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Nuclear stress perfusion imaging *versus* computed tomography coronary angiography for identifying patients with obstructive coronary artery disease as defined by conventional angiography: insights from the CorE-64 multicenter study

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ABSTRACT

We investigated the diagnostic accuracy of computed tomography angiography (CTA) versus myocardial perfusion imaging (MPI) for detecting obstructive coronary artery disease (CAD) as defined by conventional quantitative coronary angiography (QCA). Sixty-three patients who were enrolled in the CorE-64 multicenter study underwent CTA, MPI, and QCA imaging. All subjects were referred for cardiac catheterization with suspected or known coronary artery disease. The diagnostic accuracy of quantitative CTA and MPI for identifying patients with 50% or greater coronary arterial stenosis by QCA was evaluated using receiver operating characteristic (ROC) analysis. Pre-defined subgroups were patients with known CAD and those with a calcium score of 400 or over. Diagnostic accuracy by ROC analysis revealed greater area under the curve (AUC) for CTA than MPI for all 63 patients: 0.95 [95% confidence interval (CI): 0.89-0.100] vs 0.65 (95%CI: 0.53-0.77), respectively (P<0.01). Sensitivity, specificity, positive and negative predictive values were 0.93, 0.95, 0.97, 0.88, respectively, for CTA and 0.85, 0.45, 0.74, 0.63, respectively, for MPI. In 48 patients without known CAD, AUC was 0.96 for CTA and to 0.67 for SPECT (P<0.01). There was no significant difference in AUC for CTA in patients with calcium score below 400 versus over 400 (0.93 vs 0.95), but AUC was different for SPECT (0.61 vs 0.95; P<0.01). In a direct comparison, CTA is markedly superior to MPI for detecting obstructive coronary artery disease in patients. Even in subgroups traditionally more challenging for CTA, SPECT does not offer similarly good diagnostic accuracy. CTA may be considered the non-invasive test of choice if diagnosis of obstructive CAD is the purpose of imaging.

Keywords: Cardiac computed tomography, Myocardial perfusion imaging, Myocardial ischemia.

Introduction

Myocardial stress perfusion imaging (MPI) using single photon emission computed tomography (SPECT) is the most common initial imaging test in patients complaining of chest pain for the diagnosis of coronary artery disease (CAD) (1, 2). While single center study results suggest good diagnostic accuracy for SPECT for identifying patients with CAD as defined by invasive quantitative coronary angiography (QCA) (3, 4), recent multicenter trials revealed modest-to-poor diagnostic performance (5-7). Rapid advances in multidetector computed tomography (CT) technology now permit non-invasive CT coronary angiography (CTA) which yields high diagnostic accuracy for detecting CAD in both single and multicenter studies compared to QCA (8). Pooled data from several small, mostly retrospective, studies revealed substantially better diagnostic accuracy for CTA than SPECT in direct comparison (with QCA as reference standard) (9). As the patient populations in these studies were heterogenic, it remained unclear whether SPECT may be

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better suited than CTA to assess patients with known CAD or severe calcification since CTA performs less well in these groups. Accordingly, we investigated the hypothesis that CTA diagnostic accuracy for identifying patients with obstructive CAD is only superior to SPECT in patients without history of CAD or high calcium score but that there is no difference in accuracy between the two methods when these types of patients are included.

Materials and Methods

Study design

The Coronary Artery Evaluation Using 64-Row Multi-Detector Computed Tomography Angiography (CorE-64) study is a prospective, multicenter study performed at nine hospitals in seven countries to evaluate the diagnostic accuracy of CTA for detecting coronary artery stenoses in patients with suspected obstructive CAD (10). All centers received study approval from their local institutional review boards and all patients gave written informed consent. In a subset of patients, clinically driven myocardial stress perfusion studies were performed prior to CTA and conventional coronary angiography. These patients make up the study population.

Patient population

The patient population of the CorE-64 international study has been described in detail elsewhere (11). In brief, 405 study participants were selected for the study according to the following criteria: i) age at least 40 years; ii) symptoms of relevant coronary artery disease; and iii) indication for conventional coronary angiography. Patients were not eligible if they had history of cardiac surgery, allergy to iodinated contrast or contrast-induced nephropathy, multiple myeloma, organ transplantation, renal insufficiency, atrial fibrillation, New York Heart Association class III or IV heart failure, aortic stenosis, percutaneous coronary intervention within the past six months, intolerance to beta-blockers, or body mass index (BMI) over 40. It was pre-determined that patients with Agatston calcium scores of 600 or greater were to be excluded from the primary analysis of the CorE-64 study but were to be included for secondary analyses performed identically to the main cohort (12). Thus, in contrast to the main study cohort, patients with calcium score of 600 and over were included in this investigation. For the purpose of this study, only patients who underwent SPECT imaging in addition to CTA and QCA were considered for this analysis.

Image acquisition and data analysis by 64-row computed tomography angiography

Methods applied in the CorE-64 study have been described in detail elsewhere (10). In brief, patients underwent two multi-detector CT tests (coronary calcium scoring and angiography) using 64-row scanners with a slice thickness of 0.5 mm (Aquilion, Toshiba Medical Systems). Calcium scoring was performed with the use of prospective electrocardiographic (ECG) gating with 400-msec gantry rotation, 120-kV tube voltage, and 300-mA tube current. Total calcium score was determined by the Agatston method. For CTA, retrospective ECG gating was used with heart rate-adjusted gantry rotations of 350 to 500 msec to enable adaptive multi-segmented reconstruction. Sublingual nitrates were given before CTA angiography. Iopamidol (Isovue 370®, Bracco Diagnostics, Milan, Italy) was the intravenous contrast medium used for this study. Beta blockers were given if the resting heart rate was above 70 beats per minute. Raw image data sets from all acquisitions were analyzed by an independent core laboratory. Using a modified 29 to 19 segments reduced coronary artery segmentation, 2 experienced independent observers who were blinded to all clinical and stress testing findings visually assessed each of 19 non-stented segments that were 1.5 mm or more in diameter, for the presence of a stenosis of 30% or more. Then, segments with at least one visible stenosis of 30% or more were manually quantified with the use of commercially available software (Vitrea®2 version 3.9.0.1, Vital Images, Minnetonka, USA). For this purpose, readers used electronic calipers and/or semi-automatic coronary artery lumen contour detection (SUREPlaque™, Vital Images, Minnetonka, USA) to identify the minimum lumen diameter and proximal and distal disease-free reference sites for each lumen stenosis (10). Both the caliper tool and the semi-automatic arterial contour detection algorithms were used in longitudinal as well as cross-sectional projections at the discretion of the readers. Resultant percent diameter stenoses were averaged for the 2 readers. Inter-reader visual and quantitative differences exceeding 50% were resolved by a third observer.

Image acquisition and data analysis by conventional coronary angiography

Conventional coronary angiography was performed no later than 30 days after CTA using conventional techniques of quantitative coronary angiography (QCA). All coronary segments with 1.5 mm or more in diameter were analyzed visually and quantitatively using the classification of a 29-segment standard model which was condensed to 19 segments for the equivalence of the number of coronary segments used in evaluation by CTA (10). Evaluation by QCA was performed by 2 experienced readers blinded to the results of CTA and MPI using the software (CAAS II version 2.0.1 Research QCA, Pie Medical Imaging, Maastricht, Netherlands) in all coronary segments revealing diameter stenoses of 30% or more by visual inspection.

Image acquisition and data analysis by myocardial perfusion imaging

All myocardial perfusion imaging (MPI) studies were performed and interpreted at the CorE-64 study sites according to the standards recommended by the American Society of Nuclear Cardiology (13). Myocardial perfusion imaging studies were performed using 1- or 2-day protocols with either pharmacological agents (dipyridamole, adenosine or dobutamine) or exercise stress. The radiotracers utilized were 99m Tc-sestamibi, 99m Tc-tetrofosmin and thallium-201 at doses from 2 to 3 mCi for thallium-201, 7 to 10 mCi for 99mTc-sestamibi or 99m Tc-tetrofosmin at rest and approximately three times more (21 to 30 mCi) radiotracers in the last stress stage. Only one patient underwent myocardial perfusion using a dual isotope protocol with the intravenous administration of thallium-201 during rest and 99mTc-setamibi during the stress stage. Standard perfusion stages of rest and stress were performed at baseline and with exercise or pharmacological stress. Attenuation correction was not routinely performed. Myocardial perfusion was visually evaluated by the attending physician at the study sites. Assessment for myocardial perfusion abnormalities was performed based on the intensity of tracer uptake compared to a normal reference segment and based on the size of the affected myocardium area in relation to the entire myocardium. A perfusion defect was defined as reversible if the change in regional activity was not evident on rest images. A final assessment that integrated all perfusion findings determined whether the study was positive or negative for perfusion abnormalities suggestive of CAD. Results were sent to the CorE-64 core laboratory for analysis and comparison with CTA and QCA.

Statistical analysis

Statistical analyses were performed with Stata Statistical Software (Release 10.0 2007, Stata® Corporation, College Station, TX, USA). The diagnostic performance of coronary artery stenosis assessment by quantitative CTA and the presence of perfusion abnormalities by MPI for identifying patients with at least one 50% or greater stenosis by QCA (reference standard) were evaluated. ROC analysis was applied to assess the diagnostic performance of CTA for identifying patients with 50% or greater stenosis by QCA. In a secondary analysis, we performed the same analysis in a subgroup of patients without any history of coronary artery disease. Also, we performed the same analysis in a subgroup of patients with a calcium score of 400 or over *versus* those with a score below 400. All tests were two-tailed. $P<0.05$ was considered significant and confidence intervals were 95%.

Because the SPECT test was performed before the patient was referred for catheterization, it is possible that the SPECT result influenced the referral decision. Usually, when verification bias occurs, the test is given to everyone and only a subsample is referred for verification. In the present case, we have the opposite situation: the gold standard procedure was performed on everyone and only a subsample had the test. This means that the roles of the diagnostic test and the gold standard are reversed, and consequently it is the predictive values that are biased by the selection rather than the sensitivity and specificity (14). We, therefore, applied the usual adjustment based on Bayes' rule to the positive and negative predictive values for SPECT.

Results

Patient characteristics

The demographic characteristics of the study population are presented in Table I. Mean age was 62.3 ± 9.2 years and 79% were men. MPI studies were performed using exercise stress in 76% of the participants while the remaining 22% received pharmacological stress/vasodilators. Twenty-one of the 63 study subjects had a calcium score of 400 or greater. The median calcium score was 221 (interquartile range 36-478). The flow chart of patient enrollment and results is presented in Figure 1.

TABLE I - Patient characteristics

Characteristics	Values
Age, mean ± standard deviation	62.3 ± 9.2
Gender, %	
Female	21 (13/63)
Male	79 (50/63)
Smoking, %	
Current	5 (3/63)
Former	49 (31/63)
Never	46 (29/63)
Body mass index, %	
<25	27 (17/63)
25-30	38 (24/63)
30-39	32 (20/63)
40	3 (2/63)
Hypertension, %	73 (46/63)
Dyslipidemia, %	79 (50/63)
Family history of premature CAD, %	33 (21/63)
Diabetes mellitus, %	30 (19/63)
Previous MI, %	20 (13/63)
MPI exam parameters	
Exercise stress, %	76 (48/63)
Pharmacological stress, %	22 (14/63)

Data presented as mean ± standard deviation (SD) or percentage.
CAD = coronary artery disease; MI = myocardial infarction; MPI = myocardial perfusion imaging.

Diagnostic accuracy of computed tomography angiography for detecting coronary artery disease

For a 50% stenosis threshold by QCA, the diagnostic accuracy for CTA assessment revealed an AUC of 0.95 (95% confidence interval (CI): 0.89-1.00) (Fig. 2) and sensitivity, specificity, positive predictive value, and negative predictive value were 0.93, 0.95, 0.97, and 0.88, respectively, (Tab. II). Analysis of the subgroup of patients without history of CAD revealed an AUC of 0.96 (95%CI: 0.90-1.00) (Fig. 3) and sensitivity, specificity, positive predictive value, and negative predictive value of 0.97, 0.95, 0.97, and 0.95, respectively. Analysis of the subgroup of patients with Agatston score below 400 revealed sensitivity, specificity, positive predictive value, and negative predictive value of 0.91, 0.95, 0.95, and 0.90, respectively.

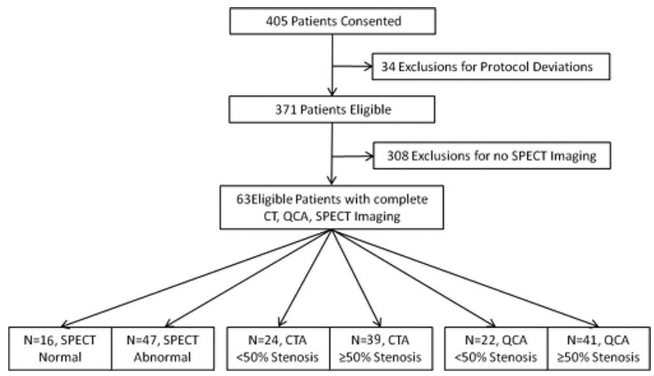

Fig. 1 - Flow chart of patient enrollment and results.

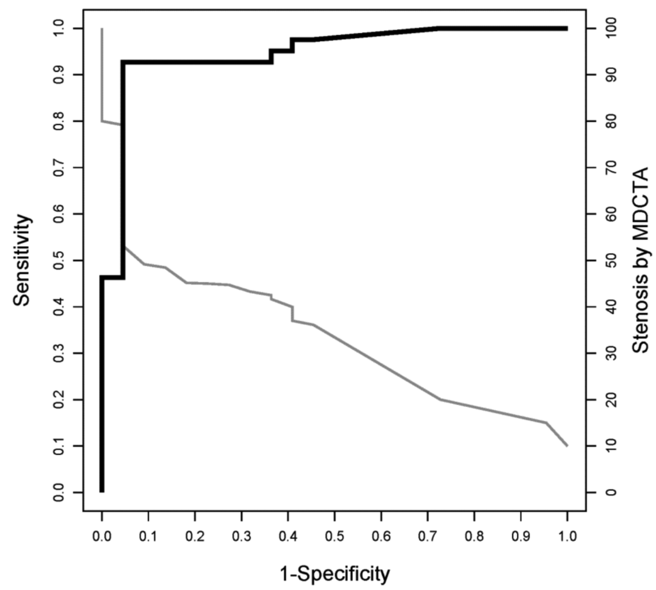

Fig. 2 - Receiver operator characteristic (ROC) curve along with the calibration curve for stenosis threshold describing the diagnostic performance of quantitative CT angiography (CTA) to identify patients with at least one 50% or more coronary arterial stenosis by quantitative coronary angiography (QCA). Area under the curve (AUC) 0.95 (95%CI: 0.89-1.00).

Diagnostic accuracy of myocardial perfusion imaging for detecting coronary artery disease

Diagnostic accuracy analysis of MPI to identify patients with at least one 50% stenosis or greater by QCA revealed an AUC of 0.65 (0.53-0.77) with sensitivity, specificity, positive predictive value, and negative predictive value of 0.85, 0.45, 0.74, and 0.63, respectively (Tab. II). Analysis of the subgroup of patients without history of CAD revealed an AUC of 0.67 (0.54-0.80) with sensitivity, specificity, positive predictive value, and negative predictive value of 0.86, 0.47, 0.71, and 0.69, respectively. Analysis of the subgroup of patients with Agatston score below 400 revealed an AUC of 0.61 (0.47-0.75) with sensitivity, specificity, positive predictive value, and negative predictive value of 0.82, 0.40, 0.60, and 0.67, respectively.

Statistical adjustment for potential referral bias resulted in only minimal changes for positive predictive value (73% vs 74%) and negative predictive value (65% vs 63%) when all studies are included with similarly minor changes for the subanalyses (67% and 73% vs 71% and 69%, 61% and 66% vs 60% and 67%, 100% and 59% vs 100% and 50%).

Comparing the diagnostic accuracy of computed tomography angiography versusmyocardial perfusion imaging

Table II summarizes the diagnostic accuracy of coronary artery stenosis assessment by CTA and MPI. Diagnostic accuracy by AUC is significantly greater for CTA compared to MPI for the entire cohort, patients without history of CAD, and patients with calcium score below 400 (P<0.05 for all). Specificity is significantly greater for CTA compared to MPI in the main analysis (P = 0.0010), the CAD-excluded analysis (P = 0.0039), and the group with calcium below 400 (P = 0.0010).

Table II - Diagnostic accuracy of computed tomography angiography and myocardial perfusion imaging by SPECT for identifying patients with at least one 50% or greater coronary arterial stenosis by quantitative coronary angiography (n=63).

Analysis	N.	Disease, %	Sensitivity	Specificity	PPV	NPV	AUC
CTA	63	65	93 (80-98)	95* (77-100)	97 (87-100)	88 (68-97)	95* (89-100)
SPECT	63	65	85 (71-94)	45 (24-68)	74 (60-86)	63 (35-85)	65 (53-77)
CTA, CADexcluded	48	60	97 (82-100)	95* (74-100)	97 (82-100)	95 (74-100)	96* (90-100)
SPECT, CADexcluded	48	60	86 (68-96)	47 (24-71)	71 (54-85)	69 (39-91)	67 (54-80)
CTA, Calcium<400	42	52	91 (71-99)	95* (75-100)	95 (76-100)	90 (70-99)	93* (85-100)
SPECT, Calcium<400	42	52	82 (60-95)	40 (19-64)	60 (41-77)	67 (35-90)	61 (47-75)
CTA, Calcium>400	21	90	95 (74-100)	100 (16-100)	100 (81-100)	67 (9-99)	95 (84-100)
SPECT, Calcium>400	21	90	89 (67-99)	100 (16-100)	100 (80-100)	50 (7-93)	95 (88-100)

Point statistics and 95% confidence intervals. PPV = positive predictive value; NPV = negative predictive value; AUC = area under the curve; SPECT= single photon emission computed tomography; CTA = computed tomography angiography; CAD = coronary artery disease.
*Statistically significant difference to myocardial perfusion imaging (P<0.05).

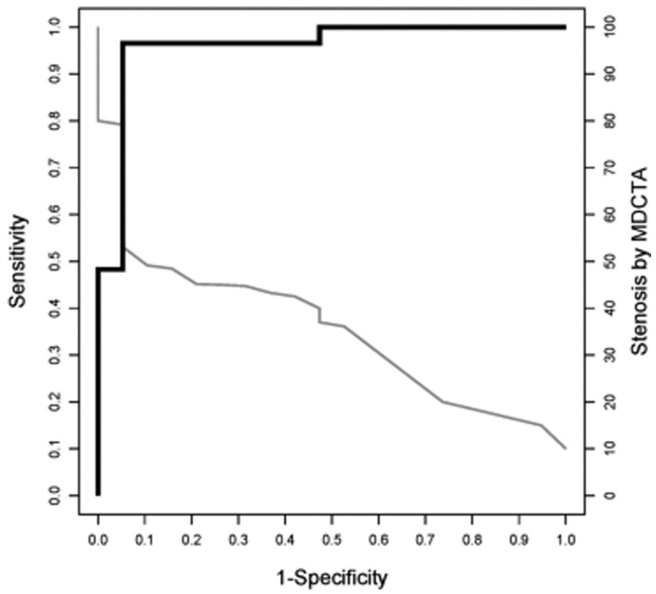

Fig. 3 - Receiver operator characteristic (ROC) curve along with calibration curve for stenosis threshold describing the diagnostic performance of quantitative CT angiography (CTA) to identify 50% or more coronary arterial stenosis by quantitative coronary angiography (QCA) in patients without history of coronary artery disease. Area under the curve (AUC) 0.96 (95%CI: 0.90-1.00).

Discussion

In this subanalysis of the CorE-64 multicenter, international study, we found CT coronary angiography to be superior to MPI for identifying patients with 50% or greater stenosis by QCA despite a patient population that included almost 25% patients with known CAD and one-third of patients with severe coronary calcification, i.e. patients who have been shown to pose challenges to CTA for diagnostic performance (12). When only patients without known CAD were considered (the target group for clinical CTA assessment) CTA yielded close to 100% accuracy for sensitivity, specificity and predictive values while SPECT performed poorly for specificity with modest positive and negative predictive values. Even in patients with severe coronary calcification (a known obstacle for CTA coronary assessment), SPECT did not offer any advantage for diagnostic accuracy over CTA.

Our results follow those of several multicenter studies in recent years which separately tested the diagnostic accuracy of CTA and MPI (8, 9). Three multicenter studies, involving patients with very different characteristics, revealed high diagnostic accuracy for CTA *versus* QCA (12, 15, 16). On the other hand, three multicenter studies comparing MPI and MRI with QCA reported only modest diagnostic accuracy for MPI (5-7). The few studies directly comparing CTA with SPECT for diagnostic accuracy confirmed the notion from indirect comparison on the diagnostic performance of CTA and MPI and found superior accuracy for CTA (9). Our results extend these findings to patient cohorts which include subgroups with less favorable characteristics for optimal CTA performance, i.e. those with extensive calcification and known CAD.

The superior diagnostic accuracy of CTA over MPI to detect CAD in patients is likely to be of significance for patient management. In an analysis of a very large clinical database, only 38% of patients without known CAD who were referred for cardiac catheterization with suspected CAD indeed had significant stenoses despite the employment of non-invasive testing prior to angiography (17). Considering that millions of patients are tested for CAD each year in the US alone, the impact of inaccurate diagnoses for CAD is likely to be substantial (9). The greater diagnostic accuracy of CTA for detecting CAD in comparison with traditional non-invasive testing, such as MPI, may help reduce the number of missed diagnoses and unnecessary additional testing.

In addition to diagnostic accuracy, establishing a prognosis is critically important for patient management. Recent meta-analyses suggested excellent prognostic information from CTA when using simple result categorization of normal, non-obstructive and obstructive CAD (18). Particularly intriguing is the virtual absence of myocardial infarction and CAD-related death at follow up in patients with normal CTA results, even up to five years after testing (19). CTA confers an advantage over MPI in its ability to detect non-obstructive CAD which is associated with a low yet significant event rate considering the large number of patients affected (18).

On the other hand, some studies suggest a clinical benefit for identifying coronary artery lesions that are hemodynamically significant as opposed to those which are not (20). This concept, however, is still in evolution as recent results question such benefit (21).

Study limitations

The primary objective of the CorE-64 study was to investigate the accuracy of 64-slice CTA for detecting obstructive CAD compared to conventional angiography. Since comparison with myocardial perfusion imaging was not the primary goal, our analysis is restricted to a subset of patients in this cohort. In contrast to CTA and QCA protocols and analyses, no single protocol was followed for MPI acquisition nor was its analysis performed in an independent core laboratory. As such, SPECT results represent a real world experience as opposed to core laboratory results. On the other hand, our CTA results are very consistent with those in the bulk of literature from both single and multicenter studies, as outlined above.

Lastly, the subgroup analysis of patients with severe coronary calcification is limited by small numbers in each group and the fact that almost all patients had obstructive disease.

Conclusions

Our study adds to the existing body of literature suggesting superior diagnostic accuracy of CTA compared to MPI for identifying patients with obstructive coronary artery disease as defined by conventional invasive angiography. Our results extend these findings to subgroups, which have been challenging for CTA, such as patients with history of coronary artery disease. If the purpose of testing is the diagnosis of obstructive coronary artery disease, CTA may be considered a first-line non-invasive imaging modality.

Disclosures

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Conflict of interests: JACL discloses grant support from GE Medical Systems and Toshiba Medical Systems. No other potential conflict of interest relevant to this article was reported.

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