International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Diagnostic performance of stress perfusion cardiac magnetic resonance for the detection of coronary artery disease
A systematic review and meta-analysis

Apostolos Kiaos, Ioannis Tziatzios, Stavros Hadjimiltiades, Charalambos Karvounis, Theodoros D. Karamitsos *

1st Department of Cardiology, Aristotle University of Thessaloniki, Thessaloniki, Greece

ARTICLE INFO

Article history:
Received 28 September 2017
Received in revised form 19 November 2017
Accepted 20 November 2017
Available online xxxx

Keywords:
Cardiovascular magnetic resonance
Stress perfusion
Coronary artery disease
Diagnostic accuracy meta-analysis

ABSTRACT

Introduction: The purpose of this study was to investigate the accuracy of qualitative stress perfusion cardiac magnetic resonance (CMR) to diagnose ischemia-causing lesions according to different definitions of significant coronary artery disease (CAD), and magnetic field strength.
Methods: We searched PubMed, Web of Science, and the Cochrane Library for studies evaluating diagnostic performance of qualitative stress perfusion CMR for diagnosis of CAD versus coronary angiography or fractional flow reserve (FFR) from inception to 10 September 2017. We used hierarchical models to synthesize the available data.
Results: Sixty-seven studies (7113 patients) met the inclusion criteria. The patient-based analysis of studies using FFR as the reference standard demonstrated a mean sensitivity of 0.90 (95% confidence interval [CI], 0.85–0.93) and a mean specificity of 0.85 (95% CI, 0.80–0.89). The patient-based analyses for detecting coronary stenosis ≥50% and coronary stenosis ≥70% at 1.5 T and for detecting coronary stenosis ≥50% and coronary stenosis ≥70%, at 3 T, demonstrated a mean sensitivity of 0.82 (95% CI, 0.79–0.84), 0.86 (95% CI, 0.83–0.89), 0.90 (95% CI, 0.82–0.95), and 0.91 (95% CI, 0.79–0.96), respectively; with a mean specificity of 0.75 (95% CI, 0.71–0.80), 0.77 (95% CI, 0.71–0.81), 0.79 (95% CI, 0.69–0.86), and 0.74 (95% CI, 0.59–0.85).
Conclusion: Qualitative stress perfusion CMR has high accuracy for the diagnosis of CAD, irrespective of the reference standard and the magnet strength. Studies using FFR as the reference standard had higher diagnostic accuracy on a patient level compared to studies using coronary angiography, with a notable difference in specificity.

1. Introduction

Current European and American guidelines support the use of non-invasive stress testing for the diagnosis of ischemic heart disease, particularly in patients with intermediate to high pre-test probability [1,2]. Stress perfusion cardiac magnetic resonance (CMR) is an attractive imaging technique to identify myocardial ischemia with high spatial resolution but no exposure to ionizing radiation.

Previous meta-analyses have explored the diagnostic accuracy of stress perfusion CMR for the detection of coronary artery disease (CAD) [3–12]. A major limitation of these meta-analyses is that they included in the same analysis, studies that employed different cut-off values to define ischemia i.e. ≥50% and ≥70% diameter stenosis or fractional flow reserve (FFR) <0.75 and <0.80. This differential demarcation precludes definitive evaluation of significant CAD in the 'gray zone' i.e. coronary stenosis between 50% and 70%, and FFR between 0.75 and 0.80. Furthermore, previous meta-analyses included not only studies with qualitative but also semi-quantitative interpretation of stress perfusion CMR, although the latter is not used in clinical practice. Finally, most of the previous meta-analyses did not use hierarchical modeling in their statistical analysis, which is considered the most rigorous approach for systematic reviews of diagnostic test accuracy [13].

For all these reasons, and given that several original research studies have recently been published, we conducted a systematic review and meta-analysis using hierarchical models, based on cross-sectional studies that used invasive coronary angiography (ICA) or FFR as reference standard. Our aim was to update and expand the evidence base of the diagnostic performance of qualitative stress perfusion CMR for CAD detection.

2. Methods

We pre-specified objectives and methods and report the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [14].

2.1. Data sources and searches

We identified eligible studies by searching PubMed, Web of Science, and the Cochrane Library from inception to 10 September 2017. The search syntax is presented in the

* Corresponding author at: 1st Department of Cardiology, Aristotle University of Thessaloniki, AHEPA Hospital, 54636 Thessaloniki, Greece.
E-mail address: tkaramitsos@auth.gr (T.D. Karamitsos).

https://doi.org/10.1016/j.ijcard.2017.11.066
0167-5273/

Supplementary material. No search restrictions were applied. We also examined reference lists of included articles and relevant reviews to identify potential studies missed by our search strategy [3–12].

2.2. Study selection

We included cohort studies, if they met all of the following criteria: 1) they used qualitative stress perfusion CMR as a diagnostic test for ischemic CAD in adult patients; 2) CAD was defined as at least ≥50% diameter stenosis in quantitative coronary angiography (QCA) or FFR <0.80; 3) adenosine or dipyridamole was used as a stressor; 4) a 1.5-Tesla (T) or 3-T MR scanner was used; and 5) the absolute numbers of true positive (TP), false positive (FP), false negative (FN), and true negative (TN) were reported, or could be derived.

Studies were excluded if they met one of the following criteria: 1) semi-quantitative assessment was used 2) they included patients with unstable clinical status; 3) three-dimensional stress perfusion CMR was used as a diagnostic test for ischemic CAD; and 4) they had a case-control design. When studies stemmed from overlapping populations, the study with the largest population was included.

Two reviewers independently screened titles and abstracts and subsequently examined the full text for potentially eligible reports. Discrepancies at each stage of selection were arbitrated by a third reviewer and resolved by consensus.

2.3. Assessment of methodological quality

Two independent reviewers used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool to assess the quality of included studies [15]. Seven domains of QUADAS-2 evaluation sheet were scored. Discordances between reviewers were resolved by consensus discussion. Assessment for every domain was based on a rule that the overall risk of bias was equal to the highest risk of bias for any of the respective signaling questions.

The domain patient selection was scored "high risk of bias", if either >20% of patients had been excluded, or patients were not enrolled in a consecutive or random pattern. The domain index test was scored "high risk of bias", if either there was not a pre-specified threshold, or the interpretation of the index test results was not blinded. The domain reference standard was scored "high risk of bias", if the interpretation of the reference standard results was not blinded. The domain flow and timing was scored "high risk of bias", if the interval between the index test and the reference standard was >30 days. A study without high risk of bias and high applicability concerns was regarded as a non-high-risk study.

2.4. Data extraction

Data extraction was performed independently by 2 reviewers using a predesigned data collection form. For each eligible report, we extracted data on study characteristics such as first author and year of publication. Further extracted variables consisted of patient characteristics, technical information and absolute numbers of TP, FP, FN, and TN test results. If available, data were recorded on patient and coronary artery territory level (i.e. left anterior descending [LAD], left circumflex [LCx], and right coronary artery [RCA]). We tried to contact authors of original studies for missing or unclear data.

If a study presented data for both stress perfusion alone and stress perfusion combined with late gadolinium enhancement (LGE), we selected data for stress perfusion alone. When results for multiple protocols were available within the same study, we used data for the protocol that is used more frequently in the clinical setting (e.g. if a study had data for both standard and high resolution we used data for standard resolution). If a study reported pairs of sensitivity and specificity at different cut-off points, we extracted the pair with the highest diagnostic accuracy. When a study reported sensitivities and specificities for different observers, the 2 × 2 table was calculated according to the mean sensitivity and specificity of the observers.

2.5. Statistical analysis and data synthesis

A paired forest plot was made using Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Summary receiver-operating characteristic (SROC) curves were obtained using the bivariate model [16]. We identified the average operating point and computed average sensitivities, specificities, and likelihood ratios (LRs) of positive (LR+) and negative test results (LR−) [17]. The LR of a test result is the probability of that result in patients with significant CAD divided by the probability of the same result in patients without significant CAD. We calculated the diagnostic odds ratio (DOR, which is computed as the ratio of positive to negative likelihood ratios and provides an estimate of how much greater the odds of having significant CAD are for patients with a positive test result compared with a negative one) using a DerSimonian-Laird random-model and the AUC (area under SROC curve) using Holling's proportional hazards model. To evaluate heterogeneity between studies, the I^2 index was used, with I^2 values higher than 50% representing high heterogeneity [18]. Possible publication bias was assessed graphically by drawing funnel plots and statistically via the Egger test for funnel plot asymmetry [19]. Analyses were performed using the software R version 3.4.1 combined with the package 'mada' (meta-analysis of diagnostic accuracy) [20,21].

Among studies using ICA as reference standard, we performed 4 subgroup analyses based on magnet strength (1.5-T or 3-T) and based on the threshold used to define significant CAD (≥50% or ≥70% diameter stenosis). We also performed a subgroup analysis for studies that used FFR as the reference standard. Studies that provided data for patients with known CAD (i.e. with prior revascularization or myocardial infarction) were evaluated in a separate analysis. When feasible, we performed further subgroup analyses based on the protocol used (stress perfusion alone or stress perfusion combined with LGE) and the stressor used (adenosine or dipyridamole). We performed a sensitivity analysis excluding studies with <40 patients and a sensitivity analysis based on methodological quality, including non-high-risk studies. Finally, we conducted meta-regression analysis on sensitivity and specificity in the bivariate model to identify predefined sources of heterogeneity (prevalence of CAD, age, gender and prevalence of diabetes), by using a threshold p value of <0.05 for statistical significance.

3. Results

We found 67 studies that met eligibility criteria with a total of 7113 patients (Supplementary references 1–67). Fifty-eight studies used ICA as reference standard. Ten studies used FFR as reference standard. The literature process is summarized in Fig. S1 (Supplementary material). The study and population characteristics are presented in Tables S1-S4 (Supplementary material).

Fig. S2 (Supplementary material) summarizes the methodological quality of the studies according to the QUADAS-2 tool. Table S5 (Supplementary material) shows how the studies scored on each domain.

The patient-based analysis of studies using FFR as the reference standard demonstrated a mean sensitivity of 0.90 (95% CI, 0.85–0.93) and a mean specificity of 0.85 (95% CI, 0.80–0.89). The patient-based analyses for detecting coronary stenosis ≥50% and coronary stenosis ≥70% at 1.5-T and for detecting coronary stenosis ≥50% and coronary stenosis ≥70%, at 3-T, demonstrated a mean sensitivity of 0.82 (95% CI, 0.79–0.84), 0.86 (95% CI, 0.83–0.89), 0.90 (95% CI, 0.82–0.95), and 0.91 (95% CI, 0.79–0.96), respectively; with a mean specificity of 0.75 (95% CI, 0.71–0.80), 0.77 (95% CI, 0.71–0.81), 0.79 (95% CI, 0.69–0.86), and 0.74 (95% CI, 0.59–0.85) (Fig. 1). The results of our analyses at the patient level are presented in Tables 1–3. SROC curves and forest plots are depicted in the Supplementary material (Figs. S3–S8).

At the vessel level, analysis of studies using FFR as the reference standard demonstrated a mean sensitivity of 0.81 (95% CI, 0.73–0.87) and a mean specificity of 0.90 (95% CI, 0.87–0.93). The vessel-based analyses for detecting coronary stenosis ≥50% and coronary stenosis ≥70% at 1.5-T and for detecting coronary stenosis ≥50% and coronary stenosis ≥70%, at 3-T, demonstrated a mean sensitivity of 0.72 (95% CI, 0.67–0.76), 0.77 (95% CI, 0.72–0.81), 0.85 (95% CI, 0.78–0.90), and 0.87 (95% CI, 0.72–0.95), respectively; with a mean specificity of 0.87 (95% CI, 0.80–0.91), 0.84 (95% CI, 0.81–0.87), 0.89 (95% CI, 0.83–0.94), and 0.89 (95% CI, 0.86–0.92) (see Fig. 1 in Ref [22]). The results of our analyses at the vessel level are presented in Tables 1–3 in Ref [22].

3.1. Stress perfusion CMR in patients with known CAD

Seven studies assessed the diagnostic accuracy of qualitative stress perfusion CMR in patients with known CAD, using ICA as reference standard. Six of these studies reported data at the patient level (790 patients) and 5 of them reported data at the artery level (651 arteries) (Supplementary material, Fig. S9). All studies were performed at 1.5-T. On a patient level, the mean sensitivity, specificity, LR+ and LR− were 0.83 (95% CI, 0.74–0.90), 0.85 (95% CI, 0.80–0.90), 5.79 (95% CI, 4.22–7.84) and 0.20 (95% CI, 0.13–0.29), respectively. DOR was 27 (95% CI, 17–45), I^2 0.3% and the AUC 0.908. On a vessel level, the mean sensitivity, specificity, LR+ and LR− were 0.73 (95% CI, 0.63–0.81), 0.84 (95% CI, 0.78–0.89), 4.66 (95% CI, 3.20–6.65) and 0.33 (95% CI, 0.23–0.44), respectively. DOR was 15 (95% CI, 8–27), I^2 7.3% and the AUC 0.861.

3.2. Direct comparisons within the same study population

We found 8 studies (598 patients) reporting diagnostic performance of stress perfusion CMR at both ≥50% and ≥70% coronary stenosis

Please cite this article as: A. Kiaos, et al., Diagnostic performance of stress perfusion cardiac magnetic resonance for the detection of coronary artery disease, Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2017.11.066