe AS and LVEF > 50%, LV-GLS cutoff value of – 14.7% was well associated with higher risk of death (sensitivity, 60%; specificity, 70%). Also, a 2-year survival was significantly lower in patients with impaired LV-GLS than in those with preserved LV-GLS (81 ± 4% versus 94 ± 1%; $p < 0.0001$) [30]. LV-GLS demonstrated its strong impact on mortality and may suggest a better risk stratification value than LVEF in this cohort. With regard to symptomatic patients with severe AS and preserved LVEF treated with surgical aortic valve replacement, a baseline LV-GLS worse than – 14.5% showed significant association with more long term-deaths in proportion of those patients with a baseline LV-GLS better than – 14.5%. Moreover, the addition of LV-GLS values to the Society of Thoracic Surgeons score provided incremental prognostic utility in the reclassification of longer term mortality risk [31].The impairment of LV-GLS post-operatively, despite a preserved post-operative LVEF, was associated with worse long-term prognosis [32].

In sum, these data suggest that valve intervention before subclinical LV dysfunction, as identified on echo strain imaging, may help to better inform the optimal timing of valve replacement and may offer improvements in long-term outcomes.

Chronic aortic regurgitation

Similar to aortic stenosis, management of symptomatic severe aortic regurgitation (AR), or asymptomatic severe AR with LV dysfunction, is well informed by current guidelines, with recommendations for aortic valve replacement [25]. The timing for aortic valve replacement in patients with severe asymptomatic chronic AR remains challenging. When chronic AR progresses to reduced ejection fraction or symptoms, prognosis is poor, with an annual mortality rate of approximately 25% without intervention [33]. Echocardiographic strain has emerged as a tool that can help to identify subclinical LV dysfunction to inform timing for valve replacement. In a cohort of asymptomatic patients with severe AR, preserved EF, and normal LV systolic dimensions, LV-GLS values worse than – 19.5% have significantly longer term mortality compared with those with LV-GLS ≥ – 19.5% in 5 years of follow-up. Specifically, for every unit of worsening of LV-GLS, there was higher mortality with a HR (95% CI) of 1.11 (1.04–1.19) [34]. Furthermore, a subgroup analysis with Kaplan-Meier's survival curves showed that patients with an abnormal LV-GLS who did not undergo aortic valve replacement had markedly decreased survival, while patients with a normal LV-GLS who did not undergo aortic valve replacement had a survival curve similar to those who underwent surgery [34]. These findings suggest that LV-GLS can help inform the timing of surgery to improve long-term survival. Furthermore, a recent study revealed that patients with aortic valve replacement an abnormal LV-GLS value in the follow-up was significantly associated with increased mortality. LV-GLS values worse than – 19% at 3 to 12 months post-surgery had a significantly higher longer term mortality than those with LV-GLS values better than – 19%. A worsening of 5 absolute percentage points of LV-GLS from the baseline was demonstrably associated with significantly increased longer term mortality [35].

Chronic mitral regurgitation

Similar to aortic valve diseases, strain can help to identify asymptomatic patients with severe primary mitral regurgitation (MR) who would benefit from early

intervention. In asymptomatic patients with severe myxomatous mitral regurgitation, any strain worse than − 21% was progressively associated with increased mortality at 8.3 years of follow-up with a HR (95% CI) of 1.60 (1.47–1.73) for every incremental unit worsening of strain [36]. Even in individuals with normal age-matched exercise capacity, individuals with strain worse than − 21% had decreased survival on Kaplan-Meier's analysis, suggesting they may benefit from early intervention [36]. Another study also demonstrated that resting LV-GLS was independently associated with functional capacity in stress testing. In asymptomatic patients with severe MR, normal left ventricular dimension, and preserved LVEF, a worse LV-GLS was independently associated with not achieving 100% age-gender predicted METs (Wald statistic 39.6, $p < 0.001$). Resting LV-GLS had independent and incremental association with exercise above other known factors like right ventricular systolic pressure and body mass index [37].Strain imaging can help to stratify prognosis after mitral valve surgery. In asymptomatic patients with severe primary MR with preserved LVEF undergoing mitral valve surgery, any strain worse than − 21% was associated with progressive and incremental post-operative mortality with a HR (95% CI) of 1.17 (1.08–1.27) for every unit worsening of strain over 7.7 years of follow-up [38]. Abnormal LV-GLS is a marker of early myocardial dysfunction and may be used as an additive tool in identifying impaired LV myocardium early and before the onset of LV systolic dysfunction in patients with mitral regurgitation.

Acute ischemic heart diseases

Strain imaging is often abnormal in ischemic heart disease, with regional abnormalities following coronary distributions. Strain imaging can provide incremental value by providing a quantitative measure of subtle LV dysfunction within the framework of preserved LVEF. In patients admitted for myocardial infarction and LVEF > 40%, a LV-GLS worse than − 14% was associated with increased cardiovascular death with a HR (95% CI) of 12.7 (3.0–54.6) [39]. Thus, strain may help to identify high-risk patients among those with preserved ejection fraction who may benefit from more aggressive treatment to prevent maladaptive cardiac remodeling after infarct. In patients with non-elevation myocardial infarction and occluded coronary arteries, strain imaging was the best parameter for predicting acute coronary occlusion and facilitating a faster interventional strategy [30].

Chronic ischemic heart disease

The quantification of myocardial infarcts provides important diagnostic and prognostic information because mortality closely relates to infarct size and location. LV-GLS correlated significantly with global infarct mass and distinguished among small, medium-sized, and large myocardial infarcts being superior to LVEF in the identification of small and medium-sized infarcts [32].

Heart transplantation

Patients with orthotropic heart transplant (OHT) require meticulous surveillance to identify acute graft rejection. Reductions in LV-GLS after

OHT is associated with early graft dysfunction, coronary allograft vasculopathy, and early mortality. Immediately after OHT, LV and RV longitudinal strain values decrease [40]. Thereafter, the strain improves gradually during the first year after transplant. Subsequently, a reduction in LV-GLS can be suggestive of progressing underlying graft dysfunction, warranting further investigation. If LV-GLS fails to improve 3 months after transplantation, this is associated with a higher incidence of cardiac events and death [41]. In transplant patients with a new LV-GLS worse than − 17%, there was a sensitivity of 77% and specificity of 79% in later detecting rejection on biopsy [42]. Strain assessment of the right ventricular free wall of a transplanted heart, with values worse than − 16.4%, are associated with worse medium to long-term prognosis as well [43].

Pericardial diseases

Strain imaging can help in the differentiation of constrictive pericarditis and restrictive cardiomyopathy. Speckle tracking with strain follows muscle layers and can help to distinguish myocardial versus pericardial pathology [44]. In constrictive pericarditis, the myocardium itself is largely normal, but under the influence of adjacent pericardial adhesions. This manifests as normal strain in septal regions of the left ventricle, but reduced strain of the lateral wall as it is tethered by adhesions from the adjacent pericardium (Fig. 1e). This contrasts most restrictive cardiomyopathies which generally have reduced strain globally, or with apical sparing in the case of amyloid [44].

Limitations of strain assessment

As previously described, strain values vary between vendors [45]. Current guidelines recommend using the same vendor software and machine over the course of follow-up [46]. Additionally, strain is influenced by technical factors. The temporal stability of the echo probe relative to the heart is required for clarity and accuracy of speckle tracking [47]. Standardization of imagine acquisition is essential for reducing variability of tracking data, i.e., frame rates, reduce foreshortening, correct selection of end-diastole time, end-systole, measurement points, etc. Clinical factors can affect strain values as well. Strain values are age related (lower in elderly people) [48] and lower in male patients [49]. Strain varies depending on preload, afterload, and heart rate [2, 50].

Future directions

Currently, abnormal longitudinal strain measurements can predict and prognosticate many cardiac pathologies. However, there remains a significant heterogeneity as to normal strain values and strain values associated with pathology. These differences owe to measurement and software differences. Future standardization and normal range quantification are needed for clinical

implementation and widespread validation of this imaging tool. Additionally, there is paucity of large-scale multicenter prognostic data, with independent measurement of strain in a core-laboratory setting.

Conclusion

Across numerous cardiac pathologies, abnormal strain is universally associated with poor outcomes and need for aggressive risk factor modification or treatment. Strain is particularly helpful in cases where LVEF is normal, as strain can identify individuals at high risk of poor outcomes, in a population otherwise considered to have low risk.

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Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

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

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