Diagnostic Performance of Two-Dimensional Speckle Tracking Echocardiography for Detection of Obstructive Coronary Artery Disease: A Meta-Analysis.

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Abstract

Background: Two-dimensional speckle tracking echocardiography (STE) is a quantitative myocardial strain imaging technique in evaluating global and segmental myocardial deformation. The aim of the meta-analysis was to determine the diagnostic accuracy of STE in the detection of significant coronary artery disease (CAD) in patients undergoing resting or stress echocardiography. Methods: We performed a literature search in PubMed and Medline until March 2020 for studies evaluating the role of STE in diagnosing CAD. We assessed the diagnostic performance of STE in detecting CAD by using the pooled estimate of sensitivity, specificity, likelihood ratio, diagnostic odds ratio and diagnostic accuracy. We analyzed longitudinal strain data that were reported in resting and stress echocardiography. Results: A total of 17 studies (n=1762) were included for the analysis. 12 studies (n=1239) reported global longitudinal strain (GLS) in resting echocardiography and 5 studies (n=523) reported GLS in stress echocardiography. Overall, in resting echocardiography studies, pooled GLS sensitivity and specificity for predicting obstructive CAD data were calculated to be 79% (95% confidence interval 74-83%) and 77% (95% confidence interval 72-82%), respectively. The pooled odds ratio was 13.6 (95% confidence interval 8.7-21.5). When we considered the dobutamine stress echocardiograms alone, the sensitivity and specificity in predicting obstructive CAD was 77% (95% confidence interval 59-89%) and 78% (95% confidence interval 53-92%), respectively. The odds ratio was 12.6 (95% confidence interval 2.7-58.5). Conclusions: In this meta-analysis of patients with suspected CAD, we found that STE could effectively detect obstructive CAD with a high diagnostic sensitivity, specificity and diagnostic accuracy

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Running Head: Speckle tracking Echo in diagnosing CAD

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Abstract:

Background: Two-dimensional speckle tracking echocardiography (STE) is a quantitative myocardial strain imaging technique for evaluation of global and segmental myocardial deformation. The aim of the meta-analysis was to determine the diagnostic accuracy of STE in the detection of significant coronary artery disease (CAD) in patients undergoing resting or stress echocardiography.

Methods: We performed a comprehensive literature search in PubMed and Medline until March 2020 for studies evaluating the role of STE in diagnosing significant coronary artery disease. We assessed the diagnostic performance of STE in detecting CAD by using the pooled estimate of sensitivity, specificity, likelihood ratio, diagnostic odds ratio and diagnostic accuracy. We separately analyzed longitudinal strain data that were reported in resting and stress echocardiography.

Results: A total of 17 studies (n=1762) were included for the analysis. Out of 17 studies, 12 studies (n=1239) reported global longitudinal strain (GLS) in resting echocardiography and 5 studies (n=523) reported GLS in stress echocardiography. Overall, in resting echocardiography studies, pooled GLS sensitivity and specificity for predicting obstructive CAD data were calculated to be 79% (95% confidence interval 74-83%) and 77% (95% confidence interval 72-82%), respectively. The pooled odds ratio was 13.6 (95% confidence interval 8.7-21.5). When we considered the dobutamine stress echocardiograms alone, the sensitivity and specificity in predicting obstructive CAD was 77% (95% confidence interval 59-89%) and 78% (95% confidence interval 53-92%), respectively. The odds ratio was 12.6 (95% confidence interval 2.7-58.5).

Conclusions: In this meta-analysis of patients with suspected CAD, we found that STE could effectively detect obstructive CAD with a high diagnostic sensitivity, specificity and diagnostic accuracy. Combined assessment of the wall motion analysis and STE may have a significant incremental diagnostic value.

Keywords:

Speckle Tracking Echocardiography, Coronary Artery Disease, Myocardial ischemia; Coronary stenosis, Wall motion abnormalities.

Introduction:

Stress and resting echocardiography plays an important role in providing clues to the presence of CAD.[1] Multiple studies have shown the diagnostic and prognostic ability of echocardiography in diagnosing CAD based on segmental myocardial function and wall motion abnormalities.[2] In patients with no prior extensive myocardial infarction and atypical presentation, the diagnostic ability of echo decreases.[3,4]Speckle tracking based two-dimensional strain imaging echocardiography (STE) is an advanced diagnostic technique providing quantitative analysis of global and regional myocardial deformation. Speckle-derived strain is superior to tissue Doppler strain, particularly with regard to dependency on beam angle.[5] Two-dimensional (2D) STE can measure global and regional strain, strain rate, displacement, and velocity in longitudinal, radial, and circumferential directions. Although it can also quantify rotational movements such as rotation, twist, and torsion of the myocardium, longitudinal deformation is most reproducible and has the best association with clinical outcomes.[5] Recently, STE utilizing GLS has gained a mainstream role in diagnosing multiple cardiac conditions. In the last several years, multiple studies evaluated the predictive capability of STE imaging in the diagnosis of coronary artery disease.[6,7]We performed a meta-analysis to determine diagnostic accuracy of STE in the detection of CAD in patients undergoing rest or stress echocardiography.

Methods:

A literature search was performed independently by 2 investigators using PubMed and MEDLINE databases until March 2020. We used a combination of keywords, which included the following: "speckle tracking", "coronary artery disease," "strain imaging". All searches were limited to studies of human subjects. We utilized PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for data extraction.[8] Studies were included if they compared the diagnostic accuracy of STE to standard diagnostic modalities or presence of myocardial ischemia. Presence of obstructive CAD was defined by either anatomic imaging (cardiac catheterization with $> 50\%$ stenosis) or functional (SPECT) or clinical presence of myocardial ischemia. We reviewed the bibliographies of the included studies and previous reviews to identify additional citations. After the trial selection process, 457 studies were reviewed, and 17 eligible studies were included for the final analysis. Figure 1 demonstrates the selection process for the studies included.

Data Extraction:

Two researchers (JS and AK) reviewed all included papers and abstracted all of the relevant data from them into formatted Windows Excel database. A third researcher (AA) reviewed extracted data from all of the papers. Data were extracted from each selected article using standard electronic sheets. Disagreement between the extracting investigators was resolved by consensus. The following data were extracted from the eligible studies: author of the study, publishing journal, year of publication, demographics of the sample population, modality of strain utilized, vendor details of the echocardiography machines, sensitivity, specificity, diagnostic modality used for comparison, methodology of echocardiography performed (stress and rest) and any utilization of pharmacological stress agents.

Quality Assessment:

Two authors (AK and JS) independently reviewed each included study. The study quality and risk for bias in individual studies were assessed by evaluating selection bias, performance bias, detection bias, attrition bias and selective reporting or other biases. Then we objectively scored the bias using Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.[9]Disagreements were resolved by consensus and by review with third researcher (AA). QUADAS-2 tool consists of four domains: patient selection, index test, reference standard, and flow/timing. The patient selection bias is assessed by the methods of patient selection, index test evaluated by how the index testing was performed, reference standard by assessing how the comparison studies were done and flow and timing bias assessed by whether if there are any interventions between index test and reference standards. Risk of bias was scored for all the domains, and applicability concerns were defined for the first three domains. The risk was quantified by stratifying them into low, high and unclear bias.

Statistical Analysis:

We conducted a meta-analysis assuming random effects by using RevMan[10] (Version 5.3.5 Copenhagen, Denmark) and Open Meta-Analyst[11] (Version 10.10, USA). One study[12] had longitudinal and circumferential strains separately reported and analyzed. There were no studies that were subsets of patients from prior reports and therefore we did not have to exclude any study for inclusion of duplicate patients. In the studies that did not report positive (true positives and false positives) and negative proportions (false positives and false negatives), we computed them by utilizing the proportion of people with disease, sensitivity and specificity in RevMan. Diagnostic odds ratio was defined as a comprehensive diagnostic measure of effectiveness of a study that is estimated by either (sensitivity/[1-sensitivity])/([1-specificity]/specificity) or (PPV/[1-PPV])/([1-NPV]/NPV).[13]When significant heterogeneity was suspected, we used a random effects model (DerSimonian and Laird method), otherwise, a fixed effect model (Mantel–Haenszel method) was considered.[14]

We performed meta-analyses separately for studies that reported longitudinal strain data on resting echocardiograms (12 out of 17 included studies), studies that evaluated the speckle tracking on stress echocardiograms (5 out of 17 included studies) and in stress echocardiograms. Table 3 shows the QUADAS-2 tool application to assess the bias in our meta-analysis.

Results:

Study selection results:

Seventeen studies (n=1762) were included for the final analysis. We included studies reporting longitudinal strain compared to angiography alone to maintain homogeneity of the analysis. All the studies were in English. All but one study were conducted in prospective design. Twelve studies reported STE data from resting echocardiography (n=1239), whereas five studies utilized dobutamine stress echocardiography (n=523) to obtain STE data. Pooled study population comprised of 1074 male and 651 female patients. The mean age of the patients in the included studies was 61 $\pm$ 4.2 years.

Table 1 represents the demographic details of the studies included for the analysis. Table 2 demonstrates reported diagnostic outcome variables that were used to perform this meta-analysis.

Results of quality and bias assessment:

When QUADAS-2 tool was used to assess the quality of the studies and risk of bias, one study revealed high bias in patient selection, 6 studies showed high bias towards index testing and all the studies showed low bias towards reference standard. In general, all the studies revealed some bias but most them had low bias potential.

Studies reporting longitudinal strain in resting echocardiography:

For 12 of 17 studies[6,15-25]that reported GLS alone, the sensitivity and specificity in predicting obstructive CAD were calculated to be 79% with a 95% confidence interval (74-83%) (p=0.068) and 77% with a 95% confidence interval (72-82%) (p=0.048) respectively. The Odds Ratio was calculated to be 13.6 [(95% confidence interval (8.7-21.5) (p=0.014)]. The positive and negative likelihood ratios were calculated to be 3.4 [(95% confidence interval (2.7-4.3) (p=0.019)] and 0.24 [(95% confidence interval (0.18-.32) (p<0.001)] respectively.

Studies reporting longitudinal strain in stress echocardiography:

A total of 5[26-30]studies reported the stress STE data. The sensitivity and specificity were to be 77% with a 95% confidence interval (59-89%) (p<0.001) and 78% with a 95% confidence interval (53-92%) (p<0.001) respectively. The odds ratio was calculated to be 12 [(95% confidence interval (2.72-58) (p<0.001)]. The positive and negative likelihood ratios are calculated to be 3.3 [(95% confidence interval (1.3-8.6) (p<0.001)] and 0.30 [(95% confidence interval (0.16-0.57) (p=0.001)] respectively.

Discussion:

In this meta-analysis, we report diagnostic performance of STE based on a pooled data from 17 original peer-reviewed studies with a total population of 1762 patients. We found that GLS using resting STE has an overall sensitivity of 79% and specificity of 77 % for prediction of obstructive CAD. With stress strain imaging data, the sensitivity of GLS was 77% and specificity was 78%.

These values appear to be comparable to other diagnostic stress testing methods[31,32]. However, STE has the advantage of no additional radiation exposure or extensive postprocessing. Standard echocardiographic assessment is usually inherently limited by its dependency on operator ability, body habitus and hemodynamic characteristics.[33]

Role of STE in Detecting CAD:

Multiple studies have shown that STE can be used reliably to assess global and regional myocardial deformation.[34,35]Abnormalities in myocardial deformation can be seen in the various pathophysiologic states, including myocardial ischemia, thus aiding in assessing myocardial dysfunction. Jamal[36] et al noted that longitudinal systolic strain was abnormal in normokinetic segments of LV supplied by stenotic (with an obstruction of>70%) arteries. In a prospective study, systolic and early diastolic strains of the segments supplied by left anterior descending (LAD) artery remained deformed (suggestive of regional post ischemic dysfunction) up to 60 minutes after exercise in patients with angiographically proven CAD compared to patients with normal angiography, suggesting role of STE imaging in patients with chest pain with a normal EKG.[37] Another study evaluated the role of early diastolic deformation in diagnosing significant CAD (>70% stenosis) and noted its sensitivity and specificity to be 77% and 93%[19]Choi[6] noted that a longitudinal strain value of -17.9% discriminated the severe (LAD or 3 vessel disease) from milder disease with a sensitivity and specificity of 79%.

Added value of STE in Dobutamine Stress Echocardiography:

Dobutamine stress echocardiography (DSE), despite its clinical utility in diagnosing coronary artery disease, has its own limitations including subjective interpretation and decreased diagnostic ability with moderate coronary stenosis. STE imaging has shown to increase the clinical utility of DSE. We have noted that STE has high diagnostic sensitivity and specificity and incremental diagnostic value when utilized along with DSE. In a prospective study[38], 44 patients with known or suspected CAD underwent DSE along with analysis of strain rate and segmental strain. All patients underwent a subsequent angiogram. In the segments with proven ischemia, strain rate increased and the longitudinal strain values were significantly reduced along with post systolic shortening. Compared to DSE alone, strain imaging improved diagnostic ability. In a multicenter study[29] involving 102 patients, the authors compared strain measurements and wall motion analysis. The diagnostic accuracy of longitudinal strain analysis was found to be comparable with wall motion score indices and the diagnostic ability increased incrementally when longitudinal strain analysis and wall motion score indices were combined.

Circumferential deformation also revealed promising results in diagnosing myocardial ischemia.[39] We performed the analysis on longitudinal deformation alone as most of the studies reported only longitudinal STE.

Incremental value of STE in overall interpretation of echo exam for coronary ischemia:

Nucifora et al[7] reported that while combining longitudinal strain to wall motion analysis, the sensitivity, specificity and the diagnostic accuracy increased compared to wall motion analysis alone. Similar results were noted by Ng et al[29] when combining strain imaging to Duke clinical score. Thus, combined assessment of clinical and echocardiographic data with added STE information likely increases the independent and incremental value as well as the diagnostic certainty in revealing obstructive CAD similar to that which is known in the combined assessment of the ECG, hemodynamic and imaging data in nuclear myocardial perfusion imaging .[40] More research is needed to assess effectiveness of strain imaging in diagnosing the presence and the severity of coronary artery disease in patients who cannot undergo stress testing.

Limitations:

Our findings should be interpreted with caution, due to smaller sample size in the included studies and due to presence of significant heterogeneity noted. Also, many studies did not routinely report cardiac risk factors, use of medications and characteristics of cardiac symptoms, that could have confounded the results. Also, many studies have not reported the diagnostic information for CAD such as ECG changes and diagnostic markers such as cardiac troponins (Tn-I) limiting our ability to assess the magnitude of CAD. Also, different vendor and corresponding software systems were used to calculate the STE data that could also have had possibly variable outcomes from this study.

Conclusion:

In this meta-analysis of patients with known or suspected CAD, we found that STE could effectively diagnose obstructive CAD with a high diagnostic sensitivity, specificity and diagnostic accuracy. The results were comparable with resting and stress echocardiography data. Larger prospective studies are warranted to determine the role of this methodology in diagnosing coronary artery disease especially evaluating its incremental value.

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Authorship credit: Conceived and designed the meta-analysis (AA, JS, AK, VS), extracted and analyzed the data (AK, JS and AA), interpretation of results (AK, JS, VS and AA), drafted the article or revised it critically for important intellectual content (AK, JS, VS and AA), final approval of the version to be published (AK, JS, VS and AA). The authors would like to acknowledge Ahlam A. Saleh, MD, MLS for helping with literature search.

Author	Year of publication	Study type	Total number of patients	Mean age	Male	Female	N
Choi[6]	2009	Prospective	96	59	68	40	3
Dahlslett[15]	2014	Prospective	64	55	44	20	2
Deng[16]	2010	Prospective	74	57.1	54	20	4
Eek[17]	2010	Prospective	150	58.1	110	40	3
Grenne[18]	2010	Prospective	111	60.5	77	34	2
Hanekom[26]	2007	Prospective	150	66	100	50	8
Hwang[27]	2014	Prospective	44	65	23	21	1
Ingul Rest[41]	2005	Prospective	60	65	19	11	3
Ingul Stress[42]	2007	Prospective	197	58	99	98	7
Kusunose[43]	2011	Prospective	118	71	NR	NR	6
Lee[44]	2015	Prospective	69	55	NR	NR	2
Liang[19]	2006	Prospective	54	64	35	26	3
Montgomery[20]	2012	Retrospective	123	60	73	50	5
Ng[29]	2009	Prospective	102	65.1	73	29	7
Nucifora[7]	2010	Prospective	182	54	108	74	6
Shimoni[21]	2011	Prospective	97	62.8	74	23	6
Smedsrud[22]	2012	Prospective	86	64	45	43	4
Tsai[23]	2010	Prospective	152	67	77	75	7
Weidemann[30]	2007	Prospective	30	62	NR	NR	1
Yang[24]	2011	Prospective	107	57.8	57	22	7
Zuo[25]	2015	Prospective	125	56	65	60	7

Legends:

- Table 1- Demographic details of the patient population of the included studies
- Table 2- Results of quality assessment and estimation of bias utilizing QUADAS 2 tool
- Figure 1- Flow chart summarizing the number of articles reviewed and the reasons for excluding them from the meta-analysis.

- Figure 2:
- Panel A: Forest plot assessing the pooled sensitivity of longitudinal STE studies in resting echocardiography
- Panel B: Forest plot assessing the pooled specificity of longitudinal STE studies in resting echocardiography
- Panel C: Forest plot assessing the positive likelihood ratio of longitudinal STE studies in resting echocardiography
- Panel D: Forest plot assessing the negative likelihood ratio of longitudinal STE studies in resting echocardiography

Figure 3:

- Panel A - Forest plot assessing the pooled sensitivity of longitudinal STE studies in stress echocardiography
- Panel B - Forest plot assessing the pooled specificity of longitudinal STE studies in stress echocardiography
- Panel C- Forest plot assessing the positive likelihood ratio of longitudinal STE studies in stress echocardiography
- Panel D - Forest plot assessing the negative likelihood ratio of longitudinal STE studies in stress echocardiography

Figure 4:

Panel A: Forest plot assessing the pooled odds ratio of GLS during resting echocardiography

Panel B: Forest plot assessing the pooled odds ratio of GLS during stress echocardiography

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