Myocardial Contrast Echocardiography has Favorable Sensitivity and Specificity for Coronary Artery Disease Diagnosis in Patients with LBBB: A Meta-analysis

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Abstract

Background: Conflicting evidence exists on the ideal choice of non-invasive pharmacologic stress imaging for coronary artery disease (CAD) diagnosis in patients with left bundle branch block (LBBB). The aim of this meta-analysis is to compare data that examine the sensitivity and specificity of non-invasive pharmacologic stress imaging in patients with LBBB for obstructive CAD diagnosis.

Methods: We performed a literature search in MEDLINE, embase.com and Cochrane (CENTRAL) without publication type or language restrictions. Both pharmacologic stress echocardiography (SE) and nuclear myocardial perfusion imaging (MPI) searches were restricted to the period between January 2004 and review time. Exclusion criteria included studies that lacked sensitivity and specificity data. The primary objective was to compare the sensitivities and specificities of all pharmacologic SE, MPI, myocardial contrast echocardiography (MCE), stress cardiac magnetic resonance (CMR) and positron emission tomography (PET) for identifying significant CAD in patients with LBBB.

Results: 10 studies met the inclusion criteria for analysis. The sensitivity and specificity odds ratio of MCE was 92% (95% CI 81-97%), 93% (95% CI 86- 97%); Dobutamine (D)-CMR 64% (95% CI 42-82%), 94% (95% CI 85-98%); pharmacologic SE 73% (95% CI 55-86%), 84% (95% CI 75-91%); and pharmacologic MPI 83% (95% CI 72-91%), 56% (95% CI 42-70%).

Conclusion: MCE and D-CMR appear to have improved diagnostic accuracy in comparison to pharmacologic SE and MPI in patients with LBBB. Additional MCE and D-CMR studies are warranted given their potential to become the non-invasive gold standard for the diagnosis of CAD in this population.

Introduction

Pharmacologic stress imaging of the heart is considered to be the non-invasive test of choice for the diagnosis of obstructive coronary artery disease (CAD) in patients with left bundle branch block (LBBB) because of the non-specificity of exercise stress testing [1]. Pharmacologic stress echocardiography (SE) and nuclear myocardial perfusion imaging (MPI) are both widely available and less expensive than other forms of testing such as myocardial contrast echocardiography (MCE), positron emission tomography (PET), and cardiac magnetic resonance imaging (CMR). The current guidelines recommend pharmacologic stress testing with either MPI or SE as Class IB tests for stable ischemic heart disease evaluation in patients with LBBB, regardless of the ability to exercise [2]. Several studies attest to the diagnostic utility of both SE and MPI but the false positive rate remains higher in patients with than without LBBB [3,4]. In 2006, a meta-analysis pooling both exercise and pharmacologic data of stress imaging concluded that the MPI had higher overall sensitivity than SE (88.5% vs. 74.6% respectively, p<0.0001) but had significantly lower specificity (41.2% vs. 88.7% respectively, p<0.0001) for CAD in patients with LBBB [5]. More recent studies evaluated several interpretation strategies of stress imaging tests in patients with LBBB and reported less false positive rates in some of the studies than previously described.

For example, incorporating diastolic parameters during dobutamine SE increased the specificity for CAD diagnosis, and accounting for the presence of fixed LV cavity dilatation and LAD territory ischemia evaluation improved the diagnostic power of MPI in patients with suspected CAD and LBBB at baseline [6,7]. Moreover, technological advances such as MCE, stress CMR and PET imaging widened the options of non-invasive evaluation in this selected population with promising results [8]. Accordingly, we conducted this meta-analysis in order to compare the sensitivity and specificity of pharmacologic SE and MPI for obstructive CAD diagnosis over the past 10 years. In addition, we performed a literature search for studies that examined the sensitivity and specificity of the newer modalities, MCE, stress CMR, and PET for CAD in patients with LBBB.

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Methods we published the research protocol of this systematic review online on PROSPERO systematic review database prior to data extraction and analysis on Feb-6-2015. The PROSPERO registration number is CRD42015016495.

The reference URLs for the published protocols are: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016495.

Eligibility

Inclusion criteria: We included studies that evaluated the sensitivity and specificity of pharmacologic SE, MPI, D-CMR, MCE, and PET for CAD diagnosis in patients with pre-existing LBBB. Exclusion criteria were case reports; reviews; studies that included patients with pacemaker or exercise induced LBBB, valvular heart disease, or that used exercise as a form of stress; and studies that did not compare non-invasive scan results to coronary angiography. The primary outcomes were comparisons of the sensitivities and specificities of DSE, adenosine MPI, MCE, and PET for identifying obstructive CAD (≥50%) in patients with LBBB.

Literature search: A literature search in MEDLINE, Embase.com, and Cochrane (CENTRAL) was conducted on February 2 2014. Language or publication type filters were not applied to the search strategy. We restricted the SE and MPI search to the period from 2004 until the current time of this review. The search was done under the supervision of the librarian (LH) and reviewed by the biostatistician (NM) and the co-authors; the search strategy was revised multiple times until the best strategy was achieved. A balanced combination of MeSH terms and keywords utilizing the various search options of the searched databases as shown in Appendix 1 was used. Ongoing research trials about the subject were searched in http://www.controlled-trials.com/isrctn/ and http://www.clinicaltrials.gov. The detailed search strategy is summarized in Appendix 1. The search strategy was developed in compliance with the guidelines of peer review of electronic searches described by Sampson et al. [9].

Selection process two reviewers (WA, AB) screened the titles and abstracts of identified citations independently and in duplicate. The full texts for citations that were judged by at least one of the two reviewers as potentially eligible were subsequently retrieved and screened independently. The results of the screening process were compared, and any disagreement was resolved by either discussion or with the help of a third reviewer. Calibration exercises were conducted and standardized screening forms based on the eligibility criteria were used.

Data extraction Data were abstracted from eligible studies using standardized forms in duplication. Data collected included the type of study design, characteristics of the population, control, and outcomes.

Study characteristics: For each study, the noted characteristics included the year of publication, number of enrolled individuals, mean or frequency of male gender, age, cardiac risk factors, type of pharmacologic agent, the method of test interpretation used, QRS duration, and significant CAD definition. The non-invasive test was defined as positive for Ischemia when nuclear scans had any perfusion defect or wall motion abnormality; SE had any stress related regional wall motion abnormality (RWMA) or abnormal diastolic parameters; MCE had myocardial contrast opacification defect or impaired flow; or if CMR had any of the following: stress induced RWMA on cine exam, perfusion abnormality, or late gadolinium enhancement (LGE). Significant CAD definition was accepted if there was ≥50% stenosis in any major coronary artery by coronary angiography.

Quantitative data synthesis: The weighted mean frequency or mean for each of the mean age, male gender percent, angiographic CAD, hypertension, diabetes, LBBB definition, and QRS duration were calculated.

From each report, a 2×2 table was constructed summarizing the number of true/false positive results and true/false negative test results. The sensitivity and specificity were calculated from the 2×2 frequency data for pharmacologic MPI, SE, CMR, and MCE. Calculated values included the diagnostic sensitivity/specificity for each study along with the weighted (proportional to the sample size) mean sensitivity (number of true positives/number of patients with angiographically significant CAD) and specificity (number of true negatives/total number of patients without angiographically significant CAD) from the combined data.

Risk of bias (quality) assessment: A risk of bias in each of the eligible studies was performed independently and in duplicate among two authors of this review using the Cochrane Risk of Bias tool. This tool includes the following criteria: lack of blinding of participants or study personnel; incompleteness of outcome data; selective outcome reporting, and other bias (Table 1). All studies were cross sectional and non-randomized. Two MPI and one MCE studies had unclear blinding of study personnel [10-12]. One had high risk for detection bias due to exclusion of patients who did not undergo coronary angiography within 6 month [7]; another excluded 6 patients from analysis due to suboptimal images [13]. One study had high risk attrition bias due to exclusion of basal segment data from analysis of all patients because of suboptimal images [10].

Otherwise, the remaining studies were considered low risk for bias for non-randomized data.

Statistical analysis

Methods: A meta-analysis of the diagnostic odds ratio (DOR) using the Der Simonian Laird approach was performed using Edgars test with funnel plots on the log(DOR) to assess publication bias [14]. Because there is typically a tradeoff between sensitivity and specificity, it is generally accepted that specialized methods are needed for the meta-analysis of diagnostic test data [15]. The bivariate approach [15,16] as implemented in the mada package in R [17,18] which uses a multivariate normal prior was utilized to account for the correlation between sensitivity and specificity. The sensitivity of all included studies and the subgroup analysis of classes of the diagnostic tools were summarized.

Heterogeneity and Publication Bias Assessment There was evidence of study heterogeneity in the diagnostic odds ratio with a P-value of 0.007 for Cochran's Q Test of Heterogeneity and I2=51%. After accounting for the four diagnostic tools using meta-regression, the evidence for heterogeneity disappeared (P-value=0.29, I2=14.91%). Thus other causes of heterogeneity were not investigated. There was not any convincing evidence of publication bias from Edgars test of funnel plot asymmetry (P-value=0.1234) or from visual inspection of the funnel plot (Figure 1).
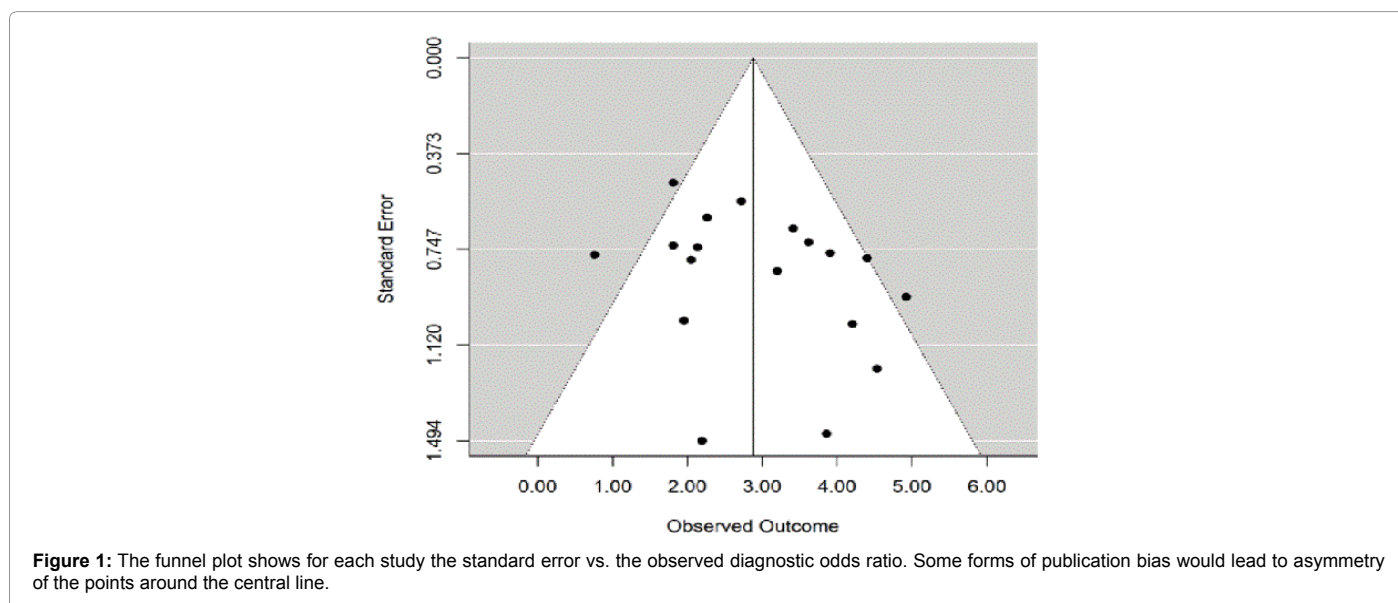
Results

The search strategy identified 3013 citations (369 were duplicates and were removed). Of the 2644 titles, 2499 were non-relevant and excluded. Of the 145 abstracts, 135 were excluded (34 case reports, reviews of poster presentations and editorials, 32 prognosis, 20 excluded or lacked data on LBBB, 35 lacked sensitivity and specificity

Study	Selection Bias		Performance Bias	Incomplete Outcome Reporting (Attrition Bias)		Reporting Bias
	Random Sequence Generation	Allocation Concealment	Blinding of Participant and Personnel	Short Term (2-6Weeks)	Long Term (>6 Weeks)	Selective Outcome Reporting
Badran et al. [6]	-	-	+	?	?	+
Fal.lahi et al. [7]	-	-	+	?	?	+
Hayat et al. [8]	-	-	+	?	?	+
Karavidas et al. [10]	-	-	?	?	?	-
Feola et al. [11]	-	-	?	?	?	+
Felis et al. [12]	-	-	?	?	?	+
Soylu et al. [13]	-	-	+	?	?	-
Pavlovic et al. [21]	-	-	?	?	?	-
Mordi et al. [22]	-	-	+	?	?	+
Vigna et al. [27]	-	-	+	?	?	-

(-) High risk for bias; (?) Unclear risk for bias; (+) Low risk for bias.

Table 1: Cochrane tool for risk of bias scores of the various studies.

Figure 1: The funnel plot shows for each study the standard error vs. the observed diagnostic odds ratio. Some forms of publication bias would lead to asymmetry of the points around the central line.

data, 8 stress or pacing induced LBBB, 4 right bundle branch block (RBBB), 1 cardiac CT, 1 post MI) leaving 10 papers for analysis. A flow chart is attached in Appendix 1. The 10 eligible studies included: 3 SE (n=171), 7 Nuclear MPI (n=326), 3 MCE (n=125), and 1 dobutamine CMR (n=82) (Figure 2 and Table 2). Two SE studies addressed at the same time MPI and CMR, one for each. Two MCE studies also evaluated MPI sensitivity and specificity. All studies enrolled patients who were undergoing testing for suspected CAD with no prior history of myocardial infarction. The forest and crosshair plots [19]. Figures 3 and 4A show the sensitivity and specificity of each study as well as the summarized sensitivity, specificity from the bivariate analysis. Characteristics of the study populations are summarized in Table 3.

Sensitivity of non-invasive imaging for CAD detection in LBBB

The overall sensitivity odds ratio of pharmacologic non-invasive stress imaging for CAD diagnosis in patients with LBBB was 77% (95% CI, 68-84%). The overall highest odds ratio for sensitivity stratified by non-invasive test was for MCE 92% (95% CI, 81-97%); this was followed by MPI with 83% (95% CI, 72-91%); pharmacologic SE with 73% (95%

CI, 55-86%); and D-CMR with 64% (95% CI, 42-82%) (Figure 3). PET scan had no data on sensitivity to answer our inquiry.

Specificity of non-invasive imaging for CAD detection in LBBB

The overall specificity odds ratio of pharmacologic non-invasive stress imaging for CAD diagnosis in patients with LBBB was 82% (95% CI, 72-89%). The overall specificities of individual non-invasive tools were highest for D-CMR and MCE with 94% (95% CI, 85-98%) and 93% (95% CI, 86-97%), respectively; this was followed by pharmacologic SE with 84% (95% CI, 75-91%); and MPI with 56% (95% CI, 42-70%) (Figure 3). PET scan had no data on specificity to answer our inquiry.

Summary of ROC curves, positive predictive and negative predictive values

The cross hair plot analysis of sensitivity and 1- specificity with the 95% confidence interval for each study demonstrates the relatively wider and lower range of specificities of nuclear MPI in comparison to the other modalities (Figure 4A). Analysis of the estimated sensitivity and 1- specificity and the associated underlying receiver operator curve
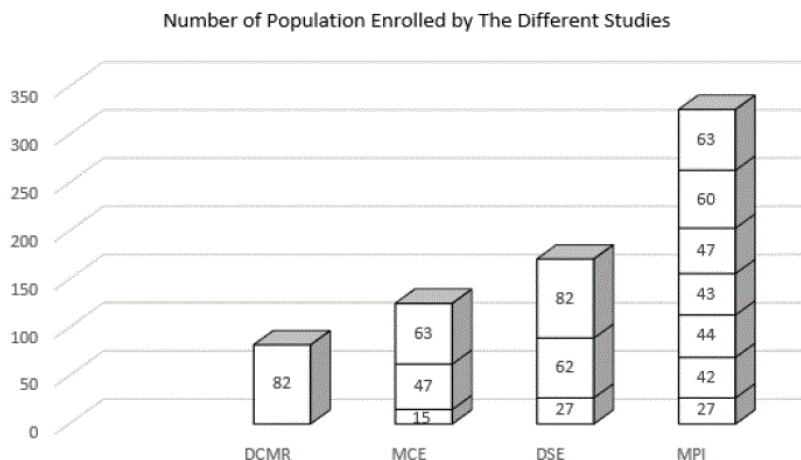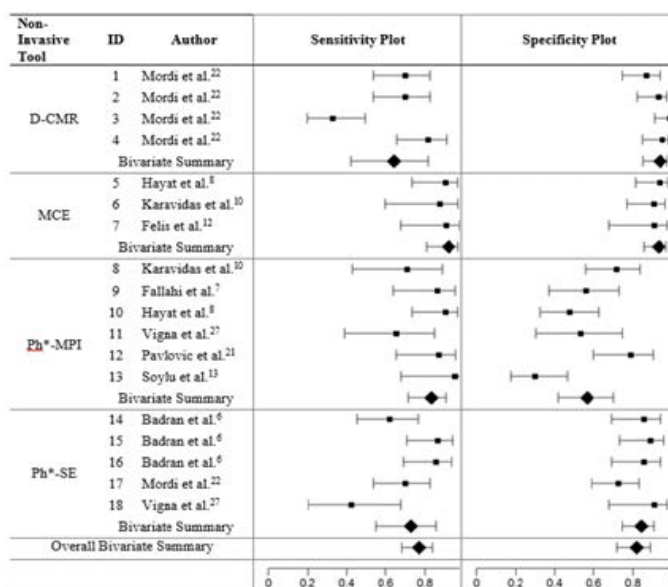
Figure 2: Stacked bar chart representing the sample size included in the individual studies stratified by non-invasive pharmacologic imaging tool.

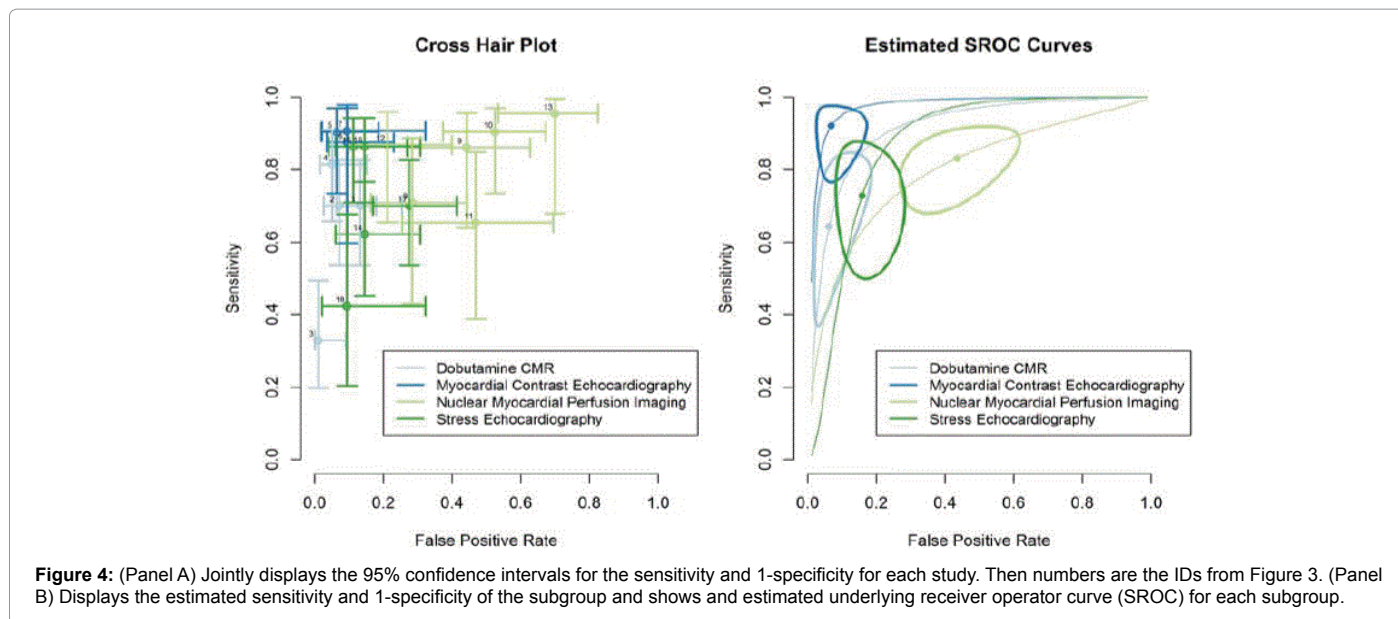| Study	Pharmacologic MPI	Pharmacologic SE	Pharmacologic CMR	MCE
Badran et al. [6]	(-)	62	(-)	(-)
Fal.lahi et al. [7]	42	(-)	(-)	(-)
Hayat et al. [8]	63	(-)	(-)	63*
Karavidas et al. [10]	47	(-)	(-)	47*
Feola et al. [11]	60	(-)	(-)	(-)
Felis et al. [12]	(-)	(-)	(-)	15
Soylu et al. [13]	44	(-)	(-)	(-)
Pavlovic et al. [21]	43	(-)	(-)	(-)
Mordi et al. [22]	(-)	82	82*	(-)
Vigna et al. [27]	27	27*	(-)	(-)

(-) No patients underwent this form of non-invasive testing; *Number of overlapping patients.

Table 2: Number of patients examined in each study with each non-invasive tool.

Repeated studies used the same population included in that study-1: Sensitivity and specificity by regional wall motion abnormality during D-CMR; 2: Sensitivity and specificity of myocardial perfusion by D-CMR; 3: Sensitivity and specificity of late gadolinium enhancement by D-CMR; 4: Sensitivity and specificity of comprehensive D-CMR (RWMA+perfusion+LGE); 14: Sensitivity and specificity of regional wall motion abnormality by echocardiography; 15: Sensitivity and specificity of peak systolic velocity of posterior septum, anterior septum, posterior, lateral, inferior, and anterior walls by tissue Doppler echocardiography; 16: Sensitivity and specificity of early diastolic velocity of posterior septum, anterior septum, posterior, lateral, inferior, and anterior walls tissue Doppler echocardiography.

Figure 3: Forest plots of sensitivities and specificities of the various studies stratified by the type on non-invasive stress imaging tools. *Ph: Pharmacologic.

Figure 4: (Panel A) Jointly displays the 95% confidence intervals for the sensitivity and 1-specificity for each study. Then numbers are the IDs from Figure 3. (Panel B) Displays the estimated sensitivity and 1-specificity of the subgroup and shows and estimated underlying receiver operator curve (SROC) for each subgroup.

	Pharmacologic MPI	Pharmacologic SE	Pharmacologic CMR	MCE
Year of Enrollment	- Aug/1998-Jun/2009 - N/A* [7,8,13]	- Jan/2002-Apr/2003 N/A* [6,22]	- N/A [22]	- Mar-Sep 2003 N/A* [8,12]
Total. Number (n)	- 326	- 171	- 82	- 125
Pharmacologic Agent	- Adenosine [10,11] - Dipyridamole [7,8,13,21,27]	- Dobutamine [6,22] - Dipyridamole [27]	- Dobutamine [22]	- Adenosine [10] - Dipyridamole [8] - N/A* [12]
Indication	- CAD Diagnosis	- CAD Diagnosis	- CAD Diagnosis	- CAD Diagnosis
Pretest Probability	- Intermediate [7,8,13,21] - N/A [10,11,27]	- Intermediate [22] - N/A [6,27]	- Intermediate [22]	- Low [12] - Intermediate [8] - N/A [10]
QRS Duration (ms)	- 129.6 ± 26.4 [11] - N/A* [7,8,10,11,13,21]	- 133.0 ± 8.1 [22] - N/A* [6,27]	- 133.0 ± 8.1 [22]	- N/A* [8,10,12]
Significant Stenosis Definition	- ≥50% in any vessel [7,8,10,11,13,21] - ≥70% in any vessel [27]	- ≥50% in any vessel [6] - ≥70% in any vessel except LM ≥50% [22] - ≥70% in any vessel [27]	- ≥70% in any vessel except LM ≥50% [22]	- ≥50% in any vessel [8,10,12]
Clinical. Data				
Mean Age ± SD (years)	- 59.9 ± 10.6	- 60.6 ± 10.9	- 56.5 ± 7.8	- 62.8 ± 10.6
% Mal.e	- 27	- 41	- 53	- 30
LVEF (%)	- 50.3 ± 13.6	- 49.3 ± 6.7	- N/A*	- 47.5 ± 16.0
% HTN	- N/A*	- 36	- 38	- 22
% DM	- N/A*	- 27	- 19	- 12
% DL	- N/A*	- 28	- 39	- 21
% Smoker	- N/A*	- 33	- 33	- 13

*Weighted average characteristics of study populations (NA when more than hal.f the studies did not report, or no data was provided in an individual study).

Table 3: Characteristics of the studies and the enrolled population stratified by the non-invasive stress testing tool.

(SROC) for the four different non-invasive pharmacologic imaging tests revealed that the diagnostic accuracy of MCE was more favorable (Figure 4B). The C-index was highest for MCE with 0.97, followed by D-CMR with 0.91, pharmacologic SE with 0.868, and pharmacologic MPI with 0.795. The positive predictive value is defined as the probability that an individual has CAD given that the test is positive, while a negative predictive value is the probability that an individual does not have CAD given that the test is negative. Both of these numbers may differ broadly depending on the prior probability that the individual has CAD (i.e., the prevalence of CAD in the individual's sub-population). Based on the point estimates of sensitivity and specificity, Figure 5 displays the positive and negative predictive values for a range of possible prior values.

Discussion

The meta-analysis described herein is the first to the best of our knowledge that compares the performance of contemporary pharmacologic stress tests for the initial CAD diagnosis in patients with pre-existing LBBB. It also serves as an update of a previous meta-analysis examining the diagnostic role of DSE and stress MPI in this same population [5].
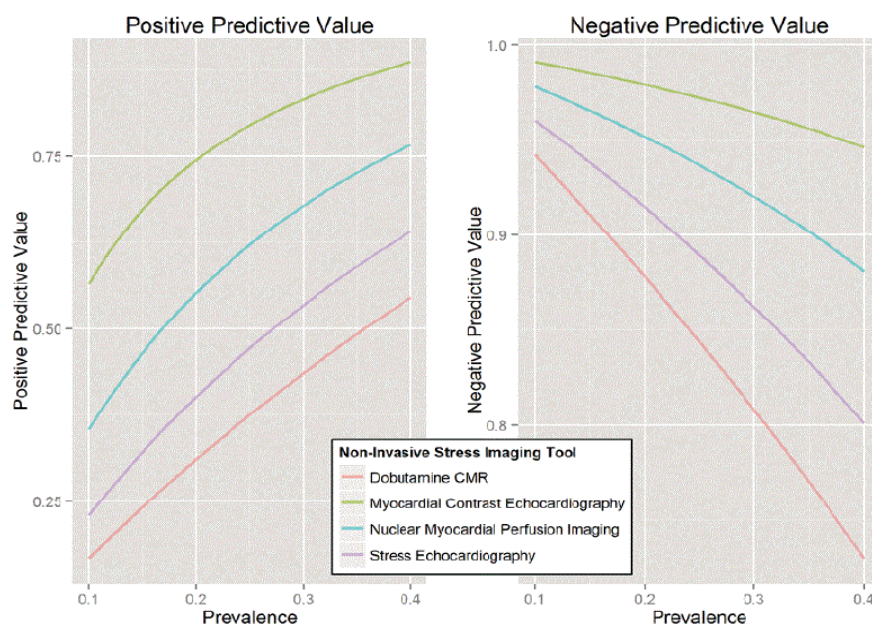
Figure 5: Both positive and negative predictive values may differ broadly depending on the prior probability that the individual has CAD (e.g. the prevalence of CAD in the individual's sub-population). These graphs display how (a) the positive predictive values and (b) the negative predictive values of the test change as a function of prevalence.

The main findings of this meta-analysis were 1) MCE has superior sensitivity and specificity characteristics compared to D-CMR, MPI and SE; 2) D-CMR and MCE have equally high specificity, but MCE is more sensitive; 3) Consistent with the older meta-analysis by Biagini et al. [5], MPI is more sensitive, but less specific than SE. These data suggest that MCE is a promising non-invasive imaging tool for CAD diagnosis in patients with LBBB. Also, the findings of this meta-analysis are supported by the findings of Hayat et al., Karavidas et al., Vigna et al., and Mordi et al. individual studies which compared more than one non-invasive tool.

Non-invasive testing choice for obstructive CAD diagnosis in LBBB

The non-invasive detection of obstructive CAD in patients with LBBB poses a diagnostic challenge. A careful choice of testing is warranted in order to avoid false positive results and unnecessary subsequent testing. Despite the current recommendation against exercise stress in general and ECG in particular for CAD diagnosis in this population, the ideal choice of non-invasive testing is not clear in the medical literature. At present, the pharmacologic MPI or SE is recommended in patients with LBBB. However, the detection of significant CAD by MPI is limited by the false positive rates of perfusion defects, particularly in the interventricular septum. Similarly, the diagnosis of RWMA involving the septum and apex during SE is frequently difficult in this population owing to pre-existing septal wall motion abnormalities. Non-invasive testing for CAD diagnosis can be achieved either by direct measurement of coronary flow utilizing perfusion scans (MPI, D-CMR or MCE) or indirectly by surrogates of coronary flow such as RWMA (CMR, SE) and diastolic function (SE). Unlike MPI, MCE and D-CMR offer real time assessment of flow. PET studies in LBBB reveal that asynchronous LV contractility leads to reduced septal vs. lateral wall contractility; as a result, in absence of flow limiting stenosis, counts appear more intense in lateral wall than septum. Similarly, low specificity characterizes MPI [20]. Based

on the studies included in this meta-analysis, the performance of MPI seems to be highly affected by scan interpretation strategy. Soylu et al. reported that accounting for any reversible perfusion defect had high sensitivity 100% but at the expense of poor specificity 29%, mostly due to defects in LAD distribution [13]. In addition, specificity was improved when scans were considered positive for defects with summed rest score (SRS) $\geq$ 12.4 $\pm$ 5.5 and summed difference score(SDS) $\geq$ 3.7 $\pm$ 1.2 with 89% sensitivity, and 80% specificity [21]. This observation warrants larger studies that compare the diagnostic accuracy of several MPI interpretation strategies in LBBB in order to make more accurate guideline recommendations as for how MPI scans need to be interpreted in LBBB.

In contrast, based on this meta-analysis, the real time assessment of coronary flow by CMR and MCE are more specific in LBBB. This may be related to the fact that these real time flow measurements are less subjected to the effect of LV asynchrony on flow than MPI or PET. First pass perfusion CMR has higher specificity (93.8%) than cine CMR RWMA (87.5%) with similar sensitivities of ~70% [22]. Gadolinium-enhanced CMR can assess myocardial opacification and washout durations in real time, which are markers of blood flow. The presence of late gadolinium enhancement carries a 100% specificity but at the sacrifice of a much lower sensitivity (41.5%) in LBBB [22]. While surrogate ischemic markers by SE and CMR perform better that MPI, they do less favorably than methods that directly measure flow. The best overall performance in this meta-analysis was achieved with MCE. MCE perfusion imaging detects abnormalities that antedate RWMA by measuring the rate of echocardiographic contrast replenishment (reflecting myocardial red blood cell velocity; normal<5 seconds) following a destructive high energy ultrasound pulse. Replenishment takes longer when regional flow is reduced and is faster in hyperemic states [23]. Blood flow represents the product of velocity and plateau intensity, and when plateau intensity is normalized to LV cavity intensity, absolute myocardial blood flow can be calculated [23]. Indirect surrogates of ischemia detect CAD by uncovering RWMA or

diastolic dysfunction. LV asynchronous contraction also complicates RWMA assessment and makes the indirect types of tests more subject to inter-observer variability in LBBB. Diastolic dysfunction in LBBB, particularly in the presence of LV hypertrophy, may be a poor surrogate of impaired coronary flow. Despite the fact that the diagnostic superiority of MCE similar to that revealed in this meta-analysis has not been demonstrated in large multicenter trials, the POINT BioMedical [24], RAMP-1 and 2 [25] did not address patients with LBBB. In a large multicenter study, Senior et al. reported superior sensitivity but lower specificity of MCE in comparison to SPECT [26]. However, this trial too did not include patients with LBBB [26]; the lower specificity was attributed to microvascular disease in the population studied [27]. Although the results of this meta-analysis are promising, further investigation in large multicenter trials is warranted to confirm the apparent diagnostic superiority of MCE in LBBB. Special population restrictions can limit the choice of testing. For example, CMR may not be applicable in patients with metal implants. Similarly, stress echo or MCE may not be an option for patients with poor acoustic windows. Future research examining the role of stepwise testing starting with MPI and proceeding to more specific non-invasive tools such as D-CMR or MCE prior to coronary angiography during the diagnostic algorithm for CAD in LBBB may be a reasonable approach. Limitations

Several potential limitations to this analysis should be acknowledged. First, the number of studies was quite small, especially for the subgroup analysis. This opens the possibility that estimates of study heterogeneity may be unreliable. Second, some of the studies used multiple ischemic markers and approaches; these studies were included in our analysis as independent studies. The small number of independents studies reflects a deficiency of the current literature. Third, several of the included studies suffered from multiple design limitations. Finally, the C-index summary measures as estimated by the bivariate analysis should not be over-interpreted as they involve extrapolation over areas of the ROC curve for which no data exist.

Conclusion

MCE and D-CMR appear to be promising tools in LBBB with superior diagnostic utility in comparison to DSE and nuclear MPI. Current datasets to guide informed decisions and guideline changes in LBBB are limited and additional studies using MCE and D-CMR in this population are warranted. CAD remains a diagnostic challenge in presence of LBBB and careful selection of non-invasive testing is necessary in order to avoid subsequent unnecessary testing given the high false positive rates in this population. Anatomic diagnosis remains the gold standard, and in selected cases, CAD diagnosis by coronary angiography may be necessary.

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Appendix1:

A.	Search strategy:

1	exp Bundle-Branch Block/ or exp heart conduction system/ or exp "bundle of his"/ or LBBB.mp. or (left* adj3 (bundl* or block*)).mp. or (conduction* adj3 disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

2	((cardiac* or heart* or myocardi* or coronar* or ischemi* or ischaemi* or stress* or dobutamin* or adenosin* or dipyridamol* or vasodilat* or pharmacolog*) adj3 (nuclear* or perfusion* or SPECT* or imag* or echo*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

3	exp echocardiography, stress/ or myocardial perfusion imaging/ or exp cardiac-gated imaging techniques/ or exp cardiac-gated single-photon emission computer-assisted tomography/

4	1 and (2 or 3)

5	limit 4 to yr="2004 -Current"

6	((cardiac* or heart* or myocardi* or coronar* or ischemi* or ischaemi* or stress* or dobutamin* or adenosin* or dipyridamol* or vasodilat* or pharmacolog*) adj3 (MRI or CMR or PET or ((contrast* adj3 echo*) or MCE))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

7	(cardiac* or heart* or myocardi* or coronar* or ischemi* or ischaemi* or stress* or dobutamin* or adenosin* or dipyridamol* or vasodilat* or pharmacolog*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

8   exp magnetic resonance imaging/ or exp magnetic resonance imaging, cine/ or exp positron-

emission tomography/

9   6 or (7 and 8)

10   5 or 9

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B.   Flow Chart representing the number of citations retrieved by the search strategy and the

number of the screened titles, abstracts and papers.

3013 Citation

          ———————— 369 Duplicates

2644 Titles

          ———————— 2499 Non-Relevant

145 Abstracts   135 Excluded
                        -    5 Case Reports
                        -    29 Reviews, poster presentations and editorial
                        -    32 Prognosis
                        -    20 Excluded or lacked data on LBBB
                        -    35 Lack sensitivity and specificity data
                        -    8 Stress or pacemaker induced LBBB
10 Studies   -   4 RBBB
-    Badran et al[6]   -   1 cardiac CT
-    Fallahi et al[7]   -   1 post MI
-    Hayat et al[8]
-    Karavidas et al[10]
-    Feola et al[11]
-    Felis et al[12]
-    Soylu et al[13]
-    Pavlovic et al[21]
-    Mordi et al[22]
-    Vigna et al[27]