Cardiovascular computed tomography for diagnosis and risk stratification of coronary artery disease

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Chapter 6

Comparison of Non-Invasive Multi-Slice Computed Tomography Coronary Angiography versus Invasive Coronary Angiography and Fractional Flow Reserve for the Evaluation of Men with Known Coronary Artery Disease

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Abstract

Computed tomography coronary angiography (MSCT) can accurately detect the presence of atherosclerosis non-invasively. However, a discrepancy has been observed between MSCT and non-invasive functional imaging. The purpose of the present study was to evaluate the correlation between MSCT and invasive fractional flow reserve (FFR) in men with known coronary artery disease (CAD). 33 patients (average age 57±11 years) clinically referred for coronary angiography underwent MSCT and FFR. Coronary angiography and MSCT were evaluated for non-significant (30-50% luminal narrowing) and significant stenosis (>50% luminal narrowing). Abnormal FFR was defined as ≤ 0.75. A total of 36 vessels were evaluated with FFR, with 8 (22%) showing reduced FFR. MSCT was normal (completely normal or <30% luminal narrowing in 11 (31%), non-significant lesions were observed in 13 vessels (36%), and significant stenosis in 12 vessels (33%). Abnormal FFR was observed in only 58% of vessels with lesions >50% on MSCT. Nevertheless, the agreement between normal MSCT and FFR was excellent; FFR was normal in all 11 vessels with normal MSCT. In conclusion, significant stenoses on MSCT frequently do not result in reduced FFR. A normal MSCT study however can accurately rule out the presence of hemodynamically significant lesions in men with known CAD.

Introduction

Multi-slice computed tomography coronary angiography (MSCT) is increasingly used as a non-invasive imaging technique capable of accurately detecting the presence of atherosclerosis.[1-6] However, a considerable discrepancy has been observed when comparing anatomic imaging with MSCT to myocardial perfusion imaging (MPI).[7-10] In these comparative studies, a large proportion of significant lesions on MSCT were not associated with a perfusion defect on MPI. Possibly, invasive functional testing using fractional flow reserve (FFR) may provide a more accurate comparison, since measurements are performed directly in the coronary arteries.[11] Only one previous study has addressed the diagnostic accuracy of MSCT to predict the presence of reduced FFR.[12] The purpose of the present study was to further assess the relationship between the anatomic information observed on MSCT and invasive functional testing using FFR in men with known coronary artery disease (CAD).

Methods

In total 33 patients were included in the study. Patients were clinically referred for coronary angiography and underwent additional testing including 1) FFR measurements during the cardiac catheterization procedure and 2) MSCT within 2 months before or after conventional coronary angiography. Conventional coronary angiography, FFR and MSCT results were obtained in 36 vessels. Patients were excluded from the study if they met one of the following exclusion criteria for MSCT: cardiac arrhythmia, renal insufficiency (serum creatinine > 120 mmol/L), known allergy to iodine contrast media, and pregnancy. Patients were also excluded if a cardiac event (worsening angina, revascularization, or myocardial infarction) occurred between the procedures. The study was part of an ongoing research protocol approved by the hospitals medical ethics committee, and all patients gave informed consent.

Patients were scanned using a 64-slice scanner (Aquillion 64, Toshiba Medical Systems, Tokyo, Japan) using a previously published scan protocol.[13] Before each examination, heart rate and blood pressure were monitored. In the absence of contraindications, patients with a heart rate exceeding the threshold of 65 beats per minute were given beta-blocking medication (50-100 mg metoprolol, oral).

The presence of calcium and the status of the coronary arteries were both evaluated using a dedicated workstation (Vitrea 2, Vital Images, USA, and Advantage, GE healthcare, USA). All studies were interpreted by two experienced observers blinded to the results of coronary angiography and FFR. Discrepancies in interpretation were resolved by consensus.

The coronary calcium score was calculated using the Agatston method. MSCT coronary angiography studies were evaluated using an intention to diagnose strategy regardless of image quality. In each vessel the presence of atherosclerosis was evaluated, and lesions were graded as having a diameter stenosis of either >30% or >50% luminal narrowing. Lesions with a stenosis >50% were deemed significant. A normal MSCT was defined as completely normal or <30% luminal narrowing.

Conventional coronary angiography was performed according to standard techniques. Quantitative analysis by an observer blinded to the MSCT and FFR results using an offline software program (QCA-CMS, version 6.0, Medis, Leiden, The Netherlands). After catheter based calibration, quantitative coronary angiography of the most severe lesions was performed with automated vessel contour detection in end-diastolic frames. Vessels were classified as having a diameter stenosis of either >30% or >50% luminal narrowing, and lesions with a stenosis >50% were deemed significant. A normal coronary angiography was defined as completely normal or <30% luminal narrowing. FFR measurements were performed in the distal and very proximal coronary artery during maximal hyperaemia obtained by intravenous injection of a bolus of adenosine (6 ug/ml in 7 ml). A 0.014 inch pressure guidewire (Brightwire 2, Volcano Corps., San Diego, USA) was advanced 1-2 mm into the proximal artery to measure proximal pressure, and advanced further, into the distal coronary artery to measure distal pressure. The FFR of the vessel was calculated as the ratio of distal pressure to proximal pressure, and a value of ≤ 0.75 was used as a cutoff point for significantly impaired coronary function.

Continuous variables were expressed as mean with standard deviation, and where compared using the student's t-test. Proportions were expressed in percentages. First MSCT observations were compared to coronary angiography. Secondly, MSCT and conventional coronary angiography were compared to FFR to determine the relation between stenotic lesions and FFR measurements. All comparisons were performed on a vessel basis. Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, IL, USA). A p-value <0.05 was deemed significant.

Results

In total 33 patients were included in the study. An overview of the characteristics of these patients is provided in Table 1. During conventional coronary angiography, an FFR measurement was obtained in the left anterior descending artery (n= 25), the right coronary artery (n = 9), and the left circumflex artery (n = 2), resulting in 38 vessels for analysis.

Table 1. Patient characteristics

Age (years)	57±11
Known coronary artery disease	30 (91%)
Diabetes mellitus	3 (9%)
Hypertension	14 (42%)
Hypercholesterolemia†	12 (36%)
Current Smoker	7 (21%)
Positive family history of cardiovascular disease	12 (36%)
Body mass index ≥ 30 Kg/m^2	8 (24%)
Heart rate during scan (beats per minute)	59±12
Average calcium score (Agatston units)	554±1588
Significant stenosis on coronary angiography	19 (58%)

Using the contrast enhanced MSCT images, 11 (31%) of 36 vessels were classified as normal (completely normal or <30% luminal narrowing). Atherosclerotic lesions exceeding 30% luminal narrowing were detected in 25 (69%) vessels. Of these 25 vessels, 13 (36%) vessels had atherosclerotic disease between 30% and 50% diameter stenosis, and in 12 (33%) vessels the diameter stenosis exceeded 50% luminal narrowing.

A total of 18 (50%) coronary arteries were normal (completely normal or <30% luminal narrowing) on conventional coronary angiography. Lesions with a diameter stenosis >30% were detected in the remaining 18 vessels (50%), of which 9 (25%) showed a non-significant stenosis (30-50% luminal narrowing) and 9 (25%) a significant stenosis (>50% luminal narrowing). Using the pressure guidewire, an average FFR of 0.83 ± 0.13 was measured. Normal FFR (>0.75) was observed in 28 (78%) vessels while FFR was abnormal in the remaining 8 (22%) vessels.

On MSCT 11 vessels were graded as normal (completely normal or <30% luminal narrowing). All 11 vessels were also graded normal on conventional coronary angiography. MSCT showed non-significant lesions (30-50% diameter stenosis) in 13 vessels, of which 5 were normal and 8 showed non-significant disease on conventional coronary angiography. Thus MSCT correctly identified 30-50% luminal narrowing in 8 of 13 vessels (62%). A significant lesion was observed in 12 vessels on MSCT. All 9 vessels with luminal narrowing >50% on conventional coronary angiography were detected; however MSCT overestimated the severity of disease in 3 vessels. Significant lesions were therefore correctly identified in 9 of 12 vessels (75%). Although an overestimation of disease was observed in some cases, MSCT correctly ruled out significant disease in all 25 vessels classified as <50% on MSCT.

Hemodynamically significant disease on FFR was observed in 7 of 12 vessels (58%) with >50% luminal narrowing on MSCT. Of note, abnormal FFR was also observed in 1 of 13 vessels (8%) with atherosclerosis between 30% and 50% luminal narrowing. Importantly, FFR was normal

in all 11 coronary arteries classified as normal on MSCT. Finally, on average FFR decreased significantly with increasing stenosis severity; further details are provided in Figure 1.

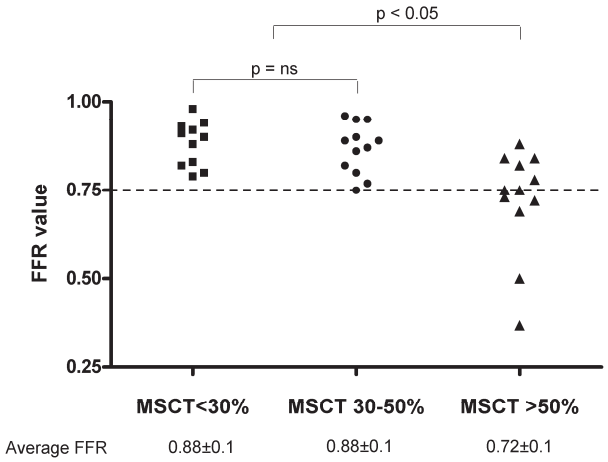

Figure 1. Scatter plot of FFR values in vessels with <30%, 30-50% and >50% luminal narrowing on MSCT. Average FFR was significantly reduced in patients with >50% luminal narrowing on MSCT.

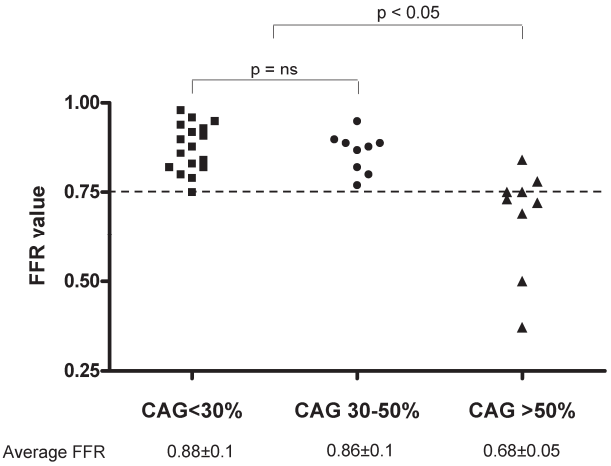

Figure 2. Scatter plot of FFR values in vessels with <30%, 30-50% and >50% luminal narrowing on conventional coronary angiography. Average FFR was significantly reduced in patients with >50% luminal narrowing on conventional coronary angiogrpahy.

When evaluating the relation between conventional coronary angiography and FFR, 7 of 9 vessels with >50% luminal narrowing on conventional coronary angiography were associated with hemodynamically significant disease on FFR.(Figure 2) Abnormal FFR was observed in 1 of 18 vessels (6%) with normal or <30% luminal narrowing on conventional

coronary angiography. On average the FFR was significantly decreased in vessels with >50% stenosis on conventional coronary angiography compared to vessels with normal or non-significant CAD.

Discussion

The main findings of this comparative study between MSCT and coronary angiography with FFR in men with known CAD are as follows: Although non-invasive anatomical imaging with MSCT correlates well with conventional coronary angiography, the agreement between an abnormal MSCT (>50% luminal narrowing) and FFR is relatively low. A large proportion (42%) of significant (>50%) lesions on MSCT did not result in a functional abnormality on FFR. Importantly however, the absence of any lesion exceeding 30% luminal narrowing on MSCT, was associated with consistent normal FFR values, suggesting that normal coronary anatomy on MSCT can accurately rule out the presence of hemodynamically significant CAD.

One previous study has been published comparing non-invasive anatomical imaging with 64-slice MSCT to FFR.[12] In this retrospective study the diagnostic accuracy of MSCT and coronary angiography using FFR as the reference standard was assessed. In total 89 stenoses were evaluated and a poor correlation was observed between MSCT and FFR. These results are in line with the current study in which a large proportion of significant stenoses on MSCT did not result in reduced FFR as well.

The inaccuracy of MSCT to precisely estimate degree of stenosis has been suggested as a potential cause of this discrepancy. Indeed, several studies have shown that MSCT has a tendency to overestimate the degree of stenosis.[1] Also in the present study, MSCT more frequently classified patients as having stenosis either 30-50% or >50% luminal narrowing as compared to conventional coronary angiography. However, similar to MSCT, conventional coronary angiography also fails to accurately predict reduced coronary flow reserve. In the current study 78% of vessels with a significant stenosis (>50% luminal narrowing) on conventional coronary angiography were associated with reduced FFR. In a meta-analysis by Christou et al. combining 18 studies with 1316 patients, a concordance of 61% between the presence of intermediate lesions of 30-70% luminal narrowing on coronary angiography and an abnormal FFR (using a cutoff value of 0.75) was observed.[14] When considering only lesions exceeding 70% luminal narrowing, the concordance increased slightly to 67%, indicating still a poor relation between degree of stenosis and reduced flow reserve. In the current study the concordance between significant stenosis on conventional coronary angiography and abnormal FFR seemed higher compared to the concordance between

significant stenosis on MSCT and FFR. To some extent this may be explained again by the tendency of MSCT to overestimate the degree of stenosis. Nevertheless, also conventional coronary angiography still frequently failed to accurately predict reduced FFR.

Comparable values have been reported in previous studies comparing MSCT to non-invasive MPI. In general, abnormal MSCT studies were associated with ischemia in approximately only 40% to 60% of studies.[7-10] In line with these observations, only 58% of significant (>50% stenosis) lesions on MSCT resulted in abnormal FFR in our current study as well. These findings highlight the fact that even on a vessel basis using invasive measurements, the relation between significant epicardial coronary stenosis and functional consequences is poor. Accordingly, in the presence of an abnormal MSCT study, functional testing remains essential to determine appropriate management.

An important finding of this study is that a normal MSCT (completely normal or <30% luminal narrowing) was consistently associated with a normal FFR. Also in previous comparisons of MSCT to MPI, MSCT has been shown to have a high negative predictive value for ischemia.[15] However, in contrast to our study, still small but not negligible proportions of normal MSCT studies were associated with abnormal MPI studies in these investigations.[8, 10] A recent study reported that abnormal MPI was observed in 10% of patients having coronary arteries without any evidence of luminal narrowing or coronary plaque on MSCT.[10] In some of these patients, the occurrence of attenuation artefacts may have hampered accurate evaluation of myocardial perfusion. More likely however, findings may have been influenced by intrinsic differences between FFR and MPI. While FFR detects epicardial coronary lesions that are severe enough to result in ischemia, MPI is also affected by abnormalities occurring at smaller levels of the coronary circulation. As a consequence, dysfunction of microvascular arterioles - which can occur in the presence of longstanding arterial hypertension and diabetes mellitus – can also result in abnormal MPI despite the absence of epicardial stenosis.[16] Accordingly, one may intuitively expect a higher agreement between MSCT and FFR as both technique evaluate and exclude CAD at macrovascular level. Indeed, comparisons of conventional coronary angiography and FFR have also indicated excellent concordance over 95% between normal coronary arteries and FFR values, [14] in line with the current study. These are important observations, as a normal FFR has been demonstrated to confer excellent prognosis and can safely defer patients from percutaneous intervention.[17, 18] Consequently, one may presume that also patients with a normal MSCT study have a low likelihood of coronary events and do not require invasive coronary angiography with possible intervention. Thus far only limited prognostic data on MSCT are available although preliminary data suggest that a normal MSCT study is indeed associated with excellent prognosis.[19-21]

Conclusion

Significant stenoses on MSCT frequently do not result in reduced FFR. A normal MSCT study however can accurately rule out the presence of hemodynamically significant lesions in men with known CAD.

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