

Diagnostic Performance of Combination Cardiac Computed Tomography Angiography with Perfusion with Fractional Flow Reserve as Standard Reference: Systematic Review and Meta Analysis

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Abstract

Background: Previous meta-analyses have confirmed the high diagnostic performance of Computed Tomography Perfusion (CTP) for detecting coronary artery disease, which, nevertheless, was compared with Quantitative Coronary Angiography (QCA).

Methods: We searched PubMed for all published literature for all published studies that evaluated the consistence between catheter Fractional Flow Reserve (FFR) and CTP. The studies were included if the coherence between FFR and CTP was investigated. The basic information and numbers of true-positive, true-negative, false-positive, and false-negative values were extracted by two investigators independently.

Results: Five studies were finally identified. Among the included references, 4 studies included data with hybrid CTP and CT angiography (CTA). The publication biases were not significant for studies with CTP ($P = 0.88$) and hybrid CTP/CTA ($P = 0.21$). The pooled positive likelihoods were 5.39 (95%CI 2.65-10.99) and 13.97 (95%CI, 9.62-20.30) for CTP and CTP/CTA, respectively, and negative likelihoods were 0.30 (95%CI, 0.19-0.49) and 0.23 (95%CI, 0.15-0.34). With hybrid imaging, the overall accuracy increased ($P < 0.05$, the area under the summary ROC curve was 0.88 for CTP and 0.95 for hybrid CTP/CTA, respectively). The sensitivity analysis indicated that no study influenced the pooled results significantly.

Conclusion: With FFR as standard reference, CTP cannot be applied as an effective tool for diagnosing suspected coronary ischemic disease alone. Rather, hybrid CTP/CTA is suggested to improve the overall accuracy.

Introduction

Although many efforts have been made to prevent Coronary Artery Disease (CAD), CAD continues to be a major health problem threatening human beings' health in developed countries. A reasonable treatment guided by the precise diagnosis of ischemia is a critical problem that is generally evaluated by Quantitative Coronary Angiography (QCA), a technique for measuring vessel characteristics during angiography procedures. Although QCA offers an evaluation of the plaque surface and stenotic lumen, it may not reliably detect whether a stenosis leads to ischemia [1].

Relatively, as a noninvasive imaging modality, Computed Tomographic Coronary Angiography (CTA) has been applied widely in routine detection clinically with good sensitivity and specificity for coronary anatomy and nearby coronary plaque characteristics [2]. Moreover, QCA is also available clinically and often used as the gold standard in most studies of evaluating CTA, showing excellent coincidence between QCA and CTA in the estimation of coronary stenosis [3]. What's more important is the identification of myocardial ischemia suffering from coronary stenosis that is critical for guiding clinical treatment and subsequent prognosis. However, an increasing number of recent evidence indicated that relationship between severity of coronary artery disease and myocardial ischemia is unreliable, [4], presenting that 50% to 90% severity category based on angiography is inaccurate in evaluating the functional significance of coronary stenosis [5]. Therefore, a definite diagnosis of myocardial ischemia or perfusion deficit should not be made by anatomic assessment based on coronary CTA alone.

Fortunately, following the emergency of Fractional Flow Reserve (FFR), the functional ischemia caused by coronary stenosis can be evaluated simultaneously during the QCA procedure. Moreover, several randomized and observational studies have confirmed the practicality of FFR for detecting functional ischemia in single- or multi-vessel stenosis [6-8]. Investigators of the Fractional Flow Reserve Versus Angiography for Multi vessel Evaluation study (FAME) further demonstrated that an FFR-guided Percutaneous Coronary Intervention (PCI) approach would be superior to invasive coronary angiography guided PCI [1,9]. In addition, a large-scale study demonstrated that patients who have stable CAD, whose initial treatment is medical therapy, May also benefit from FFR-guided PCI [10]. Therefore, FFR is believed to be a gold standard for detecting the ischemic lesion.

However, a recent multi-center study, with FFR as a reference, indicates that CTA has a low accuracy for diagnosing ischemic stenosis, although coronary CTA has been widely applied as a gatekeeper to exclude morphologic stenosis [5,11]. Luckily, the emergency of noninvasive cardiac CT perfusion (CTP), a new CT technique processed synchronously with CTA, makes the detection of the functional significance of coronary stenosis available [12]. Moreover, with FFR as standard reference, lots of studies demonstrate that CTP could provide reliable information to define an ischemic CAD [13-15]. However, there is limited number of enrolled patients in these single-center studies and no study to date has systematically reviewed the literatures to investigate whether this claim is justified.

In the current study, we sought to systematically explore the potential of Computed Tomography (CT) for diagnosing hemodynamically significant CAD with FFR as standard reference and directly compare two most commonly used techniques of CT: CTP and CTA.

Materials and methods

The present analysis was conducted following the Quality of Reporting of Meta-analyses statement guidelines [20] and the Standards for Reporting of Diagnostic Accuracy statement [21].

PubMed was searched for all published English literature by using medical search terms “Fractional Flow Reserve” or “FFR”, “Computed Tomography” or “CT” and “Myocardial Perfusion” without further restrictions. In addition, the references of previous systematic review were also screened.

Two investigators carefully examined the studies to ensure that potential duplicate data or overlapping data were excluded. Disagreements were resolved by consensus.

Table 1: Baseline characteristics of included studies.

Author	Modality	Year	Age	Male/ Female	BMI	Prevalence			TP (No.)	FP (No.)	TN (No.)	FN (No.)	Threshold to diagnose ischemia
						Multi- vessel	MI	Diabetes mellitus					
Ki Seok Choo [16]	CTP/CTA	2013	61.7±20.5	28/9	0.24	27	3	49	2	0.75
Ko, B. S.(JACC) [17]	CTP/CTA	2012	62.1±9.9	27/13	28.2±4.9	0.30	...	0.13	27	4	74	11	0.80
Ko, B. S.(JACC) [17]	CTP/CTA	2012	62.1±9.9	27/13	28.2±4.9	0.30	...	0.13	34	4	75	5	0.80
Ko, B. S.(EURHEART J) [15]	CTP/CTA	2012	65.1±8.3	27/15	27.9±6.5	0.25	0.12	0.21	28	1	44	13	0.80
Bettencourt N [18]	CTP/CTA	2013	62.0±8.0	68/33	28.0±4.5	0.25	...	0.39	52	24	206	21	0.80
Ki Seok Choo [16]	CTP	2013	61.7±20.5	28/9	0.24	27	5	47	2	0.75
Ko, B. S.(JACC) [17]	CTP	2012	62.1±9.9	27/13	28.2±4.9	0.30	...	0.13	28	22	43	10	0.80
Ko, B. S. (EURHEART J) [15]	CTP	2012	65.1±8.3	27/15	27.9±6.5	0.21	0.12	0.21	31	7	38	10	0.80
Bettencourt, N [18]	CTP	2013	62.0±8.0	68/33	28.0±4.5	0.25	...	0.39	40	11	219	33	0.80
Alexia Rossi [19]	CTP	2013	60.0±10.0	63/17	27.0±4.0	0.16	...	0.20	21	8	35	4	0.75

Study eligibility

The studies were included for the following reasons: (a) the consistence between FFR and CTP was evaluated and (b) the absolute numbers of True Positive (TP), False Positive (FP), True Negative (TN), and False Negative (FN) could be calculated from the detailed data, or could be obtained by contacting authors. Studies were excluded if they included patients who had Undergone Coronary Artery Bypass Graft (GABG), PCI, or prior heart transplantation or if they were retrospective.

The articles were firstly screened based on their titles and abstracts. The full text was reviewed if it was considered to be suitable or if it could not be excluded during the first screening step.

Data synthesis and statistical analysis

The publication bias was assessed using a regression line, outlined by Deeks et al. [22]. To assess heterogeneity across studies, we used the Cochran Q statistic and measured Inconsistency (I²) [23]. The impact of prevalence of multi-vessel disease, CTP and hybrid CTP/CTA modalities were examined using meta-regression.

Besides the sensitivity and specificity, we mainly evaluate the accuracy by synthesizing the positive and negative Likelihood Ratios (LRs) in order to evaluate the diagnostic role of CTP and hybrid CTP/CTA. They have advantages for the following reasons: They are less likely to change with the pre-test probability of CAD, and they can be calculated for several levels of the symptom/sign. Therefore, the main results may not be influenced by the prevalence of CAD of different references.

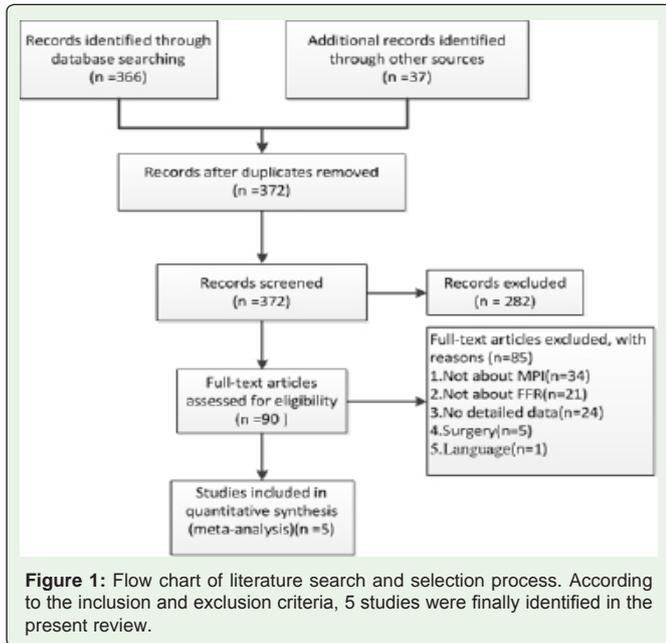
LRs can be pooled by using the Mantel-Haenszel method (fixed effects model) or by the DerSimonian Laird method (random effects model) to incorporate variation among studies [24]. Based on parameters estimated by the bivariate model, a hierarchical summary ROC (sROC) curve was constructed, the area under which serves as a global performance.

We used STATA, version 12 (StataCorp, College Station, Texas) with the Meta-DiSc 1.4 to analyze data.

Results

The characteristics of studies

A total of 366 potentially relevant references from PubMed searching and 37 additional studies from screening relevant reviews were firstly confirmed. Thirty-one duplicate studies were then excluded. Following title and abstract assessment, we retrieved 90 studies and excluded 282 references. According to the inclusion and exclusion criteria, 5 studies were finally identified in our review (Figure 1). Shows the flow chart of the literature search and selection



process. Five studies performed CTP (1 study) and hybrid CTP/CTA (4 studies) separately. The detailed data were presented in (Table 1).

Methodological quality

According to the QUADAS tool, the methodological qualities were satisfactory. Five studies had a score > 10, during which none fulfilled all of the items (Table 2). Shows the detailed information of methodological quality.

Data synthesis and statistical analysis

We classified the data according to CTP and hybrid CTP/CTA separately. Totally, 560 patients were included. The publication biases were not significant for CTP (P = 0.88) and for hybrid CTP/CTA (P= 0.21).

At the vessel level, the pooled sensitivity and specificity for CTP were 71% (95%CI 65-77%) and 88% (95%CI 84-91%), and the positive and negative LR were 5.39 (95%CI 2.65-10.99) and 0.30 (95%CI, 0.19-0.49), respectively. Statistical heterogeneity positive LR and negative LR across the included studies were found(I² = 85.30%, P<0.001 and I² = 69.00%, P<0.05 (Figure 2). The area under the summary ROC curve was 0.88 (95%CI, 0.85–0.91) (Figure 3).

The synthesized sensitivity and specificity of hybrid CTP/CTA imaging were 79% (95%CI, 73-84%) and 94% (95%CI, 92-96%), respectively. Also, the positive and negative LR were 13.97 (95%CI,

9.62-20.30) and 0.23(95%CI, 0.15-0.34), respectively. Between-study differences in diagnostic performance of CTP/CTA were evaluated, and heterogeneity was found at the vessel level for both sensitivity and specificity (I²= 0.00%, P = 0.86 and I²= 53.80%, P = 0.07). The area under the summary ROC curve was 0.95 (95%CI, 0.94–0.96) (Figure 3).

The sensitivity analysis was conducted to investigate the influence of each individual study on the overall meta-analysis summary estimate. No study influenced the pooled sensitivity and specificity results significantly.

Discussion

The present study suggests that: (a) With FFR as the standard reference, diagnostic performance of CTP is moderate to effectively confirm and exclude ischemic CAD. (b) The diagnostic accuracy of hybrid CTA/CTP is comparatively higher than that of CTP alone in the detection and exclusion of ischemia.

In view of cost-effectiveness, the biomarker and exercise ECG, as a noninvasive tool, has a low accuracy for avoiding unnecessary invasive examination, although ECG has been generally applied to diagnose suspected CAD [25]. Similarly, the accuracy for diagnosing ischemic stenosis by coronary CTA, as a gatekeeper to exclude morphologic stenosis, is not high, even with FFR as a reference [11].

Cardiac perfusion, such as CTP, is a method excogitated for diagnosis of myocardium ischemia. The current study indicates that the overall diagnostic accuracy of CTP is moderate. The subgroup analysis suggests that the prevalence of multi-vessel disease is a significant factor that influenced the capacity of CTP to exclude ischemic CAD. But unlike FFR, which is derived from the ratio of distal (post-stenotic) to proximal coronary pressure, CTP compares myocardial flow supplied by the stenotic artery with hyperemic flow subtended by a non-stenotic vessel in order to detect perfusion defects. CTP, therefore, requires at least 1 non-ischemic coronary artery for accurate interpretation and diagnosis [26]. As a result, CTP tends to underestimate the hemodynamic importance of coronary stenosis in patients who have multi-vessel disease. Another important factor in the inconsistency between CTP and FFR may be the false assessment of FFR in patients who have microvascular ischemia that is generally caused by diabetes or by prior myocardial injury, as FFR is determined by the assessment of the flow in the major epicardial arteries alone without taking into account microvascular disease [15]. Specifically, although the negative diagnostic ability decreased greatly in populations with higher prevalence of multi-vessel disease, the positive diagnostic capability slightly increased. In fact, the negative diagnostic ability of CTP to exclude hemodynamical stenosis in patients who have suspected CAD and to avoid an unnecessary

Table 2: Quality assessment of diagnostic accuracy studies.

Authors	Item1	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Item9	Item10	Item11	Item12	Item13	Item14	ALL
Ki Seok Choo [16]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	13
Ko, B. S(JACC) [17]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	13
Ko,B. S. (EURHEART J) [15]	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	12
Bettencourt, N [18]	Y	Y	Y	U	Y	Y	Y	U	Y	Y	Y	Y	U	Y	11
Alexia Rossi [19]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	13
ALL	5	5	5	4	5	5	5	3	5	5	5	2	3	5	62

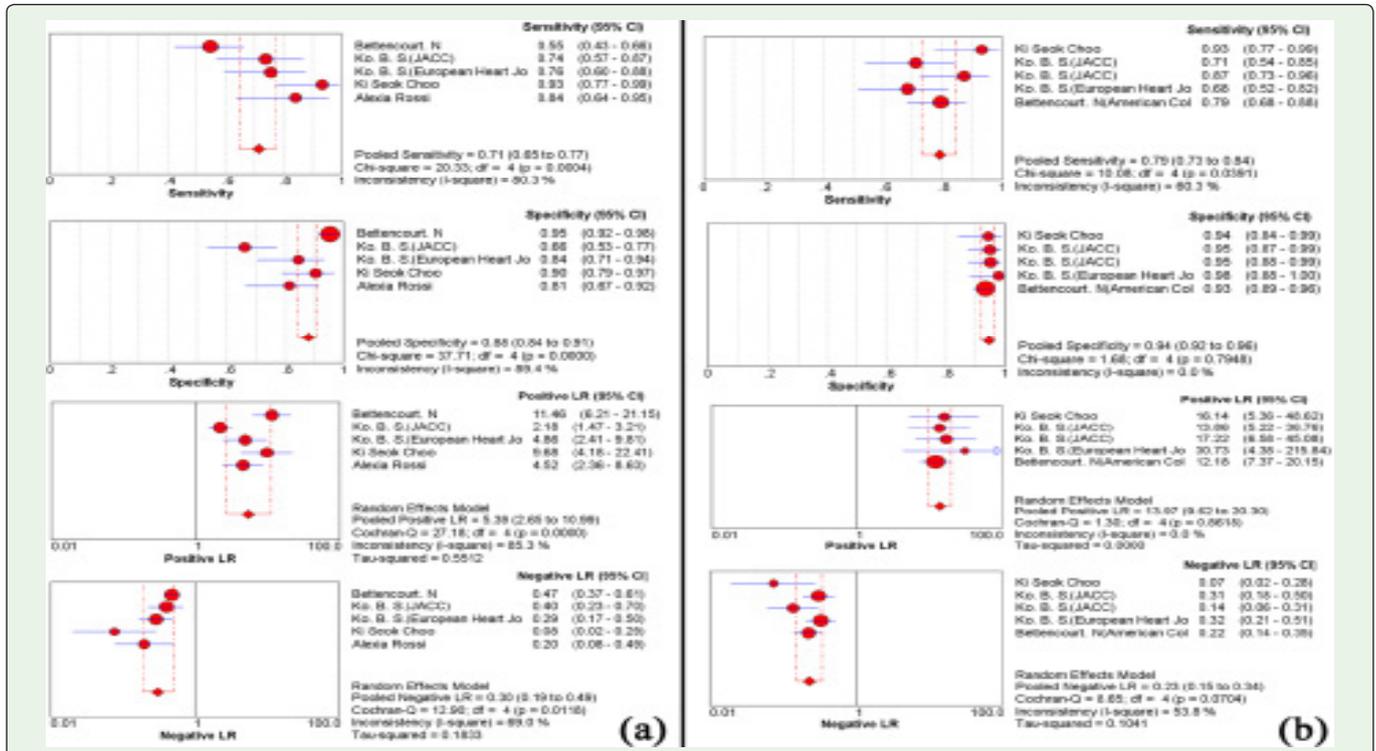


Figure 2: Pooled positive and negative LRs. The pooled positive and negative LRs, calculated by the random effects model, were 5.39 (95%CI 2.65-10.99) and 0.30 (95%CI, 0.19-0.49) for CTP (a) and 13.97 (95%CI, 9.62-20.30) and 0.23(95%CI, 0.15-0.34) for CTP/CTA (b), respectively.

invasive test is the key index of a noninvasive test [27]. The clinical application value of CTP is, therefore, weakened.

It is worthy to note that the accuracy of CTP varies with different FFR cutoffs for diagnosing an ischemic disease. With a higher threshold of FFR, the positive diagnostic ability of CTP decreased, while the negative performance increased. The potential reason may be that an FFR value between 0.75 and 0.80 often has an abnormal myocardial blood supply [28]. Although CTP may lead to a better negative diagnostic value with 0.8 as the threshold, it remained low to be applied as an exclusive test.

With the utility of advanced CT scanners, hybrid CTP/CTA imaging could be executed simultaneously. Several studies tried to combine the anatomic information of noninvasive CTA to improve the diagnostic accuracy, which applied the following criteria:

positive CTA and CTP, ischemia; positive CTA and negative CTP, non-ischemic stenosis; and negative CTA and positive CTP, micro vascular dysfunction-considered to be non-significantly stenosed [15,29,30]. The overall diagnostic increased accordingly, as accordant results may lead to higher accuracy [29]. However, four aspects can improve the present criteria. First, the computing method regards inconsistent results as non-ischemic stenosis, which improves the positive diagnostic value more than negative performance. Clinically, when the results of non-invasive tests are inconsistent, an invasive catheter is generally suggested [31]. Just as non-diagnostic imaging of CTA is generally classified as positive by these studies [15,29,30]; further study should calculate the accuracy of a hybrid test with inconsistency between CTP and CTA as positive, which mainly improves the critical negative diagnostic value of a non-invasive test. Second, the present criteria of CTA did apply stenosis, with 50% as

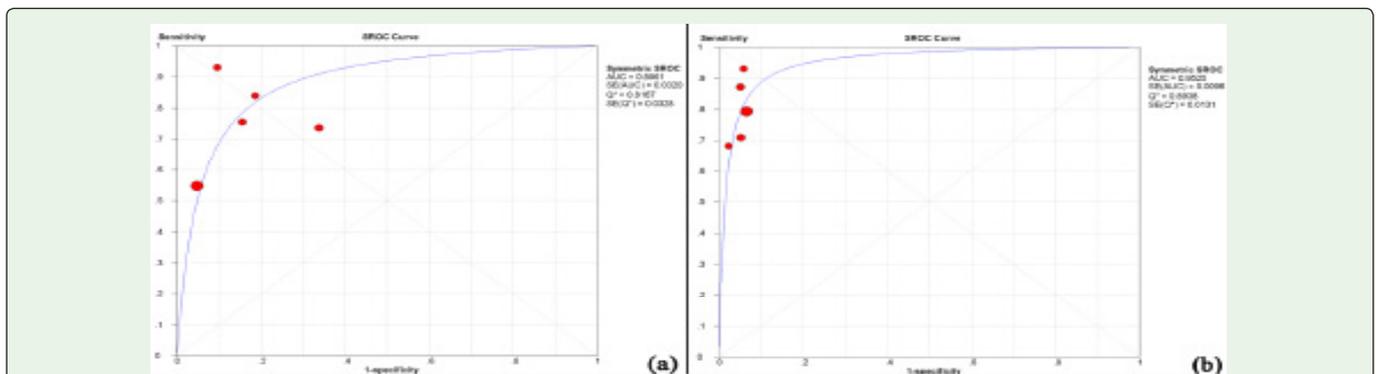


Figure 3: Summary receiver operating characteristic (sROC) curve for myocardial perfusion single CTP and hybrid CTP/CTA. The sROC curve areas were 0.88 for CTP (a) and 0.95 for CTA/CTA (b), respectively.

the cutoff value. In fact, FFR has the advantage over QCA mainly in intermediate stenosis [11]. The interpretation of CTA should be classified as mild stenosis (<30%), which rarely influences the blood supply; intermediate stenosis (30%-70%), and severe stenosis (>70%), which generally leads to inconclusive ischemia and requires further evaluation by FFR [32]. Third, the main defect of a false negative in patients who have multi-vessel stenosis is still unresolved. Clinically, multi-vessel stenosis might be regarded as positive, as further invasive tests will be suggested to avoid a false diagnosis. Fourth, although the hybrid test could improve the accuracy at artery level, a limitation still exists that we cannot correctly evaluate myocardial segments as FFR does. Combination with noninvasive calculation of FFR from CT (FFRCT), which could provide information of an ischemic index by calculating fluid dynamics [33], could reach a high diagnostic accuracy with regard to lesion-specific ischemia [34].

Two limitations should be declared. First, the number of studies that deal with hybrid CTP/CTA is limited. Further multi-center study that applies the suggested criteria is required in order to illustrate the practicability and superiority of hybrid imaging. Second, although subgroup analysis greatly decreased the heterogeneity, certain heterogeneity still existed. However, we applied the random effects model to resolve the problem.

Conclusion

Although CTP can lead to better performance than QCA can in predicting hemodynamical coronary disease, it still cannot be applied as an effective tool for diagnosing suspected coronary ischemic disease alone. Rather, hybrid CTP/CTA is suggested to improve the overall accuracy.

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