Speckle Tracking Echocardiography in Non–ST-Segment Elevation Acute Coronary Syndromes

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Abstract: Non–ST-segment elevation acute coronary syndromes (NSTE-ACSs) are a group of clinical conditions characterized by acute myocardial ischemia. Conventional echocardiography is generally used to evaluate cardiac function using wall motion analysis and left ventricular ejection fraction but may be insufficient to explore all the complex features of NSTE-ACSs, which may vary substantially from patient to patient in terms of severity of ischemia and extent of involved myocardium. In the last years, speckle tracking echocardiography (STE) has become a widely available technique for the non-invasive assessment of cardiac function and has been repeatedly applied in the setting of NSTE-ACSs. In this review we summarize current evidence about the use of STE in patients with NSTE-ACSs, trying to underline advantages and limitations in comparison with conventional echocardiography for: diagnosis of NSTE-ACS, differential diagnosis, identification of high-risk patients, and prediction of outcome. (Curr Probl Cardiol 2021;46:100418.)

Introduction

The term non–ST-segment elevation acute coronary syndrome (NSTE-ACS) refers to a group of clinical conditions characterized by acute myocardial ischemia and absence, at the surface

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electrocardiogram (ECG), of ST-segment elevation. The pathological correlate at myocardial level is cardiomyocyte necrosis (non−ST-segment elevation myocardial infarction [NSTEMI]) or, less frequently, myocardial ischemia without cell loss (unstable angina).[1]

Conventional echocardiography is generally used to evaluate cardiac function in patients with NSTE-ACS.[1] However, it may be insufficient to explore all the complex features of this condition, which may vary substantially in terms of severity of ischemia and extent of involved myocardium.[1] Doppler tissue imaging has been applied to the study of ischemic myocardial dysfunction but it is limited by the angle-dependency and noise of the myocardial deformation analysis based on the Doppler signal.[2] In the last years, speckle tracking echocardiography (STE) has become a widely available technique for the noninvasive assessment of global and regional cardiac function providing a number of myocardial strain and strain rate measures. STE is a relatively operator-independent technique and has a lower interobserver variability[3] compared to that of left ventricular ejection fraction (LV-EF).[4] The latest guidelines on NSTE-ACS suggest that reduced regional myocardial function demonstrated using strain and strain rate might improve the diagnostic and prognostic value of conventional echocardiography.[1] However, a specific review of the literature supporting use of ultrasound deformation imaging in NSTE-ACS has not been conducted so far.

The aim of this review, therefore, is to verify whether the use of STE in NSTE-ACS patients has additional value over conventional echocardiography for: (1) diagnosis of NSTE-ACS; (2) differential diagnosis; (3) identification of high-risk patients, and, (4) prediction of outcome.

Technical Features and Parameters

STE provides a non-Doppler, relatively angle-independent measurement of myocardial deformation or strain. The most used strain parameter in clinical practice is global longitudinal strain (GLS), which is obtained by averaging longitudinal strain (LS) of all myocardial segments from the 3 standard apical views. In addition, peak systolic LS calculated throughout the myocardium can be reported spatially, from base to apex and circumferentially, in a polar diagram using a color-coded parametric representation,[5,6] which has the advantage to facilitate distribution assessment of regional LV myocardial dysfunction (Fig 1). A multilayer approach can be utilized to visualize separately subendocardial and subepicardial layers (Figs. 2 and 3).[7] Other parameters used to study LV myocardial deformation are global circumferential strain and global radial

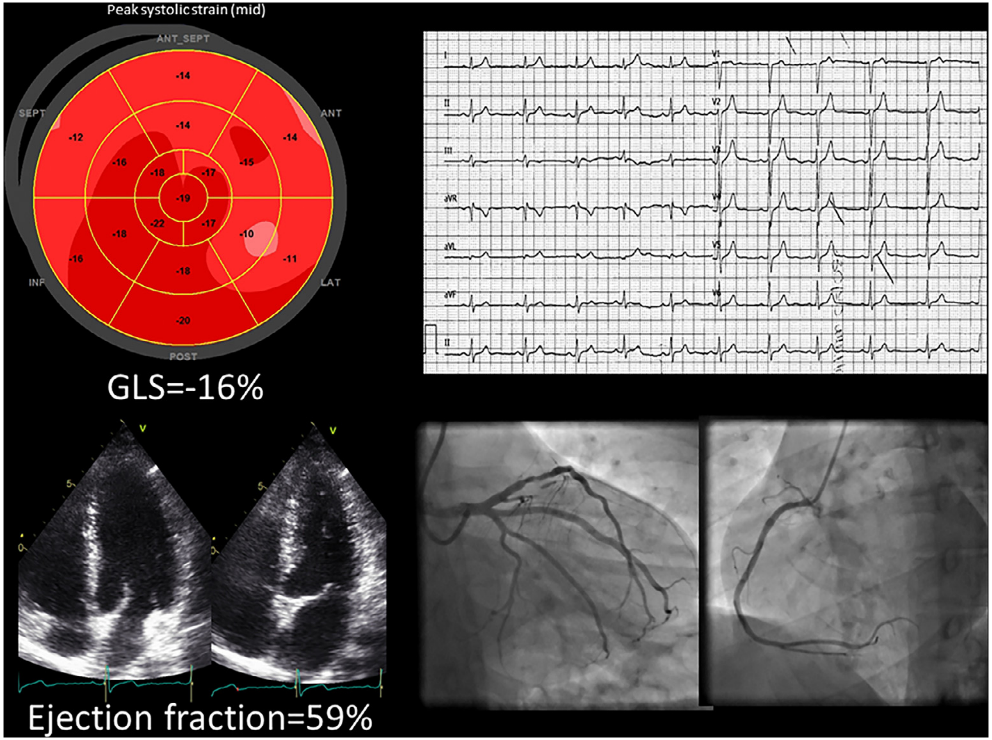

FIG 1. A 27-year old man with chest pain, troponin I increase (1.67 ng/mL) and tall T waves in V2-V3 leads at electrocardiogram. A wide area of reduced longitudinal strain (clear red at septal, anterior, and lateral wall) was observed on polar speckle tracking echocardiography, with decreased global longitudinal strain (GLS), despite no wall motion abnormalities and normal left ventricular ejection fraction at conventional echocardiography. Coronary angiography found a thrombotic left anterior descending coronary artery. (Color version of figure is available online.)

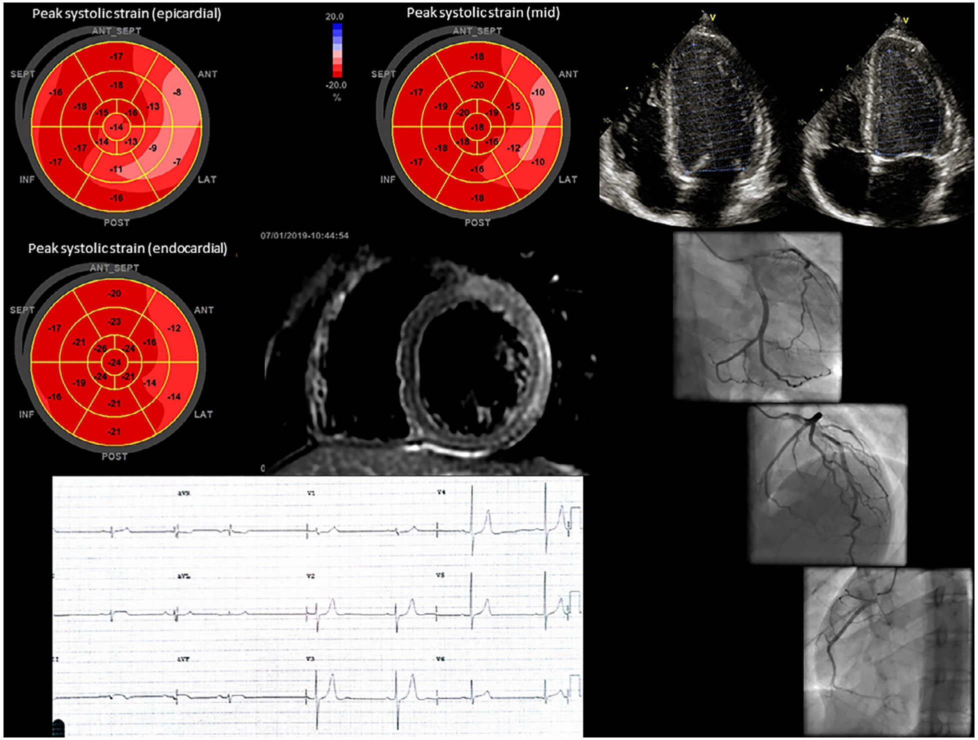

FIG 2. A 19-year old man with chest pain, troponin T increase (0.663 ng/mL) and normal electrocardiogram. Conventional echocardiography showed absence of wall motion abnormalities. Polar speckle tracking echocardiography documented reduction of longitudinal strain at posterolateral and anterior wall (atypical for single coronary artery distribution), particularly on epicardial layer, consistent with nonischemic disease. Cardiac magnetic resonance revealed edema on posterolateral and anterior wall, suggesting myocarditis. Coronary angiography demonstrated absence of coronary artery stenosis.

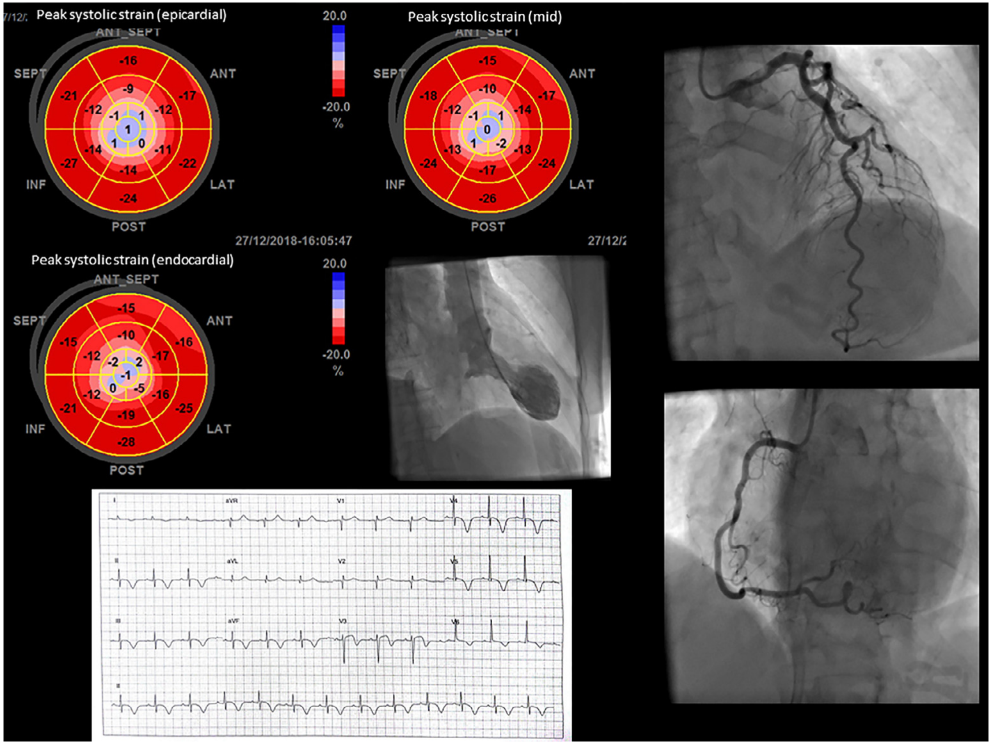

FIG 3. A 68-year old woman with chest pain, high-sensitivity troponin I increase (2789 ng/L), and negative T-waves on inferior/lateral leads at electrocardiogram. Ventriculography showed apical akinesia. No coronary artery stenosis was evidenced at coronary angiography. Polar speckle tracking echocardiography indicated tako-tsubo cardiomyopathy pattern, with longitudinal strain reduction also at inferoposterior wall and similar involvement of epicardial and endocardial layers.

strain, obtained from analysis of LV short-axis views and calculated averaging all local strains.

Diagnosis of NSTE-ACS

During myocardial ischemia mechanical abnormalities generally precede ECG findings and symptoms. The first fibers that become ischemic are the subendocardial ones (oriented mainly in the longitudinal oblique direction), thus LS worsening during ischemia precedes the decrease in radial deformation and wall thickening.[8] Diagnostic sensitivity of different echocardiographic techniques may vary according to their capability to selectively assess longitudinal contraction of myocardium.

Wall motion score index (WMSI) and LV-EF are based on assessment of endocardial motion and ventricular volume change, respectively. A subtle ischemia may not be detected by these 2 methods, mainly because nonischemic circumferential and longitudinal subepicardial fibers may have a compensatory effect in maintaining inward wall motion (radial strain) and LV-EF. Conversely, STE can evaluate ischemic changes measuring LS (Table 1, Fig 1). Interestingly, in NSTE-ACSs myocardial strain can be reduced for a prolonged period of time,[9] although the mechanism of such a behavior remains unknown.[10]

Single-center studies showed that, in patients presenting with acute chest pain without prior cardiac events, GLS by STE has a sensitivity of 81%-87% and a specificity of 67%-88% for CAD diagnosis and performs better than visual wall motion assessment and LV-EF.[9,11-15] The GLS cut-off value suggested for ACS diagnosis varies from −17.5% to −19.7%, while a value of −20% or better has been reported to rule out a significant CAD. These studies, however, are limited by a different angiographic definition of CAD and by the small sample size.

In a multicenter prospective study, Shiran et al[16] evaluated 605 patients presenting at the emergency department with chest pain and suspected ACS but without initial troponin elevation. CAD was defined as coronary narrowing ≥70%. GLS was significantly worse in patients with ACS than in those without, but had a low diagnostic accuracy (area under the curve of 0.6). The authors concluded that LS was not a useful tool to rule out NSTE-ACS in the emergency department. This study has limitations: (1) most of the NSTE-ACS patients had a relatively mild ischemic disease (unstable angina 86.5% and single vessel CAD 69.7%), therefore their disease may have been more difficult to detect by STE; (2) only 19% of patients without NSTE-ACS underwent coronary angiography; and (3) echocardiography was performed an average of 10 hours after the

TABLE 1. Role of STE in diagnosis and differential diagnosis of NSTE-ACS

Author	No. of pts	Cut-off value	Sens. (%)	Spec. (%)	PPV	NPV	AUC	*P*
Diagnosis of NSTE-ACS								
Shimoni et al (2011)[9]	97	GLS ≥ −19.7%	81	67			0.8	
Lee et al (2015)[15]	104	RLS ≥ −13%	92	77.3	69.7	94.4		
Schroeder et al (2016)[12]	268	GLS ≥ −18.8%	86	73			0.823	
		GCS ≥ −21.7%	87	76			0.835	
Alves et al (2017)[13]	61	GLS ≥ −17.5%	87	82			0.86	
Caspar et al (2017)[14]	58	GLS ≥ −19.7%	81	88			0.92	
Shiran et al (2017)[16]	605	PSS20% > −17%	81.1	26.4	90.9	13.3	0.59	
Exclusion of NSTE-ACS								
Dahlslett et al (2014)[11]	64	GLS ≤ −20%	93	78	74	92	0.87	<0.05
Identification of culprit lesion								
Shimoni et al (2011)[9]	97	RLS ≥ −14% (LAD)	74	51			0.68	
		RLS ≥ −17% (LCx)	77	64			0.78	
		RLS ≥ −14.3% (RCA)	79	57			0.75	
Caspar et al (2017)[14]	58	RLS ≥ −19.4% (LAD)	90.9	86.1			0.93	
		RLS ≥ −16.4% (LCx)	86.7	81.4			0.88	
		RLS ≥ −18% (RCA)	82.4	78			0.85	
Identification of complex lesions								
Choi et al (2009)[10]	108	GLS ≥ −19.4%	76.3	74.1			0.803	<0.001
		RLS ≥ −17.9% (mid/basal)	78.9	79.3			0.828	<0.001
Hoshi et al (2014)[22]	50	GLS ≥ −19.4%	86.6	62.9			0.745	
Cai et al (2016)[23]	59	GLS ≥ −11.76%	82.6	83.3			0.882	<0.001

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TABLE 1. (*continued*)

Author	No. of pts	Cut-off value	Sens. (%)	Spec. (%)	PPV	NPV	AUC	*P*
Multilayer STE								
Sarvari et al (2013)[17]	77	Endo RLS ≥ −16.4%	89	81	73	93	0.91	<0.05
		Mid RLS ≥ −14.7%	82	88	79	89	0.91	<0.05
		Epi RLS ≥ −12.6%	78	69	58	85	0.79	<0.05
Liu et al (2016)[18]	113	Endo RLS ≥ −23.52% (LAD)	89	80			0.874	<0.001
		Endo GLS ≥ −22.69% (LAD)	86	88			0.905	<0.001
Zhang et al (2016)[19]	139	Endo GLS ≥ −21.35% (complex CAD)	72	84			0.846	<0.05
		Endo RLS ≥ −20.15% (complex CAD)	72	88			0.852	<0.05
Differential diagnosis with myocarditis								
Di Bella et al (2010)[29]	13	RLS ≥ −21%*	100	62	72	100		
Hsiao et al (2012)[28]	45	GLS ≥ −15.1%	78	93			0.93	<0.001
		GLS ≥ −16.9% (EF ≥ 50%)	84	68			0.83	<0.001
Kostakou et al (2018)[27]	25	RLS ≥ −17% (lateral)	95	95			0.99	
Differential diagnosis with stress-induced cardiomyopathy								
Cai et al (2016)[32]	92	RLS ≥ −11.5% (LV mid-inferior)					0.7	
		RLS ≥ −10.5% (LV apical-inferior)					0.7	
		RLS ≥ −12.5% (RV apical)					0.7	

GCS, global circumferential strain; GLS, global longitudinal strain; PSS20%, 20th percentile of peak systolic strain; RLS, regional longitudinal strain.
*In at least 2 contiguous myocardial segments.

last episode of chest pain. Results of this study, therefore, cannot be equally applied to a population of patients with a more severe ischemic disease (NSTEMI) or evaluated shortly after their chest pain.

In principle, a multilayer approach could increase the diagnostic capability of STE in the setting of a suspected NSTE-ACS, lying on the concept that a nonocclusive coronary lesion causes prevalent endocardial ischemia and longitudinal dysfunction. According with this view, several studies indicated that assessment of regional longitudinal strain (RLS) of the endocardial layer improves NSTE-ACS diagnosis.[17-19] However, there are NSTEMI with occlusive coronary lesions causing transmural ischemia, therefore leading to an equal dysfunction in all myocardial layers (ie, circumferential and longitudinal dysfunction). In addition, there are technical issues to take into account: (1) deformation of a layer may affect that of the others (eg, active contraction of a layer with viable myocardium may determine passive deformation of the near layer; conversely, a layer with nonviable myocardium may reduce the active deformation of the others) and (2) it may be difficult to hook the speckles, mostly at the basal segments (lower density echo beams) due to the limitation of lateral resolution. Therefore, the role of multilayer STE to diagnose NSTE-ACSs needs further clarification.

When evaluating STE findings in the setting of patients with suspected NSTE-ACS, there are nonischemic factors to consider that may reduce GLS values, thus decreasing the specificity of this parameter. They include diabetes, hypertension, myocardial fibrosis,[20-21] as well as impaired myocardial relaxation, male gender, higher heart rate, and higher body mass index, also at a young age.[16] Therefore, interpretation of GLS alterations in patients without acute ECG and troponin abnormalities may be complex, even in absence of a previous cardiac ischemic disease, and should take into account patient clinical history in detail.

Finally, some authors applied STE to identification of culprit and complex coronary lesions in NSTE-ACS patients. Shimoni et al[9] and Caspar et al[14] evaluated the capability of regional RLS to predict the culprit coronary lesion. The RLS cut-off value for recognition of the stenotic coronary artery varied according to the coronary territory, making a RLS-based approach difficult to apply in practice. Other investigators[10,22,23] suggested the potential for STE to identify the complexity of the coronary lesions but data are insufficient to drive conclusions. As already pointed out, the reduction of LS, either regional or global, is not specific to severe CAD and may be present in other cardiomyopathic conditions.

The potential role of STE for initial management of patients presenting at the emergency department for chest pain and suspected NSTE-ACS has been summarized in Figure 4. In some subgroups of patients (those with left bundle branch block, atrial fibrillation, paced rhythm, significant valvular disease, and history of myocardial infarction) the role of STE has not been tested, thus for these subgroups specific investigations are needed.

Differential Diagnosis of NSTE-ACS

In the emergency department setting with a patient complaining a chest pain of cardiac origin, there are 2 main differential diagnoses: myocarditis and stress-induced cardiomyopathy (SCM).

Myocarditis

Acute myocarditis is characterized by an inflammatory myocardial damage that can cause myocardial dysfunction. Although some studies showed that STE can recognize contraction abnormalities due to myocarditis,[24-29] the small size of those studies and the different LS cut-off values proposed for diagnosis are a limit. Regarding the differential diagnosis with NSTE-ACSs, there are no investigations with direct comparison with STE alterations in myocarditis. A key diagnostic feature of myocarditis is the patchy territorial involvement unrelated to the distribution of a coronary artery. Also, a selective or predominant involvement of the subepicardial layer is expected in nontransmural myocarditis as opposed to the predominant subendocardial involvement in ischemia (Fig 2). However, as endocardial and epicardial layer deformations interact, a passive deformation of an impaired subepicardial segment can mask the real damage. On the other hand, longitudinal deformation is already lower in the epicardium of a normal heart[7] and this should be known to avoid overinterpretation of STE findings in myocarditis. In patients at lower risk of CAD (young patients, women in childbearing age without coronary risk factors), STE findings may support indication to cardiac magnetic resonance.

Stress-induced Cardiomyopathy

SCM, including tako-tsubo cardiomyopathy, is characterized by a generally transient LV wall motion abnormality (mostly involving the apical segments) in the absence of obstructive epicardial CAD. In about 25% of cases there is also involvement of the right ventricle, while right ventricle dysfunction only is very rare. Generally, in SCM patients GLS is reduced and this decrease may involve all the 3 LV myocardial layers.[30] In 2 studies STE was used to differentiate SCM from an NSTE-ACS involving the

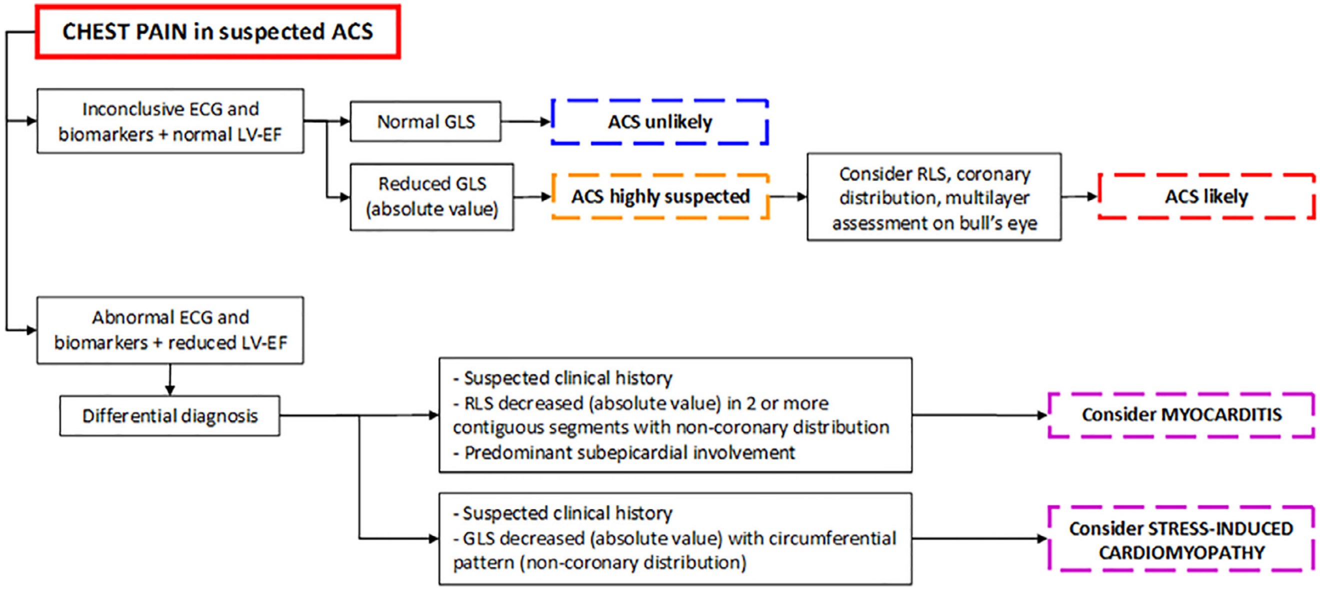

FIG 4. Flow chart for use of speckle tracking echocardiography in suspected acute coronary syndrome (ACS). ECG, electrocardiogram; GLS, global longitudinal strain; LV-EF, left ventricular ejection fraction; RLS, regional longitudinal strain.

left anterior descending coronary artery territory[31,32]: in SCM patients myocardial dysfunction extended beyond the left anterior descending territory (Fig 3) and often to the inferior wall.[32] However, in patients with multiple ischemic myocardial territories differentiation between NSTE-ACS and SCM may be difficult.

In summary, STE may suggest diagnosis of myocarditis and SCM (Fig 4, Table 1) but, at present, does not avoid the need for coronary angiography when NSTE-ACS is strongly suspected.

Identification of High Risk Patients

Current guidelines suggest strategies for treatment of NSTE-ACSs according to the initial risk stratification in very-high, high, intermediate, and low-risk patients.[1] Criteria to define very-high-risk and high-risk patients are clinical, and the only echocardiographic criterion for intermediate-risk patients is a LV-EF $<40\%$. Because STE identifies myocardial dysfunction due to ischemia/necrosis better than WMSI or LV-EF, it is expected to stratify more precisely patients awaiting coronary angiography (Table 2).

Grenne et al[33] observed that in patients with NSTEMI and acute coronary occlusion, both GLS and global circumferential strain deteriorated from admission to coronary angiography and a regional circumferential strain $\geq -10\%$ could identify acute coronary occlusions.[34] Eek et al[35] reported that NSTE-ACS patients with coronary artery occlusion had reduced GLS compared to patients without. An area of ≥ 4 adjacent segments with a LS $\geq -14\%$ could identify patients with acute coronary occlusion.

Recently, it has been observed that ischemic myocardium tends to lengthen before the onset of systolic shortening, probably due to its

TABLE 2. Role of STE in identifying NSTE-ACS patients at higher risk

Author	No. of pts	Cut-off value	Sens. (%)	Spec. (%)	PPV	NPV	AUC	*P*
Eek et al (2010)[35]	150	LS $\geq -14\%$ for ≥ 4 adjacent segments	85	70	44	94	0.81	<0.05
Grenne et al (2010)[34]	111	RCS $\geq -10\%$	90	88			0.83	<0.05
Zahid et al (2014)[37]	150	GLS $> -17.2\%$	64	77			0.71	<0.0001
		DESL $>$ 100 ms	33	91			0.65	0.009
Eek et al (2010)[39]	61	GLS $\geq -13.8\%$	85	96	85	96	0.95	<0.02

DESL, duration of early systolic lengthening; GLS, global longitudinal strain; LS, longitudinal strain; RCS, regional circumferential strain.

reduced ability to endure the LV pressure rapidly rising during the isovolumic contraction. In ST-segment elevation myocardial infarction (STEMI) patients, the duration of early systolic lengthening has been shown to be proportional to the infarct size.[36] In 150 retrospectively evaluated NSTEMI patients, a duration of early systolic lengthening cut-off value of 100 ms could recognize patients with coronary occlusion.[37] WMSI, GLS, and LV-EF, all had better sensitivity but worse specificity.

Infarct size assessed by contrast-enhanced cardiac magnetic resonance is considered a strong predictor of mortality and major adverse cardiovascular events after STEMI, where an increased mortality rate is associated with infarct size $\geq$12%.[38] Eek et al[39] examined 61 NSTE-ACS patients immediately before revascularization (on average 2.1 days after hospitalization) and found that a GLS obtained before coronary angiography $>-13.8\%$ could identify patients with final infarct size $\geq$12% at the cardiac magnetic resonance 9 months later.

In brief, STE has the potential to improve risk stratification in patients with NSTEMI. Its use to select patients who may benefit from urgent reperfusion therapy has been recently reported.[40]

Prediction of Outcome

Presence of viable myocardium is one of the most powerful indicators of LV functional recovery after a myocardial infarction (MI) and can be evaluated by STE calculating postsystolic shortening (PSS). This has been shown both in STEMI[41] and NSTEMI[42] patients. Bainin et al also documented that PSS predicts heart failure following an NSTE-ACS.[43]

D'Andrea et al[44] evaluated 70 patients with a recent NSTEMI undergoing coronary angiography for recurrent angina. They found that a baseline GLS value of $\geq-12\%$ and lack of improvement of GLS soon after percutaneous coronary intervention were independent predictors of LV remodeling at 6 months (Table 3). In a subsequent study, the same authors reported similar findings using the 4-dimensional X-Strain technique (Table 3).[45]

Wang et al[46] considered prospectively 248 patients from the VALIANT study with first MI (30% non−Q-wave) and LV-EF <35%, for a 20-month follow-up period. The number of segments with abnormal LS was significantly associated with all-cause mortality and death or hospitalization for HF, and was also a better indicator in predicting clinical outcomes than WMSI.

Ersbøll et al[47] prospectively studied 988 patients referred for coronary angiography (31.5% NSTEMI) for a median follow-up of 30 months.

TABLE 3. Predictive role of STE in NSTE-ACS patients

Author	No. of pts	Cut-off value	Sens. (%)	Spec. (%)	PPV	NPV	AUC	*P*
D'Andrea et al (2011)[44]	70	Segmental strain ≥ −10%	78	84			0.88	<0.001
		GLS ≥ −12%	84.8	87.8			0.89	<0.0001
D'Andrea et al (2016)[45]	75	GLS ≥ −12%	84.7	88.8			0.91	<0.0001
Haugaa et al (2013)[49]	569	MD > 75 ms		96	17			
		MD > 75 ms + GLS > −16%			21			

GLS, global longitudinal strain; MD, mechanical dispersion.

Both GLS and mechanical dispersion (MD) were independent predictors of outcome. In the subgroup of 904 patients with LV-EF >35%, only GLS maintained a prognostic value. In another study, the same authors[48] evaluated prospectively 849 patients with MI (32% NSTEMI) and LV-EF >40% for a median follow-up of 30 months. Patients with GLS >−14% had a 3-fold increase in risk for the combined endpoint defined as all-cause mortality and hospitalization for HF.

Haugaa et al[49] studied prospectively 569 MI patients (53% NSTEMI) after at least 40 days from the cardiac event for a median follow-up of 30 months. MD was an independent predictor of ventricular arrhythmic events and sudden cardiac death (Table 3). In patients with NSTEMI, GLS and PSS index were markers of arrhythmias, whereas LV-EF was not.

Other predictors of outcome have been identified in addition to LV systolic function, such as the ratio between peak E wave on the transmitral Doppler curve and peak e' wave on the strain rate curve by STE (global E/e'sr ratio).[50]

In summary, several parameters have been proposed to predict outcome in patients with NSTE-ACS (number of segments with abnormal LS, PSS, GLS, MD, global E/e'sr ratio). However, in most studies the effect on NSTEMI and STEMI patients cannot be clearly distinguished and end-points varied in different investigations. Therefore, further data are needed before drawing definitive conclusions.

Limitations of STE

It should be underlined that a correct interpretation of STE findings requires knowledge and expertise, especially in an acute setting, thus adequate training of the operators using this diagnostic tool is needed. Fortunately, the learning curve appears to be short.[51]

Another issue is the vendor-specific variability in evaluating strain and strain rate, especially when using quantitative measures.[52,53] This may obstacle diagnostic and prognostic application of predefined cut-off values of myocardial deformation indices. In the future, calibration of strain and strain rate measures among different vendors could facilitate use of ultrasound deformation imaging when assessing cardiac function in clinical practice.

GLS as well as global radial and circumferential strain are load dependent, but this limitation is shared with all ejection-phase indices, including LV-EF and also assessment of WMSI.

Conclusions

Establishing if a patient presenting at the emergency department with chest pain, inconclusive ECG, and laboratory findings has a NSTE-ACS may be difficult. Several small single-center studies suggested that STE can be a helpful adjunct to conventional echocardiography to improve NSTE-ACS diagnosis but the only multicenter investigation in this field concluded that LS was not a useful tool to rule out NSTE-ACS in the emergency department. Therefore, the definitive diagnostic role of STE in the setting of NSTE-ACS remains to be demonstrated.

Regarding the differential diagnosis with myocarditis and SCM, although STE does not avoid the need for coronary angiography, it objectively displays typical strain patterns that may suggest alternate diagnosis to NSTE-ACS.

Improving identification of high-risk patients with NSTE-ACS is important for interventional decision-making. Single-center investigations showed that STE has the potential to accomplish this challenging task but published reports are only preliminary and further studies are needed before drawing definitive conclusions.

As far as outcome prediction is concerned, there are studies showing that STE may improve assessment of prognosis in ACS patients over conventional echocardiographic evaluations but dedicated multicenter investigations on NSTE-ACS only are lacking. Moreover, due to the number of STE predictors which have been proposed, additional trials should clarify which is the most powerful parameter to use.

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