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Dynamic stress computed tomography myocardial perfusion for detecting myocardial ischemia: A systematic review and meta-analysis

Minjie Lu [a,b,*], Shuli Wang [a], Arlene Sirajuddin [b], Andrew E. Arai [b,*], Shihua Zhao [a,*]

[a] Department of Magnetic Resonance Imaging, Cardiovascular Imaging and Intervention Center, Fuwai Hospital, State Key Laboratory of Cardiovascular Disease, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, China

[b] Department of Health and Human Services, National Heart, Lung and Blood Institute (NHLBI), National Institutes of Health (NIH), Building 10, Room B1D416, MSC 1061, 10 Center Drive, Bethesda, MD, 20892-1061, USA

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ABSTRACT

Background: Comparing to SPECT and MRI, with higher temporal and spatial resolution and development of radiation dose reduction, myocardial computed tomography perfusion has emerged as a potential method for evaluation of hemodynamic myocardial ischemia. This meta-analysis systematically analyzed the performance of dynamic CT myocardial perfusion (DCTMP) to diagnose myocardial ischemia (MI) with clinically established reference methods [MR/SPECT/PET perfusion and fractional flow reserve (FFR)] as the reference standard.
Methods: We searched PubMed, Embase and web of science databases for all published studies that evaluated the accuracy of DCTMP to diagnose MI met our inclusion criteria. An exact binomial rendition of the bivariate mixed-effects regression model with test type as a random-effects covariate was performed to synthesize the available data.
Results: The search revealed 13 eligible studies including 482 patients. The pooled sensitivity and specificity of myocardial blood flow (MBF) were 0.83 (95% CI: 0.80 to 0.86) and 0.90 (95% CI: 0.88 to 0.91) at the segment level, 0.85 (95% CI: 0.80 to 0.88) and 0.81 (95% CI: 0.78 to 0.84) at the artery level, and 0.93 (95% CI: 0.82 to 0.98) and 0.82 (95% CI: 0.70 to 0.91), at the patient level, respectively. The high area under the sROC curves of MBF were 0.944 at segment level, 0.911 at vessel level and 0.949 at patient level, respectively.
Conclusions: DCTMP has a high diagnostic accuracy in detecting myocardial ischemia and it may increase significantly at segment level in combined use of coronary CTA.

1. Introduction

Computed tomography angiography (CTA) is currently included among recommended diagnostic modality for the identification and management of patients suspected of stable CAD in guideline [1]. However, specificity has been shown to be lower than the sensitivity of CTA [2]. Myocardial perfusion imaging by single-photon emission computed tomography (SPECT) [3–5] and magnetic resonance imaging (MRI) [3,6] have been world-widely utilized routinely to evaluate myocardial ischemia. Comparing to SPECT and MRI, with higher temporal and spatial resolution and development of radiation dose reduction, myocardial computed tomography perfusion (CTP) has emerged as a potential method for evaluation of hemodynamic myocardial ischemia. In recent years, numerous studies in relatively small patient groups have been published on both static [7–14] and dynamic myocardial perfusion CT [15–23]. Several meta-analysis have been published on static CTP [24] or mixed (static and dynamic) CTP [25–27], however, despite the promising results of these studies, most of them were limited by the absence of quantitative evaluation, as well as by the acquisition of images during a predefined single frame during early myocardial perfusion. Dynamic techniques for quantitatively detecting myocardial perfusion imaging—most commonly with MRI, PET, or, recently, CT [17,28,29]—may allow for noninvasive quantification of myocardial blood flow (MBF), which may further improve identification of hemodynamic significance of coronary artery stenosis. However, up-to-date, there is limited meta-analysis only focusing on the diagnostic accuracy of stress dynamic CT myocardial perfusion (DCTMP) for evaluation of hemodynamically relevant CAD.

This systematic review and meta-analysis sought to summarize all the published studies on this issue and evaluate the diagnostic accuracy of stress DCTMP with or without coronary CTA, in comparison to clinically established reference methods.

2. Methods

The meta-analysis was performed using a standard protocol based on the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines [30] and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement [31]. No industry support was provided for this systematic review and meta-analysis.

* Corresponding authors.
E-mail addresses: coolkan@163.com, minjie.lu@nih.gov (M. Lu), araia@nhlbi.nih.gov (A.E. Arai), cjr.zhaoshihua@vip.163.com (S. Zhao).

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2.1. Search strategy

A search through PubMed, Embase, and Web of Science from January 2008 to April 2017 was performed. Published studies that examined the diagnostic accuracy of dynamic stress myocardial CT perfusion in patients suspected of or with known CAD compared to SPECT, MRI, invasive coronary angiography plus fraction flow reserve (FFR) were screened. The following keywords in different combinations were used: computed tomography, angiography, coronary artery, stress perfusion and dynamic myocardial perfusion. All relevant published systematic reviews and meta-analyses on CT perfusion were identified and their reference lists were screened. Reference lists of the retrieved articles were screened as well.

2.2. Study eligibility

To identify eligible studies for inclusion in the current systematic review and meta-analysis, two independent reviewers (M Lu. and S. Li) independently screened all abstracts and performed data extraction. Any disagreement was resolved by discussion and referring the study to a third reviewer (Dr. A. Arai). We included a study if: (1) dynamic myocardial perfusion CT was studied as a diagnostic test to detect hemodynamic coronary artery disease; and (2) diagnostic accuracy of dynamic myocardial perfusion CT was compared to another myocardial perfusion imaging modality (SPECT/PET/MRI) or to invasive coronary angiography (ICA) with FFR measurement as reference standard; (3) at least 16-multidetector CT (MDCT) was used; (4) reference standard was either SPECT, PET, MRI or invasive coronary angiography (ICA) plus FFR; and (5) numbers of true positive, false positive, true negative and false negative cases were reported or could be calculated on patient, vessel or segment basis. A study was excluded if: (1) it concerned a review, protocol, letter or case report; (2) it involved only a laboratory, phantom or animal study. In possible duplicate reports, the report with the largest sample size was included.

2.3. Quality assessment

The study design, patients recruited and reference applied in each study were considered primarily for the quality assessment of the study by referring to the items in The Quality Assessment of Diagnostic Studies (QUADAS) guidelines [32], which was updated to QUADAS-2 in 2011 [33]. Fourteen items were evaluated with this tool to rate the index and reference standard tests. Two readers independently evaluated QUADAS items for all included studies; if they disagreed, a third reader adjudicated.

2.4. Data extraction

Data extraction was performed by one reviewer (S. Wang) and subsequently verified by a second reviewer (M. Lu). The following data categories were extracted from the included studies: patient characteristics, stressor used for index test, index test characteristics, and reference threshold (ICA + FFR, MRI/SPECT/PET). True positive, false-positive, false-negative, and true negative numbers were extracted. Data were recorded separately, whenever available, at the segment, vessel/artery territory and patient levels.

2.5. Data synthesis and analysis

The meta-analysis was performed at the segment, vessel and patient level if possible. For each study, the sensitivity, specificity, positive and negative likelihood ratio (NLR), and the diagnostic odds ratio, along with the 95% confidence interval (CI), were calculated to express the diagnostic accuracy of the stress DCTMP techniques in diagnosing hemodynamically significant CAD when compared with reference. Because methodological heterogeneity between included studies was anticipated, a random-effects (DerSimonian and Laird) model was used for pooling the data [34]. Pooled results were used to determine the area under the receiver operating characteristic curve and the Q^* statistic. Heterogeneity among study result was quantified by calculating the I^2 statistic. The degree of heterogeneity was considered low ($I^2 < 50\%$), moderate ($I^2 = 50\%$–75%), or high ($I^2 > 75\%$) [35]. Statistical analysis was performed by using Review Manager (RevMan) 5 version 5.3.5 freeware package (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) and the dedicated meta-analysis software Meta-DiSc version 1.4 (Universidad Complutense, Madrid, Spain).

3. Results

3.1. Characteristics of the dynamic stress CT myocardial perfusion

Our literature search in PubMed, Embase, ISI Web of Knowledge and additional citation tracking in review and original articles identified 257 potentially relevant abstracts of full-text articles. Of those, 108 articles were duplicates and were therefore removed. 124 articles were excluded after title and abstract screening. Twenty-five articles were read full-text. Finally thirteen articles were subsequently included in the meta-analysis [9,15–17,19–23,28,29,36,37]. Supplemental Fig. 1 shows the flowchart of the search process. The 13 included studies had a total of 482 patients. The mean age was 61.7, of whom 378 (78.4%) were male (Table 1). 62.7% had hypertension, 26.0% had diabetes, 62.5% had dyslipidemia, 39.4% were smokers, 39.1% had a family history of CAD, and the mean BMI was 26.4 kg/m^2. The studies used either MDCT (4/13, 30.8%) [19,23,28,37] or dual-source CT scanners (9/13, 69.2%). The majority of the studies used a 3–5 min infusion of adenosine at a dose of 140 mg/kg/min for the vasodilator protocol (76.9%). Mean radiation dose ranged from 5.3 to 10.5 mSv per dynamic perfusion and 9.3 to 18.1 for the entire CT scan protocol (Supplemental Table 1).

3.2. Methodological quality

Our inter-rater reliability for assessing quality items was perfect (kappa = 0.89). The quality assessment results are presented in Supplemental Fig. 2 and the items are shown in Supplemental Table 2. Although all studies provided detailed information pertaining to the reference standard, evaluating levels, as well as the scan protocol they used, some of studies did not clearly state the time interval between DCTMP and the reference test. Eleven out of 13 studies were declared that the analyses of the images were blinded.

3.3. Data synthesis and statistical analysis

The diagnostic performance of the stress dynamic CT perfusion was tested at different levels including segment, vessel and patient levels. Pooled analyses were also performed for the combination of CTA and CTA alone.

In detail, MBF was meta-analyzed at segment level in five articles (2381 segments), at vessel level in 5 studies (697 vessels) and in 2 studies in patient level (110 patients), respectively. MBF plus CTA was meta-analyzed at segment level in two articles (1050 segments), at vessel level in four studies (427 vessels) and in 3 studies at patient level (96 patients), respectively. MPR (myocardial perfusion ratio) was meta-analyzed in 2 studies on vessel level (58 vessels). We also performed a meta-analysis on CTA alone at vessel level in 4 studies (606 vessels) and at patient level in 3 articles (143 patients).

3.4. Diagnostic performance

3.4.1. Segment level

Overall, 2381 segments by MBF and 1050 segments by MBF plus CTA were analyzed in 5 and 2 studies. The results showed that 33.5% of the segments (798 of 2381; range 7.7% to 52.0%) by MBF and 11.6% of the segments (126 of 1050; range 6.6% to 11.8%) by MBF plus CTA had hemodynamic CAD. The pooled sensitivity and specificity were 0.83 (95% CI: 0.80 to 0.86) and 0.90 (95% CI: 0.88–0.91) for MBF, respectively (Supplemental Fig. 3, Table 2). No heterogeneity was found for sensitivity ($I^2 = 0\%$; $p = 0.948$), whereas the heterogeneity was significant for specificity ($I^2 = 93.5\%$, $p < 0.001$). Addition of DCTMP to coronary CTA significantly improves both sensitivity and specificity to 0.85 (95% CI: 0.76 to 0.92) and 0.96 (95% CI: 0.95–0.97), respectively. Only low heterogeneity was found for sensitivity ($I^2 = 49.7\%$; $p = 0.159$), whereas the heterogeneity was high for specificity ($I^2 = 92.0\%$, $p < 0.001$).

3.4.2. Vessel/Artery territory level

Overall, 697 arteries by MBF in 5 studies, 427 arteries by MBF + CTA in 4 studies, 104 arteries by MPR in two studies and 606 arteries by CTA alone in 4 studies were analyzed. 38.3% of vessels (267 of 697; range 22.2% to 56.3%) by MBF, 30.9% of vessels (132 of 427; range 17.2% to 47.2%) by MBF plus CTA, 49.0% of vessels (51 of 104; range 46.2% to 49.5%) by MPR and 32.5% of vessels (197 of 606; range 22.2% to 47.2%) by CTA alone had hemodynamic CAD (Supplemental Fig. 4, Table 2).

The pooled sensitivity and specificity were 0.83 (95% CI: 0.80–0.86) and 0.90 ((95% CI: 0.88–0.91) for MBF, 0.83 (95% CI: 0.75–0.87) and