Clinical Applications of Left Ventricular Global Longitudinal Strain by 2D-Speckle Tracking Echocardiography

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Abstract:

Evaluation of myocardial strain may be able to circumvent several of the LVEF measurement drawbacks when evaluating LV systolic performance. Regardless of the ultrasound beam's angle of insonation, speckle tracking echocardiography enables the measurement of myocardial strain in three different spatial directions: longitudinal, radial, and circumferential. In clinical practise, longitudinal strain is most likely the strain type most often utilised to describe LV systolic function and has significant prognostic and diagnostic roles in evaluating different myocardial diseases.

Keywords: GLS, echocardiography, speckle tracking.

Tob Regul Sci. ™ 2023;9(1): 4825-4839

DOI: doi.org/10.18001/TRS.9.1.336

Introduction:

The echocardiographic assessment of regional myocardial function plays a critical role in the diagnosis and management of ischemic heart disease and in most laboratories relies on the visual detection of endocardial wall motion abnormalities and assessment of left ventricular (LV) ejection fraction. However, this approach is subjective and operator dependent, demands complete visualization of the endocardium and is subjected to the cardiac loading and heart rate. Thus, there is a need for an objective, comprehensive, noninvasive measurement of myocardial performance and contractility with acceptable interpretative variability **(1)**.

Measurements of myocardial strain and strain rate (SR) are newer indices those have the potential to overcome these limitations. Strain and SR represent the magnitude and rate, respectively, of myocardial deformation, which is an energy requiring process that occurs in both systole and diastole. Abnormalities of myocardial deformation are seen early in the development of many pathophysiologic states including ischemia and thus provide a sensitive means for detecting regional myocardial dysfunction **(2)**.

Tissue Doppler also allows indirect computation of myocardial deformation by the use of velocity gradients along the myocardial tissue. This allows an accurate assessment of myocardial deformation and thus enables quantification of myocardial strain and strain rate (SR). These deformation indices are not affected by the tethering phenomenon and are therefore direct indices of myocardial contractility **(3).**

Speckle tracking echocardiography (STE) has emerged as a new noninvasive ultrasound modality for quantifying myocardial mechanics. It evaluates tissue motion by tracking natural acoustic reflection and interference patterns within a defined ultrasound window. This tracking is performed by an image processing algorithm which tracks blocks of 20–40 pixels (Kernels), which contain markers or fingerprints also called Speckles **(4).**

This modality is therefore an angle independent analysis of tissue motion and deformation. Thus STE is inherently evaluates myocardial deformation or strain, as opposed to tissue Doppler strain, which indirectly computes strain from velocity gradients**,** Doppler derived strain is highly dependent on the angle of interrogation and is therefore likely to be reliable only in the apical imaging planes and unpredictable in the parasternal long axis and short axis planes **(5)**.

Main technical considerations:

The term "speckle tracking" denotes that this method is focused primarily on the study of speckles during the cardiac cycle. Single speckles are fused into functional units (kernels), which are then unambiguously recognisable due to the speckles' distinctive arrangement. As a consequence, each kernel acts as an ultrasonic fingerprint that can be followed by software throughout the cardiac cycle. Without using the Doppler signal, the system can calculate displacement, rate of displacement (velocity), deformation (strain), and rate of deformation (strain rate) of selected myocardial segments and LV rotation by analysing the motion of each kernel that composes a routine 2-dimensional grey scale image **(6)**.

To decrease random noise, each sample for a speckle tracking echocardiographic analysis must be generated by averaging at least 3 consecutive cardiac cycles and setting the frame rate of the routine 2-dimensional picture capture between 60 and 110 frames per second, as indicated in the literature. Because of the close association between speckle tracking echocardiography and single-cardiac-cycle strain analysis, it is unable to perform research in patients with non-sinus rhythms **(7)**. The results produced from speckle tracking echocardiography have been confirmed against sonomicrometry and tagged MRI, demonstrating good feasibility and repeatability. The stringent reliance on frame rate and good quality 2-dimensional pictures, which are required for establishing an adequate characterization of the endocardial boundary, are significant potential limits of this innovative approach **(8)**.

1- Strain:

Strain represents a measure that evaluates the degree of deformation of the analyzed segment in relation to its initial dimensions. It is expressed as a percentage. ***The strain equation (ε) is as follows:*** $\varepsilon = L - L0/L0$, where L is the length of the object after deformation and L0 is the basal length of the object. A lengthening or thickening deformation is given a positive value depending on the direction, whereas a shortening or thinning deformation is given a negative value **(9)**.

2- Strain rate:

The strain rate (ε′) represents the myocardial deformation rate. It is expressed as second S^{-1}; in other words, if the same strain value is reached in half the time, the strain rate value will be doubled. Experimental studies have shown that the strain rate is less dependent on LV load variations than strain. However, because the strain rate signal is noisier and less reproducible, most clinical studies still use strain measurements **(10).**

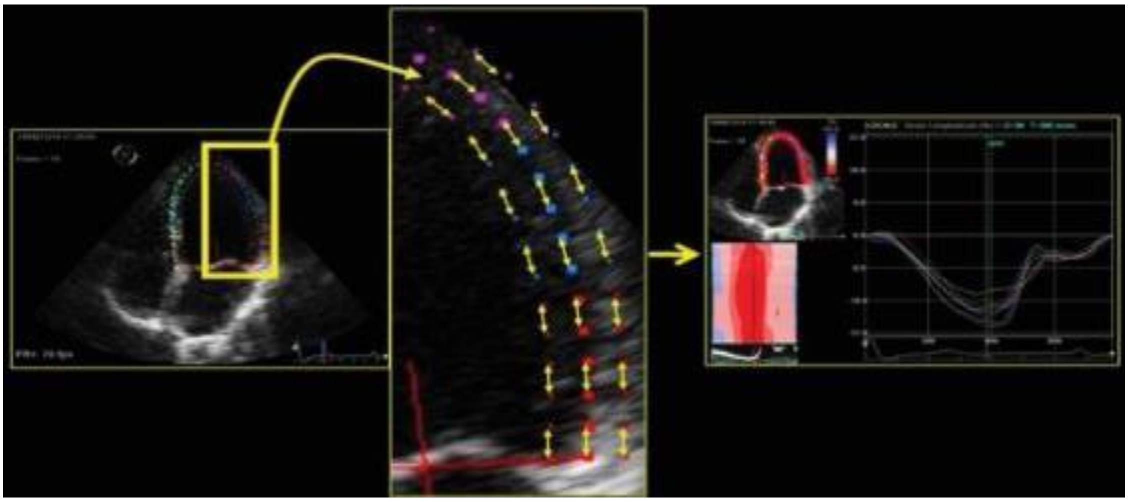
3- Longitudinal strain:

Longitudinal strain represents myocardial deformation directed from the base to the apex. During systole, ventricular myocardial fibers shorten with a translational movement from the base to the apex; the consequent reduction of the distance between single kernels is represented by negative trend curves (figure 1A) **(8)**.

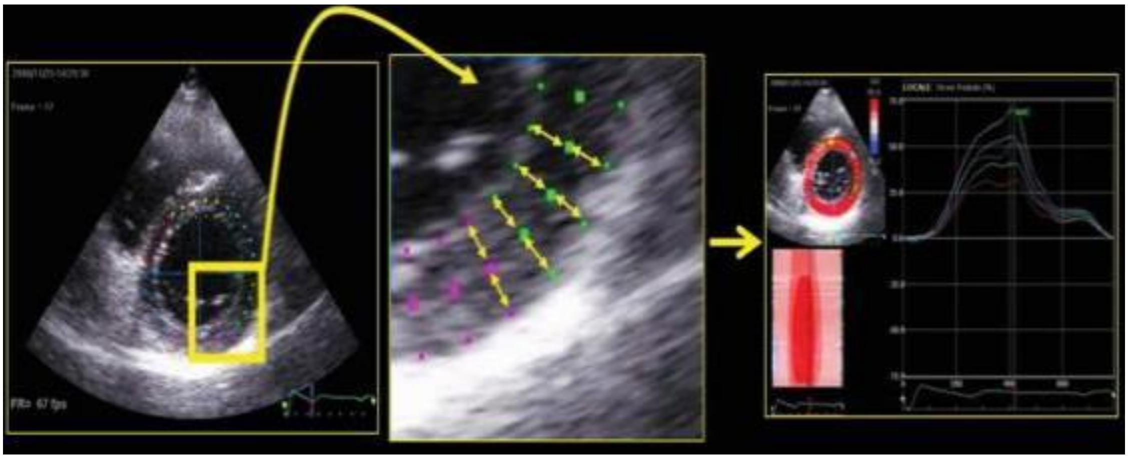
Through longitudinal strain analyses in 4-chamber, 2-chamber, and apical long axis views, both regional (relative to each of the17 LV segments) and global strain values (global longitudinal strain) can be obtained. Global longitudinal strain recently has been validated as a quantitative index for global LV function **(8)**.

The same measurement can be applied to the speckle tracking echocardiographic analysis of longitudinal myocardial deformation of the left atrium (LA) and right ventricle (RV), obtaining the peak atrial longitudinal strain and the RV longitudinal strain, respectively **(11)**.

A



B



C

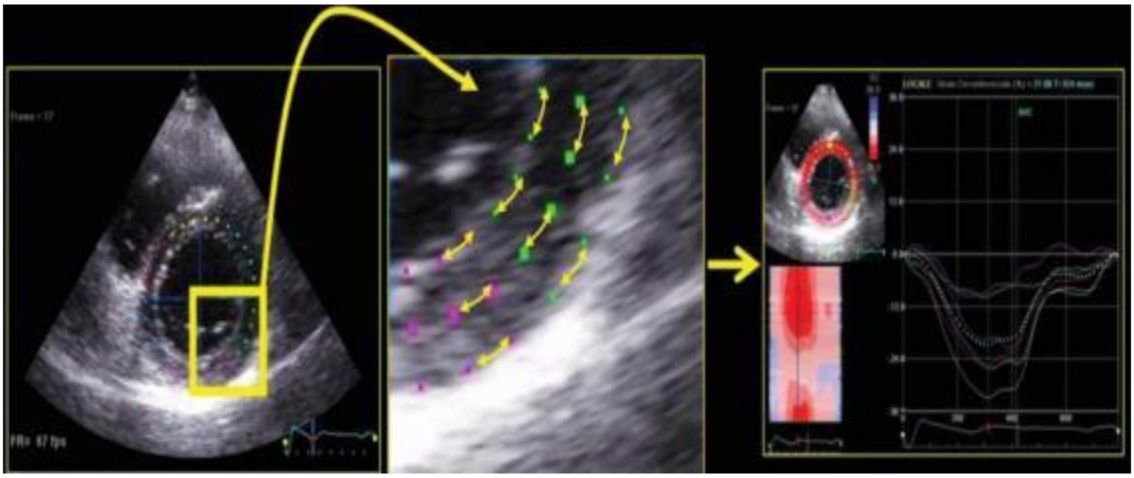


Figure (1): Speckle-tracking echocardiographic analysis of myocardial deformation showing measurements of longitudinal strain (A), radial strain (B), and circumferential strain (C) **(8)**

4- Radial strain:

Radial strain illustrates the LV thickening and thinning motion during the cardiac cycle by representing radially directed myocardial deformation, i.e. toward the center of the LV chamber. As a result of the increasing radial propulsion of single kernels during systole, radial strain values are depicted by positive curves (figure 1B) **(8).**

5- Circumferential strain:

On a short-axis image (figure 1C), circumferential strain shows LV myocardial fiber shortening throughout the circular perimeter. As a result, during systole, circumferential strain data are represented as negative curves for circumferential speckle-to-speckle distance reduction. In the case of longitudinal strain, a global circumferential strain value may be calculated **(12).**

6- Twisting and torsion:

The only way to assess LV twisting was to use an MRI scanner. Speckle-tracking echocardiography has just developed as a novel method for assessing LV twisting. The reciprocal rotation of the LV apex and base during systole causes left ventricular twisting, which is an essential part of cardiac biomechanics **(8)**.

The measurement of LV twisting by speckle-tracking echocardiography is made feasible by evaluating the reciprocal rotation of the LV apex and base during systole, which is intrinsic to its physiologic properties. The net difference in mean rotation between the apical and basal levels is then used to compute left ventricular twisting (figure 2). Torsion of the left ventricle is defined as LV twisting normalized by the base-to-apex distance **(13)**.

7- Untwisting:

Untwisting's significance in diastolic LV filling mechanics has recently gotten a lot of attention. Untwisting velocity is regarded to be a vital first expression of active relaxation, making it useful for studying diastole and, in particular, isovolumic relaxation, because it appears to be less load-dependent than other diastolic measures **(14).**

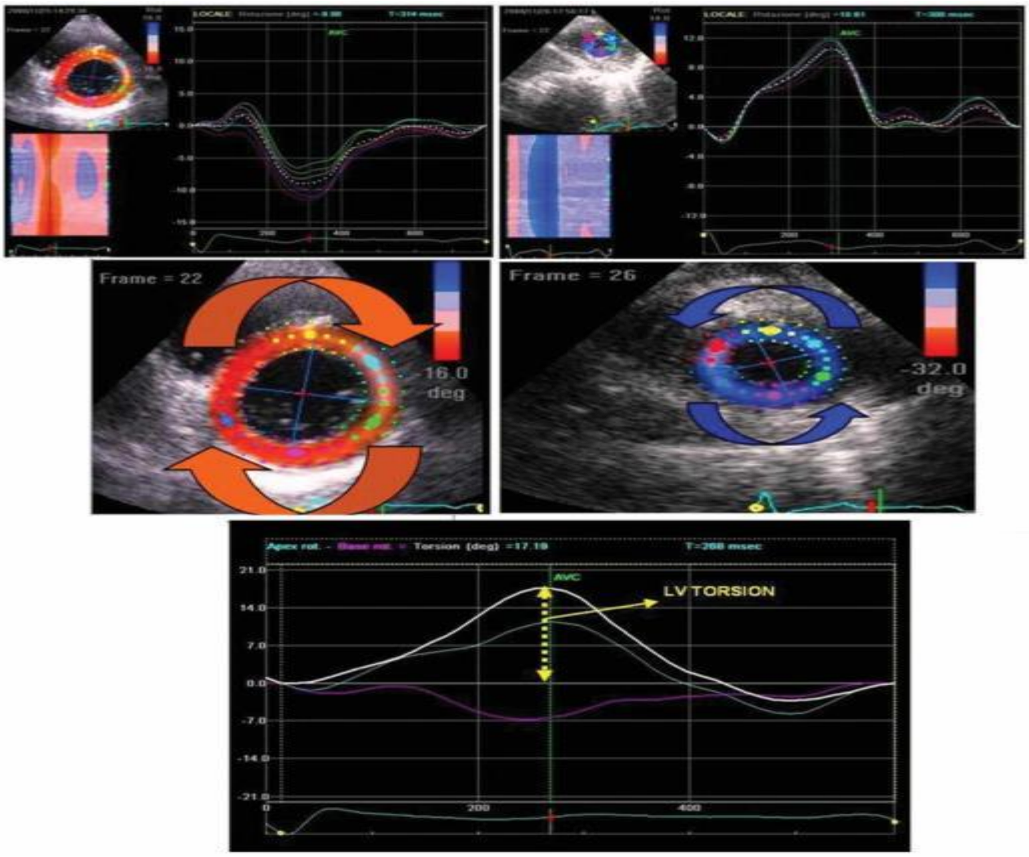


Figure (2): Graphic depiction of left ventricular rotational dynamics showing rotation of the cardiac base (**left**) and apex (**right**). In the bottom panel, a diagram of left ventricular (LV) twisting measurement is represented as the net difference between mean apical and basal rotation; left ventricular torsion is calculated by normalizing left ventricular twisting with the base-to-apex distance. AVC indicates aortic valve closure **(8).**

Other measurements:

Such as peak systolic strain, end-systolic strain, post-systolic strain (PSS), and peak strain (figure 3). A can be seen, the definition of end-systolic of particular interest, as derived parameters such as post-systolic shortening directly depend on it **(15).**

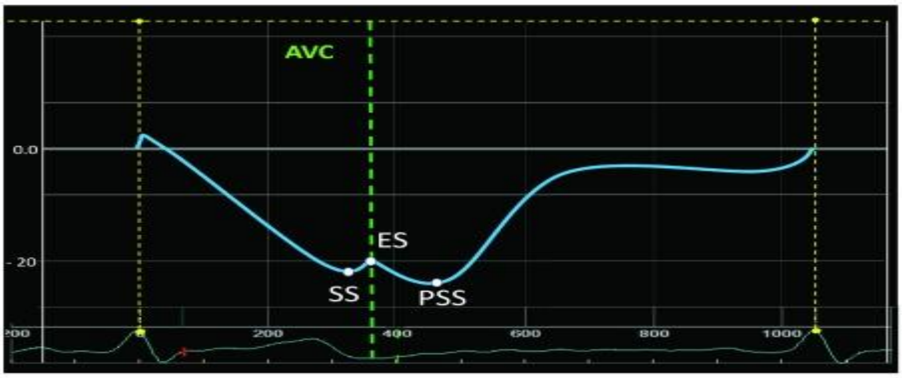


Figure (3): Overview and definition of commonly used strain measurements. Peak systolic strain (SS) is always measured before aortic valve closure (AVC). End-systolic strain (ES) is measured on AVC. Post-systolic strain (PSS) peaks after AVC **(15).**

2D-STE is although a useful and validated technique, it is based on assumptions that speckles always remain within the confines of the 2D image planes and can be accurately tracked throughout the cardiac cycle. This assumption may not be always being valid because of the 3D motion of cardiac chambers. 2D-STE is unable to measure one of the three components of displacement vectors, and this adversely affects the accuracy of various derived strain indices **(16).**

How to obtain strain parameters?

1- Image acquisition:

Images for speckle-tracking echocardiographic analysis are acquired and recorded using traditional 2-dimensional grey scale echocardiography during breath holding with steady electrocardiographic tracing, which is currently done offline. In order to obtain true apical and short-axis images using standard anatomic landmarks in each view and avoid foreshortening of the analysed myocardial structure, care must be taken to obtain true apical and short-axis images using standard anatomic landmarks, care must be taken to avoid foreshortening of the analysed myocardial structure, allowing for a more reliable delineation of the endocardial border. For 2-dimensional picture capture, the ideal frame rate is between 60 and 110 frames per second **(17).**

These parameters are suggested for combining high temporal resolution with adequate spatial definition and improving the frame-to-frame tracking technique's viability. It's best to start with a speckle tracking echocardiographic analysis of an apical long-axis chamber view to find the frame that corresponds to aortic valve closure, since this will serve as a valuable reference for the rest of the investigation. For longitudinal strain and peak atrial longitudinal strain investigations, apical 4- and 2-chamber views are required. Short-axis recordings are collected from a typical parasternal probe location for the basal plane and a more distal anterior or anterolateral position for the apical plane, which are beneficial for radial strain, circumferential strain, and rotation analysis. To standardize acquisitions, the basal plane is defined as the plane that includes the tips of the mitral leaflets, whereas the apical plane is defined as the plane just proximal to the level at which the LV cavity end-systolic obliteration occurs distally to the papillary muscles. It is also important to make the LV cross section as round as possible **(8).**

2- Offline analysis:

Specific acoustic-tracking software, normally accessible on specialized workstations, is used to analyze recordings, allowing for an offline semi-automated analysis of speckle-based strain. A point-and-click method is used to manually trace the endocardial surface of the investigated myocardial segment in apical and/or short axis views. The algorithm then automatically generates an epicardial surface tracing, resulting in the creation of a region of interest. **(18).**

The program separates the region of interest into 6 segments after human modification of the region's breadth and shape, and the resulting tracking quality for each segment is automatically assessed as either acceptable or unacceptable, with the option of manual rectification. The software rejects segments for which no acceptable picture quality can be achieved and excludes them from the analysis. Finally, once the region of interest has been optimized, the program provides strain curves for each myocardial segment that has been selected **(19).**

The operator can derive regional and global peak and time-to-peak values from these curves (by averaging values recorded in all segments). The program automatically creates a topographic depiction of all 17 investigated segments if the longitudinal strain analysis is conducted in all three apical perspectives **(20).**

The operator can also obtain the longitudinal strain time to peak and the post systolic index (ie, the percentage of the post systolic strain value compared to the maximum strain peak of the evaluated segment) bull's-eye with a simple input, both of which have been shown to be useful in preliminary studies for the analysis and detection of potentially ischemic or dys-synchronous myocardial areas **(21).**

Clinical applications of speckle tracking echocardiography:

Prognostic implications:

In the general population, lower GLS was shown to be a powerful and independent predictor for vascular events such as stroke and myocardial infarction and for new onset of atrial fibrillation **(22).**

Myocardial disease:

The various myocardial diseases result in either an increased collagen deposition causing fibrosis, e.g. hypertension, myocarditis, ischemia, infarction and cardiomyopathy or could result myocardial infiltration, e.g. amyloidosis or glycogen storage disease. The various myocardial diseases which affect the myocardium and can be evaluated by strain and twist mechanics are:

- Coronary artery diseases (CADs) including acute and chronic ischemia, acute infarction and ischemic cardiomyopathy and viability studies.
- Hypertension.
- Idiopathic dilated CMP.
- Hypertrophic cardiomyopathy.
- Restrictive cardiomyopathy.
- Diabetic cardiomyopathy.
- Amyloidosis.
- Valvular heart disease.
- Dyssynchrony.
- Heart failure with preserved EF (**12)**.

Clinical applications in CAD:

A. Chronic ischemic disease:

Although strain imaging has a potential role in the diagnosis and management of virtually any disease that affects the myocardium, arguably its greatest potential is in the detection of ischemic heart disease. Because longitudinal mechanics predominate in the ischemia-vulnerable subendocardium, either Doppler- or 2D-derived strain can be used because both analyze the longitudinal component of deformation. In the appropriate patient at rest, subclinical LV systolic dysfunction has been shown to correlate with the presence of obstructive coronary disease. Thus, Doppler longitudinal systolic strain and strain rate (SRs) were significantly abnormal in visually normokinetic segments supplied by stenotic (>70%) arteries **(23)**.

In a prospective, observational study, tissue Doppler systolic and early diastolic strains in the basal anterior segment of patients with left anterior descending (LAD) coronary artery disease remained depressed for 1 hour after exercise (whereas velocity and strain rate (SR) quickly normalized), suggesting that strain-identified regional post-ischemic dysfunction (ie, myocardial stunning) may be diagnostic in patients with chest pain in whom the ECG has normalized **(24)**.

In a study of 2D strain imaging, a peak systolic longitudinal SR of 0.83 s-1 and an early diastolic SR of 0.96 s-1 predicted significant (>70%) stenosis with a sensitivity and specificity of 85% and 64% and 77% and 93%, respectively, suggesting the potential for early diastolic deformation to improve diagnostic accuracy **(25)**.

In another study of 108 patients undergoing coronary angiography, a 2D longitudinal strain of -17.9% discriminated severe 3-vessel or left main disease from lesser coronary artery disease with a sensitivity and specificity of 79% and 79%, respectively **(26)**.

Finally, in a cohort of patients with normal ejection fraction at increased atherosclerotic risk and /or with stable chest pain, a progressive impairment of 2D global strain and SR (the former with lower variability and higher reproducibility than the latter) was directly related to increasing severity of coronary disease as determined from multislice computed tomography. A global longitudinal strain (the average of segmental longitudinal strains) (-17.4%) provided high sensitivity and specificity (83% and 77%, respectively) in identifying patients with obstructive coronary disease **(27)**.

B. Acute ischemia (acute myocardial infarction):

This is usually an emergency room scenario where an immediate coronary intervention has highest priority. The echocardiographic examination should therefore be limited to the necessary minimum which is needed to clarify remaining clinical questions. Conclusions will be usually drawn from the immediate visual analysis of the image data **(28)**.

Longitudinal strains are reduced in patients with myocardial infarctions and correlate with infarct size and ejection fraction and predict LV remodeling and clinical events and response to reperfusion strategies **(29)**.

In a study of patients with recent first myocardial infarctions and matched control subjects, Strain and strain rate (SR) but not tissue Doppler velocities could differentiate normal from abnormally contracting segments **(30)**.

In a subpopulation of the same study who also underwent both Doppler Strain Imaging (DSI) and coronary angiography, longitudinal Doppler strain data displayed 85% sensitivity and specificity for the detection of infarct- involved segments using strain and SR cutoffs of -13% and -0.8 s-1, respectively. DSI and regional myocardial blood flow (contrast echo) predicted LV remodeling (> 20% increase in end-diastolic diameter) in 10 patients 4 to 6 months after reperfused ST-elevation myocardial infarction (area under the curve [AUC] for strain, 0.95; SR, 0.85; and regional myocardial blood flow, 0.90) and correlated with an LV functional improvement (ejection fraction increase > 10%) in an additional 19 patients **(30)**.

In 27 patients, percutaneous coronary intervention increased the early diastolic Strain Rate (SR) in ischemic (but not non-ischemic) segments and was associated with an increase in the early diastolic trans-mitral filling velocity; systolic SRs in ischemic and non-ischemic segments were unchanged **(31)**.

In 20 patients with severe angina ineligible for revascularization, an improvement in New York Heart Association angina class was associated with improvement in DSI (peak systolic strain), and systolic and diastolic myocardial and diastolic trans-mitral velocities with enhanced external counterpulsation **(29)**.

Extent of myocardial infarction:

A related issue-differentiating non trans-mural from trans-mural infarction has important implications for management, in so far as trans-mural segments worsen prognosis are unlikely to improve after revascularization. Radial SR and Strain responses to dobutamine infusion were compared in a study of closed-chest pigs with chronic non trans-mural and trans-mural infarctions **(32)**.

Before infarction, dobutamine produced a linear increase in SR and a biphasic (increase with low dose, decrease with high dose) Strain response. In non trans-mural infarcts, baseline SR and Strain were reduced compared with control; during dobutamine infusion, Strain did not change and the SR response became biphasic. In trans-mural infarctions, both SR and Strain were considerably reduced and failed to respond to dobutamine. Post-systolic deformation occurred in both non trans-mural and trans-mural infarctions (although markedly so in the latter). DSI and contrast enhanced (ceMRI) were compared in 47 patients with a first myocardial infarction (21 trans-mural, 15 non trans-mural >50%, and 11 subendocardial < 50%) and 60 volunteers. An SR > - 0.59/s detected trans-mural infarction with high sensitivity and specificity (90.9% and 96.4%, respectively) and a - 0.98/s > SR >-1.26/s discriminated subendocardial infarction from normal myocardium with very good sensitivity and specificity (81.3% and 83.3%, respectively) **(32)**.

The ability of Speckle Tracking Echocardiography (STE) to assess infarct scar size (histology) and infarct-induced LV remodeling (end-systolic diameter) was examined in rats 4 to 10 weeks after LAD ligation. Circumferential and radial strains were both significantly decreased after infarction and were lowest in the infracted segments, but segmental circumferential strain was dependent to a similar extent on segmental fibrosis and end-systolic diameter, whereas segmental radial strain was more dependent on end-systolic diameter **(33)**.

The ability of Speckle Tracking Echocardiography (STE) to differentiate the transmural extent of infarction measured with ceMRI and dobutamine stress echo was tested in 80 patients with chronic LV ischemic dysfunction. Segments with trans-mural scar had lower circumferential strain and SRs than subendocardial (1% to 50% wall thickness) infarcts and normal myocardium. However, neither radial nor longitudinal deformation indices discriminated transmural from subendocardial scar, although longitudinal strain and SR (unlike dobutamine stress wall motion analysis) distinguished subendocardial infarct from normal segments **(34)**.

In contrast, a regional longitudinal strain cutoff value of - 4.5% distinguished non trans-mural from transmural infarction with high sensitivity and specificity (81.2% and 81.6%, respectively) **(35)** and a segmental radial strain cutoff value of 16.5% distinguished non transmural from transmural infarctions with reasonable sensitivity and specificity (70.0% and 71.2%, respectively), as did a circumferential strain cutoff value of - 11.1% **(36)**.

Global strains derived from Doppler Strain Imaging (DSI) and Speckle Tracking Echocardiography (STE) were assessed acutely and at 10 days in 36 patients after ST-elevation myocardial infarction treated with thrombolysis and were compared with infarct size and transmurality using ceMRI. LV global circumferential strain (from 6 segments) and particularly LV global peak systolic longitudinal strain (from 16 segments) correlated with infarct size; segmentally, circumferential strain better distinguished transmural from sub-endocardial necrosis than longitudinal strain (sensitivity and specificity of segmental circumferential strain to predict transmural necrosis of 80% and 74%, using a cutoff of -13.3%). Reproducibility was better with STE than DSI **(37)**.

In a study of 61 patients with non ST-elevation myocardial infarction, LV global longitudinal strain before revascularization (28% surgical, 69 % percutaneous coronary intervention) predicted infarct size (as did wall motion score index) 9 months after infarction. A global longitudinal strain >-13.8% (and a wall motion score index >1.3) identified patients with infarcts involving >12% of myocardium. Global circumferential and global radial strains were not as predictive. Thus, measurement of regional deformation and global strains with either DSI or STE, ideally in multiple directions, has the potential to identify infarct size and the trans-mural extension of a myocardial scar and therefore the extent of nonviable myocardium. Variable cutoffs between laboratories that may be explained in part by methodologic, analytic, and experimental design differences remain problematic **(38)**.

Viability:

The assessment of myocardial viability based on wall motion scoring during low-dose dobutamine infusion is subjective and often difficult. STE parameters identify viable myocardium. The viability of myocardial segments (96 segments, 12 rats) after coronary occlusion-reperfusion was assessed with histology (TTC staining) and 2D strain imaging. Segments with greater than 50% area of infarct had lower end-systolic radial and circumferential strains and longer time to peak strains than those with lesser degrees or no infarct, and an end-systolic radial strain less than 2% had a sensitivity and specificity of 88% and 95% for detecting infarcted areas greater than 50% **(39)**.

A study in patients compared the ability of STE radial strain and contrast- enhanced MRI (ceMRI) to predict recovery of 463 segments in 53 patients 9 months after revascularization. Segments that failed to recover had lower peak radial strain (15.2% versus 22.6%) and greater hyper-enhancement, and, using a cutoff of 17.2% for peak radial strain, functional recovery was predicted with high accuracy (AUC, 0.859) similar to MRI (AUC, 0.874) **(36)**.

The same group later reported similar findings in 512 dysfunctional segments at baseline; the accuracy to predict functional recovery 9 months after revascularization was similar for peak systolic radial strain (AUC, 0.846) and ce-MRI (AUC, 0.834). The combination of strain and hyper-enhancement improved diagnostic accuracy (AUC, 0.861) and their predictive power **(40)**.

Global LV strain (averaged peak systolic strain using semi-automated software) in 147 patients with an acute myocardial infarction was correlated with a viability index derived from single-photon mission-computed tomography (r = 0.79) and predicted an improvement in ejection fraction 1 year after the index infarction (sensitivity and specificity for improved ejection fraction > 5% of 86% and 74%, respectively) using a global LV strain cut-off -13.7% **(41)**.

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