Quantitation of stress echocardiography by tissue Doppler and strain rate imaging: a dream come true?

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Tissue Doppler (TD) is an ultrasound tool providing a quantitative agreement of left ventricular regional myocardial function in different modalities. Spectral pulsed wave (PW) TD, performed online during the examination, measures instantaneous myocardial velocities. By means of color TD, velocity images are digitally stored for subsequent off-line analysis and mean myocardial velocities are measured. An implementation of color TD includes strain rate imaging (SRI), based on post-processing conversion of regional velocities in local myocardial deformation rate (strain rate) and percent deformation (strain). These three modalities have been applied to stress echocardiography for quantitative evaluation of regional left ventricular function and detection of ischemia and viability. They present advantages and limitations. PWTD does not permit the simultaneous assessment of multiple walls and therefore is not compatible with clinical stress echocardiography while it could be used in a laboratory setting. Color TD provides a spatial map of velocity throughout the myocardium but its results are strongly affected by the frame rate. Both color TD and PWTD are also influenced by overall cardiac motion and tethering from adjacent segments and require reference velocity values for interpretation of regional left ventricular function. High frame rate (i.e. > 150 ms) post-processing-derived SRI can potentially overcome these limitations, since measurements of myocardial deformation have not any significant apex-to-base gradient. Preliminary studies have shown encouraging results about the ability of SRI to detect ischemia and viability, in terms of both strain rate changes and/or evidence of post-systolic thickening. SRI is, however, Doppler-dependent and time-consuming. Further technical refinements are needed to improve its application and introduce new ultrasound modalities to overcome the limitations of the Doppler-derived deformation analysis.

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Introduction

The interest in stress echocardiography (SE) began at the onset of the '80s with the introduction of B-mode imaging, which provided a much more complete assessment of left ventricular (LV) regional wall function compared to the pre-existing M-mode technique. At the beginning, B-mode echo was successfully used in conjunction with supine or upright bicycle exercise[1,2], treadmill post-exercise[3-5], handgrip[6], and cold pressure test[7]. A further innovative progress in SE was the introduction of pharmacologic agents to induce ischemia, both vasodilators – such as dipyridamole and adenosine[8,9] – and sympathomimetic drugs, such as dobutamine[10,11]. Low-dose dipyridamole[12] and dobutamine[13] were also recognized capable of enhancing regional wall motion in akynetic or hypokynetic myocardial segments, and therefore were introduced into clinical practice for the identification of viable myocardium.

The major revolutionary development in SE, however, was the introduction of digital recording, with the possibility of obtaining a side-by-side display of rest and stress images using cine-loops of selected cardiac cycles, facilitating the recognition of even subtle wall motion changes[14-16]. More recent technologic improvements include tissue harmonic imaging[17] and last-generation contrast agents[18] that strongly improve the detection of endocardial borders.

To date, SE is largely applied in the clinical setting as an alternative and/or an integration of stress myocardial scintigraphy. Clinical cardiologists may apply SE for risk stratification of patients with ischemic heart disease by identifying both myocardial ischemia and viability[19-26]. A negative SE makes the occurrence of an adverse event unlikely, while a positive test

identifies patients at high risk[27]. Further prognostic information can also be obtained considering the time of ischemia during stress testing and the therapy at the testing time[28,29]. A prognostic impact of transthoracic Doppler-derived coronary flow reserve, better if combined with regional wall motion score (WMS) assessment[30], is also reasonably expectable.

In this view, the reliability of SE is a crucial issue. Current approaches to SE are subjective and semiquantitative, based on visual analysis of wall motion and thickening on gray-scale images, whose accuracy is strongly dependent by the operator[31] and his experience[32]. A more objective, less operator-dependent evaluation is therefore needed, which goes with the dream to achieve a true quantitative, parametric analysis of SE.

Tissue Doppler (TD) is an ultrasound tool that provides quantitation of regional myocardial function[33-37] and is obtained by modifying the filter setting and reducing the velocity range of standard Doppler signal. Different TD modalities are possible, including spectral pulsed wave (PW) and color TD. PWTD is performed on-line during the examination, and gives measurements of instantaneous systolic and diastolic myocardial velocities and time intervals[33,37]. Color TD is also performed on-line but images are generally stored digitally in cine-loop format for subsequent off-line analysis[38]. By using this approach, regional myocardial Doppler velocity profiles can be extracted at any sampled point and mean systolic and diastolic velocities can be measured. A sophisticated implementation of color TD is strain rate imaging (SRI), whose analysis consists in a post-processing conversion of myocardial velocities in deformation rate and percent deformation of the myocardium in a given region of interest[39,40].

One of the most interesting aspects of application of TD and deformation imaging to SE is that these techniques allow the study of the longitudinal function of the heart in the apical views. This is extremely important from the pathophysiologic point of view because the subendocardial layer of the LV myocardium is more sensitive to ischemia: this layer is formed by longitudinal muscle fibers, whose contraction can therefore be appropriately studied with TD and deformation imaging in the long-axis direction.

Although all TD modalities (PWTD, color TD and SRI) have been tested for quantitative SE in several studies, up to date their clinical application remains still under examination. Therefore, a critical review of TD SE may be useful to point out current advantages, limitations and future perspectives of these tools.

Pulsed wave tissue Doppler and stress echocardiography

Spectral PWTD has the peculiarity of measuring instantaneous peak velocities and time intervals by placing the sample volume at a myocardial or annular level. Three velocities are generally measured: peak systolic S_m (upon the baseline), early diastolic E_m, and atrial A_m, under the baseline. When the sample volume is positioned at the level of the mitral annulus, PWTD measures the amplitude and timing of longitudinal motion of the overall LV chamber[41]. Conversely, when it is located on a given myocardial segment, it allows the study of regional myocardial function[37] (Fig. 1). Both these approaches have been applied to SE.

Annular PWTD performed at the lateral, septal and posterior site of the mitral annulus and combined with the long-axis M-mode examination, has been recently used to differentiate ischemic from non-ischemic dilated cardiomyopathy[42]. In this experience, failure to increase M-mode systolic amplitude (total amplitude minus post-ejection shortening) by 2 mm or annular E_m velocity by 1.1 cm/s at peak dobutamine stress were the best discriminator for coronary artery disease (CAD). The predictive accuracy of the E_m velocity increase was higher than that achieved by the WMS in patients without left bundle branch block (sensitivity of 71 vs 67%, specificity of 94 vs 76%, both $p < 0.001$) (Table I)[42-48]. In another study, resting mitral annular S_m velocities at the sites corresponding to myocardial infarct regions were significantly lower than in the control group (5.5 ± 0.4 vs 11 ± 0.8 cm/s, $p < 0.001$) and exercise stress-derived S_m velocities corresponding to remote regions were lower in patients with multivessel disease[49]. In 45 patients with previous myocardial infarction, an increase of the mitral annular S_m velocity in myocardial infarct regions (lateral, posterior septal, inferior, anterior, postero-lateral, anterior septal region) > 2.0 cm/s at low-dose dobutamine SE predicted the presence of myocardial viability with a 92% sensitivity and a 90% specificity (Table II)[45,50,51].

Myocardial PWTD has also been used in SE. In 70 patients with known or suspected CAD, ischemic segments had the lowest increment in rest-to-peak dobutamine S_m velocity (< 90% in comparison with 148% of healthy controls); using an S_m velocity < 12 cm/s to define an abnormal response at peak dose, the sensitivity and specificity of PWTD for ischemia was 86 and 96% for basal segments, and 81 and 89% for mid-level segments[43] (Table I). In a territory-based analysis, failure to achieve a S_m velocity ≥ 10.5 cm/s at peak stress in the left anterior descending coronary artery and circumflex artery territories and a velocity ≥ 10.0 cm/s in the right coronary artery (RCA) territory, predicted the presence of CAD (stenosis > 50%) in the corresponding arteries with a sensitivity of 63% and a specificity of 76%; however, no incremental value was found in comparison with WMS analysis[44]. On the other hand, the combination of PWTD and wall motion analysis at the level of the infero-basal segment during dobutamine SE reduced false-positive results for inducible ischemia in 50 subjects undergoing coronary angiography, with a sensitivity of 81.8% and a specificity of

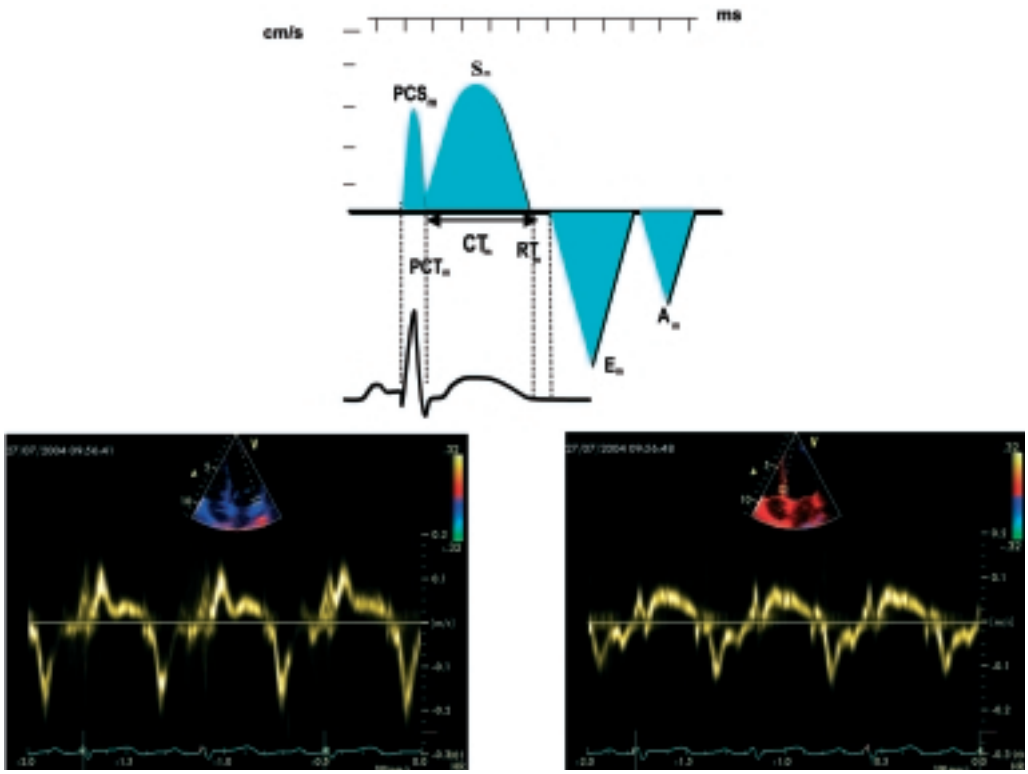

Figure 1. *Pulsed tissue Doppler of myocardial and mitral annular longitudinal velocities. In the* upper panel *a scheme of methodology for pulsed wave tissue Doppler is shown, with a positive pre-systolic velocity (PCS_m) occurring during pre-contraction time (PCT_m), a positive myocardial systolic velocity (S_m) occurring during contraction time (CT_m), and two negative early (E_m) and atrial (A_m) diastolic velocities. Relaxation time (RT_m) occurs between the end of contraction and the onset of early diastolic filling, i.e. between aortic valve closure and mitral valve opening. In the* lower panel *pulsed tissue Doppler recording by sampling the left ventricular lateral mitral annulus* (left lower panel) *and a given myocardial wall, which in this case is the posterior septal wall* (right lower panel).

Table I. Cut-off values at peak stress for the detection of myocardial ischemia, sensitivity and specificity of tissue Doppler (TD) and strain rate imaging (SRI) for the diagnosis of myocardial ischemia during high-dose dobutamine stress echocardiography.

TD modality	Cut-off value (at peak stress)	Sensitivity (%)	Specificity (%)	Reference
PWTD	Annular E_m < 1.1 cm/s	71	94	Duncan et al.[42]
	Myocardial S_m < 12 cm/s			Yamada et al.[43]
	- basal segments	86	96	
	- mid segments	81	89	
	$S_m \leq 10.5$ cm/s for LAD and CX $S_m \leq 10.0$ cm/s for RCA	63	76	Peteiro et al.[44]
	S_m increase < 25% for RCA	82	78	Rambaldi et al.[45]
Color TD	Septum and inferior wall - basal segments $S_m \leq 7$ cm/s - mid segments $S_m \leq 5$ cm/s Anterior, lateral and posterior wall - basal segments $S_m \leq 6$ cm/s - mid segments $S_m \leq 4$ cm/s	83	72	Cain et al.[46]
	S_m adjusted for HR, age, female gender (only on 7 LV segments):			Madler et al.[47]
	- LAD territory	80	80	
	- CX territory	91	80	
	- RCA territory	93	82	
SRI	$\varepsilon_{PSM}/\varepsilon_{max} \geq 35\%$	86	90	Voigt et al.[48]

CX = circumflex coronary artery; E_m = myocardial early diastolic velocity; HR = heart rate; LAD = left anterior descending coronary artery; LV = left ventricular; PWTD = pulsed wave tissue Doppler; RCA = right coronary artery; S_m = myocardial systolic velocity; $\varepsilon_{PSM}/\varepsilon_{max}$ = post-systolic motion/maximal strain ratio.

Table II. Cut-off values at low-dose dobutamine, sensitivity and specificity of tissue Doppler (TD) and strain rate imaging (SRI) for the diagnosis of myocardial viability during low-dose dobutamine stress echocardiography.

TD modality	Cut-off value (at low-dose dobutamine)	Sensitivity (%)	Specificity (%)	Reference
PWTD	Annular S_m of MI region > 2.0 cm/s	92	90	Matsuoka et al.[50]
	Regional S_m > 1.0 ± 0.5 cm/s	87	52	Rambaldi et al.[45]
SRI	Systolic SR increase > -0.23 s^{-1}	83	84	Hoffmann et al.[51]

MI = myocardial infarction; PWTD = pulsed wave tissue Doppler; S_m = myocardial systolic velocity; SR = strain rate.

97.4%[52]. A progressive increase of the S_m velocity (> 25% from 10 μg/kg/min to peak dobutamine) was predictive of a normal RCA, whereas a blunted increase and/or decrease (< 25%) was predictive of significant RCA narrowing (Table I) with a sensitivity of 82% (confidence interval-CI 68-96%), specificity of 78% (CI 67-93%), positive predictive value of 69% (CI 52-86%), negative predictive value of 88% (CI 75-100%), and accuracy of 79% (CI 65-94%)[45].

Myocardial PWTD also improves the diagnostic accuracy of dobutamine SE for the identification of viable myocardium in patients with severe LV dysfunction. Rambaldi et al.[53] observed that a S_m velocity increment ≥ 1.0 ± 0.5 cm/s at low-dose dobutamine predicted myocardial viability (defined by ^{18}F-fluorodeoxyglucose imaging) with a higher sensitivity (87 vs 75%, $p < 0.05$) but a similar specificity (52 vs 51%, p = NS) compared to WMS assessment (Table II). In addition, in 30 patients with previous myocardial infarction examined at low-dose dobutamine, the S_m velocity was significantly different between segments defined as normal (2.71 ± 1.91 cm/s), viable (1.86 ± 2.15 cm/s) and non-viable (0.99 ± 1.16 cm/s) ($p < 0.001$) on the basis of the conventional B-mode dobutamine SE, as well as between normal, mismatch, and match segments defined by positron emission tomography (2.72 ± 1.96, 1.01 ± 0.96, and 0.80 ± 1.07 cm/s respectively, $p < 0.001$)[54].

It is important to note that the feasibility of PWTD during exercise SE is optimal for the S_m velocity of the basal posterior septum but an adequate detection of myocardial E_m diastolic velocity at this level can be obtained only in 74% of the assessed patients[55]. Similar results are observed during dobutamine SE, even at the level of the right ventricular walls, which are not easily explorable by standard B-mode echocardiography[54]. It should also be considered that myocardial velocities at the apex are lower than those at the basal segments and are also more prone to the effect of Doppler angle dependency, with a low signal-to-noise ratio[56]. This is observed in healthy subjects and in cardiac patients, at rest as well as during SE. Therefore, apical velocities should not be considered for quantitative analysis. Moreover, PWTD does not allow the simultaneous recording of myocardial velocities at different levels, and is too time-consuming to be reliably performed on all 16 conventional LV segments during each stage of SE. These factors strongly limit the application of this tool to SE in clinical practice.

Color tissue Doppler and stress echocardiography

Currently, digitally stored color TD images allow post-processing extraction of myocardial velocity profiles at a regional level[38]. Color TD acquisition of longitudinal myocardial velocities is performed using the apical views and tissue velocities are superimposed on the B-mode images in real time during the examination. The subsequent off-line quantitative analysis of the stored images is done on selected cine-loops triggered to QRS. Similar to PWTD, the typical velocity profile extracted from the color TD cine-loop includes a positive S_m and two negative diastolic velocities, the first during early diastole (E_m) and the second during atrial contraction (A_m). These velocities can be measured both at rest and during SE (Fig. 2). They are mean velocities on repetitive loops. The great advantage of color TD compared to PWTD is the possibility of analyzing multiple myocardial segments simultaneously, at rest as well as during exercise or pharmacologic SE.

Pasquet et al.[57] were the first to apply color TD to SE, by using a conventional 16-segment LV model in 116 patients. They compared color TD with single-photon emission computed tomography (SPECT), both at rest and after treadmill exercise. Segments with a rest SPECT defect had significantly lower rest and stress S_m velocities than normal segments; segments with a stress SPECT defect had a marked reduction in maximal exercise S_m velocity and a lower S_m increment than normal segments.

Subsequently, attempts have been made to apply color TD to dobutamine SE and to provide normal reference values for multiple walls. Taking into account the base-to-apex variation of velocity, Cain et al.[46] found the following cut-off values of S_m velocity at peak dobutamine SE: ≥ 7 cm/s at the basal segments and ≥ 5 cm/s at the mid-level segments of the posterior

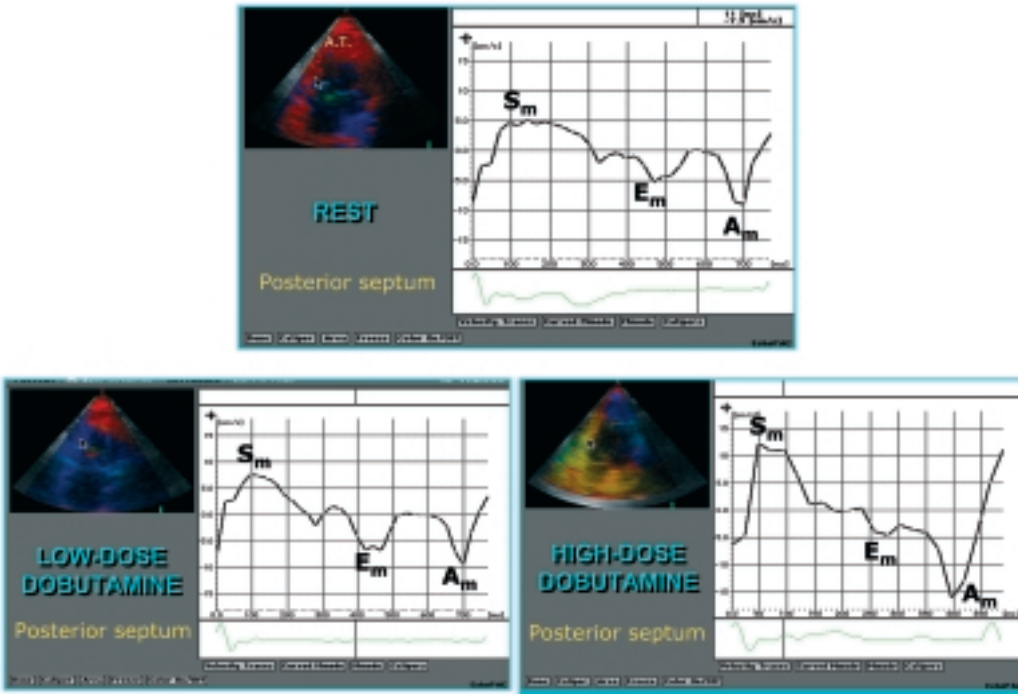

Figure 2. *Color tissue Doppler off-line analysis of the posterior interventricular septum at rest* (upper panel)*, at low-dose dobutamine* (left lower panel) *and at high-dose dobutamine* (right lower panel). *A gradual increase of peak myocardial systolic velocity (S_m) amplitude is detectable from resting conditions to high-dose dobutamine stress. A_m = myocardial atrial velocity; E_m = myocardial early diastolic velocity.*

septum, anteroseptum, and inferior wall; ≥ 6 cm/s at the base and ≥ 4 cm/s at the mid-portion of the free walls (anterior, lateral and posterior walls). By using these cut-off values, comparable results between color TD and WMS were obtained for the detection of significant CAD in terms of sensitivity (83 vs 88%), specificity (72 vs 81%), and accuracy (80 vs 86%). On these grounds, it is not surprising that combining various strategies for integration of WMS and color TD, the accuracy of SE interpretation could be improved among novice observers (from 75 ± 2 to 77 ± 5%, $p < 0.01$) and not among expert readers[58].

The possibility of off-line analysis also shifted the attention of researchers to the evaluation of diastolic parameters, which cannot be explored by standard Doppler transmitral inflow during dobutamine SE, due to the overlap of E and A velocities at the faster heart rates. Although a similar merging of TD E_m and A_m velocities is observed during tachycardia, in a study involving 63 patients with suspected or ascertained CAD the LV segments subtended with significant coronary stenosis showed a lower E_m and a shorter E deceleration time at rest and peak stress[59]. The assessment of myocardial diastolic velocities may also be useful in patients without epicardial CAD to understand the pathophysiologic mechanisms underlying the association between diastolic dysfunction and alteration of coronary flow reserve in arterial hypertension[60] as well as the impairment of myocardial diastolic reserve in diabetic cardiomyopathy[61].

The greatest effort to validate quantitative color TD SE for the diagnosis of CAD has been performed by the investigators of the multicenter MYDISE (Myocardial Doppler in Stress Echocardiography) study[47], who acquired color TD digital data during dobutamine SE in 289 subjects, and measured myocardial response by off-line analysis of 11 LV segments. In this study, the optimal diagnostic accuracy was achieved by logistic regression models, using the S_m velocity at maximal stress in 7 myocardial segments, after adjustment for the independent correlates (heart rate, age and female gender, all $p < 0.001$). Best cut-off values from receiver-operator characteristic (ROC) curves diagnosed left anterior descending coronary artery, circumflex coronary artery and RCA disease with sensitivities and specificities of 80 and 80%, 91 and 80%, and 93 and 82%, respectively. All models performed better than the S_m cut-off velocity values alone ($p < 0.001$).

The MYDISE study has shown important limitations of color TD, that is, its poor feasibility and reproducibility. In fact, the choice to quantify TD velocity only in 11 LV segments raised from a previous data analysis by the same researchers[62], who observed a very low feasibility and reproducibility of measures at the level of 5 LV segments (the 4 apical segments and the basal anterior septum in the parasternal view). Coefficients of variation for the S_m velocity in the other LV segments were acceptable (basal segments: 9-14% at rest and 11-18% at peak stress; mid-level segments: 10-24% at rest and 14-28% at peak stress), and justified further analysis. Similar results were obtained for other myocardial systolic parameters such as velocity time integral of S_m, time to peak S_m velocity (from ECG

QRS onset to peak S_m), and myocardial acceleration (peak S_m/time to peak S_m, cm/s^2). Coefficients of variation of myocardial diastolic velocities were considered too high already at rest (11-40%) to perform further analysis during SE.

Possible sources of variability hypothesized by the MYDISE investigators include: difficulty in visual evaluation of timing of global systole and diastole, especially when a post-systolic motion is detectable during a prolonged isovolumic relaxation time; difficulty in reproducing the position of the sample volume (in fact, myocardial velocity gradients occur between subendocardial and subepicardial layers[63] as well as from base to apex[38]); some loss of lateral resolution, especially at the higher frame rates.

The findings of the MYDISE study, obtained in a large patient population and using strict criteria, strongly blunt the enthusiasm deriving from other studies showing good feasibility during SE for color TD-derived systolic measurements[64,65] but not for diastolic velocities[59,65]. In this view, the reported ability of S_m velocity to identify myocardial viability at low-dose dobutamine[66,67] in selected patient populations should be considered with caution. There is, however, interest in the prognostic implications of myocardial velocities as pointed out by Marwick et al.[68], who showed in 251 patients with abnormal dobutamine SE that S_m velocity can discriminate patients with events (4.9 ± 1.7 cm/s) from those without events (6.4 ± 6.5 cm/s, $p < 0.001$) during a follow-up of 16 ± 12 months.

Finally, a further limitation of TD should be mentioned, that is the effect of cardiac translation motion or tethering effect by adjacent segments on regional myocardial velocities. This limitation is particularly evident when LV longitudinal velocities are measured from the apical views. During the cardiac cycle the LV apex is stationary while the mitral annulus moves toward the apex in systole (sum of all systolic shortenings) and away from the apex in diastole (diastolic lengthening). Thus, in presence of an apical myocardial infarction, a reduction of myocardial velocities can be measured at the apex as well as in the non-ischemic basal segments, although at this latter level lower velocities may not correspond to a "true" depressed myocardial function[39,40]. Likewise, owing to tethering, vigorous contractions of non-ischemic segments can determine higher velocities in neighboring ischemic regions, giving a false-positive result of myocardial viability[39]. This limitation, which may be present at rest, becomes crucial during SE, where not *motion* but *thickening* of myocardial segments has to be carefully evaluated to detect ischemia and/or viability.

Strain rate imaging and stress echocardiography

From digitally recorded color TD cine-loops containing velocity data from the entire myocardium, SRI can be derived from regional Doppler velocity gradients[39,40]. Strain rate (SR), i.e. the local rate of deformation of the myocardium, corresponds to the local spatial velocity gradient and can therefore be obtained from myocardial velocities measured at two different neighboring locations separated by a distance ($SR = V_1 - V_2/L$, where V_1 and V_2 are local velocities and L is the intervening distance). If V_1 and V_2 are different, there is a spatial velocity gradient which implies a deformation of the tissue included between the two different locations (Fig. 3)[39,40,69-72]. SR is calculated as the instantaneous spatial velocity gradient and is measured in seconds^{-1}. Strain is the local percent deformation caused by an applied force and is calculated as the time integral of SR, most often using end-diastole as reference point[39,40,69-72] (Fig. 3). In the longitudinal direction (i.e., in the standard echocardiographic apical views), when the two locations are getting closer, a shortening of myocardial tissue in between occurs and both systolic SR and strain have a negative value ("rate of shortening" in systole); conversely, when the locations are moving apart and the segment elongates, there is a myocardial lengthening and both diastolic SR and strain correspond to a positive value ("rate of lengthening" in diastole)[68-70] (Fig. 3). In the short-axis direction, SR and strain have positive value during systole (= regional thickening rate and regional thickening respectively) and negative value during diastole but their measurements are more technique-dependent and therefore less robust than longitudinal parameters[70-72] (Fig. 3). Similar to ejection fraction, myocardial strain is affected by load changes and LV geometry[72]. SR appears to be less load-dependent and, therefore, can be considered a stronger index of myocardial contractility. In fact, it is closely related to invasively determined myocardial elastance[73], able to respond negatively to beta-blockade and positively to inotropic stimuli as dobutamine[73-76] and cardiac pacing[75]. Due to these favorable characteristics, SRI may potentially overcome the limitations of color TD, discriminating between active and merely passive wall motion, and therefore appears as a more suitable technique for quantitative analysis of SE. In this view, SRI can improve the evaluation of regional wall motion compared with TD and conventional ultrasound techniques in patients with myocardial infarction, mainly because it identifies segments that are moving passively but not shortening normally[77]. The normal values of TD-derived SRI have been calculated in reference populations and the reproducibility of SRI has been tested, ranging between 11.8 and 14.4% for longitudinal systolic SR[70,71] and being > 15% for diastolic SR.

The application of SRI, both at rest and during SE, implies a correct identification of systolic and time intervals. This can be performed marking end-diastole and end-systole by the aid of previously performed pulsed Doppler imaging of the mitral inflow and LV output flow. By this method the markers of mitral valve

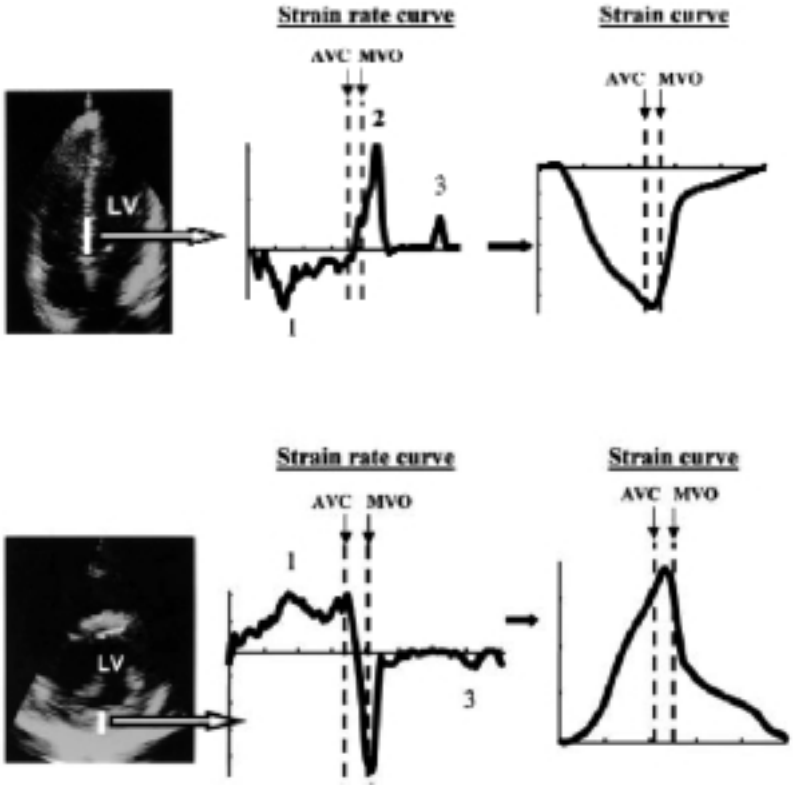

Figure 3. *Methodology for off-line calculation of both longitudinal strain rate imaging from the basal segment of the septum* (upper panel) *and radial strain rate imaging from the posterior wall* (lower panel). *Peak systolic strain rate (1) is used as an index of systolic contraction while peak early (2) and late (3) diastolic strain rate is the expression of diastolic function. AVC = aortic valve closure; LV = left ventricle; MVO = mitral valve opening. From Weidemann et al.[71], modified.*

opening and closure as well as of aortic valve opening and closure are superimposed to SRI imaging (Fig. 4). Alternatively systolic and diastolic time intervals can be identified by the method proposed by Voigt et al.[78]: LV end-systole, i.e. the aortic valve closure, is derived by color TD M-mode, as the end-systolic thin blue line which, caused by a brief backward motion of the mitral valve secondary to aortic valve closure, is visualized within the otherwise red-colored mitral anterior leaflet.

SRI has been applied to SE. Although it failed to increase sensitivity of dobutamine SE in a study of false-negative results[79], Voigt et al.[48] tested curved M-mode SRI analysis to detect ischemia during dobutamine SE in 44 patients with known or suspected CAD by measuring amplitude and timing of myocardial deformation. In non-ischemic segments, peak systolic SR increased during dobutamine SE (from -1.6 ± 0.6 to -3.4 ± 1.4 s^{-1}, $p < 0.01$), whereas strain changed minimally (from -17 ± 6 to -16 ± 9%, $p < 0.05$). SR increase (-1.6 ± 0.8 vs -2.0 ± 1.1 s^{-1}, $p < 0.05$) and strain increase (-16 ± 7 vs -10 ± 8%, $p < 0.05$) were significantly reduced in all ischemic segments (defined by perfusion scintigraphy) in comparison with the non-ischemic segments. SRI parameters showed no significant apex-to-base gradient[80] and, compared with conventional wall motion evaluation, curved M-mode SR assessment improved sensitivity/specificity from 81/82% to 86/90%[48]. It is of particular interest the ability of SRI to recognize the evidence of a post-systolic thickening (PST), that is a systolic contraction of a myocardial region occurring after aortic valve closure, during myocardial relaxation time. The identification of PST needs the above reported timing of SRI measurements, to distinguish clearly PST from normal S_m velocity. PST was observed in all ischemic segments and a PST/maximal strain ratio at high-dose dobutamine ≥ 35% was the best quantitative parameter to identify stress-induced ischemia. PST has shown to be a sensitive index of myocardial ischemia in both dyskinetic and hypokinetic segments[81]. In addition, a gradual increase of PST amplitude from moderate to severe ischemia, parallel to the decrease of systolic shortening and to the influence exerted by changes in afterload, was observed[82] in experimental models. If myocardial wall segment does not deform during isovolumic contraction – when LV pressure rises – but shortens markedly when LV pressure is failing during isovolumic relaxation "*is not likely to be passive*". Therefore, the higher the PST compared to the total systolic shortening the higher the probability for its active contraction[83].

SRI was also successfully used to improve assessment of myocardial viability in patients with depressed LV function[51]. In particular, a systolic SR increase from

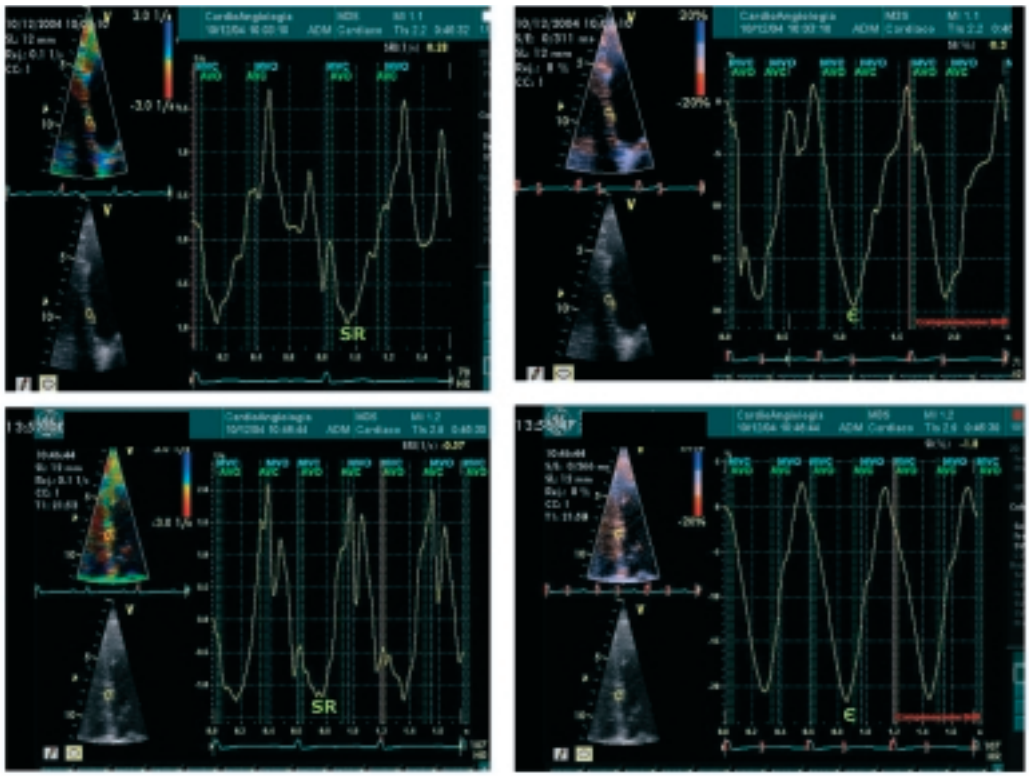

Figure 4. *Strain rate (SR) and strain (ε) at rest* (upper panel, left *and* right *respectively) and during dobutamine stress echocardiography* (lower panel, left *and* right *respectively). An increase of both SR (from 1.00 to 1.3 s^{-1}) and ε (from 18.0 to 23.0%) respectively is detected from resting conditions (heart rate 70-71 b/min) to dobutamine infusion (heart rate 102 b/min). End-diastole and end-systole are identified superimposing markers of mitral valve opening (MVO) and closure (MVC) by standard Doppler mitral inflow imaging (apical 4-chamber view) and markers of aortic valve opening (AVO) and closure (AVC) by standard Doppler left ventricular out-tract systolic flow (apical 5-chamber view). The measure of both ε and SR are performed at end-systole.*

rest to low-dose dobutamine > -0.23 s^{-1} allowed accurate discrimination of viable from non-viable myocardium, using ^{18}F-fluorodeoxyglucose positron emission tomography as gold standard, with a sensitivity of 83% and a specificity of 84%[51]. The ROC curve analysis showed an area under the curve for prediction of non-viable myocardium of 0.89 using SRI (95% CI 0.88-0.90), whereas the area under the ROC curve using TD was 0.63 (95% CI 0.61-0.65). Also the evidence of a PST during SE has been considered as a possible marker of myocardial viability[81,83].

A further interesting use of SRI during dobutamine SE may be the evaluation of inotropic reserve related to incremental heart rates (force-frequency relation) during dobutamine SE in conditions where coronary artery stenosis may be excluded[84].

These results are encouraging but a recent study has shown that, although SR measurement was suboptimal in only 54/1936 assessed segments, feasibility of SRI depends on appropriate data recording (high frame rate, narrow sector, correct beam orientation to avoid the Doppler angle) and post-processing algorithms, which are rigid and time-consuming[85]. In this regard, a visual, semiquantitative assessment of myocardial deformation may improve the use of deformation imaging applied to SE, simplifying and shortening both recording and analysis[86].

Conclusions and perspectives

Conventional SE is a validated approach for the assessment of both myocardial ischemia and viability despite the use of a semiquantitative interpretation based on visual analysis of segmental wall motion, which can sometimes be difficult even with good image quality. In its conventional application, therefore, SE remains a highly subjective technique and this may affect its clinical diagnostic value and reproducibility in individual patients. This may also explain why SE has become a theater for testing innovative technologies, such as anatomical M-mode, automatic boundary detection and color kinesis, contrast enhancement of myocardial perfusion, tissue characterization, TD and SRI[87]. These two latter techniques, in particular, are very attractive for cardiologists since they may quantify myocardial systolic and diastolic function by measuring velocities, time intervals, deformation, and rate of deformation of the myocardium.

Some applications of TD already entered into clinical practice, especially for the evaluation of diastolic dysfunction, such as the estimation of the LV end-diastolic pressure through the use of the E/E_m ratio (the ratio between the transmitral Doppler E velocity and the mitral annulus TD E_m velocity)[88], recognition of the pseudonormal transmitral Doppler pattern[89] and differentiation

of constriction from restriction[90]. Other interesting applications are rising, such as TD and SRI selection of candidates for cardiac resynchronization therapy[91,92].

The application of these Doppler techniques to SE has been tested in several studies, both in laboratory and clinical settings. Among the various TD modalities, all have potential advantages but also important limitations that may affect the clinical application to SE. PWTD, which has the highest temporal resolution, does not permit the simultaneous assessment of multiple LV myocardial regions and its application to all 16 LV segments during each SE stage requires a time duration incompatible with clinical SE. Color TD and PWTD are both influenced by overall cardiac motions and tethering effects, which may limit accurate detection of myocardial ischemia and viability and prevent from application to the apical segments. Moreover, the existence of a base-to-apex velocity gradient, the loss of resolution at higher cardiac rates and the angle dependency of velocities are additional problems which hesitate in suboptimal feasibility and reproducibility of TD in the setting of clinical SE. SRI can potentially provide myocardial deformation indexes that represent regional contractility much closer than myocardial velocities. The current calculation of strain and SR from Doppler velocities is time-consuming and also affected by some limitations: local SR, for example, is even more influenced by the Doppler angle than velocity. However, it should be mentioned that the introduction of new sophisticated software for calculation of SR from analysis of ultrasound B-mode gray-scale images, which does not rely on Doppler velocities anymore, may potentially improve the reproducibility of myocardial deformation parameters, leading in the future to a more widespread use of strain and SR in clinical SE.

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