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Role of left ventricle deformation analysis in stress echocardiography for significant coronary artery disease detection: A diagnostic study meta-analysis

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Abstract

Background: We compared the diagnostic accuracy of longitudinal strain (LS) imaging during stress echocardiography with visual assessment of wall-motion (WM) for detecting significant coronary artery disease (CAD).

Methods: Our systematic search included studies reporting diagnostic measures for LS imaging and visual assessment of WM for detecting significant CAD during stress echocardiography. Summary diagnostic accuracy measures including area under the curve (AUC), sensitivity, specificity, diagnostic odds ratio (DOR), and, likelihood ratios (LRs) were estimated.

Results: In thirteen studies with 978 patients, ten studies used invasive coronary angiography as the reference standard. Pooled AUC for diagnosing significant CAD was 0.92 [95% confidence

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Drafting of the manuscript: AG, AS, SA, KG, NSB, JB, FGH, SDP, NCN, RH

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interval (CI) 0.89 to 0.94] for LS imaging as compared to 0.83 (95% CI 0.80 to 0.86), $p=0.000$ for visual assessment of WM. LS imaging had higher sensitivity [88% (95% CI 84 to 92) vs. 74% (95% CI 68 to 80), $p=0.000$] and comparable specificity to visual assessment of WM [80% (95% CI 72 to 87) vs. 83% (95% CI 74 to 90), $p=0.592$]. The DOR for LS imaging and visual assessment of WM was 31 and 15, $p=0.254$, respectively. The positive LR was 4.5 for both; negative LR was 0.14 and 0.31, $p=0.002$ for LS imaging and visual assessment of WM, respectively.

Conclusions: LS imaging during stress echocardiography has better diagnostic accuracy for detecting significant CAD as compared to visual assessment of WM. Studies using larger sample size and standardized techniques of strain measurement are required to further ascertain the added advantage of strain measurement over visual assessment alone.

Keywords

Longitudinal strain imaging; deformation analysis; wall-motion analysis; meta-analysis

Introduction

Stress echocardiography is a well-established modality for identifying myocardial ischemia.¹ Detection of wall-motion (WM) abnormalities during stress echocardiography are a cornerstone for diagnosing myocardial ischemia.² Wall motion abnormalities occur later in the ischemic cascade, and may be transient. Therefore, technical limitations of WM abnormality detection during stress echocardiography include the inability to obtain images at peak heart rate due to the rapid return of heart rate after stress, as well as off-axis imaging, and observer dependency.^{3,4} Hence, sensitivity and overall diagnostic accuracy of visual assessment during stress echocardiography are thought to be lower than other non-invasive imaging modalities.⁵

Myocardial deformation analysis using longitudinal strain (LS) analysis with stress echocardiography is an objective and reliable modality to detect abnormalities of myocardial motion better than visual assessment given its quantitative nature, ability to differentiate tethering from surrounding segments, and the fact that deformation abnormalities are seen early in the natural history of ischemic heart disease which may help detect at-risk territories earlier.^{6–8} Several studies have evaluated the role of LS imaging in diagnosing significant coronary artery disease (CAD) but these studies had a small sample size(s),^{8,9} reported the varying degree of diagnostic accuracy,^{10–12} and used different LS parameters.^{1,8,13–15} Given the lack of systematic evaluation of LS imaging during stress echocardiography, we conducted the current study to assess the diagnostic performance of LS imaging during stress echocardiography compared to visual assessment of WM in patients with suspected significant CAD. We hypothesized that the addition of LS analysis will improve the diagnostic accuracy of stress echocardiography beyond the visual assessment of WM.

Methods

Given this is a meta-analysis of the previously published literature, ethics committee approval is not applicable.

Study Protocol and Search strategy

Studies reporting diagnostic measures including sensitivity and specificity of LS imaging as well as a visual assessment of WM for myocardial ischemia detection during stress echocardiography in patients with suspected significant CAD were included. This study was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplemental Table 1). A systematic PubMed/MEDLINE database search from origin till September 1, 2018, was performed by two independent investigators (KG and TSK) for studies comparing LS imaging to visual assessment of stress echocardiography images to detect significant CAD using predefined criteria (Supplement). Studies in a language other than English, animal studies, studies reporting results taking myocardial segments as the unit of the study and those with <5 subjects in each group were excluded. Disagreements, if any, were resolved through consensus and after discussion with a third author (NSB).

Reference standard, stress echocardiography protocols, and LS imaging

Reference standard—Ten studies used invasive coronary angiography (ICA) as the reference standard. One study used single-photon emission computed tomography (SPECT) and another used coronary computed tomography angiography (CCTA) as the reference standard. One study used both ICA and adenosine-stress myocardial perfusion imaging. The angiographic cut-off for the diagnosis of significant CAD varied; >50% obstruction in seven studies, >70% in three studies and fractional flow reserve <0.75 in one study.

Stress echocardiography—Pharmacological stress was utilized most commonly (9 studies), followed by exercise stress (3 study) and one study reporting both exercise and pharmacological agents for stressing patients. Stress echocardiographic images were obtained from within one minute to five minutes after termination of exercise (Table II).

Left ventricular deformation with LS imaging—LS measurements were performed in all thirteen studies to assess left ventricular deformation. In all studies, the investigator interpreting LS analysis was blinded to the results of the reference standard. For plotting LS curves, tissue velocity imaging (TVI) was utilized in four studies and whereas nine studies used 2D speckle tracking (Table II). Two out of thirteen studies reported diagnostic accuracy of longitudinal strain at rest compared to WM abnormality at stress.^{15,16} Ten studies used global LS (GLS) whereas three studies used segmental LS measures. Variable LS measures and cut-offs for LS measures were used across studies for the detection of significant CAD (Table II). The most commonly utilized software for LS measurement was EchoPAC Workstation software provided by General Electric (GE) Medical systems (9 studies) other software including QLAB 9.0 (1 study), TVI® by GE (1 study), TomTec (1 study) and GcMat by GE (1 study) were also used.

Outcome measures

The outcomes evaluated in this meta-analysis were the area under the curve (AUC) for receiver operator characteristic (ROC), sensitivity, specificity, diagnostic odds ratio (DOR) and likelihood ratios (LRs). These were compared between LS imaging and visual assessment of WM during stress echocardiography.

Data items

Data items extracted from each study included demographic and clinical characteristics, the risk of bias items, the reference standard for diagnosis, software for LS assessment, LS parameters, positive (PPV) and negative predictive value (NPV), sensitivity, specificity, and AUC. Data for subgroup analyses by type of LS measure, strain measurement technique, the timing of strain measure, stress modality, and reference standard for CAD diagnosis was also extracted.

Data extraction

Two authors (KG and TSK) independently extracted the relevant data from the studies. Inconsistencies were resolved by a third author (NSB).

Quality assessment

We used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria to assess the quality of studies.¹⁷ Based on the data required for the present meta-analysis, studies were classified as having a low, unclear or high risk of bias and were classified according to the concerns regarding applicability by two independent authors (KG, TSK). The discrepancy, if any, were resolved through consensus as described above. Domain flow and timing was marked as high-risk of bias if the interval between the LS imaging and reference standard was >6 months.

Statistical analysis

A bivariate mixed-effects binary regression modeling was used to estimate summary sensitivity, specificity, DOR and LR for LS imaging and visual assessment.¹⁸ The summary measures were compared using LR tests. Summary ROC curves were constructed to assess the overall accuracy of each technique from the aforementioned model.¹⁸ Data were analyzed for heterogeneity using the I^2 statistic proposed by Higgins and Thompson.¹⁹ Deek's funnel plot asymmetry test was used for assessment of publication bias.²⁰ We also constructed Fagan's plots to understand the effect of the diagnostic likelihood ratios for LS and visual analysis on the post-test probability of significant CAD.^{18,21} All of the p-values were two-tailed, with statistical significance specified at $p < 0.05$. Sub-group analyses were performed to evaluate the effect of the type of LS measure (global or segmental), strain measurement technique (2D speckle tracking or TVI), timing of strain measure (stress or rest), stress modality (pharmacological or exercise), and reference standard for CAD diagnosis (invasive or non-invasive) on sensitivity and specificity of strain measures. All analyses were conducted in STATA version 15.0 (StataCorp, College Station, Texas).

Results

Of the 317 records screened from the PubMed database, we found 13 studies^{1,8–13,15,16,22–25} (9 prospective and 4 retrospective studies) with 978 patients that were eligible for (Figure 1). The included studies were published from 2007 to 2018. The sample size of individual studies ranged from 20-137 patients and the mean age ranged from 60-73 years. Among the included studies 53.3% of patients were confirmed to have significant CAD as per reference standard. Three studies included patients with a previous history of myocardial infarction

and four studies included patients with a history of coronary revascularization. Table I highlights the baseline characteristics across the included studies. The items of the PRISMA checklist are presented in Supplement Table 1. The risk of bias and applicability concerns were assessed using QUADAS-2 and were deemed acceptable (Supplement Figure 1). Stress echocardiography and strain imaging protocols with cut-offs to define significant CAD are given in Table II. Sensitivity and specificity of individual studies and derived values are presented in Supplement Table 2.

Meta-analysis of diagnostic measures for visual assessment of WM for significant CAD detection

All studies had an AUC for ROC of greater than 0.5 for visual assessment; indicating in most of the studies visual assessment was better than random prediction. The summary AUC for visual assessment was 0.83 [95% confidence interval (CI), 0.80 to 0.86] (Figure 2, panel a) indicating good diagnostic accuracy. Sensitivity and specificity in individual studies for visual assessment varied from 44 to 89% and 55 to 100%, respectively. Pooled sensitivity and specificity for visual assessment for diagnosing significant CAD were 74% (95% CI 68 to 80) and 83% (95% CI 74 to 90), respectively (Figure 3, panel a & Figure 4, panel a). The positive and negative LR was 4.5 (95% CI, 2.6 to 7.7) and 0.31 (95% CI, 0.23 to 0.41) for visual assessment, respectively. The summary DOR (ratio of LR+/LR-) of 15 (95% CI, 7 to 32) indicated good discriminating power for visual assessment.

Meta-analysis of diagnostic measures for LS imaging for significant CAD detection

All studies had AUC of greater than 0.5 for LS analysis to detect significant CAD; indicating LS imaging was better than random prediction in all included studies. The summary AUC for LS imaging was 0.92 (95% CI, 0.89 to 0.94) (Figure 2, panel b) indicating excellent diagnostic accuracy. Sensitivity and specificity in individual studies for LS imaging varied from 77 to 100% and 49 to 93%, respectively. Pooled sensitivity and specificity for LS imaging were 88% (95% CI 84 to 92) and 80% (95% CI 72 to 87), respectively (Figure 3, panel b & Figure 4, panel b). The positive and negative LR was 4.5 (95% CI, 3 to 6.6) and 0.14 (95% CI, 0.10 to 0.22) for LS imaging, respectively. The summary DOR for LS imaging was 31 (95% CI, 15 to 64) indicating excellent discriminatory power.

Comparison of diagnostic performance of visual assessment of WM and LS imaging

Pooled data from included studies show that out of 521/978 patients with significant CAD as per reference standard, LS imaging was able to detect 458/521 (88%) patients with true significant CAD as compared to 386/521 (74%) with visual assessment. Summary ROC curves suggest that LS imaging had a higher diagnostic accuracy for significant CAD detection than visual assessment of WM summary AUC (0.92 vs 0.83, $p < 0.001$) (Figure 2) which was driven by an improved sensitivity (88% vs. 74%, $p < 0.001$) (Figure 3) for LS imaging as compared to visual assessment and a comparable specificity (80% vs. 83%, $p = 0.592$) (Figure 4). These findings suggest that for every 100 patients referred for stress echocardiography, LS imaging will pick-up ~ 14 more patients with significant CAD as compared to visual assessment alone, with a comparable number of false positives. Interestingly, the variability in sensitivity by LS imaging was lower than visual assessment as indicated by I^2 statistic (52% vs. 62%) likely driven by quantitative and objective nature

of LS imaging. LS imaging had a numerically higher but statically non-significant summary DOR of 31 (95% CI, 15 to 64) as compared to 15 (95% CI, 7 to 32) for visual assessment of WM, $p=0.524$. The positive LR was 4.5 for both; while the negative LR was lower for LS imaging as compared to visual assessment of wall motion (0.14 vs. 0.31, $p=0.002$).

We did not observe any publication bias with Deeks test for both LS imaging and visual assessment, $p>0.05$ (Supplement Figure 2).

Post-test probabilities for LS imaging and visual assessment

We constructed Fagan's plots to explore the effect of LS imaging and visual assessment on post-test probabilities given the test was positive or negative (Figure 5). Considering a pretest probability of significant CAD to be 50%, if LS imaging was positive for significant CAD, the post-test probability of truly having significant CAD was 80% (similar to the post-test probability of 80% if visual assessment suggested significant CAD). Given the same pre-test probability, if LS imaging was negative for significant CAD, the chances of having significant CAD were only 13% as compared to 23% in case visual assessment showed normal WM. These results suggest that LS imaging helped ruling-out significant CAD better than ruling-in significant CAD as compared to visual assessment alone.

Sub-group analyses

We grouped studies by the type of LS measure, strain measurement technique, timing of strain measure, stress modality, and reference standard for CAD diagnosis and calculated the pooled sensitivity and specificity in the aforementioned sub-groups. We did not observe any significant effect of type of LS measure, strain measurement technique, the timing of strain measure, stress modality, and reference standard for CAD diagnosis on sensitivity and specificity] (all $p>0.05$). (Table III).

Discussion

Our systematic review and meta-analysis suggest that myocardial deformation analysis by LS imaging is feasible and has a higher diagnostic accuracy for detection of significant CAD, as compared to visual assessment of WM alone in patients undergoing stress echocardiography. This was primarily driven by improved sensitivity with LS imaging, given the specificity was similar to visual assessment.

There are several potential explanations which may have led to improved sensitivity for LS imaging. Abnormalities in LS parameters are found earlier in the natural history of CAD before WM gets affected.²⁶ LS abnormalities are independent of tethering motion and hence likely to detect abnormalities in myocardial motion due to ischemia better than visual assessment.^{3,26} Ability to detect WM abnormalities is limited by the sensitivity of the human eye (which is observer dependent); LS imaging by TVI or speckle tracking is able to detect subtle deformation changes which, on their own, are insufficient to cause visible WM changes and therefore, may escape detection.^{15,27} When exercise stress echocardiography is used to detect myocardial ischemia, the delay in acquisition of post-stress images may lead to resolution of ischemia and recovery of normal WM in myocardial segments that have experienced only mild ischemia and/or have extensive collateral blood flow.²⁸ In addition,

the increased respiratory rate with exercise makes image acquisition and interpretation difficult.²⁹ Strain abnormalities are known to persist for a longer time after stress which may also help overcome this limitation.^{1,30} On the other hand specificity of LS imaging was similar to visual assessment, indicating strain imaging did not reclassify those patients which were abnormal on visual analysis. Poor visualization of the endocardial border, especially of the basal segments leads to false positive results in visual assessment; the same segments show reduced LS in patients without significant ischemia.^{31,32} Aforementioned along with wide dispersion in specificity (55-100% for visual assessment of WM and 49-93% for LS imaging) might have resulted in a similar specificity in our meta-analysis.

Sub-group analysis suggests that the accuracy of LS measurement to diagnose significant CAD does not change if either 2D speckle tracking or TVI is used to measure strain. Though 2D speckle tracking is less angle dependent and has higher intra-observer or inter-observer agreement, both techniques are found to correlate well and can be used to measure strain reliably.³³

Strain imaging was feasible in more than 80% cases with high intra- as well as inter-observer co-relation.^{10,12,13,15} Feasibility of both 2D and tissue-velocity based strain imaging has been demonstrated in both animal as well as human studies, with good correlation between stenosis and strain during stress.^{34,35}

To the best of our knowledge, this is the first meta-analysis to estimate and compare the diagnostic accuracy of LS imaging with visual assessment during stress echocardiography for the detection of significant CAD. All the studies indicated the feasibility of performing LS imaging with stress echocardiography and indicate that implementation of LS protocols for regular clinical use is possible. The results of this meta-analysis strengthen the conclusion that sensitivity to detect significant CAD was higher with LS imaging when compared to WM assessment, apart from the aforementioned mechanistic explanations for this improvement. In this meta-analysis, all studies except one¹¹ reported increased sensitivity with LS imaging lending directional consistency to the observation of improvement in sensitivity. The included studies were directionally inconsistent in terms of incremental benefits of LS imaging over visual assessment on specificity to detect significant CAD.^{8,12,24} When these studies were pooled the specificity of LS imaging was high (~80%) but similar to visual assessment. Interestingly, there was lower variability in the reported sensitivity for LS analysis among the studies (77 to 100%) as compared to the reported sensitivity for visual assessment (44 to 89%) which is likely an attestation to quantitative and objective nature of LS imaging as compared to visual assessment.

Our findings have several clinical implications as follows: use of LS imaging with stress echocardiography is 1) feasible, 2) may help improve the sensitivity of stress echocardiography, 3) may serve as a fallback tool when the visual assessment is equivocal, and 4) may serve as an objective marker for serial assessments.

Our study has several limitations. Different LS parameters, type and timing of LS ascertainment, reference standards, cut offs of strain measures, software, and stress protocols were utilized across studies, which may have led to unquantifiable biases. Although when

studies were grouped to assess the effect of several of the aforementioned variables we did not observe any significant change in diagnostic performance of LS to detect significant CAD, indicating that the relative change of LS measures from stress to rest may be more important than absolute values of these measures. Furthermore, with all aforementioned differences in protocol, the addition of LS analysis parameters led to improved sensitivity for significant CAD detection in all studies as well in our meta-analysis. Despite the directional consistency in results it is not possible to utilize LS imaging in clinical practice unless protocols, parameters, and software are standardized to determine true clinical accuracy of LS imaging.

Conclusions:

Myocardial deformation analysis by LS imaging during stress echocardiography is feasible and has better diagnostic accuracy for detecting significant CAD as compared to visual assessment of WM alone. There is a need for larger studies, with standardized definitions and protocols, prior to widespread clinical use of LS imaging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Flow diagram for study selection

Figure 2 (a) and (b):

Summary receiver-operating curves (SROC) and area under the curve (AUC) for (a) visual assessment of wall motion and (b) LS imaging. Confidence contour highlights possible combinations of mean sensitivity and specificity

Figure 3 (a) and (b):
 Forest plot of sensitivity of included studies for (a) visual assessment of wall motion and (b) LS imaging. Squares represent point estimates of the sensitivity of each study. Solid lines represent 95% confidence interval (CI) around the point estimate. The diamond represents a summary estimate of pooled sensitivity.

Figure 4 (a) and (b): Forest plot of specificity of included studies for (a) visual assessment of wall motion and (b) LS imaging. Squares represent point estimates of the specificity of each study. Solid lines represent 95% confidence interval (CI) around the point estimate. The diamond represents a summary estimate of pooled specificity.

Figure 5 (a) and (b):

Fagan's nomogram for calculating the post-test probability (PTP). The solid red line extends from prevalence to positive LR and PTP; dashed blue line extends from prevalence to negative LR and PTP.

In each plot, a vertical axis on the left showed the fixed pre-test probability (PTP) (50%). Using the likelihood ratio in the middle axis, post-test probability (patient's probability of having the disease after the index test result was known) was acquired. (a) With a PTP being 50%, the post-test probability of significant coronary artery disease (CAD) on angiography, given a positive and negative visual assessment of wall motion results, were 80% and 23%. (b) With a PTP being 50%, the post-test probability of significant CAD on angiography, given positive and negative LS imaging results, were 81% and 13%.

Baseline characteristics

Table 1:

Author/year	Reference standard/cut-off	Total subjects (n)	CAD (n)	No CAD (n)	Mean Age (in years)	Males (n)	Htn (in %)	DM (in %)	Previous MI included	Previous PCI/CABG	Mean LVEF (%)
Wiedemann et al. ^{24/2007}	ICA/FFR<0.75	30	17	13	NR	NR	86.7	16.7	No	Yes	59.5
Björk Ingul et al. ^{36/2007}	ICA>50%	137	76	61	NR	NR	39.8	15.3	NR	NR	NR
Ng et al. ^{12/2009}	ICA>50%	62	48	14	65	48	NR	NR	Yes	NR	58.8
Takagi et al. ^{1/2010}	ICA>50%	45	30	15	73	37	87	51	NR	Yes	NR
Takagi et al. ^{8/2011}	SPECT	20	8	12	65	14	40	40	NR	NR	NR
Montgomery et al. ^{3/2012}	ICA>50%	123	56	67	60	73	68	27	NR	Yes	NR
Gaibazzi et al. ^{26/2014}	ICA>50%	82	49	33	64	46	62.2	24.4	No	No	NR
Cusma-Piccione et al. ^{10/2015}	ICA>50%	52	38	14	65	22	44	30	NR	NR	55.2
Aggeli et al. ^{13/2015}	ICA>70%	100	67	33	61	72	59	23	No	No	55
Nagy et al. ^{11/2015}	ICA>50%	60	35	25	63	46	63.3	26.7	Yes	Yes	NR
Rumbinaite et al. ^{23/2016}	ICA/ 70%, adenosine stress MPI	127	60	67	NR	67	49.6	14.9	No	NR	NR
Yang et al. ^{25/2017}	ICA>70%	37	25	12	73	21	65	43	Yes	NR	68
Mansour et al. ^{14/2018}	CCTA>70%	103	12	91	52	84	35.9	21.3	NR*	NR	64

CAD: Coronary artery disease Htn: Hypertension; DM: Diabetes mellitus; ICA: Invasive coronary angiography; SPECT: Single photon emission computed tomography; MPI: Myocardial perfusion imaging; CCTA: Coronary computed tomographic angiography; FFR: Fractional flow reserve; 2D: 2-dimensional; NR: Not reported; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention.

* excluded recent MI (< 6 months)

Table II:

Stress echocardiography and LS imaging protocols

Author/year	Stress	LS imaging technique	LS	Strain at	LS parameter	Diagnostic values (to detect significant CAD)
Wiedemann et al. ^{24/2007}	P	TVI	G	Rest, Stress	peak systolic strain rate	$< -0.6 \text{ s}^{-1}$
Bjork Ingul et al. ^{36/2007}	P	2D speckle tracking	G	Stress	Peak systolic strain rate	$< -1.3 \text{ s}^{-1}$
Ng et al. ^{12/2009}	P	2D speckle tracking	G	Stress	Peak GLS	$< -20\%$
Takagi et al. ^{1/2010}	E	TVI	G	Rest, Stress	Time to peak strain (TPS) ratio	1.10
Takagi et al. ^{8/2011}	E	TVI	G	Rest, Stress	time-to-peak strain 5 min after stress echocardiography	$> 70 \text{ ms}$
Montgomery et al. ^{15/2012}	P, E	2D speckle tracking	G	Rest	Rest systolic strain rate	< -0.95
Gaibazzi et al. ²⁰¹⁴ ¹⁶	-	2D speckle tracking	G	Rest	Rest GLS	$< -20.7\%$
Cusma-Piccione et al. ^{10/2015}	P	2D speckle tracking	G	Rest, Stress	GLS between low and peak dose	Not available
Aggeli et al. ^{13/2015}	P	2D speckle tracking	G	Rest, Stress	GLS between stress and rest	0%
Nagy et al. ^{11/2015}	P	TVI	S	Stress	Post-systolic index, peak systolic strain rate	$\text{PSI} < 35\%$; peak systolic strain rate $< -1.3^{-1}$
Rumbinaite et al. ^{23/2016}	P	2D speckle tracking	G	Stress	Peak GLS	$> -21.6\%$
Yang et al. ^{25/2017}	P	2D speckle tracking	S	Rest, Stress	strain between stress, post-systolic shortening	$> 1\%$ reduction in LS, new post-systolic shortening
Mansour et al. ^{14/2018}	E	2D speckle tracking	S	Rest, Stress	Peak GLS	$> -16\%$

LS: Longitudinal strain; CAD: Coronary artery disease; P: Pharmacological; E: Exercise; TVI: Tissue-velocity imaging; G: Global; S: Segmental GLS: Global longitudinal strain; TPS ratio: Defined as TPS at delayed post-exercise/baseline; Post-systolic index is the ratio of post-systolic to maximal systolic strain

Sub-group analyses to determine the effect of timing of strain measures, stress modality, strain technique and reference standard for CAD diagnosis on diagnostic performance measures for strain imaging

Table III:

Variable (no. of studies)	No. of studies	Subjects (n)	Pooled Sensitivity (%) (95% CI)	Pooled Specificity (%) (95% CI)
Longitudinal strain type				
Overall pooled estimate	13	978	88 (84 to 92)	80 (72 to 87)
Global	10	744	90 (84 to 94)	81 (72 to 87)
Segmental	3	234	84 (75 to 90)	73 (39 to 92)
Strain measurement technique				
Overall pooled estimate	13	978	88 (84 to 92)	80 (72 to 87)
2D speckle tracking	9	823	88 (82 to 93)	81 (70 to 88)
TVI	4	155	86 (77 to 91)	75 (64 to 84)
Timing of LS analysis				
Overall pooled estimate	13	978	88 (84 to 92)	80 (72 to 87)
Stress	11	773	90 (85 to 94)	81 (72 to 88)
Rest	2	205	81 (72 to 88)	74 (45 to 91)
Stress modality				
Any stress	11	773	90 (85 to 94)	81 (72 to 88)
Pharmacological	8	605	90 (84 to 94)	84 (71 to 92)
Exercise	3	168	86 (77 to 91)	75 (64 to 84)
Reference Standard for CAD diagnosis				
Overall pooled estimate	13	978	88 (84 to 92)	80 (72 to 87)
Invasive angiography	10	728	87 (82 to 90)	79 (69 to 87)
Non-invasive methods [*]	3	250	89 (66 to 97)	81 (61 to 92)

TVI: Tissue velocity imaging; LS: Longitudinal strain; CI: Confidence interval; CAD: Coronary artery disease; Echo: Echocardiography

^{*} Non-invasive methods include CT coronary angiography and myocardial perfusion imaging