Incremental Value of Two Dimensional Speckle Tracking Echocardiography in the Functional Assessment and Characterization of Subclinical Left Ventricular Dysfunction

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Abstract: Subclinical left ventricular (LV) dysfunction refers to subtle abnormalities in LV function which typically precede a reduction in the left ventricular ejection fraction (LVEF). The assessment of myocardial function using LVEF, a radial metric of systolic function, is subject to load dependence, intra-observer and inter-observer variability. Reductions in LVEF typically manifest late in the disease process thus compromising the ability to intervene before irreversible impairment of systolic performance sets in. 2-Dimensional speckle tracking echocardiography (2D-STE), a novel strain imaging modality has shown promise as a sensitive indicator of myocardial contractility. It arms the clinician with a powerful and practical tool to rapidly quantify cardiac mechanics, circumventing several inherent limitations of conventional echocardiography. This article highlights the incremental utility of 2D-STE in the detection of subclinical LV dysfunction.

Keywords: Subclinical left ventricular dysfunction, 2-dimensional speckle tracking echocardiography, Global longitudinal strain.

INTRODUCTION

Strain refers to the change in the length of a segment of the myocardium relative to its original length and strain rate refers to the net change in strain per unit time. 2-Dimensional speckle tracking echocardiography (2D-STE), an angle-independent technique, employs automated algorithms to analyze temporal variations (frame to frame) in the mobility of acoustic speckle markers of 20-40 pixels size along different spatial orientations such as longitudinal, circumferential and radial planes to then quantitatively derive respective strain or deformational parameters. The endocardium contributes maximally to longitudinal strain (LS). Location of the endocardium farthest away from the epicardial coronary arteries and its exquisite sensitivity to ischemia makes it vulnerable to a variety of insults thereby making LS a highly sensitive indicator of LV dysfunction. In contrast, radial strain (RS), circumferential strain (CS) and torsional strains (TS) are affected later in the disease and are widely acknowledged to have lower inter- and intra-observer reproducibility [1].

One of the utilities of myocardial strain might be timely identification of subclinical left ventricular (LV) dysfunction, which could provide the clinician with a wider therapeutic window to potentially arrest or delay progression to clinically evident cardiovascular disease or impairment of myocardial performance. In this article, subclinical LV dysfunction refers to a compromise in LV function prior to reduction in LVEF ≤ 50%. The focus of this article is to highlight: 1. The clinical entities where subclinical LV dysfunction has been described by 2D-STE and 2. The potential incremental value of 2D-STE over conventional 2D-echocardiography in the management of these patients.

APPLICATIONS OF STRAIN
i) Valvular Heart Disease

A clear consensus on the timing of valve repair or replacement in asymptomatic patients with preserved LVEF is currently lacking [2]. In addition to the detection of subclinical LV dysfunction, strain parameters have shown promise for the prediction of post-surgical LV dysfunction. Myocardial strain could plausibly assist in the identification of high-risk patients who might benefit from early surgical intervention prior to a decline in the LVEF below guideline recommended threshold levels for surgical intervention (Table 1). Adaptive remodeling in early aortic regurgitation (AR) preserves LVEF by a compensatory rise in RS and CS for the...
Table 1. Studies evaluating strain in valvular heart disease with speckle tracking echocardiography.

| Study                  | Sample size with description | Imaging modality (vendor name) | Objective | Outcomes                                                                 |
|------------------------|------------------------------|--------------------------------|-----------|---------------------------------------------------------------------------|
| **Aortic Regurgitation**|                              |                                 |           |                                                                           |
| Mizarini et al. [41]   | Chronic AR:NT-proBNP<400 (n=44) vs. >400 vs. controls (n=64) | 2D-STE (EchoPac-GE)            | Effect of LV strain on NT-proBNP | GLS>-16% predicts levels>400                                              |
| Olsen et al. [5]       | Chronic AR: Surgical (n=29) vs. conservative (n=35) | 2D-STE (EchoPAC-GE)            | Strain indices in AR progression | Progression correlates with reduced systolic (-1.04 vs. -1.19%), early diastolic (1.2 vs. 1.6s⁻¹) and myocardial SR (-16.3 vs. -19%) |
| Smedsrud et al. [6]    | Chronic AR (n=47) vs. controls (n=31) | 2D-STE (EchoPAC-GE)            | GLS impairment and early LV dysfunction | Reduced GLS (-17.5 vs.-22.1%) identifies subclinical LV dysfunction; GLS and not LVEF correlates with post-operative LV function |
| Kaneko et al. [37]    | Chronic AR (n=36) vs. controls (n=15) | 2D-STE (Toshiba)              | GRS decline-marker of myocardial dysfunction? | Endocardial GRS loss (28.9 vs. 37.1%) predicts myocardial dysfunction |
| Di Salvo et al. [4]   | Stable (n=17) vs. progressive AR (n=9) | 2D-STE (EchoPAC)              | Strain parameters and AR progression | LV LS (cut-off>-19.5%) - only predictor for AR Progression               |
| **Aortic Stenosis**    |                              |                                 |           |                                                                           |
| Van Dalen et al. [11]  | AS (n=60) vs. controls (n=30) | 2D-STE (QLAB-Philips)         | Twist indices and severity of AS, subendocardial ischemia | Elevated peak systolic LV twist (13.6 vs. 11.4) and endocardial twist-shortening ratio (0.6vs.0.4) correlates with ischemia and AS severity |
| Ng et al. [9]          | Aortic sclerosis (n=118) vs. Mild (n=81) vs. moderate (n=109) vs. severe (n=112) AS | 2D-STE (EchoPAC-GE) | Strain and severity of AS | Sequential deterioration in LS, CS, RS and SR correlates with progressive reduction in valve area |
| Levy et al. [42]      | Severe symptomatic AS        | 2D-STE (EchoPAC-GE)           | GLS on post-surgical atrial fibrillation rates | GLS>-15% predicts post-surgical atrial fibrillation |
| Delgado et al. [10]   | Severe AS (n=73) vs. controls (n=40) | 2D-STE (EchoPAC-GE)           | Changes in LV strain pre and post-surgery | GLS (-14.6 vs. -20.3%) and SR-impaired despite pEF. LS, CS and RS improved following valve replacement |
| **Mitral Stenosis**    |                              |                                 |           |                                                                           |
| Ozdemir et al. [12]   | Mild-moderate MS (n=60) vs. controls (n=52) | 2D-ECHO, STE (EchoPAC-GE) | LV dysfunction in MS with pEF | GLS (-17 vs.-19%) and GLS rate compromised in MS |
| **Mitral Regurgitation**|                              |                                 |           |                                                                           |
| Isla et al. [7]        | Chronic severe MR (n=38)     | 2D, 3D-ECHO, Doppler ECHO and 2D-STE (Q-Lab) | Preoperative strain on post-operative LV dysfunction | Longitudinal SR at mid interventricular septal level <-0.8s⁻¹ best predictors of LVEF reduction >10% |
| Kim et al. [43]        | Chronic severe MR (n=59) vs. controls (n=34) | 2D-ECHO,angiography and 2D-STE (EchoPac-GE) | Strain assessment of latent LV dysfunction | Peak systolic radial SR of 2.0 s⁻¹ best correlates with peak dp/dt; short axis function offers better prediction |
(Table 1) Contd….

| Study | Sample size with description | Imaging modality (vendor name) | Objective | Outcomes |
|-------|-----------------------------|--------------------------------|-----------|----------|
| Florescu et al. [8] | Severe primary MR (n=28) vs. controls (n=10) | 2D-ECHO, TVI and STE (EchoPac-GE) | Pre-op strain and post-valve replacement LV function | Systolic TVI and the combination of systolic TVI and LS are main independent predictors of post-operative LVEF drop >10% |
| Pandis et al. [44] | Degenerative MR (n=40) | 2D, 3D-ECHO, and 2D-STE (TomTec) | Predictors of recurrent MR post-surgery | Mid-lateral RS≤-27 and apical lateral RS ≤-25-significant predictors |
| Mascle et al. [45] | Severe degenerative MR: post op LVEF≥50% (n=73) + LVEF<50% (n=15) | 2D-ECHO, 2D-STE and TDI (EchoPAC-GE) | Pre-operative GLS on post-operative LV dysfunction | GLS >-18% predicts post-operative LVEF drop to <50% |

2D, 2 dimensional; 3D, 3 dimensional; AS, aortic stenosis; AR, aortic regurgitation; CS, circumferential strain; ECHO, echocardiography; GLS, global longitudinal strain; GRS, global radial strain; LS, longitudinal strain; LV, left ventricle; LVEF, left ventricular ejection fraction; MS, mitral stenosis; MR, mitral regurgitation; NT-proBNP, N terminal-pro brain natriuretic peptide; pEF, preserved ejection fraction; RS, radial strain; SR, strain rate; TDI, tissue Doppler imaging; TVI, tissue velocity imaging.

Fig. (1). Paradoxical longitudinal strain in inferior and inferolateral walls in a patient admitted with uremic pericarditis and found to have newly reduced systolic function without any wall motion abnormalities, suggestive of perimyocarditis. The systolic function recovered following treatment for pericarditis in an echocardiogram performed 2 weeks later.

early loss of LS with additional compensation provided by LV hypertrophy and increase in LV volume [3]. Reduction in LVEF to <50% in asymptomatic AR heralds an increase in the rate of progression to symptoms, a surgical indication, from 4.3% to 25% per year [2]. Amongst patients with preserved ejection fraction (pEF), LS attenuation >-19.5% is 77% sensitive and 94% specific for symptomatic progression of asymptomatic moderate-severe AR [4]. Pre-operative GLS attenuation, but not LVEF, has been associated with post-operative LV dysfunction [5, 6]. Likewise, in mitral regurgitation, pre-operative GLS impairment (GLS<-18 %) has been shown to identify subclinical LV dysfunction in patients with LVEF>60% and also predict post-operative LV dysfunction [7, 8].

In aortic stenosis (AS), the degree of strain deterioration correlates significantly with lower aortic valve (AV) area and severity of AS [9] while strain recovery has been noted post AV replacement [10], even prior to recovery of LVEF. Furthermore, altered twist mechanics in AS offers a non-invasive means of predicting subendocardial ischemia [11]. Similarly, identification of subclinical LV dysfunction by attenuated GLS and GLS rate in asymptomatic or minimally symptomatic mitral stenosis (MS) [12] might aid in optimal
2D-STE is robust in terms of its prognostic utility in coronary artery disease (CAD). Coronary Artery Disease

Myocardial remodeling and an athlete’s heart while providing excellent correlation with the magnitude of diastolic dysfunction in hypertensives [19]. Detection of LS impairment by 2D-STE precedes detection by tissue Doppler imaging (TDI) in hypertensives with preserved LVEF even prior to the development of left ventricular hypertrophy (LVH) [20] thus providing an early opportunity to arrest progression to LVH. Indeed, preserved CS and consequential wall thickening despite reduction in LS has been posited to explain preservation of LVEF in patients with systemic hypertension [21].

2D-STE derived GLS attenuation might be useful for risk stratification in asymptomatic diabetics via prediction of subclinical systolic LV dysfunction with the decrease in LS being proportional to diabetes duration [22]. Furthermore, impairment of GLS has been associated with higher coronary artery calcium scores in diabetics, a surrogate for subclinical atherosclerosis [23].

Table 2. Studies highlighting utility of speckle tracking echocardiography in subclinical coronary artery disease.

| Study | Sample size with description | Imaging modality with vendor name | Objective | Outcomes |
|-------|------------------------------|----------------------------------|-----------|----------|
| Nucifora et al. [46] | Non-obstructive (n=60) vs. obstructive (n=63) vs. no CAD (n=59) | CT angiography and 2D-STE (EchoPAC-GE) | GLS prediction of obstructive CAD | GLS>-19% predicts obstructive CAD better than diastolic dysfunction or Duke clinical scores |
| Hanekom et al. [47] | Significant CAD (150) | 2D-STE, TVI, DSE and coronary angiography (EchoPAC-GE) | Strain from STE vs. TVI during DSE in predicting obstructive CAD | STE-equally efficacious to TVI in anterior but not in posterior circulation |
| Liang et al. [17] | Obstructive (n=39) vs. non-obstructive or no CAD (n=15) | 2D-STE, coronary angiography (EchoPAC-GE) | Diastolic strain in obstructive CAD | Early diastolic SR impairment is superior to systolic strain: 77% sensitive, 93% specific |
| Tsai et al. [16] | CAD (n=75) vs. no CAD (n=77) | STE, coronary angiography (EchoPAC-GE) | LS in prediction of obstructive CAD | Sensitivity, specificity of GLS>-19%: 75%, 81%; peak segmental LS difference/peak systolic GLS ratio>1: 77%, 79% |
| Smedsrud et al. [15] | Significant (n=43) vs. non-significant CAD (n=43) | 2D-STE, coronary angiography (EchoPAC-GE) | Does duration of early systolic lengthening predict significant CAD? | Early systolic lengthening (cutoff 58 milliseconds) predicts significant CAD better than peak systolic LS attenuation |

2D-STE, 2 dimensional-speckle tracking echocardiography; CAD, coronary artery disease; CT, computed tomography; DSE, dobutamine stress echocardiography; GLS, global longitudinal strain; LS, longitudinal strain; pEF, preserved ejection fraction; SR, strain rate; TVI, tissue velocity imaging.

Timing of mitral valve (MV) interventions prior to permanent myocardial remodeling [13, 14].

Coronary Artery Disease

2D-STE is robust in terms of its prognostic utility and reproducibility in the assessment of subclinical CAD (Table 2) [15]. Various strain parameters such as early myocardial systolic lengthening (15), ratio of peak systolic LS difference to peak systolic GLS [16] and a combination of early systolic and early diastolic SR [17] provide incremental value over GLS for obstructive CAD. Strain assessment during dobutamine stress echocardiography (DSE) could enhance the sensitivity of conventional 2D-echo by minimizing interobserver variability in delineating endocardial borders and interpreting wall motion abnormalities as demonstrated by using software such as automated functional imaging (AFI). Strain rate imaging offers incremental value over DSE derived wall motion scores in the prediction of mortality [18]. Additionally, a remarkable coronary territorial correlation between AFI derived strain and angiography with a sensitivity >90% in the anterior and >79% in the posterior circulations has been demonstrated [16, 18].

Hypertension and Diabetes Mellitus

Attenuation of 2D-STE derived GLS presents a vital differentiating parameter between hypertensive heart disease and an athlete’s heart while providing excellent correlation with the magnitude of diastolic dysfunction in hypertensives [19]. Detection of LS impairment by 2D-STE precedes detection by tissue Doppler imaging (TDI) in hypertensives with preserved LVEF even prior to the development of left ventricular hypertrophy (LVH) [20] thus providing an early opportunity to arrest progression to LVH. Indeed, preserved CS and consequent wall thickening despite reduction in LS has been posited to explain preservation of LVEF in patients with systemic hypertension [21].

Although diastolic dysfunction is believed to be the underlying pathophysiology in HFpEF, recent studies have indicated abnormalities of systolic function in these patients [24]. Indeed, traditional diastolic dysfunction parameters were absent in approximately one-third of the HFpEF trial cohorts [25, 26]. Systolic impairment of strain parameters (LS, CS) has been demonstrated in HFpEF patients, with LS attenuation being associated with higher NT-pro BNP levels [27]. 2D-STE derived increases in LS delay index and time to achieve peak longitudinal velocity unveil the dysfunctional systolic component of HFpEF indicating dysynchronous and ineffective ventricular contraction [28] (Table 3). Previous studies have hypothesized that reduction of dysynchrony by cardiac resynchronization therapy could translate into energy efficient contractility and mitigate progression to systolic failure [28].
v) Perimyocarditis

Incipient myocardial dysfunction has been demonstrated in acute perimyocarditis with compromise in GLS and twist angle preceding reduction of LVEF [29] (Fig. 1). Impairment of CS and TS with intact LS in constrictive pericarditis as opposed to impaired LS and intact CS in restrictive cardiomyopathy effectively differentiates these conditions [30].

vi) Cancer Chemotherapy

Routine serial assessment of LV strain parameters could aid in earlier identification of chemotherapy-induced cardiotoxicity prior to conventional changes in LVEF (Table 4). Attenuation of 2D-STE derived LV apical cap peak systolic strain [31], GLS, torsion, twisting and untwisting rates occur as early as 1 month after anthracycline (AT) therapy, preced-
MISCELLANEOUS CONDITIONS

Apical sparing, evidenced by relative apical LS>1 (mean apical LS/mean basal LS+ mean mid-LS) discriminates cardiac amyloidosis from AS or hypertrophic cardiomyopathy induced LHV with a sensitivity>90% and specificity>80% [32] (Fig. 2). LS impairment is associated with elevated NT-proBNP in Behcet’s disease (Table 5). In Fabry’s disease, systolic strain attenuation in the basal postero-lateral segments offers a sensitivity and specificity of 90% and 97% respectively, for the identification of MRI confirmed fibrotic arrhythmogenic foci [33]. Systemic Sclerosis is characterized by impairment of global and LV longitudinal peak systolic strain (PSS) with higher attenuation in the basal segments and sparing of the apical and medial segments [34]. Moreover, reduced GLS and global CS were independently predictive of ventricular arrhythmias in systemic sclerosis patients [35].

Strain derived radial LV wall motion discoordination was shown to be an independent predictor of decline in cardiac output in acute pulmonary embolism [54]. Subclinical LV dysfunction inherent to preeclampsia has been identified by a higher decline in global LS, RS and CS than in non-proteinuric hypertension [55]. Sickle cell crisis results in transient LV dysfunction with reversal of regional LS impairment on crisis resolution [38].

OBLIGATORY NEED FOR STANDARDIZATION IN SPECKLE TRACKING ECHOCARDIOGRAPHY

Marwick et al. have described discordant strain values from different vendors to result from three components: 1) Image procurement and storage resolution; 2) Processing of image data for strain quantification and 3) Hemodynamic status [35]. Image acquisition with vendor specific ultrasound machines, heterogeneity in frame rates used for compression (30 frames/sec for vendor neutral software), differences in the methodology of algorithms used to derive strain, types of strain used (natural or Lagrangian strain), anatomical regions studied to derive strain (endocardial, epicardial or both), phase of the cardiac cycle in which images are acquired and blood pressure variations during image procurement are all sources of discrepancies [35]. Head-to-head comparisons between different combinations of ultrasound machines and vendor specific versus vendor neutral post-processing software has depicted higher variations from sound machines, heterogeneity in frame rates used for compression, different algorithms used for strain derivation, different types of strain used (natural or Lagrangian strain) and different frame rates for strain output [36]. When vendor neutral software is used, standardization of methods to derive strain has been shown to minimize GLS variations even at frame rates as low as 30 frames/second [39, 40].
A concerted effort to standardize strain software between a conglomerate of vendors supported by the American Society of Echocardiography and the European Society of Echocardiography is afoot. It is hoped that this endeavor will eventually culminate into standardization of postprocessing software to minimize variability between vendor offerings.

**FUTURE DIRECTIONS**

Barriers to use of strain imaging in routine practice include physician reluctance to adopt innovative technology with perceived complexity, lack of standardization and reimbursement limitations. Whether interventions following identification of subclinical LV dysfunction could translate into reduced cardiovascular morbidity and mortality needs further appraisal in prospective randomized controlled trials. Further technologic refinements targeting these limitations could transform 2D-STE into a robust modality for the routine detection of subclinical myocardial dysfunction, given its increasing ease of use and wide applicability.

**LIST OF ABBREVIATIONS**

- **2D-ECHO** = 2-dimensional echocardiography
- **2D-STE** = 2-dimensional speckle tracking echocardiography
- **AF** = Atrial fibrillation
- **AFI** = Automated functional imaging
- **AR** = Aortic regurgitation
- **AS** = Aortic stenosis
- **AT** = Anthracycline
- **AV** = Aortic valve
- **CAD** = Coronary artery disease
- **CS** = Circumferential strain
- **DSE** = Dobutamine stress echocardiography
- **GLS** = Global longitudinal strain

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**Table 5.** Miscellaneous conditions underscoring the clinical applicability of speckle tracking echocardiography.

| Study             | Sample size with description | Imaging modality with vendor name                  | Objective                                                                 | Outcomes                                                                 |
|-------------------|------------------------------|---------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Yagmur et al.     | Behcets disease (n=32) vs. controls (n=27) | 2D-ECHO and 2D-STE (QLab-Philips)                 | Detection of subclinical LV dysfunction                                   | Reduced LS (-17.8 ± 2.7%) in disease vs. controls (-20.5 ± 1.8%); NT-proBNP independent correlate of mean LS |
| Liu et al. [51]   | Hemodialysis patients (n=102) | 2D-ECHO, TDI and 2D-STE (EchoPac-GE)              | Predictors of significant CAD despite pEF in hemodialysis patients         | Reduction in LS ≥-15% in ≥6 myocardial segments predicts CAD             |
| Dedobbeleer et al. [52] | Friedreich’s ataxia (n=20) vs. controls (n=20) | 2D-ECHO and 2D-STE (QLab-Philips)                 | Stain profiling, detection of subclinical LV dysfunction                  | Reduced GLS (-15.3 vs. -17.5%), peak LV twist and untwisting rates      |
| Caputo et al. [53] | At least 1 cardiovascular risk factor (n=70) | 2D-ECHO, TDI and 2D-STE (EchoPAC-GE)              | Abnormal LV strain in overweight (BMI) despite pEF                       | Peak LS of LV-reduced in overweight vs. normal BMI (-17.2% vs. -18.7%)   |
| Takamura et al. [54] | Acute PE (n=25) vs. controls (n=25) | 2D-ECHO and 2D-STE (EchoPAC-GE)                  | Impact of acute RV pressure overload on LV strain                         | Global LS (-16 vs. -20), CS (-17 vs. -24) and RS (44 vs. 59) reduced in acute PE, recover with the resolution of pressure overload |
| Shahul et al. [55] | Preeclampsia (n=11) vs. non-proteinuric hypertension (n=11) vs. normotensives (n=17) | 2D-ECHO and 2D-STE (TomTec)                      | Is subclinical LV dysfunction inherent to preeclampsia?                   | Impaired GLS (-13.7 vs. -15.9 vs. -20.1), GRS (22.4 vs. 40.7 vs. 39.8) and GCS (-17.9 vs. -28.2 vs. -21.6) in preeclampsia. pEF in all groups |
| Inoue et al. [56] | RV apical pacing (n=51)+ RV septal pacing (n=52) vs. controls (n=50) | 2D-ECHO and 2D-STE (EchoPAC-GE)                  | Subclinical LV dysfunction with RV apical pacing                          | Maximal impairment of GLS with RV apical pacing [-14.3 vs. -16.8 vs. -18.2] |
| Miszalski-Jamka et al. [57-59] | Wegener's granulomatosis (n=22) vs. controls (n=22) | 2D-ECHO and 2D-STE (EchoPAC-GE)                  | Subclinical LV dysfunction identification                               | Global LS (-17.9 vs. -19.7), CS (-18.4 vs. -21.6) and RS (38.8 vs. 50.1) impairment noted, correlate with disease severity. |

2D-ECHO, 2 dimensional echocardiography; 2D-STE, 2 dimensional speckle tracking echocardiography; BMI, body mass index; CAD, coronary artery disease; CS, circumferential strain; GCS, global circumferential strain; GRS, global radial strain; LS, longitudinal strain; LV, left ventricle; PE, pulmonary embolism; pEF, preserved ejection fraction; RS, radial strain; RV, right ventricle; TDI, tissue Doppler imaging.
HFpEF = Heart failure with preserved ejection fraction
LS = Longitudinal strain
LV = Left ventricle
LVEF = Left ventricular ejection fraction
MS = Mitral stenosis
MV = Mitral valve
NT-proBNP = N terminal-pro brain natriuretic peptide
pEF = Preserved ejection fraction
PSS = Peak systolic strain
RS = Radial strain
RV = Right ventricle
SR = Strain rate
TS = Torsional strain
TDI = Tissue doppler imaging

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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