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Comprehensive Assessment of Coronary Artery Stenoses

Computed Tomography Coronary Angiography Versus Conventional Coronary Angiography and Correlation With Fractional Flow Reserve in Patients With Stable Angina

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Objectives We sought to determine the diagnostic accuracy of noninvasive visual (computed tomography coronary angiography [CTCA]) and quantitative computed tomography coronary angiography (QCT) to predict the hemodynamic significance of a coronary stenosis, using intracoronary fractional flow reserve (FFR) as the reference standard.

Background It has been demonstrated that CTCA provides excellent diagnostic sensitivity for identifying coronary stenoses, but may lack accurate delineation of the hemodynamic significance.

Methods We investigated 79 patients with stable angina pectoris who underwent both 64-slice or dual-source CTCA and FFR measurement of discrete coronary stenoses. CTCA and conventional coronary angiography (CCA), and QCT and quantitative coronary angiography (QCA), were performed to determine the severity of a stenosis that was compared with FFR measurements. A significant anatomical or functional stenosis was defined as ≥50% diameter stenosis or an FFR <0.75. Stented segments and bypass grafts were not included in the analysis.

Results A total of 89 stenoses were evaluated of which 18% (16 of 89) had an FFR <0.75. The diagnostic accuracy of CTCA, QCT, CCA, and QCA to detect a hemodynamically significant coronary lesion was 49%, 71%, 61%, and 67%, respectively. Correlation between QCT and QCA with FFR measurement was weak (R values of −0.32 and −0.30, respectively). Correlation between QCT and QCA was significant, but only moderate (R = 0.53; p < 0.0001).

Conclusions The anatomical assessment of the hemodynamic significance of coronary stenoses determined by visual CTCA, CCA, or QCT or QCA does not correlate well with the functional assessment of FFR. Determining the hemodynamic significance of an angiographically intermediate stenosis remains relevant before referral for revascularization treatment. (J Am Coll Cardiol 2008;52:636–43) © 2008 by the American College of Cardiology Foundation

Currently available 64-slice cardiac computed tomography (CT) scanners and recently introduced dual-source scanners have the ability to completely assess the entire coronary tree and have been demonstrated to have good diagnostic accuracy for the identification of anatomically important coronary artery disease (CAD), generally defined as coronary artery stenoses with a lumen diameter reduction of at least 50% (1–11). However, the anatomically significant appearance of a coronary stenosis does not always equate with functional significance, and this is particularly true for intermediate type coronary lesions (12–16). According to the guidelines (European Society of Cardiology, American College of Cardiology/American Heart Association), the decision to perform angioplasty or bypass surgery should integrate anatomical information with a test that provides objective proof of ischemia (17,18).

Only few reports have studied the relationship between the significance of a stenosis in a coronary vessel as defined by computed tomography coronary angiogram (CTCA) and the functional importance of this stenosis in that particular coronary vessel territory (19–22). This study evaluates the relationship between the anatomy and functional significance of a coronary stenosis in patients who underwent both

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CTCA and conventional coronary angiogram (CCA) using the lesion-specific intracoronary fractional flow reserve (FFR) measurement.

Methods

Study population. We retrospectively analyzed all patients who, in the period between July 2004 and March 2007, underwent both a cardiac CT scan and invasive CCA and a subsequent measurement of the FFR. The decision to measure FFR was based entirely on the appearance of a coronary narrowing on CCA and was performed at the interventional cardiologist's discretion. All patients were assessed by either a 64-slice CT scanner (period July 2004 to March 2006) or dual-source CT scanner (period April 2006 to March 2007). Contraindications for a CT scan included impaired renal function (creatinine clearance <60 ml/min as defined with the Cockroft formula), irregular heart rhythm, and known contrast allergy. Patients with previous percutaneous coronary intervention using stents or coronary artery bypass surgery were excluded from further analysis. Due to the hemodynamic interaction between 2 or more stenoses in series (23,24), we only included patients in whom FFR of a single discrete lesion had been performed. In total, 89 segments in 79 patients were included in the study. Sixteen segments were excluded due to CTCA-related artefacts and 1 because of inability to obtain a good angiographic view to perform quantitative coronary angiography (QCA).

For this retrospective analysis, all patients gave their informed consent to undergo CTCA as part of research protocols approved by the institutional review board. FFR was carried out as part of routine clinical management.

CCA. All patients underwent CCA through the femoral approach, using a 6- or 7-F guiding catheter. After intracoronary injection of 2 mg isosorbide dinitrate, an angiogram of the right and left coronary artery was performed in multiple projections using standard techniques. All angiograms were analyzed off-line by 2 cardiologists who were not involved in the patient's medical care. They independently analyzed the selected coronary artery stenosis where FFR had been informed using visual estimation and quantitative assessment, the latter using an automated edge contour detection system (Cardiovascular Angiographic Analysis System, Pie Medical Equipment, Maastricht, the Netherlands) (25). Qualitative and quantitative analysis was based on the angiographic projection showing the most severe narrowing. A coronary stenosis was defined as significant based on visual inspection or when the degree of stenosis as measured with QCA was ≥50%.

FFR measurement. Fractional flow reserve was measured with a sensor-tipped 0.014-inch guidewire (Pressure Wire, Radi Medical Systems, Uppsala, Sweden). After positioning of the pressure sensor just distal to the stenosis, maximal myocardial hyperemia was induced by a continuous intravenous infusion of adenosine in a femoral vein at an infusion rate of 140 μg/kg body weight per minute for a minimum of 2 min. During maximum hyperemia, FFR was calculated as the ratio of mean distal pressure measured by the pressure wire divided by the mean proximal pressure measured by the guiding catheter (26). A coronary stenosis with an FFR value <0.75 was considered functionally significant (27–29).

Abbreviations and Acronyms

CAD = coronary artery disease
CCA = conventional coronary angiogram
CT = computed tomography
CTCA = computed tomography coronary angiogram
FFR = fractional flow reserve
QCA = quantitative coronary angiography
QCT = quantitative computed tomography coronary angiography

CTCA. PATIENT PREPARATION. Patients scanned with the 64-slice scanner who had a heart rate exceeding 65 beats/min received additional oral and/or intravenous beta-blockers (metoprolol) before the CT scan in order to obtain a heart rate below 65 beats/min. Patients scanned with dual-source CT did not receive pre-medication irrespective of the heart rate.

SCAN PROTOCOL. Thirty-eight patients were scanned with a 64-slice CT scanner (Sensation 64, Siemens, Forchheim, Germany). Angiographic scan parameters were: 32 × 2 × 0.6 mm collimation with z-flying focal spot, 330 ms rotation time, temporal resolution 165 ms, 120 kV tube voltage, 900 mAs tube current, and 3.8 mm/rotation table feed. Prospective X-ray tube modulation was not applied.

Forty patients were scanned using a dual-source CT scanner (Somatom Definition, Siemens, Forcheim, Germany). Dual-source CT angiographic scan parameters were: 120 kV, 330 ms rotation time, temporal resolution 83 ms, and 32 × 2 × 0.6 mm collimation with z-flying focal spot for both detectors. Pitch values were adapted to heart rate based on the average of the last 10 heart beats preceding the scan. Each tube provided 412 mAs/rot. Prospective tube modulation was applied with full dose radiation only given during 25% to 70% of the RR-interval.

With the 64-slice scanner, a bolus of 100 ml of contrast material (400 mgI/ml; Iomeron, Bracco, Milan, Italy) was injected intravenously in an antecubital vein at 5 ml/s. With dual-source CT, the volume of iodinated contrast material (Ultravist 370 mgI/ml, Schering AG, Germany) was adapted to the scan time, which varied between 5 and 13 s. A bolus of contrast material (60 to 90 ml) was injected in an antecubital vein at a flow rate of 5 ml/s followed by a saline chaser of 40 ml at 5 ml/s. In both scanners a bolus-tracking technique was used to synchronize the arrival of contrast in the coronary arteries, and the scan was started once the contrast material in the ascending aorta reached a predefined threshold of +100 Hounsfield units.

IMAGE RECONSTRUCTION. Images were reconstructed with electrocardiogram gating to obtain near motion-free image

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quality. Optimal datasets were reconstructed in the mid- to end-diastolic phase and in the end-systolic phase.

QUALITATIVE EVALUATION OF THE CTCA. Two experienced observers unaware of the results of CCA evaluated the CTCA datasets on an offline workstation (Leonardo, Siemens, Forchheim, Germany). Initially, the specific lesion was evaluated with axial slices for the presence of significant disease, and additionally (curved) multiplanar reformatted reconstructions were used.

QUANTITATIVE EVALUATION OF THE CTCA. Two experienced observers performed the quantification manually. After positioning the planes orthogonally to the course of the coronaries, cross-sectional images were obtained in the most severe narrowing and in the proximal and distal reference site. In these 3 images, the minimal lumen diameter was measured. The reference diameter was calculated by averaging the proximal and distal minimal lumen diameters. The percent diameter stenosis was calculated by subtracting the reference diameter from the minimal lumen diameter, which was divided by the reference diameter. The average of both measurements by the 2 observers was reported. A 50% diameter stenosis measured with quantitative computed tomography coronary angiography (QCT) was described as significant.

Statistical analysis. The diagnostic performance of qualitative and quantitative CCA and CTCA for the detection of significant stenoses in the coronary arteries with FFR as the standard of reference is presented as sensitivity, specificity, and diagnostic accuracy (true positives + true negatives/true positives + true negatives + false positives + false negatives), with the corresponding 95% confidence intervals. The relation between anatomical (QCA and QCT) and functional parameters (FFR) were analyzed with correlation statistics. The Pearson correlation coefficient was used because QCA, QCT, and FFR were normally distributed. Bland-Altman analysis was performed by plotting the difference of QCA and QCT versus QCA (30). Interobserver variability for the detection of significant coronary stenosis and agreement between techniques to classify segments as having a functionally significant lesion was determined by κ-statistics.

Table 1 Patient and Lesion Characteristics

Patients (n = 79)	
Segments, n	89
Gender, male/female	64/15
Mean age, yrs	60 ± 9
Body mass index, mean (kg/m^2)	26.6 ± 3.9
Prior myocardial infarction	10
Angiographic data	
Affected artery	
Left main coronary artery	5
Left anterior descending coronary artery	41
Circumflex coronary artery	19
Right coronary artery	24
Reference diameter (mm)	2.82 ± 0.67
Percent diameter stenosis (%)	44 ± 11
Minimal luminal diameter (mm)	1.57 ± 0.50

Table 2 Patient Management

Therapeutic decision, n	
Medical therapy	57
Percutaneous coronary intervention	29
Coronary artery bypass grafting	3
Revascularized segments, n	
FFR <0.75	16
FFR ≥0.75 to <0.80	11
FFR >0.80, IVUS obstructive plaque	5

FFR = fractional flow reserve; IVUS = intravascular ultrasound.

Results

Patients' characteristics and angiographic data are shown in Table 1. A total of 17 segments were excluded due to the presence of heavy calcifications (11 segments), motion artifacts (2 segments), breathing artifacts (2 segments), low contrast opacification (1 segment), and absence of a good angiographic view to perform QCA (1 segment). Average heart rate during CT data acquisition was 60 ± 9 beats/min for 64-slice CT and 68 ± 11 beats/min for dual-source CT.

Overall, 89 discrete stenoses in 79 patients were included for comparison with FFR. Seventy-one percent (63 of 89) of these stenoses were of angiographic intermediate severity (between 40% and 70% diameter stenosis as determined by QCA), 29 stenoses were less than 40%, and 1 stenosis was measured as more than 70%. Of these 89 coronary stenoses, 35 had a diameter stenosis of more than 50% by QCA, but only 16 lesions were hemodynamically significant (FFR <0.75). Patient management is shown in Table 2.

Diagnostic performance of CTCA and CCA versus FFR: visual assessment. The diagnostic performance of CTCA and CCA for the assessment of a functionally important coronary stenosis (FFR <0.75) is detailed in Table 3 and Figure 1. Agreement between visual CT and FFR assessment was present in 49% (44 of 89) of the evaluated segments; 15 of the 16 hemodynamically significant stenoses were identified correctly. One functionally important lesion in the midleft anterior descending coronary artery was underestimated and classified as nonsignificant by CTCA (44% diameter stenosis by QCA) (Fig. 2). Overestimation of hemodynamic severity occurred in 44 cases (Fig. 3). Corresponding sensitivity and specificity were, respectively, 94% and 40%. Interobserver variability for detection of a functionally important coronary stenosis was good (kappa value of 0.76). Agreement between CTCA and FFR was poor (kappa value of 0.16).

By comparison, visual lesion assessment by CCA showed an agreement with FFR in 61% (54 of 89) of the segments. Visual scoring identified 10 of the 16 functionally important lesions and 44 of the 73 functionally insignificant lesions. Six functionally important lesions were underestimated (Fig. 2). In 29 lesions, the hemodynamic severity was

Table 3 Diagnostic Performance of CCA and CTCA to Detect a Functionally Significant Coronary Stenosis (FFR <0.75, FFR <0.80)

	True Positive	True Negative	False Positive	False Negative	kappa	Sensitivity, %	Specificity, %	Diagnostic Accuracy, %
FFR <0.75 (n = 16)								
CT coronary angiography, visual score	15	29	44	1	0.16	94 (82–100)	40 (29–51)	49 (39–60)
Quantitative CT coronary angiography	8	55	18	8	0.20	50 (26–75)	75 (65–85)	71 (61–80)
Conventional coronary angiography, visual score	10	44	29	6	0.15	63 (39–86)	60 (49–72)	61 (51–71)
Quantitative coronary angiography	11	49	24	5	0.25	69 (46–91)	67 (56–78)	67 (58–77)
FFR <0.80 (n = 31)								
CT coronary angiography, visual score	29	28	30	2	0.35	94 (58–100)	48 (35–61)	64 (54–74)
Quantitative CT coronary angiography	14	46	12	17	0.25	45 (28–63)	79 (69–90)	67 (58–77)
Conventional coronary angiography, visual score	17	36	22	14	0.16	55 (37–72)	62 (50–75)	60 (49–70)
Quantitative coronary angiography	17	41	18	13	0.25	57 (39–74)	69 (58–81)	65 (55–75)

CCA = conventional coronary angiogram; CT = computed tomography; CTCA = computed tomography coronary angiogram; FFR = fractional flow reserve.

overestimated (Fig. 3). Consequently, the sensitivity was 63% and the specificity 60% for CCA to detect a functionally significant lesion. Interobserver variability for the detection of a functionally important coronary stenosis was moderate (kappa value of 0.61). Agreement between CCA and FFR was poor (kappa value of 0.15). Furthermore, the

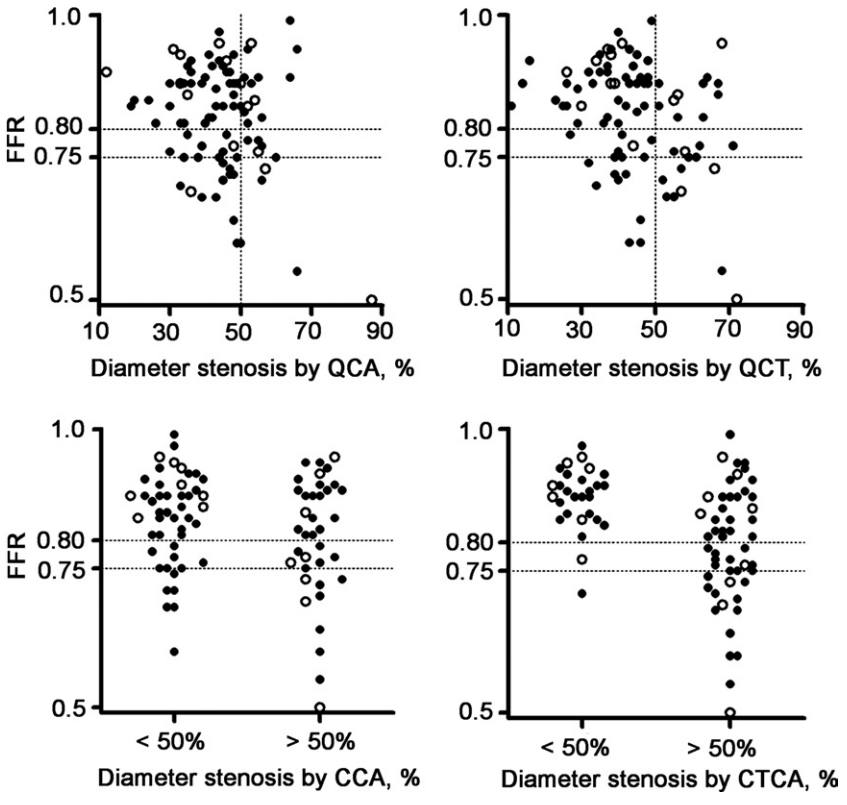

Figure 1 Scatter Plots of FFR Versus QCA, QCT, CCA, and CTCA

Quantitative coronary angiography (QCA), quantitative computed tomography coronary angiography (QCT), CCA, and CTCA are plotted versus FFR. There was a weak, but significant, negative correlation between QCA and FFR ($r = -0.30$) and between QCT and FFR ($r = -0.32$). Coronary arteries smaller than 3.5 mm are depicted as **solid circles**, coronary arteries larger than 3.5 mm as **open circles**. Abbreviations as in Figure 1.

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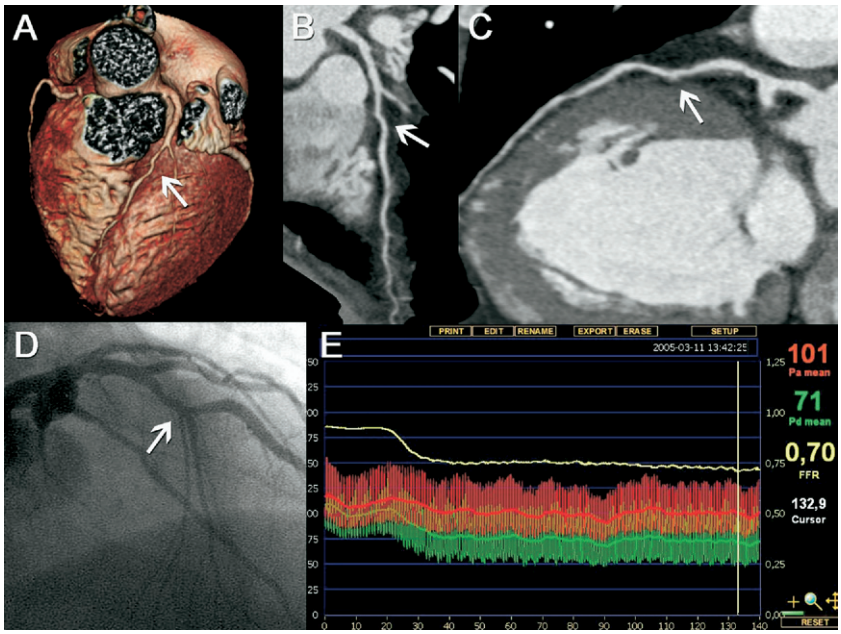

Figure 2 **CTCA and CCA With FFR Measurement of Intermediate Coronary Lesion**

Patient showing a coronary artery stenosis **(arrow)** in the left anterior descending coronary artery, as visualized with computed tomography coronary angiography (CTCA) (**A**, volume-rendered image; **B and C**, 2 orthogonal curved multiplanar reconstructions) and conventional coronary angiography (CCA) **(D)**. By visual assessment, the coronary lesion was estimated as less than 50% diameter stenosis, both by CTCA and CCA. By quantitative analysis, the diameter stenosis was measured as 44% by quantitative coronary angiography and 40% by quantitative CTCA. The fractional flow reserve (FFR) was 0.71 **(E)**. Based on the functional assessment, the patient underwent a successful percutaneous coronary intervention for this anatomically intermediate stenosis.

diagnostic performance of CTCA and CCA for the assessment of a functionally important coronary stenosis, defined as an FFR <0.80, is detailed in Table 3 and Figure 1.

Diagnostic performance of QCT and QCA versus FFR: quantitative assessment. The diagnostic accuracy of QCT and QCA for detecting functionally relevant coronary stenoses is described in Table 3 and Figure 1. Overall, the diagnostic accuracy for both quantitative measures was slightly better than when performed with visual estimation.

Agreement between QCA and FFR as well as between QCT and FFR (Table 3) was only fair (kappa value of 0.25 and 0.20, respectively). The interobserver variability for QCA (kappa value of 0.58) and QCT (kappa value of 0.69) was moderate.

The correlation between QCT and FFR was R = −0.32 and between QCA and FFR was R = −0.30. Correlation of the percent diameter stenosis as determined by QCT and QCA was significant, but only moderate (R = 0.53; p < 0.0001) (Fig. 4). The Bland-Altman analysis plot revealed important variability: the mean difference between QCA and QCT was +2% with 95% limits of agreement ranging from −21% to +25% (Fig. 4).

Discussion

Fractional flow reserve is a lesion-specific technique to determine the functional importance of a coronary stenosis and is correlated with noninvasive tests that demonstrate ischemia (27,31–34). It has been shown to be a useful guide for decision making regarding the revascularization of a specific lesion. In lesions where the FFR is ≥0.75, revascularization can be safely deferred (35–37).

Limitations of anatomical imaging. Previous reports have demonstrated that the anatomical assessment of a coronary stenosis as determined by CCA correlates poorly with the hemodynamic significance of the stenosis, in particular in intermediate severity lesions (12–16). Although QCA is accurate and reproducible, it does not reflect the hemodynamic impairment of coronary flow. The QCA does not account for the effects of factors such as collateral circulation, mass of viable myocardium, shape and length of stenosis, inflow and outflow configuration, and transient vasoconstriction with resulting dynamic changes in the diameter of a stenosis (38). The diffuseness of the atherosclerotic process often results in disease in the reference segments proximal and distal to the site of maximal diameter reduction and as a result leads to underestimation of extent and severity of coronary atherosclerosis (39).

Integrating anatomy with functional information. These findings were also demonstrated in this study, not only for CTCA, but also when assessing the severity of a coronary artery stenosis with CCA. Using visual assessment, CTCA had high sensitivity to detect lesions with functional signif-

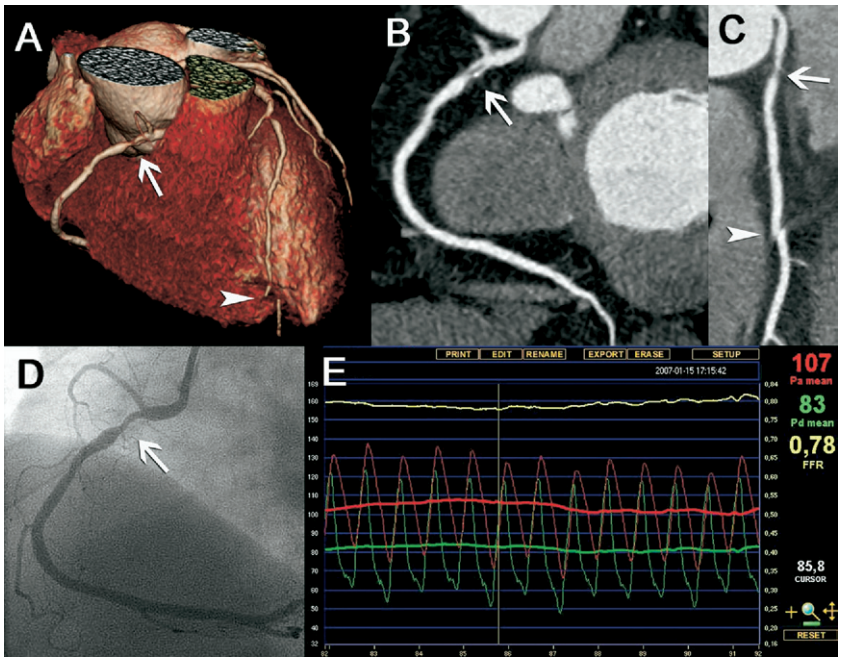

Figure 3 **CTCA and CCA With FFR Measurement of Intermediate Coronary Lesion**

Patient with a coronary artery stenosis **(arrow)** in the proximal part of the right coronary artery, as visualized with CTCA (**A**, volume-rendered image; **B and C**, 2 orthogonal curved multiplanar reconstructions) and CCA **(D)**. Visually, the diameter stenosis was estimated as more than 50%, both by CTCA and CCA. Also, after quantification (56% diameter stenosis by quantitative coronary angiography, 70% diameter stenosis by quantitative CTCA), the lesion appeared to be anatomically significant. The FFR was 0.78 **(E)**. In the distal segments, a step artefact can be seen **(A and C, arrowhead)**. Abbreviations as in Figure 1.

icance (FFR <0.75). However, it had poor specificity due to frequent false positives; CTCA overestimated the functional severity of a coronary stenosis, even when excluding segments with extensive calcifications or coronary motion. Quantification of stenosis severity by QCT and QCA improved the prediction of a functionally relevant coronary stenosis slightly.

Previous studies have compared the anatomical findings of CTCA with functional imaging using nuclear stress testing (19,20,22). These studies also showed a poor correlation between anatomy and function with only ~50% of patients with significant coronary stenosis as demonstrated by CTCA having ischemia demonstrated by nuclear stress testing. Besides methodological limitations, these noninvasive tests measure the effect of impaired coronary perfusion at the level of the myocardium and thus do not discriminate between epicardial flow impairment and microvascular perfusion abnormalities. Intracoronary measurement of the

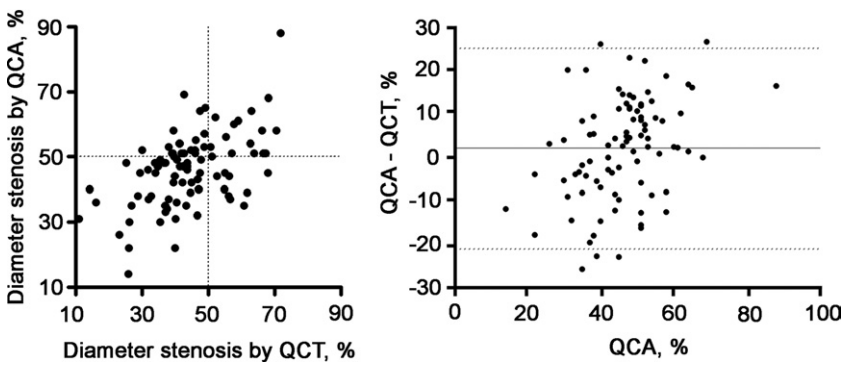

Figure 4 **Scatter Plot and Bland-Altman Analysis of QCT Versus QCA**

In the **left panel**, QCT is plotted versus QCA. A significant correlation is seen between both anatomical techniques (r = 0.53). In the **right panel**, Bland-Altman analysis showed a bias of +2% with 95% limit of agreement ranging from −21% to 25%. Abbreviations as in Figure 3.

FFR has the disadvantage of being invasive, but has the benefit of determining the ischemic potential of a specific epicardial coronary stenosis.

Clinical implementation. Given the previously discussed findings, and the consistently high negative predictive value of CTCA in different population groups, CTCA appears best suited as an effective rule-out test for significant CAD. Those patients with suspected CAD and no or minimal coronary atherosclerosis on CTCA would not need further investigation (40,41). However, patients with obstructive CAD on CTCA may best be investigated using a combined approach with a subsequent functional test such as nuclear stress testing, stress echocardiography, or magnetic resonance perfusion imaging.

Anatomical evaluation of CAD has limitations and makes functional assessment necessary. Comprehensive noninvasive anatomical and functional imaging may best identify patients who are likely to benefit most from secondary preventive measures and medical therapy (coronary atherosclerosis without ischemia) or who may be candidates for coronary revascularization (coronary atherosclerosis with ischemia). All-in-one approaches, such as single-photon emission CT-CTCA or positron emission tomography-CTCA, that provide integrated evaluation of anatomy and physiology in a noninvasive way might theoretically solve these diagnostic problems.

Now that we are able to noninvasively access coronary anatomy, we should be mindful of the limitations of noninvasive functional tests, especially in patients with multivessel disease or significant left main stenosis on CTCA, without evidence of ischemia of a noninvasive functional test (42,43). In case of doubt, it seems prudent to refer such a patient to the catheterization laboratory for further invasive assessment and definitive exclusion of the functional severity of a specific epicardial stenosis using FFR.

Study limitations. Patient inclusion was not performed in a prospectively designed study, but as a retrospective analysis. Consecutive patients were enrolled based on the access to the 64-slice or dual-source CT scanner. Seventeen segments in 15 patients had to be excluded due to the presence of heavy calcifications, motion artifacts, breathing artifacts, low contrast opacification, and absence of a good angiographic view that made it, both visually as well as quantitatively, impossible to reliably estimate stenoses severity.

Quantification of coronary artery stenoses with CTCA continues to be a challenge due to the difficulty in ascertaining the normal reference segment of the coronary artery because of atherosclerotic involvement of the vessel wall proximal and distal to the stenosis (2,3,44). Especially in the presence of extensive calcifications of the artery, it becomes impossible to accurately define the reference vessel diameters. Further improvement in spatial resolution will enhance the ability to accurately grade stenosis severity. However, particularly in coronary stenoses of intermediate severity, this may not improve the ability to predict functional significance, as is also observed with invasive CCA.

Conclusions

The correlation between stenosis severity as determined by CTCA or CCA and ischemia measured by FFR in coronary lesions of intermediate severity is poor. Functional information, whether provided by FFR or a noninvasive stress test, is essential in these circumstances for appropriate clinical decision making.

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