European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 08, Issue 03, 2021

Evaluation of Cardiac Muscle Function Using Speckle Tracking in Non-ST-Elevation Myocardial infarction Patients

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Abstract

Background:Ischemic heart disease is the number one cause of mortality worldwide resulting in 7 million of the 53 million deaths in reported in 2010. Acute coronary syndrome is divided into ST-elevation myocardial infarction (STEMI), Non ST-elevation myocardial infarction (NSTEMI) and unstable angina. NSTEMI and unstable angina share similar pathophysiology and have similar clinical presentation with the only difference is positive cardiac biomarkers (cardiac Troponins and CK-MB) in the case of NSTEMI. Two dimensional (2D) speckle tracking echocardiography is a relatively new imaging technique. Like tissue Doppler imaging (TDI), it allows calculation of myocardial velocities and distortion parameters like strain and strain rate (SR) giving important information for assessment of systolic and diastolic function, particularly longitudinal strain, which both sensitive and specific in post myocardial. The main advantage of speckle tracking analysis is its ability to assess several planes (circumferential, radial and longitudinal) giving accurate data about LV dimensions and deformation with good correlation to tagged cMR and sonomicrometry as reference methods.The accuracy and sensitivity of detecting MI visually by detecting segmental wall motion abnormalities are moderate and operator dependent but improve greatly by using speckle analysis.

Keywords:Non-ST-Elevation Myocardial infarction (NSTEMI), Speckle tracking echocardiography

Ishemic Heart Disease:

Ischemic heart disease can be classified into stable coronary artery diseases (Chronic coronary syndromes) and Acute Coronary Syndromes which can be subdivided into ST-segment elevation myocardial infarction (STEMI) and Non-ST segment elevation acute coronary syndromes (NSTE-ACS) that includes both Non-ST segment elevation myocardial infraction (NSTEMI) and Unstable Angina (UA).

Both NSTEMI and UA have similar pathophysiology, clinical picture and Electrocardiographic features with only NSTEMI having positive cardiac biomarkers (Troponins and CK-MB).

Epidemiology*:*

Globally, Ischemic heart diseases are the leading cause of mortality; resulting in around 13.2% of total deaths in 2010 (7 million of total 53 millions).

Recent trends have altered the distribution of Acute Coronary Syndromes: widespread use of preventive measures and therapies like Aspirin, Statins and smoking cessation has led to reduced incidence of STEMI while aging with the higher prevalence of diabetes and chronic kidney diseases has resulted in more cases of NSTE-ACS with a trend towards increase in diagnosis of

NSTEMI over Unstable Angina due to the development of higher sensitive cardiac Troponin assays. **(1)**

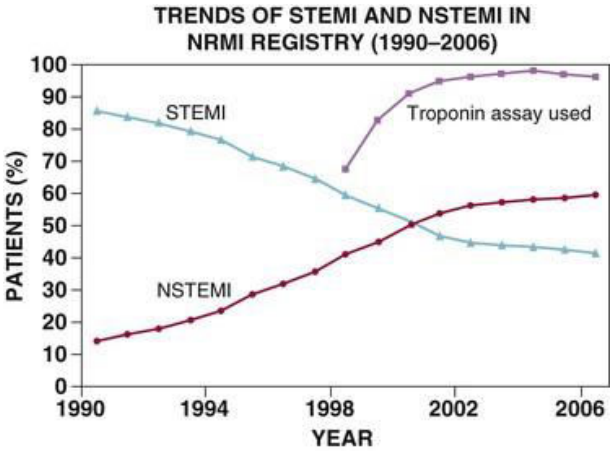

Figure 1: Trends of STEMI and NSTEMI **(1)**

Pathophysiology*:*

NSTEMI occurs due to mismatch or imbalance between myocardial O2 supply and demand mostly due to rupture or erosion of unstable atheromatous plaque leading to formation of a flow limiting but non-obstructive thrombus on top**.**

Activation of Coagulation cascade and platelets are crucial in the formation of thrombus on top of plaque rupture or erosion. The initial event is vascular injury or endothelial dysfunction leading to platelet adhesion via glycoprotein Ib and the sub endothelial Von- willebrand factor. Platelets exposure to sub endothelial collagen leads to its activation and degranulation and release of Adenosine Diphosphate (ADP) and Thromboxane A2 (TxA2) that leads to more platelet activation and expression of Glycoprotein IIb/IIIa **(2)**

In parallel, tissue factor when exposed leads to activation of coagulation cascade; Tissue factor along with activated factor VII (VIIa) and activated factor V (Va) lead to activation of factor X (Xa) which increases the production of activated factor II (Thrombin). Cascade continues when Thrombin induces activation of Fibrinogen into Fibrin which in turn leads to more platelet activation. Platelet bind to Fibrinogen via Glycoprotein IIb/IIIa (GP IIb/IIIa) leading to the formation of platelet-fibrin thrombus (Non occlusive in case of NSTEMI) which impairs blood flow leading to infarction. Several factors contribute to Plaque instability including loss of extracellular matrix in the fibrous cap which is attributed to matrix degrading enzymes. Inflammation and inflammatory factors play a central role in plaque thrombogenecity and plaque neovascularization leading to plaque expansion or hemorrhage. **(2).**

Role of Echocardiography in quantification of left ventricular function

Conventional Echocardiography

Echocardiogram can utilize one or more of three special type of echocardiography:

1)2-D (2-dimensional) echocardiography:

This technique is used to assess the actual structures of the heart and its motion.

2)M-Mode echocardiography:

It gives better temporal resolution and it is the mode of choice for some measurments, such as the chambers dimensions and the thickness of the heart walls. It produces an image that is similar to a line tracing rather than an actual picture of heart structures.

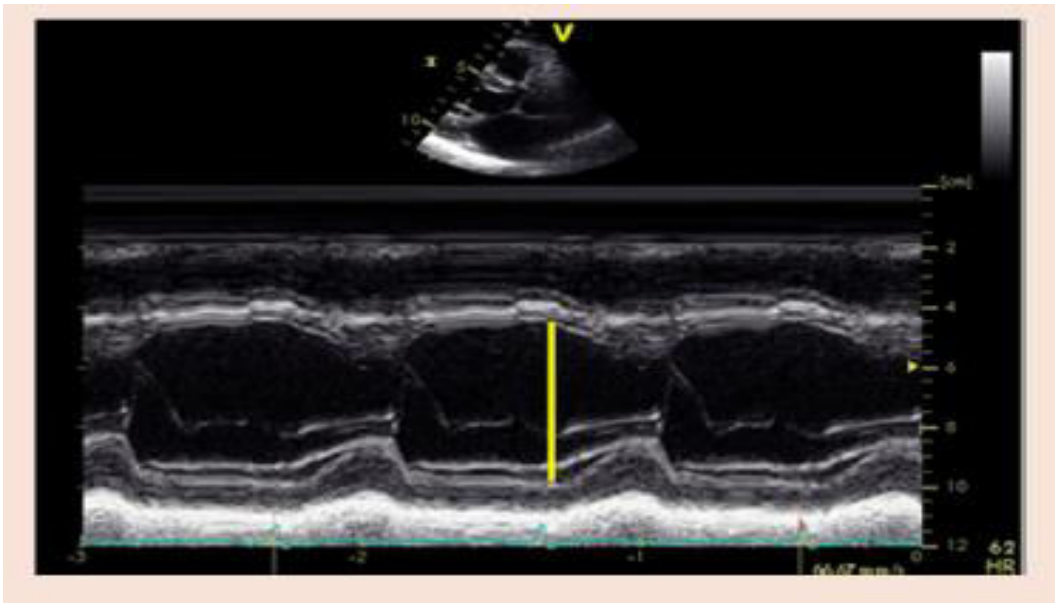

Figure 2 : M-Mode (**3**).

3) Doppler echocardiography:

This Doppler technique is used to measure and assess the flow of blood through the heart's chambers and valves. Doppler can also detect abnormal blood flow like shunts or valve regurgitations or stenoses. It has two main types pulsed-wave doppler and comntonous-wave doppler.

Color Doppler: in Color Doppler different colors are used to designate the direction of blood flow. This simplifies the interpretation of the Doppler technique

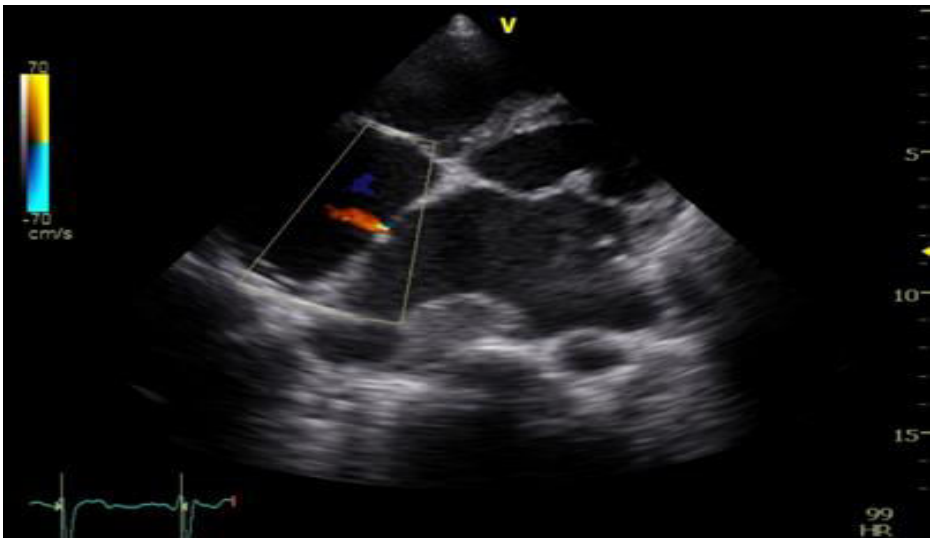

Figure 3 : Color Doppler(**3**).

Speckle Tracking Echocardiography:

Definition:

Speckle Tracking Echocardiography (STE) is a relatively new quantitative method that can be used with 2D or 3D echocardiography for studying the multi-directional components of left ventricular (LV) deformation by using the speckle pattern in the myocardium. It is a non-invasive method of definition of vectors and velocity. It is obtained automatically by measurement of the distance between 2 pixels of an LV segment during the cardiac cycle. It provides an objective, angle-independent and non-oppler method for studying LV deformation and dynamics in systole

and diastole. **(4)**

Basic definitions and terminology:

1. The Kernel:

Each cluster of speckles having a unique pattern of a specific region is known as a kernel. It is used to improve the tracking process and to avoid the inevitable loss of some speckles as a result of heart motion due to twisting or respiration. Each region of the myocardium has a unique kernel pattern and this pattern is relatively stable during the cardiac cycle. **(5)**

The machine defines a small region of kernel, and tracks its movement of the kernel in the next frames. **(6)**

2. Myocardial Strain:

It is defined as the fractional change in the length of a myocardial segment that is reported as a positive or negative percentage.In the ventriclar contraction, a negative

Strain value means shortening and a positive value means thickening. Deformation of a 3D object (myocardial segment) is complex with 3 normal strains along X,Y and Z axes and 6 shear strains. **(6)**.

Strain refers to the amount of tissue deformation normalized to its original shape. It represents the fractional change in one dimension, typically length, in response to a stress. It can be calculated as the difference between the final length (L) and the original length (L_0), divided by the original length.

$$\text{Strain} = [(L - L_0)/L_0] \times 100\%$$

Thus strain can be thought of as the percentage change in length.The instantaneous deformation expressed relative to the initial length is known as (Lagrangian strain). It could also be expressed relative to the length at a previous time instance (natural strain) and in this definition of instantaneous strain the reference value is not constant over the time but changes during the deformation process. For myocardial strain measurements it appears more appropriate to measure the natural strain because the measured values are less dependent on the definition of the initial length L_0. **(7)**

Myocardial strain can be obtained by tissue Doppler imaging (TDI) by temporal integration of the strain rate. TDI strain accuracy is subject to random noise, and suffers from Doppler angle error and under-sampling, while STE offers a direct measurement of myocardial deformation. **(8)**

3. Strain rate:

Strain rate (SR) is the rate of change in strain with units of 1 per second. It measures the time course of deformation and is the primary parameter of deformation derived from tissue Doppler **(6)**.

It is calculated as the difference in tissue Doppler velocity *(V)* between sample volumes divided by the distance (D) between them:

$$SR = (V2 - V1)/D$$

Normally, the ventricular myocardium has a negative strain rate in systole and a positive strain rate during diastole. The left atrium (LA) has a positive strain rate in ventricular systole and a negative strain rate during ventricular diastole. **(9)**.

Strain rate provides data on relative timing of myocardial motion and peak systolic and diastolic strain rates. Peak systolic strain rate is a measure of ventricular contractile function that is, unlike

strain, insensitive to changes in loading conditions. **(10)**

4. Longitudinal Strain:

Longitudinal strain represents myocardial deformation directed from the base to the apex. In 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

Through longitudinal strain analysis in 4-chamber, 2-chamber, and apical long axis views, both regional (relative to each of the17 LV segments) and global strain values

(Global longitudinalstrain) can be obtained. Global longitudinal strain recentlyhas been validated as a quantitative index for global LV function. (**11**)

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

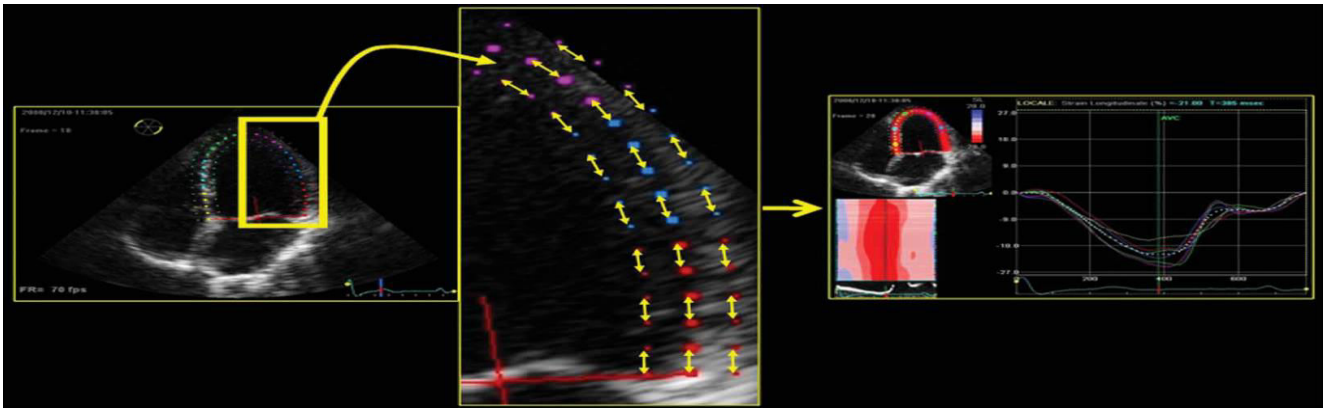

Figure 4 : longitudinal strain (LS) **(12)**

5. Radial Strain:

Radial strain represents radially directed myocardial deformation towards the center of the LV cavity, and thus indicates the LV thickening and thinning motion during thecardiac cycle. Consequently, during systole, given the progressive radial propulsion of

single kernels, radial strain values are represented by positive curves. Radial strain values are obtained by speckle-tracking echocardiographic analysis of both basal and apical LV short-axis views**. (12)**

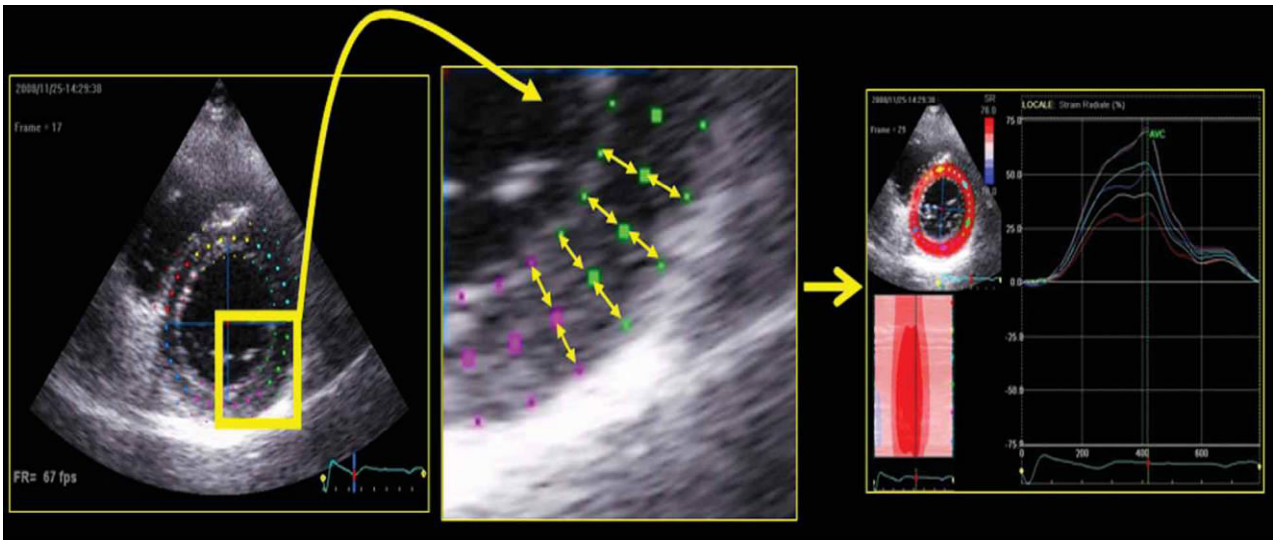

Figure 5 : radial strain (RS) **(12)**

6. Circumferential Strain :

Circumferential strain represents LV myocardial fiber shortening along the circular perimeter observed on a short-axis view **(12)**

Consequently, during systole, for circumferential speckle-to-speckle distance reduction, circumferential strain measurements are represented by negative curves. As for longitudinal strain, it is possible to obtain a global circumferential strain value.

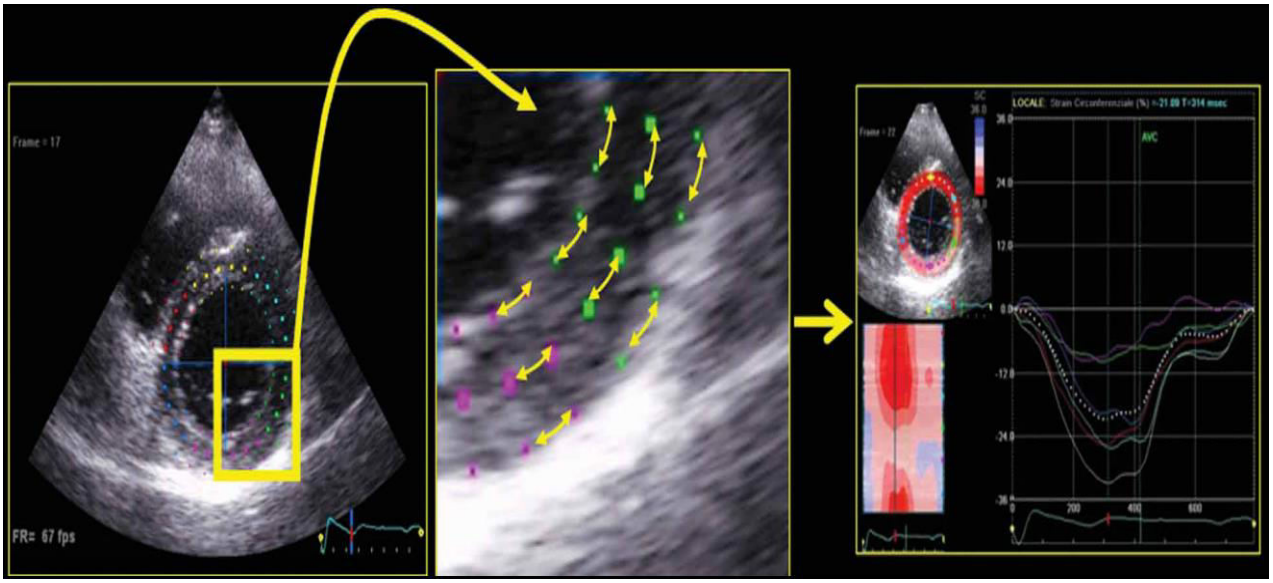

Figure 6 : circumferential strain (CS) **(12)**

7. Rotation, Torsion and Twist:

Rotation is the circular motion of the LV myocardium around its long axis, measured in degrees, while torsion is the gradient in rotation angle from base to apex, measured as degrees per cm. myocardial twist is defined as the relative rotation between the apex and base of the LV and is primarily determined by the epicardial muscle layer.

When the LV contracts or relaxes, the rotational motion of the myocardium causes lateral displacement perpendicular to the heart axis. This lateral rotational displacement of the myocardium is composed of longitudinal shear strain, in which the base of the heart is displaced laterally with reference to the apex when viewed from the side; and circumferential shear strain, in which the myocardium displays clockwise or counterclockwise rotation in the cross-sectional view. These two shear strains together form the longitudinal–circumferential shear strain of the LV **(13)**.

Although torsion mechanics are important for proper myocardial function, clinical applications of LV twist and torsion are still limited. Several studies on STE provided some interesting results. First, LV rotation and twist were not sex-related but were affected by age. Paradoxically, aging seemed to associate with higher rotation and twist. **(14)**.

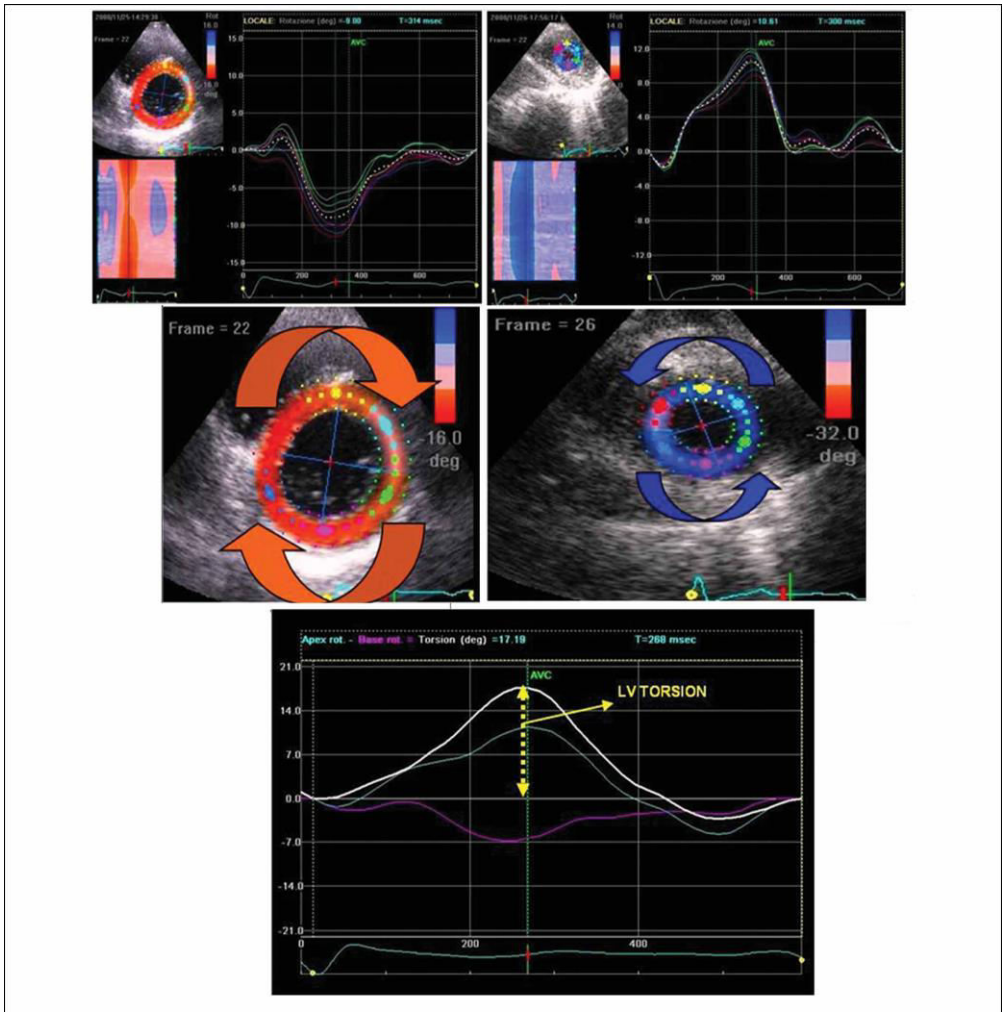

Figure 7: Graphic depiction of left ventricular rotational dynamics showing rotation of the cardiac base (left) and apex (right). In the bottom panel, a diagram of left ventricular (LV) twisting measurement is represented as the net difference between mean apical and basal rotation; left ventricular torsion is calculated by normalizing left ventricular twisting with the base-to-apex distance. **(12)**

Validation of speckle tracking echocardiography:

Speckle tracking requires a thorough understanding of echocardiographic imaging technique for both image acquisition and myocardial border tracing. Images must be of high-resolution quality to track regions of interest accurately. Myocardial strain derived from STE has been validated using tagged MRI.

Speckle-tracking strain results correlate significantly with tissue Doppler derived measurements. TDI technology is dependent on achieving a parallel orientation between the ultrasound beam and the direction of motion and therefore is applied mostly in apical views for recording longitudinal strains and from mid-anterior and mid-inferior segments of the LV in short-axis views for recording radial strains. STE, in contrast, can analyze the longitudinal and radial deformation of all LV segments from apical views and radial and circumferential strain of all LV segments from the short-axis views**(15).**

Speckle tracking–derived strain and strain rates do not require scaling for any index of LV morphology. **(16)**. Overall, speckle tracking appears to be highly reproducible and minimally affected by intra-observer and inter-observer variability.

Variations between MRI tagging and STE may be secondary to misaligned image planes and out-of-plane motion, which may not be accounted for by STE. Furthermore, initial studies using contrast echocardiography have shown wide inter-individual variability in the precision of strain quantification, suggesting that additional investigations are needed to understand thoroughly the use of strain techniques concomitant with contrast echocardiography.
Application of STE has also been extended for studying regional and global function of other cardiac chambers including the right ventricle and the left atrium. The complex geometry and thin walls of the right ventricle and left atrium may present considerable challenges in optimal positioning of the region of interest.Investigations with STE have primarily attempted to define the longitudinal deformation of the right ventricle, with some preliminary data suggesting a potential role in measuring the circumferential and rotational deformation of the right ventricle. **(17)**

Clinical uses and applications of STE:
In general, longitudinal LV mechanics, which are predominantly governed by the sub-endocardial region, are the most vulnerable component of LV mechanics and therefore most sensitive to the presence of myocardial disease. The mid-myocardial and epicardial function may remain relatively unaffected initially, and therefore circumferential strain and twist may remain normal or show exaggerated compensation for preserving LV systolic performance.
Assessment of myocardial mechanics, therefore, can be tailored per the clinical goals. The detection of altered longitudinal mechanics alone may suffice if the overall goal of analysis is to detect the presence of early myocardial disease. Further characterization of radial strains, circumferential strains, and torsional mechanics provides assessment
of the transmural disease burden and provides pathophysiologic insight into the mechanism of LV dysfunction. **(18)**

In general, speckle-tracking echocardiography may allow an unprecedented in-depth evaluation of myocardial systolic and diastolic dynamics across a broad range of physiologic and pathologic conditions beyond traditional echocardiographic techniques. Longitudinal strain provides a quantitative myocardial deformation analysis ofeach LV segment, also allowing for early systolic dysfunction detection in patients with a preserved LVEF**(18)**

1) Detection of subclinical Left ventricle dysfunction:
Global longitudinal strain (GLS) is a very promising method to identify patients with mild and subclinical systolic dysfunction that is not reflected in reduced EF. In patients with valvular heart disease, myocardial strain appears to be more sensitive than EF and can identify myocardial dysfunction before fall in EF.

In heart failure with preserved ejection fraction there may be reduction in GLS as a sign of reduced systolic function **(19)**.

In patients undergoing chemotherapy, the reduction in myocardial strain precedes the significant change in LVEF, and GLS by STE is recommended for early detection of subclinical LV dysfunction. **(20)**.

2) Detection of Left ventricle hypertrophy:

A. Physiologic Hypertrophy:

In physiological hypertrophy/athlete's heart, GLS was noted to be significantly higher than that measured in patients with pathological hypertrophy related to hypertrophic cardiomyopathy. **(21)**

B. Hypertensive Heart Disease:

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. **(19)**.

Torsional mechanics are also preserved. However, the untwisting may be abnormal and delayed. Early diastolic LV untwisting velocity during the isovolumic relaxation period is reduced and delayed and correlates with the degree of LV hypertrophy. Arterial hypertension is an ideal model for assessing the changes in different varieties of deformation occurring hand in hand with the development of LV concentric geometry (concentric remodeling and concentric LV hypertrophy). This is a crucial issue because experiences using standard echocardiography have shown that impairment of mid-wall fractional shortening of the circumferential fibers precedes the reduction of the LVEF. Speckle-tracking echocardiography has furthered the understanding that the interaction of the different deformations is much more complex under these circumstances. In particular, it seems that longitudinal and radial strain are impaired when circumferential strain is still normal and LV torsion, also maintained in the normal range, acts as mechanistic compensation to preserve a normal ejection fraction (EF)**. (22).**

These data are further sustained by the demonstration that in hypertensive patients with a preserved

LVEF, impaired longitudinal strain and increased LV torsion are associated with serum levels of the tissue inhibitor of matrix metalloproteinase 1, a marker of myocardial fibrosis, which represents the main determinant of LV diastolic dysfunction. These findings suggest that the change in collagen turnover and myocardial fibrotic process may cause early LV contractile dysfunction when the LVEF is still normal, and LV functional abnormalities seem to mainly affect the diastolic properties of the myocardium. **(23)**

3) Myocardial ischemia and coronary artery disease (CAD):

Ischemia leads to a reduction in regional myocardial function, which ranges from reduced systolic shortening (hypokinesia) to systolic lengthening (dyskinesia). Reduced systolic shortening, systolic lengthening, and post-systolic shortening, which are the three hallmarks of ischemic dysfunction, can be quantified both by velocity and deformation imaging.

LV longitudinal mechanics at rest may therefore be attenuated in patients with coronary artery disease. Reduced peak longitudinal strain rate and early diastolic strain

rate from resting echocardiography could predict >70% coronary stenosis with sensitivity of 85% and specificity of 64%, while reduced longitudinal strain (LS) was predictive of CAD with 97% sensitivity and 93% specificity during stress testing. **(24)**

4) Assessment of valvular heart diseases:

Because of adaptive remodeling of the left ventricle, patients can remain asymptomatic or minimally symptomatic for prolonged periods, even in the presence of severe valvular disease. STE improves the yield of routine 2D echocardiography (2DE) in valvular heart diseases by

providing insights into the pattern of adaptive remodeling and detecting the presence of subclinical cardiac dysfunction **(25)**

5) Assessment mechanical dyssynchrony and risk ofarrhythmias:

Normal ventricular activation spreads rapidly through the conduction system, resulting in a synchronized ventricular contraction. LV dyssynchrony, defined as non-uniform timing of peak myocardial shortening, may have several underlying mechanisms, including defects in His-Purkinje conduction, disturbances in electromechanical coupling, and purely mechanical causes. **(25)**

6) Cardiomyopathies:

In patients with non-obstructive hypertrophic cardiomyopathy and a preserved EF, speckle-tracking echocardiography has shown the capability to identify early major abnormalities of all strain components of myocardial deformation (longitudinal, circumferential, and radial strain. Another potential clinical application of speckle-tracking echocardiography is for differentiation of hypertrophic cardiomyopathy from athlete's LV hypertrophy based on the lower longitudinal strain values in patients with hypertrophic cardiomyopathy who have a normal LVEF**. (25)**

Limitations of strain imaging:

1. Technical factors:

A. Image quality:

The accuracy of speckle tracking is dependent on 2D image quality and frame rates. Low frame rates result in unstable speckle patterns, whereas high frame rates reduce scan-line density and reduce image resolution. Longitudinal strain data generally have been shown to have higher reproducibility than radial strain data. 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.

Similar to TDI, high frame rate imaging for two-dimensional (2D) speckle tracking is necessary. 2D speckle tracking frame rates are generally lower (average 80–90 Hz) than TDI which can achieve frame rates>100 Hz. This, results in under-sampling, especially in patients with tachycardia and also during strain and SR measurements performed throughout stress echocardiography. **(6)**

B. Selection of image clips:

With acquisition of multiple clips, 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).**(26)**

C. Selection of the region of interest:

Region of interest options for GLS include endocardial, midwall, epicardial, or full-wall strain, but still no evidence that favors one definition over another. GLS is highest in the endocardium and lowest in the epicardium. 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. The papillary muscles should not be included in the region of interest. **(26)**

D. Selection of timing:

GLS compares baseline lengths, generally set at end-diastole (the frame before the mitral valve closure; 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).Alteration of the end-diastolic time may be necessary in dyssynchronous hearts with conduction delay or when analyzing cardiac structures other than ventricles (e.g., atria). Also, exact systolic temporal definitions may have a major impact on strain measurements **(27)**

2. Clinical factors:

A. Race and ethnicity:

Some studies suggest that race and ethnicity mat have some impact on the reference ranges for strain values. Current 2015 American Society of Echocardiography guidelines steer clear of defining normal ranges for GLS and instead highlight the considerable heterogeneity in published reports. As a guide, a value above -20% with a standard deviation of ±2% is likely to be normal. A Japanese study of 817 healthy volunteers (mean age: 36 years; 61% male), the overall mean full-thickness, peak systolic GLS was reported as -21.3 ±2.1%. **(28)**

An Italian study of 260 Caucasian healthy volunteers (mean age: 44 years; 43% male), the mean full-thickness, peak systolic GLS was reported as -21.5 ±2.0%. **(29)**

B. Age and sex:

Significant age-related reductions in deformation have been reported (e.g., GLS was -20.3% ±1.9% in healthy subjects over 60 years of age versus -22.1 ±2.4% in those <20 years of age; $p < 0.01$). **(Zghal et al. 2011)**

Sex-related differences have been described, with lower deformation noted in males than in females across all age groups studied. **(28)**

C. Exercise:

Athletes have been shown to have significantly higher GLS than sedentary normal controls. Sinus bradycardia and LV mass were independent determinants of supernormal GLS at rest. **(29)**

D. Pregnancy:

Despite changes in hemodynamics, GLS was not found to vary significantly in comparison between pregnant patients and in non-pregnant controls during trimesters of pregnancy. **(30)**

E. Medications:

The effects of medications on GLS values are poorly studied in humans. Treatment with 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 **(30)**

F. Obesity:

Obesity is associated with lower strain values in the absence of other Comorbidities or reduction in (LVEF). **(30)**

ConflictofInterest: Noconflictofinterest.

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