

## THE PRESENT AND FUTURE

### REVIEW TOPIC OF THE WEEK

# A Test in Context: Myocardial Strain Measured by Speckle-Tracking Echocardiography



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#### ABSTRACT

Strain-based imaging techniques (and specifically speckle-tracking echocardiography) have been shown to have clinical utility in a variety of settings. This technique is being embraced and increasingly adopted in many echocardiography laboratories worldwide. This review appraised speckle-tracking echocardiography in a clinical context by providing a critical evaluation of the prognostic and diagnostic insights that this technology can provide. In particular, we discuss the use of speckle-tracking strain in selected areas, such as undifferentiated left ventricular hypertrophy, cardio-oncology, aortic stenosis, and ischemic heart disease. The potential utility of regional and chamber strains (namely segmental left ventricular strain, left atrial strain, and right ventricular strain) are also discussed. Future directions for this technology are explored. Before its clinical application, it is particularly important that physicians be cognizant of the technical challenges and inherent limitations of strain data, which are also addressed here. (J Am Coll Cardiol 2017;69:1043-56)  
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Strain is a unitless measurement of dimensional or deformational change. Imaging-based techniques have been derived and refined in order to quantify myocardial strain in clinical practice (1-3). The most widely used technique is speckle-tracking echocardiography (STE), which has been shown to have clinical utility in a variety of settings (Central Illustration) (4,5). This technique is being embraced and increasingly adopted in many echocardiography laboratories worldwide.

This review appraised this test in a clinical context by providing a critical evaluation of the prognostic and diagnostic insights that this technology can provide. Before its clinical application, it is particularly important that physicians be cognizant of the technical challenges and inherent limitations of strain data, which are also discussed here.

#### WHAT IS SPECKLE TRACKING?

Using image-processing algorithms for routine 2-dimensional digital echocardiographic images, small stable myocardial footprints, or speckles, generated by ultrasound-myocardial tissue interactions are identified within a defined region of interest. Tracked frame-to-frame over the cardiac cycle, distances between speckles or their spatiotemporal displacement (regional strain velocity vectors) provide non-Doppler information about global and segmental myocardial deformation.

#### WHAT ADVANTAGES DOES SPECKLE TRACKING PROVIDE?

The original methodology used to measure strain was tissue Doppler-based (6). A derivative of this



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## ABBREVIATIONS AND ACRONYMS

- CA** = cardiac amyloidosis
- EF** = ejection fraction
- GLS** = global longitudinal strain
- HCM** = hypertrophic cardiomyopathy
- LA** = left atrium
- LV** = left ventricle/ventricular
- RRSR** = relative regional strain ratio
- RV** = right ventricle
- STE** = speckle-tracking echocardiography
- TDI** = tissue Doppler imaging

methodology is velocity-vector tissue Doppler imaging (TDI), available software for which allows measurement on clips acquired even from different vendor machines. Limitations of this tissue Doppler-based strain assessment include angle dependency and significant noise, over which STE provides advantages. First, by estimating 2-dimensional intratissue velocities (rather than 1-dimensional transducer-tissue velocities), STE allows for discrimination between normal, active myocardial segmental deformation versus passive displacement of a dysfunctional myocardial segment due to adjacent segment tethering and global cardiac motion. This is particularly useful in non-thinned segments. Second, in contrast to

TDI-based strain, which measures deformations between time points (so-called “natural” strains), STE lends itself more readily to Lagrangian strain, which compares deformation to original length. “Normal” strains are those that occur perpendicularly or orthogonally to the surface (as distinct from tangential “shear” strains). Normal strains include “longitudinal” strains that assess apex-base deformation measured from apical views and “radial” or “circumferential” strains measured from short-axis parasternal views.

## WHAT IS THE OPTIMAL SPECKLE TRACKING TECHNIQUE?

Although there is no established gold standard method of assessing strain *in vivo*, STE has been validated in comparison with tagging harmonic phase cardiac magnetic resonance and sonomicrometry (7,8). Many of the published reports on strain have focused on global longitudinal strain (GLS) for several reasons: images obtained in the axial plane have superior resolution; the global value is obtained from mean values over the entire length of the myocardial wall, which adds robustness to this parameter; and there is a greater amount of myocardial tissue in the apical long-axis view than in the short-axis view of the nonhypertrophied heart. Although assessment of GLS is now routine practice in many echocardiographic laboratories, our experience with radial and circumferential strain analyses is that they are not sufficiently reproducible for routine clinical work.

## NOMENCLATURE

By convention, positive values are consigned to lengthening, thickening, or clockwise rotation, whereas negative values are consigned to shortening,

thinning, or counterclockwise rotation. Greater degrees of deformation therefore translate to numerically lower strain values, which proved to be a source of confusion in early published reports on strain. To avoid any such misunderstandings, current guidelines recommend presentation of the numerical data or referring to change in deformation (increased strain = more negative) (9,10).

## INTERPRETING STRAIN VALUES

**NORMAL RANGES.** In a meta-analysis of 24 studies dating from 2009 to 2011, including 2,597 healthy volunteers (mean: ~47 years of age; 51% male), GLS varied from -15.9% to -22.1% (mean: -19.7%; 95% confidence interval [CI]: -18.9 to -20.4%) (11). Current 2015 American Society of Echocardiography guidelines steer clear of defining normal ranges and instead highlight the considerable heterogeneity in published reports (see supplemental Table 6 from Lang et al. [9]). As a guide, the authors suggest a value above -20% with a standard deviation of  $\sim\pm 2\%$ , the value cited by the American Society of Echocardiography, is likely to be normal.

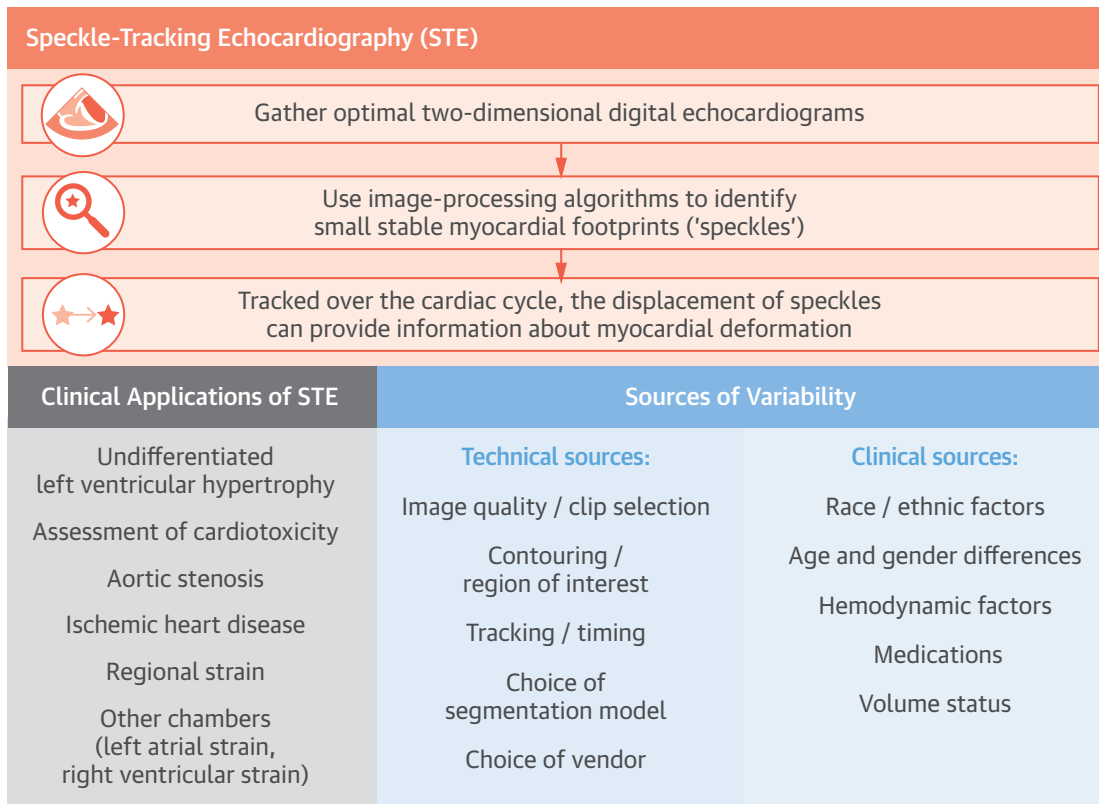
Strain values are heavily influenced by test variability, technical factors, and patient-specific clinical factors, each of which will be discussed further.

## VARIABILITY OF STRAIN: INTERVENDOR AND INTEROBSERVER/INTRAOBSERVER REPEAT TESTING.

STE variability was the prime focus of a task force convened for the purpose of standardizing STE methodology by assessing and identifying sources of variability (12). Here, 62 volunteers had strain measured under optimized conditions, using machines provided by 7 different vendors. Absolute values of GLS ranged from -18.0% to -21.5%, with absolute differences between vendors of up to 3.7% strain units ( $p < 0.001$ ). Of note, among 2 of the more commonly used vendors, strain was higher using the General Electric (Chicago, Illinois) than the Philips (Andover, Massachusetts) machine, with an absolute bias of 2.1%. Inter- and intraobserver reproducibility measurements were good (5.4% to 8.6%; 4.9% to 7.3%, respectively), superior or at least comparable to those of ejection fraction (EF) measurements and other conventional echocardiographic parameters. Importantly, intertest variability of strain was performed by assessing differences between 2 time points; variability when strain was performed more than twice was not assessed.

Primary sources of intervendedor variability relate to post-processing (rather than spatiotemporal resolution or filter setting variances) (10). In addition to such proprietary differences in quantification, there

**CENTRAL ILLUSTRATION Speckle-Tracking Strain: Clinical Utility and Future Directions**



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Speckle-tracking strain is an increasingly used echocardiographic technology that can provide additional (if not potentially incremental) clinical utility. Interpretation of speckle-tracking strain must take into consideration both technical and clinical sources of variability. This technology is a focus of much current research, with the prospect of exciting future developments that are eagerly awaited. 3D = 3-dimensional.

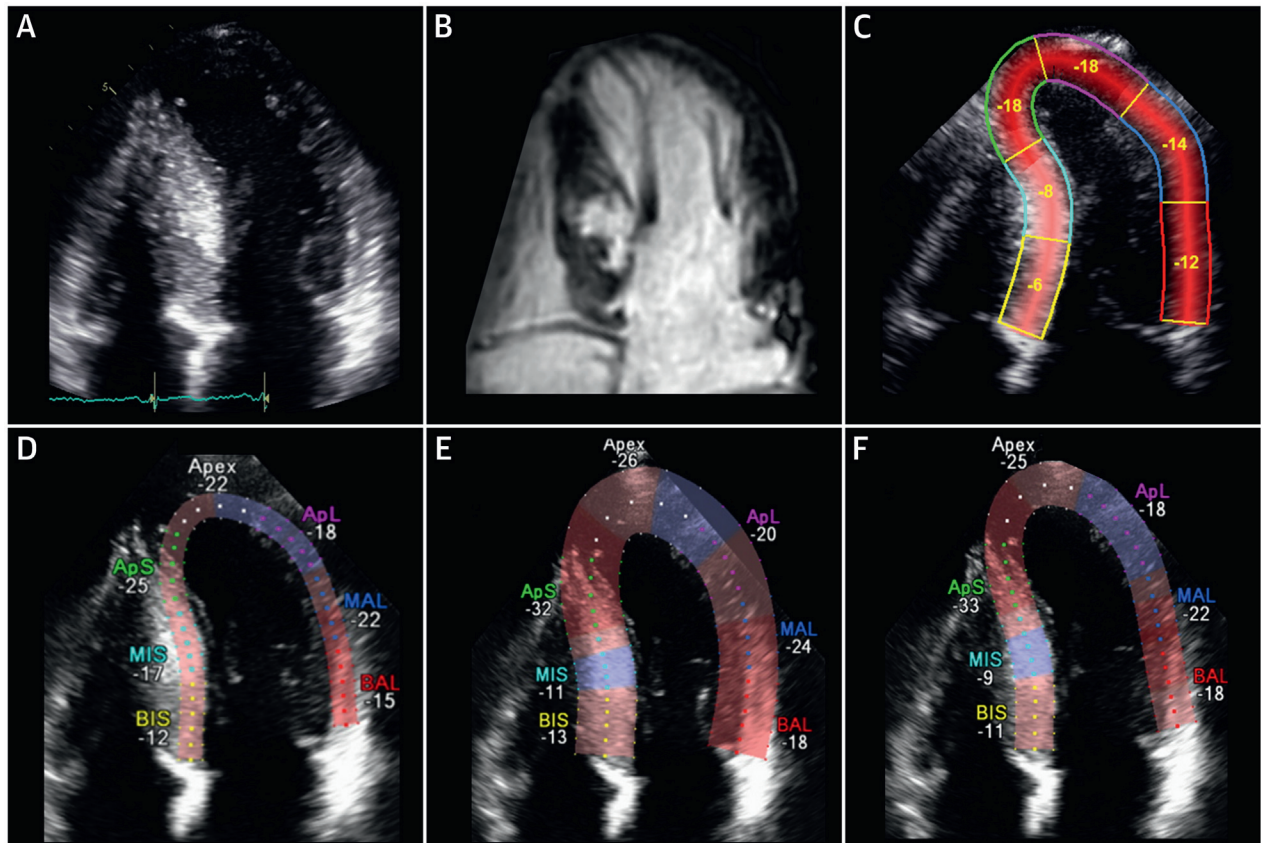
is also variation in how individual apical regional strain values are displayed within 3-, 4-, and 2-chamber apical views and within overall polar maps. This gives some optimism that variability may be amenable to improvement with further industry and academic collaboration and resultant standardization.

**TECHNICAL FACTORS THAT MAY INFLUENCE STRAIN VALUES.** The clinical case highlighted in **Figure 1** illustrates the importance of technical factors with regard to strain assessment. The semiautomated nature of longitudinal strain assessment introduces a learning curve and represents a potential source of measurement variability. Like most echocardiographic parameters, strain should be viewed as a semiquantitative technique, and the following technical sources of variability must be carefully considered.

**Image quality.** General good echocardiographic principles apply. Optimization of echocardiographic images is vital as image quality and frame rates (ideally, no less than 40 fps) remain a crucial determinant of accurate edge detection, tracking, and strain assessment (13). Echo contrast does not help STE, as microbubbles are indistinguishable from speckles, although potential compromises have been suggested (14). Because GLS exhibits a minor base-to-apical gradient (increasing toward the apex), foreshortened images may therefore result in inaccurate strain values, although less so for epicardial longitudinal strain, which is more homogenous over the left ventricle (LV) (15).

**Choice of segmentation model.** Overall and regional GLS values vary depending on the LV segmentation model used, consensus for which has not been achieved. Seventeen-segment models remain

**FIGURE 1** Case Example of Strain in Clinical Practice: Hypertrophic Cardiomyopathy



A 20-year-old male patient presented with syncope. Echocardiographic findings were consistent with hypertrophic cardiomyopathy, including marked asymmetric septal hypertrophy as well as increased echo intensity in the basal to mid inferoseptum (A). Cardiac magnetic resonance using delayed gadolinium enhancement revealed near transmural septal scar (B). Strain imaging (C to F) showed markedly reduced septal strain values. Typical intervendor differences are demonstrated, here between a GE platform (C) and a Philips platform (D to F). Automated software tracking is not always reliable, in which case, manual selection of fiducial landmarks, segmental contouring, and/or a region of interest is paramount. Here, automated detection of the apex and lateral annulus were inaccurate, and the default region of interest was inappropriately narrow (D). Too wide a region of interest will also result in inaccurate strain values (E) versus optimal manual adjustments (F). ApL = apical lateral; ApS = apical septum; BAL = basal anterolateral; BIS = basal inferoseptum; MAL = mid anterolateral; MIS = mid inferoseptum.

the most commonly used in echocardiography and in other imaging modalities, although current guidelines do not advocate their use in functional imaging because of limited views and contractility of the true apical cap segment (9). A 16-segment model offers a more proportional representation of the distal myocardium than an 18-segment model, although the latter is more intuitive from apical views (with 2 apical segments per each 3-, 4-, and 2-chamber apical view). **Selection of image clips.** Where multiple clips have been acquired, there will be at least slight variation in strain assessment simply due to clip selection. Any significant beat-to-beat variation in heart rate between clips will not allow for calculation of average GLS (limiting assessment in the setting of atrial fibrillation) (16).

**Selection of fiducial landmarks and segmental contouring.** For semiautomated strain assessment, fiducial landmarks are carefully selected, with point placement performed in apical 3-, 4-, and 2-chamber views to define the base and apex. Care must be taken to avoid placing points on the atrial side of the mitral annulus or into the LV outflow tract (both of which result in underestimation of strain). Thereafter, for most patients, manual adjustment of segmental contours is essential to optimize tracking (despite introducing potential subjective error).

**Selection of the region of interest.** Region of interest options for GLS include endocardial, midwall (our preference), epicardial, or full-wall strain, but to date, there is currently no evidence that favors one

definition over another (12). GLS is highest in the endocardium and lowest in the epicardium (15). Of note, endocardial GLS was reported by the task force when assessing intervender global strain differences, as this was the only parameter that could be provided by all vendors (12). From a technical perspective, if the region of interest thickness is set too wide, tracking may be impaired, and inclusion of the pericardium will result in a reduction of measured strain; if the region-of-interest thickness is over-focused, strain variability may be increased. Of note, the papillary muscles should not be included in the region of interest. It is recommended that the software should explicitly state what region of interest is being measured, as well as the specific spatial extent (in pixels or millimeters) over which the data have been sampled (10).

**Selection of timing.** GLS compares baseline lengths, generally set at end-diastole (the frame before the mitral valve completely closes; typically estimated using an electrocardiographic surrogate marker, such as the onset of the QRS complex) to a defined systolic length (either automatically detected or after manual frame selection of aortic valve closure, using the initial apical 3-chamber view) (10). It is recommended that software programs allow for alteration of the end-diastolic time, which may be necessary in dyssynchronous hearts with conduction delay, should mitral valve closure and electrocardiography parameters dissociate; or when analyzing cardiac structures other than ventricles (e.g., atria). Exact systolic temporal definitions may have a major impact on strain measurements (17). Options include peak systolic strain (our preference and the default timing for most vendor software) and end-systolic strain, whereas others report peak strain (not isolated to systole and so may reflect “post-systolic” deformation occurring after aortic valve closure). Although the Task Force to standardize deformation imaging recommended use of end-systolic strain in their original definitions paper, it was actually peak systolic strain that was reported in their subsequent intervender analysis document (10,12).

**Recognition of poor tracking.** How well the software tracks the myocardium throughout the cardiac cycle (tracking quality) remains a concern. For example, in one study, over 20% of patients had at least 1 segment that tracked poorly, despite involving a cohort of healthy volunteers (18). Some software vendors may provide an automatic assessment of tracking quality by providing tracking feasibility scores. Generally, it is recommended that image views where tracking is insufficient in more than

1 segment should be excluded from further analysis (12). Tracking quality has been shown to have regional variability and is typically worse in lateral/apical segments (18). Differential exclusion of badly tracked segments is an additional source of intertest variation.

**Technical differences among vendors.** As discussed earlier, a number of different vendors offer strain platforms with technical differences among proprietary post-processing algorithms. There are vendor-specific differences among how overall reported GLS values are calculated from segmental values. Because of software algorithm issues, cross-platform values are not necessarily interchangeable, and for this reason, guidelines recommend that serial assessment of GLS in individual patients should be performed using the same vendor’s equipment and the same software (9).

## CLINICAL FACTORS THAT MAY INFLUENCE STRAIN VALUES

**RACIAL, ETHNIC, AND INTERNATIONAL DIFFERENCES.** In a 2009 multicenter (Australian  $n = 94$ ; European  $n = 51$ ; American  $n = 97$ ) study of 242 healthy volunteers (mean age:  $\sim 51$  years; 44% male), mean full-thickness, peak systolic GLS (General Electric [GE]) was reported as  $-18.6 \pm 0.1\%$ , with no significant differences among sites (18). A number of additional studies have provided reference ranges for specific populations. In the 2012 JUSTICE (Japanese Ultrasound Speckle Tracking of the Left Ventricle) study of 817 healthy volunteers (mean age:  $\sim 36$  years; 61% male), the overall mean full-thickness, peak systolic GLS (GE) was reported as  $-21.3 \pm 2.1\%$  (19). In a 2014 Italian study of 260 Caucasian healthy volunteers (mean age:  $\sim 44$  years; 43% male), the mean full-thickness, peak systolic GLS (GE) was reported as  $-21.5 \pm 2.0\%$  (lower limits of normal or average: 2 SD was  $-16.9\%$  for men and  $-18.5\%$  for women) (20).

**AGE AND SEX DIFFERENCES.** Significant age-related reductions in deformation have been reported (e.g., GLS [GE] was  $-20.3\% \pm 1.9\%$  in healthy subjects over 60 years of age versus  $-22.1 \pm 2.4\%$  in those  $< 20$  years of age;  $p < 0.01$ ) (21). Similarly, sex-related differences have been described, with lower deformation noted in male patients than in female patients across all age groups studied (19).

**HEMODYNAMIC FACTORS.** GLS increases in response to early physiological heart rate increase in the setting of exercise in normal patients (22). However, decreased values are found in the setting of pathological heart rate increase, most notably in sepsis,

where such decreases have been shown to have prognostic relevance (23).

**IMPACT OF CARDIOVASCULAR RISK FACTORS.** Higher mean blood pressure has been independently associated with lower values of deformation (decreased GLS and increased afterload are also evident in patients with aortic stenosis) (11,24). Obesity is associated with lower strain values in children and adults in the absence of other comorbidities or reduction in left ventricular ejection fraction (LVEF), with significantly improved biventricular strain values demonstrated after bariatric surgery (25,26). Reduced GLS has been reported in dyslipidemic children and adolescents free of other cardiovascular risk factors or structural cardiac abnormalities compared with controls, with obesity causing an additive adverse effect on strain parameters (27). Reduced GLS is common in asymptomatic patients with type 2 diabetes mellitus and is independently associated with adverse outcome (28). After ST-segment elevation myocardial infarction, diabetic patients have consistently lower GLS values than those in a matched group of nondiabetic patients with similar infarct size and EFs (29). Neither acute nor chronic changes in GLS were reported in a study examining myocardial function in young, otherwise healthy heavy smokers (30).

**MEDICATIONS.** The effects of medications on GLS values are poorly studied in humans. Theoretically, acute effects of angiotensin-converting enzyme inhibitors should result in increased strain through afterload reduction and lower systemic blood pressure. In contrast, beta-blockers may reduce strain initially through negative inotropic and chronotropic effects. Thereafter, any reverse remodeling effects would be expected to result in increased strain values.

**DIALYSIS.** In a 2014 single-center prospective study of 107 dialysis patients (mean age: ~65 years; 69% male), the mean full-thickness, peak-systolic GLS (GE) was reported as  $-11.4 \pm 4.4\%$  (31). Mean EF was  $62\% \pm 10\%$ , serving to highlight the fact that systolic dysfunction measured using standard means may overestimate contractility in patients with LV hypertrophy, which is present in one-third of dialysis patients. Here, strain values were also found to be independent of intradialytic weight change (a surrogate of pre-load) and to show a significant correlation with survival.

**PREGNANCY.** Interestingly, despite changes in hemodynamics, GLS was not found to vary significantly in a comparison between pregnant patients and in

nonpregnant controls nor during trimesters of pregnancy (32).

**ATHLETES.** Endurance athletes have been shown to have significantly higher GLS than sedentary normal controls (33). Sinus bradycardia and LV mass were independent determinants of supernormal GLS at rest.

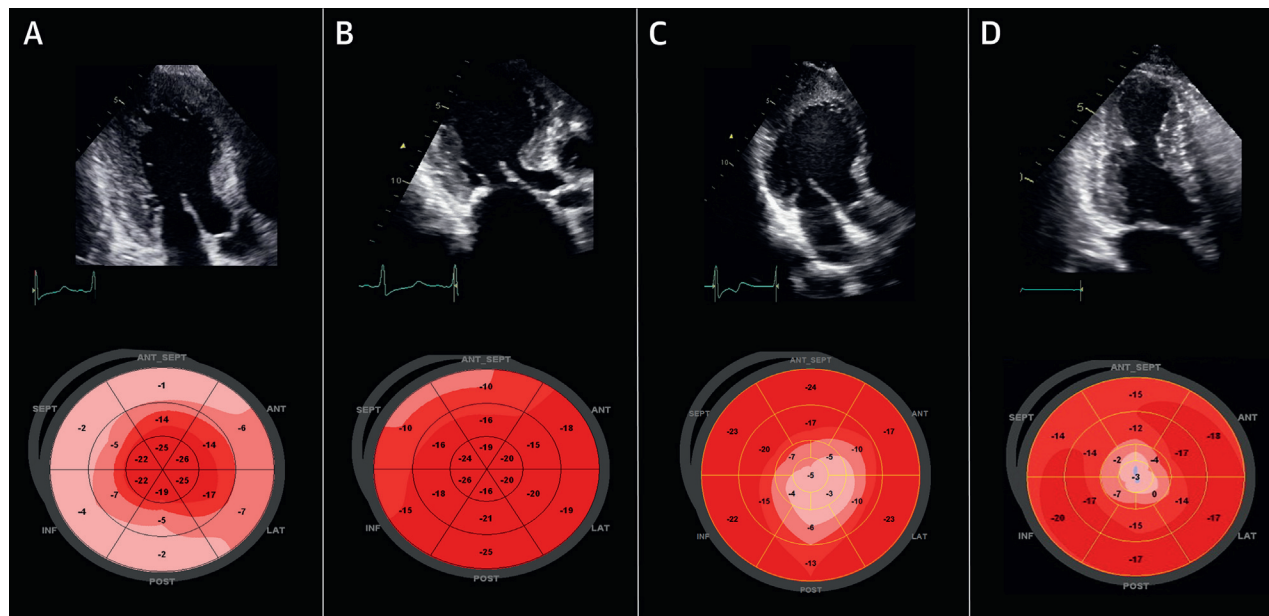
## CLINICAL UTILITY OF STRAIN

To date, most clinical strain data stems from non-randomized, retrospective studies. Reduction of absolute strain is a marker of most myocardial diseases, acute and/or chronic, and for some, portends poor prognosis and increased risk (5). When assessing the prognostic role of strain for any given pathology, it is important to understand the nuances of what is being measured (longitudinal strain assessment should at least have region of interest/timing and vendor-specific descriptors). Assessment of potential confounding differences between groups that may otherwise account for lesser deformation between cases and controls should also be looked for.

**MYOCARDIAL STRAIN PATTERNS IN UNDIFFERENTIATED LV HYPERTROPHY.** The limitations of EF in assessing systolic function and predicting prognosis in the context of LV hypertrophy (or increased LV wall thickness) are well recognized (31). STE has gained increasing clinical popularity in this setting as a means of identifying systolic dysfunction in the context of normal EF, aiding diagnosis of rarer causes of LV hypertrophy, such as hypertrophic cardiomyopathy (HCM) or cardiac amyloidosis (CA) and assessing prognosis (Figure 2).

In patient with CA, earlier studies consistently demonstrate a significant reduction in GLS that is predictive of mortality (34,35). Typically, the EF-to-GLS ratio is approximately 3. In CA, morphological and functional remodeling may impose a dissociation in these parameters, and an EF-to-GLS ratio of  $>4.1$  has been proposed as a means to distinguish CA from HCM (36). Furthermore, differences not just in GLS but also in regional longitudinal strain have proven to be clinically very useful in patients with undifferentiated LV hypertrophy and specifically CA. A regional strain pattern termed apical sparing, quantified by a relative regional strain ratio (RRSR; defined as [average apical strain]/[average basal strain + average mid strain]) of  $\geq 1$  was found to be highly sensitive and specific for the diagnosis of CA and to have prognostic implications (37,38). Qualitative polar maps demonstrating regional strain variations were also shown to have diagnostic utility in the

**FIGURE 2** Case Series Highlighting Different Scenarios for Abnormal Apical Strain Patterns



Two-dimensional images (top panels) and bull's eye plots (bottom panels) show (A) an apical sparing pattern in cardiac amyloidosis and (B) abnormal septal strain in hypertrophic cardiomyopathy; (C) reduced apical strain in apical variant hypertrophic cardiomyopathy; and (D) again a reduced apical strain in apical infarction.

differentiation of CA from other causes of LV hypertrophy (39). Normal absolute apical-basal strain differences of approximately  $-2\%$  are markedly exaggerated in CA (often  $-8\%$  or more), possibly related to the subsequently described decremental basal-to-apical gradient of amyloid deposition (40,41). We recommend assessing GLS in all patients with undifferentiated LV hypertrophy and calculating the RRSR in those who have a visual pattern suggestive of CA.

In patients with HCM, reduction in GLS is associated with worse cardiovascular outcomes, including heart failure (42,43). The lowest regional strain values are typically seen at the site of greatest hypertrophy and fibrosis (44). Such septal abnormalities can be identified on qualitative polar maps (39). Recently, mechanical dispersion (defined as the standard deviation of time to peak negative strain in all segments) has been shown to not only correlate with the degree of myocardial fibrosis but also to be an independent predictor of ventricular arrhythmia (45). STE has been assessed in apical variant disease, where GLS is generally higher with better outcomes than in nonapical variant disease (46). In a study of genotype-positive patients with HCM, abnormal STE measurements were recorded only in those with LV

hypertrophy, suggesting that GLS may not necessarily predict pre-clinical disease (47).

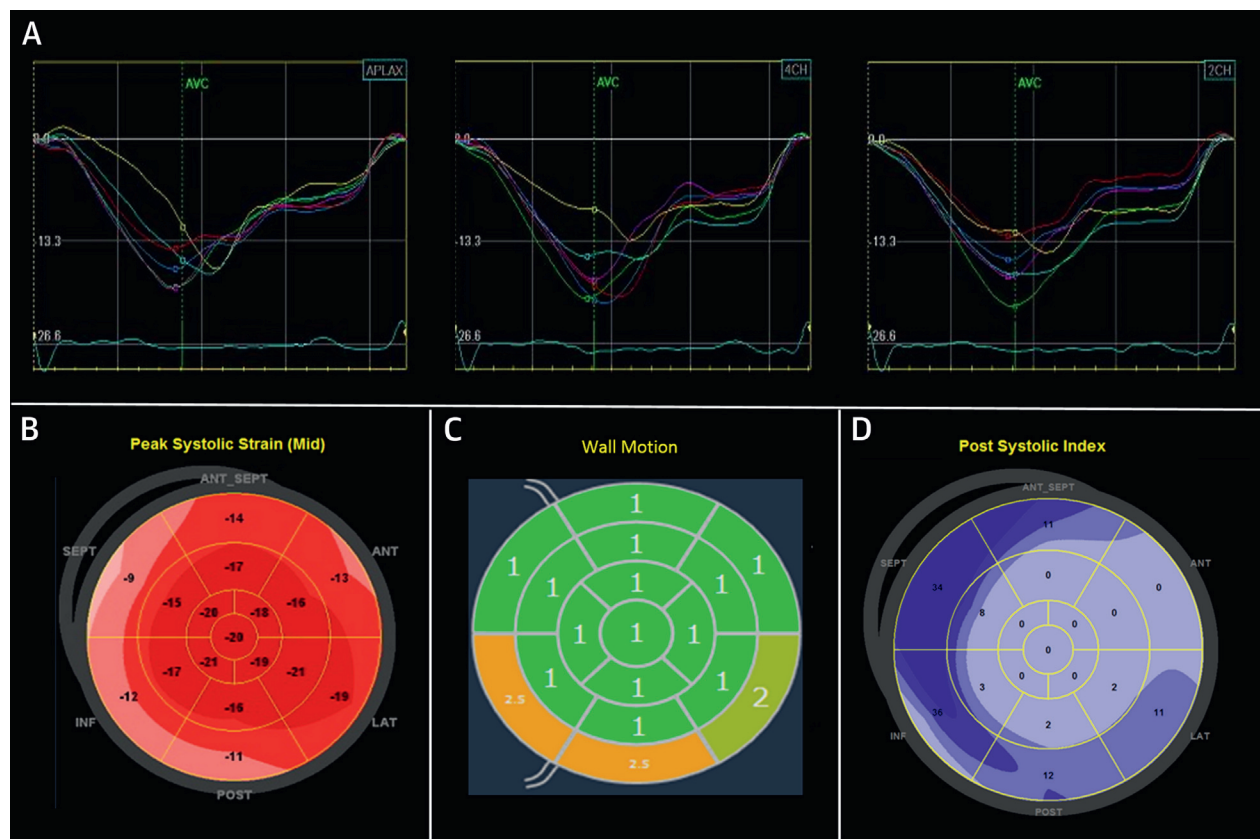
In patients with hypertension, GLS was significantly reduced compared with that in normal controls and was reduced even more in hypertensive patients with heart failure with preserved ejection fraction (48).

In physiological hypertrophy/athlete's heart, GLS was noted to be significantly higher than that measured in patients with pathological hypertrophy related to HCM (49).

### CARDIO-ONCOLOGY

To date, treatment decisions within cardiotoxicity surveillance strategies are initiated and continued primarily on the basis of EF (50). Increasingly, GLS is also being measured as part of such surveillance as an additional surrogate marker of cardiotoxicity with potential for cost effectiveness (51). Of note, quoted variability for EF and GLS has generally been derived from studies performed in healthy volunteers under controlled conditions within academic centers between 2 time points only. The actual real-world clinical variability for such parameters in sick patients undergoing chemotherapy,

**FIGURE 3** Case Example of Strain in Clinical Practice: Right Coronary Artery Infarct



Segmental strain traces recorded from apical 3-, 4-, and 2-chamber views, respectively (A); bull's eye plot displaying midwall peak systolic strain (B); regional wall motion plot (C); and post-systolic index (percentage of post-systolic increment over systolic strain) (D) in a patient with a right coronary artery infarct. Reduced regional strain values (A, B) and segmental post-systolic shortening (D) correspond to the regional wall motion plot (C). Note that the strain plots are rotated 60° clockwise compared with the regional wall motion plot.

with testing often performed multiple times (>2 studies) has the potential to overlap cutoffs defining toxicity (50,52). Thus, rather than relying on interpretation of interval changes of a single parameter in an isolated fashion, it may be advantageous to have concomitant strain assessment, in addition to EF, to provide additional supportive data with regard to suspected cardiotoxicity (53). Where there is discordance between parameters, it is important to first check the quality of the data (such as tracking), although repeat testing may ultimately be required in order to differentiate measurement variability from sustained real change.

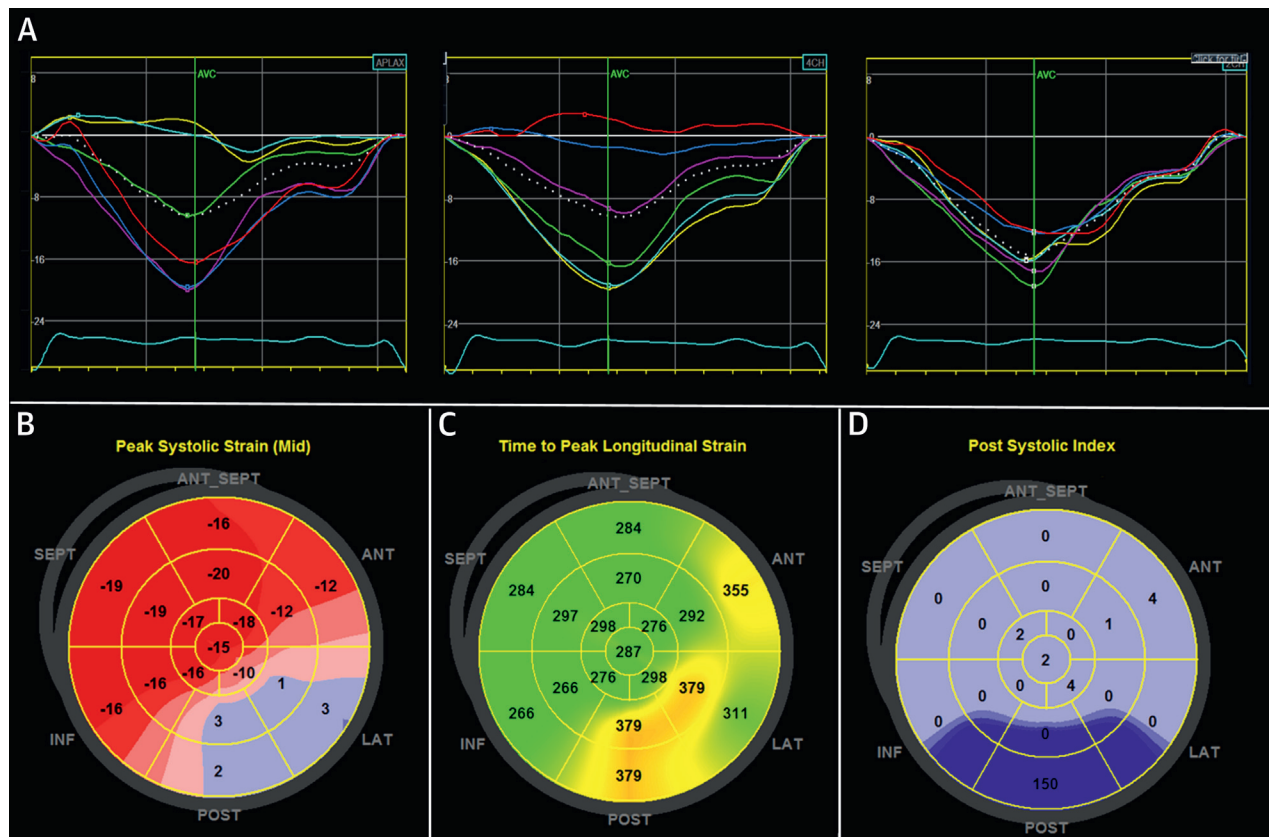
Data supporting the initiation of cardioprotection for the treatment of subclinical LV dysfunction are limited (50). Because rates of progression from subclinical LV dysfunction to symptomatic heart failure remain unknown, it is difficult to predict whether

early intervention in these patients, which may lead to improvements in long-term clinical outcomes, is warranted on the basis of strain reduction alone (54). In cancer survivors, strain abnormalities are not only common but appear to relate to both anthracycline therapy and overall radiotherapy dose (55). Indeed, prospective studies are under way that will provide information specifically regarding potential radiation dose-response relationships between functional myocardial strain measurements and myocardial-specific radiation dosages (56).

**AORTIC STENOSIS.** Major societal valve guidelines recommend surgery for patients with asymptomatic severe aortic stenosis if EF is <50% (Class I) (57). However, such patients have worse outcomes than those with preserved EF undergoing aortic valve replacement, including increased operative mortality



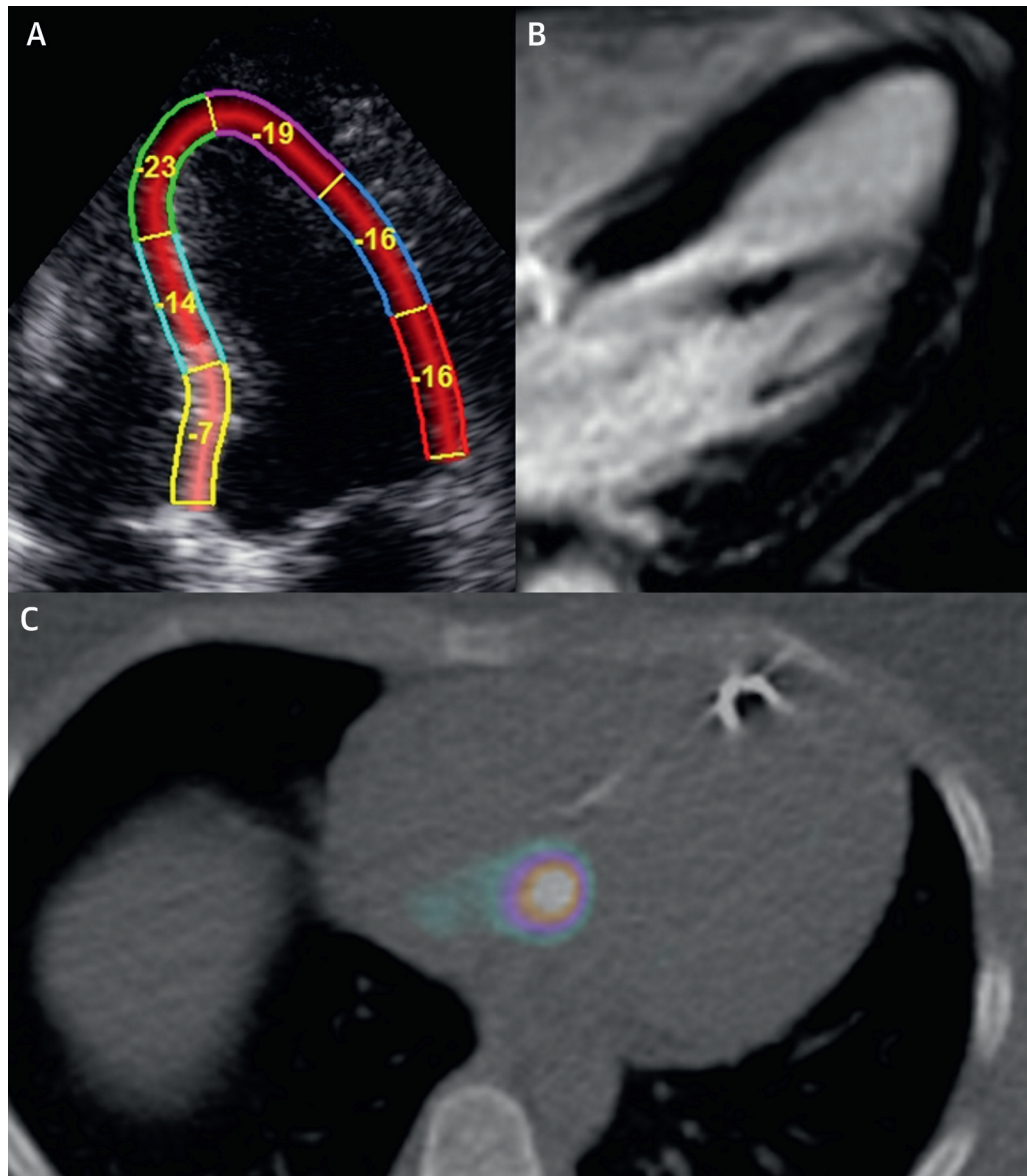
**FIGURE 4** Case Example of Strain in Clinical Practice: Left Circumflex Artery Infarct



Segmental strain traces recorded from apical 3-, 4-, and 2-chamber views, respectively (A); bull's eye plots displaying midwall peak systolic strain (B); time to peak longitudinal strain (C); and post-systolic index (percentage of post-systolic increment over systolic strain) (D) in a patient with a left circumflex infarct. Affected segments demonstrate reduced regional strain values (A, B), delayed time to peak strain (C), and segmental post-systolic shortening (D).

and worse long-term prognosis, and one-half of these patients do not recover normal EF post-operatively (58). Given its role as an alternative measurement of systolic function, it is not surprising that GLS has been getting a lot of attention in this cohort, not just as a marker of subclinical LV dysfunction but also as a means to predict composite cardiac endpoints and post-operative LV functional recovery (24,59,60). In patients with aortic stenosis, GLS has been shown to correlate with increasing disease severity (with significantly reduced values, even in patients with mild aortic stenosis, compared with normal controls) and to be a strong, independent predictor of all-cause mortality (24). In asymptomatic patients (n = 60) with severe aortic stenosis and normal EF, reduced GLS was associated with abnormal exercise response and with an increased risk of cardiac events (cardiac hospitalization, aortic valve replacement, or cardiovascular death) during a 12-month follow-up (59). In a

similar cohort (n = 163; follow-up: 20 ± 19 months), GLS <16% (defined as the average of 12 segments from apical 2- and 4-chamber views) was specifically found to be a significant predictor of symptom development, surgery, or death (60). Although GLS has not yet been formally included in major societal guidelines for aortic stenosis, more recent multimodality imaging guidelines recommend that surgery may be considered (Class IIb) in patients with asymptomatic severe aortic stenosis with either high or paradoxically low gradients, who are identified as high-risk by GLS (as well as other multimodality risk factors, such as high calcium score and extensive myocardial fibrosis) (61). The adverse prognosis associated with lower GLS values in study group patients with aortic stenosis is likely multifactorial and may relate to reduced contractility, increased afterload, and/or myocardial fibrosis, as well as increased cardiovascular risk phenotype (older age, male sex, concomitant hypertension, diabetes,

**FIGURE 5** Case Example of Strain in Clinical Practice: Inflammatory Myocarditis

A 34-year-old woman presented with chest pain and was found to have complete heart blockage with stable junctional escape. Echocardiography results were normal, apart from focally reduced basal inferoseptal strain (A). Cardiac magnetic resonance revealed a normal delayed gadolinium enhancement pattern (B), whereas a cardiac PET scan revealed a small focal area of enhanced fluorodeoxyglucose uptake in the basal inferoseptum (C), suggesting an underlying acute inflammatory myocarditis. PET = positron emission tomography.

dyslipidemia, obesity). It is unclear whether operating earlier on those asymptomatic patients with normal EF and low GLS alters outcomes. There are some indications that strain (TDI or GLS) may also have a role to play in regurgitant disease, although strain is less affected by volume, rather than pressure overload (62,63).

**ISCHEMIC HEART DISEASE.** Given that the ischemic cascade begins with flow heterogeneity in the watershed subendocardial layer, where there is a preponderance of longitudinally orientated fibers, it is not surprising that GLS abnormalities, such as early systolic stretch, low systolic shortening, and post-systolic shortening (tardokinesis) have been

reported in patients with ischemia (Figures 3 and 4). Strain imaging has also been demonstrated to facilitate a faster interventional strategy in patients with non-ST-segment elevation myocardial infarction and occluded coronary arteries (64).

With regard to stress echocardiography, the clinical use of STE is limited, not least because of interpretative difficulties but also due to preferences for stress echocardiography contrast medium usage, which hinders GLS assessment.

In chronic ischemic heart disease, GLS correlated significantly with global infarct mass and was found to be superior to LVEF in the identification of small and medium-sized infarcts (65).

**REGIONAL STRAIN.** Current guidelines also do not recommend quantitative assessment of the magnitude of regional deformation because of lack of reference values, suboptimal reproducibility, and considerable intervender measurement variability (9). Indeed, intervender differences for segmental strain values may be even higher than that reported for global values, which is partly related to vendor-specific differences in how much spatial smoothing is applied to local tracking of speckles as part of noise reduction algorithms.

In our experience, rather than focusing on numerical segment-specific strain values, we have found the most clinical utility with regional strain on assessment of base/midapical differences or comparison of regional differences in polar strain maps (37,39).

Reductions in local strain may represent areas of inflammation (Figure 5) or fibrosis (Figure 1). Regional strain patterns have been used to highlight the typical regional mechanical contraction pattern associated with left bundle branch block, namely early systolic septal shortening combined with early pre-stretch and delayed peak contraction of the lateral wall. Absence of such a pattern was independently associated with increased risk of adverse outcome after cardiac resynchronization therapy (66).

**OTHER CHAMBERS.** Acquired from apical views, left atrial (LA) strain is a research-based measurement that relates to LA deformation and has been reported to be inversely related to LA pressure (similar to LV strain and systolic blood pressure) (67). The thin LA wall poses challenges for STE, and there is again a lack of standardization among software from different vendors with regard to this application (e.g., how the mitral annulus should be handled). With a pattern similar to a normal pulmonary vein Doppler profile, peak positive values occur during ventricular systole (A-S, reservoir phase), with a second positive peak during ventricular diastole (A-D, conduit phase)

before the negative peak of LA contraction. Reference timing needs to be adjusted, which influences strain values (in sinus rhythm, the p-wave is generally the reference zero point, with peak values <30% usually indicating significant alteration) (68). LA strain is typically lowest in patients with atrial fibrillation and may predict heart failure and risk of embolic stroke. Of note, GLS has prognostic value in patients with persistent atrial fibrillation (68).

Right ventricular (RV) strain is measured using the RV free wall assessed from an RV-focused apical 4-chamber view. To avoid underestimation of strain values, it is important not to place the reference points too low (not on the atrial side of the tricuspid annulus) nor have the region of interest too wide (particularly relevant given how thin the RV free wall is). Peak RV GLS (mean of the 3 RV free wall segments) is typically slightly higher than that of the LV, and generally >−20% in absolute value. Prognostic value for RV GLS has been demonstrated under a wide variety of conditions, including heart failure, pulmonary embolism, and arrhythmogenic RV cardiomyopathy (69).

## FUTURE DIRECTIONS

Technological advancements should allow STE to continue to mature in order to play an increasingly important role in the armamentarium of future cardiologists. Improvements in tracking and border recognition may translate to shorter analysis times, whereas fuller automation of the technique may lead to more widespread adoption of time-pressed echocardiography laboratories. Continued collaboration between vendors and potential sharing of proprietary software should serve to further reduce intervender variability. Simultaneous 4-chamber strain can rapidly quantitate longitudinal strain in all 4 chambers from 1 echo view within 1 heartbeat, although this remains a monoplane representation (70). Three-dimensional strain offers an opportunity to overcome limitations imposed by out-of-plane speckle motion, although current iterations are limited by poor frame rates. Multimodality assessment of myocardial strain is a burgeoning development whereby techniques analogous to STE, such as feature tracking in cardiac magnetic resonance, may take advantage of higher relative spatial resolution of cine sequences to provide advanced myocardial mechanics data (71).

## CONCLUSIONS

Increasing use of STE within both the research and clinical realms means that this technique is likely here to stay. Continuing training, education, and quality assurance processes may help offset some of

the technical challenges and inherent limitations with this data and allow for more accurate STE interpretation. As highlighted in this review, further prognostic and diagnostic insights continue to emerge as we continue to apply this technology to different patient populations and myocardial diseases. Given that STE will not be performed as a stand-alone test in the foreseeable future but rather in conjunction with other parameters, such as EF, further research to better understand the incremental value of STE is needed.

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## PERSPECTIVES

### COMPETENCY IN MEDICAL KNOWLEDGE:

Strain-based imaging techniques (and specifically speckle-tracking echocardiography) have been shown to have clinical utility in a variety of settings. This technique is being embraced and increasingly adopted in many echocardiography laboratories worldwide. This review appraised this test in a clinical context by providing a critical evaluation of the prognostic and diagnostic insights that this technology can provide.

**TRANSLATIONAL OUTLOOK:** Before strain-based imaging techniques are applied clinically, it is particularly important that physicians be cognizant of the technical challenges and inherent limitations of strain data.

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