Radiology

ORIGINAL RESEARCH ■ CARDIAC IMAGING

Diagnostic Performance of Transluminal Attenuation Gradient and Noninvasive Fractional Flow Reserve Derived from 320–Detector Row CT Angiography to Diagnose Hemodynamically Significant Coronary Stenosis: An NXT Substudy[1]

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Purpose: To compare the diagnostic performance of 320–detector row computed tomography (CT) coronary angiography–derived computed fractional flow reserve (FFR; FFR_{CT}), transluminal attenuation gradient (TAG; TAG_{320}), and CT coronary angiography alone to diagnose hemodynamically significant stenosis as determined by invasive FFR.

Materials and Methods: This substudy of the prospective NXT study (no. NCT01757678) was approved by each participating institution's review board, and informed consent was obtained from all participants. Fifty-one consecutive patients who underwent 320–detector row CT coronary angiographic examination and invasive coronary angiography with FFR measurement were included. Independent core laboratories determined coronary artery disease severity by using CT coronary angiography, TAG_{320}, FFR_{CT}, and FFR. TAG_{320} is defined as the linear regression coefficient between luminal attenuation and axial distance from the coronary ostium. FFR_{CT} was computed from CT coronary angiography data by using computational fluid dynamics technology. Diagnostic performance was evaluated and compared on a per-vessel basis by the area under the receiver operating characteristic (ROC) curve (AUC).

Results: Among 82 vessels, 24 lesions (29%) had ischemia by FFR (FFR ≤ 0.80). FFR_{CT} exhibited a stronger correlation with invasive FFR compared with TAG_{320} (Spearman ρ, 0.78 vs 0.47, respectively). Overall per-vessel accuracy, sensitivity, specificity, and positive and negative predictive values for TAG_{320} (<15.37) were 78%, 58%, 86%, 64%, and 83%, respectively; and those of FFR_{CT} were 83%, 92%, 79%, 65%, and 96%, respectively. ROC curve analysis showed a significantly larger AUC for FFR_{CT} (0.93) compared with that for TAG_{320} (0.72; *P* = .003) and CT coronary angiography alone (0.68; *P* = .008).

Conclusion: FFR_{CT} computed from 320–detector row CT coronary angiography provides better diagnostic performance for the diagnosis of hemodynamically significant coronary stenoses compared with CT coronary angiography and TAG_{320}.

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Computed tomographic (CT) coronary angiography is an established noninvasive method for anatomic assessment of coronary stenoses (1), yet it has limited specificity for diagnosing their hemodynamic significance (2). Novel CT techniques were recently developed that include transluminal attenuation gradient (TAG) and noninvasive fractional flow reserve (FFR) derived from CT (FFR_{CT}) in an attempt to improve the diagnostic performance of CT coronary angiography (3,4).

TAG is defined as the linear regression coefficient between luminal attenuation and axial distance from the coronary ostium. The high diagnostic performance of TAG obtained by using 320–detector row CT, which enables near-isophasic single-beat imaging of the entire coronary tree, has been demonstrated (3). Computational fluid dynamics as applied to CT coronary angiography images enables prediction of blood flow and pressure in coronary arteries and calculation of lesion-specific fractional flow reserve (5). FFR_{CT} has been demonstrated to have high diagnostic performance for detection and exclusion of hemodynamically significant stenoses (4,6,7). Both techniques can be computed from typically acquired CT coronary angiography scans without need of additional image acquisition or administration of medication. However, to our knowledge, their diagnostic performance has not been compared on the basis of images acquired by using wide-detector CT. We hypothesize that both CT-based techniques will have comparable diagnostic performance in the detection of hemodynamically significant coronary stenosis.

Our primary purpose of this study was to compare the diagnostic performance of 320 multi–detector row CT coronary angiography–derived FFR_{CT}, TAG (TAG_{320}), and CT coronary angiography alone to diagnose hemodynamically significant stenosis as determined by invasive FFR. The secondary aim was to compare the incremental value of TAG_{320} and FFR_{CT} to CT coronary angiography alone in the diagnosis of hemodynamically significant stenosis.

Advance in Knowledge

- Noninvasive fractional flow reserve (FFR) derived from 320–detector row CT coronary angiography (FFR_{CT}) is superior in diagnosing hemodynamically significant coronary stenoses as determined by invasive FFR compared with CT coronary angiography and transluminal attenuation gradient derived from 320–detector row CT (TAG_{320}); receiver operating characteristic curve analysis showed a significantly larger area under the curve for FFR_{CT} (0.93) compared with that for TAG_{320} (0.72; P = .003) and CT coronary angiography alone (0.68; P = .008).

Materials and Methods

This substudy of the prospective NXT study (no. NCT01757678) was approved by each participating institution's review board, and informed consent was obtained from all participants. Consecutive patients suspected of having coronary artery disease who underwent 320–detector row CT coronary angiography and invasive coronary angiography with FFR measurement were studied. The rationale, design, and eligibility criteria of the NXT study were previously described (8). Exclusion criteria included patients in whom FFR was not performed or performed on a vessel less than 2 mm, and in whom FFR_{CT} or TAG could not performed.

CT Coronary Angiography Acquisition and Analysis Protocol

CT coronary angiography was performed by using prospective electrocardiographic gating and 320–detector row CT (Aquilion One or Aquilion Vision; Toshiba Medical Systems, Otawara, Japan). The scan protocol differed in the three recruitment sites. In Monash Medical Center, the scan was acquired by using a CT scanner (Aquilion Vision; Toshiba Medical Systems) during injection of 75 mL of 100% iohexal (Omnipaque 350; GE Healthcare, Milwaukee, Wis) at 5 mL/sec followed by 30 mL of saline at the same rate. Scans were manually triggered. Scan parameters were as follows: detector collimation, 320 × 0.5 mm; tube current was determined with use of automatic exposure control (SureExposure3D; Toshiba Medical Systems); tube voltage, 100–135 kV depending on body mass index; and temporal resolution, 135 msec. In Kyoto University, the CT scan was acquired (Aquilion One; Toshiba Medical Systems) during injection of 59 mL of 100% iomeprol (Iomeron 350; Bracco, Milan, Italy) at 4.2 mL/sec, followed by 30 mL of saline at the same rate. Scans were automatically triggered by using bolus tracking when the contrast attenuation reached 150 HU in the ascending aorta. Scan parameters were as follows: detector collimation, 320 × 0.5 mm; tube current, 300–500 mA, depending on body mass index; tube voltage, fixed at 120 kV; and temporal

Implication for Patient Care

- FFR_{CT} is an accurate noninvasive method derived from coronary CT angiography to predict the hemodynamic significance of coronary artery disease.

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Abbreviations:
AUC = area under the ROC curve
FFR = fractional flow reserve
FFR_{CT} = FFR derived from CT
ROC = receiver operating characteristic
TAG = transluminal attenuation gradient
TAG_{320} = TAG derived from 320–detector row CT coronary angiography

Author contributions:
Guarantors of integrity of entire study, B.S.K., B.L.N.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, B.S.K., D.T.L.W., J.D.C., M.M., S.K.S.; clinical studies, B.S.K., B.L.N., J.D.C., S.G., S.K., T.K., I.T.M.; experimental studies, J.D.C.; statistical analysis, B.S.K., B.L.N., D.P.L., J.D.C., I.T.M.; and manuscript editing, B.S.K., D.T.L.W., B.L.N., D.P.L., J.D.C., S.G., M.M., S.A., S.K., I.T.M., S.K.S.

Conflicts of interest are listed at the end of this article.

resolution, 170 msec. In Keio University, the scan was acquired by using the scanner (Aquilion One; Toshiba Medical Systems) during injection of 59 mL of 100% iopamidol (Iopamiron 370; Bracco) for 12 seconds at 4.9 mL/sec, followed by 30 mL of saline at the same rate. Scans were automatically triggered by using bolus tracking when the contrast attenuation reached 150 HU in the ascending aorta. Scan parameters were as follows: detector collimation, 320 × 0.5 mm; tube current, 300–500 mA depending on body mass index; tube voltage, fixed at 120 kV; and temporal resolution, 170 msec. In adherence to quality standards as defined in guidelines (9), oral and/or intravenous β-blockers were administered by targeting a heart rate of less than 60 beats per minute, and sublingual nitrates were administered immediately before the scan to optimize coronary vasodilatation. Core laboratory analysis was performed in Erlangen, Germany on all segments with a diameter of 2 mm or larger according to the 18 coronary segment model. Significant stenosis was defined as stenosis of 50% or more in a major epicardial coronary artery segment with a diameter of 2 mm or larger.

FFR_{CT} Computation

By using the most recent generation of FFR_{CT} analysis software (4), blinded analysis was performed (Heartflow, Redwood City, Calif). For each patient, a quantitative three-dimensional luminal model of the aortic root and epicardial coronary arteries was generated from CT coronary angiography images. Coronary blood flow and pressure were computed by using conditions that simulated maximal hyperemia, and FFR_{CT} was computed throughout the coronary arterial tree. For occluded arteries, FFR_{CT} of 0.50 was assigned. A FFR_{CT} of 0.80 or less was considered to be hemodynamically significant. For the combined assessment of FFR_{CT} with CT coronary angiography, vessels were classified as nonsignificant if there was a stenosis of less than 50% by using CT coronary angiography. Vessels were classified as significant if there was a stenosis of 50% or greater found by using CT coronary angiography and FFR_{CT} was 0.80 or less.

TAG_{320} Analysis

Core laboratory analysis of TAG_{320} was performed with a semiautomated method by using dedicated computer software (Toshiba Medical Systems) in a blinded method (B.K. and D.W., both with 5 years of experience with interpretation of CT images). Vessel centerline and contouring was automatically determined for each major coronary artery and was manually corrected if necessary. Cross-sectional images perpendicular to the vessel centerline were then reconstructed. The mean luminal radiologic attenuation (in Hounsfield units) was measured at 1-mm intervals, from the ostium to a distal level where the cross-sectional minimal area fell below 2 mm^2. The data points in segments with motion or blooming artifacts from luminal calcium were manually excluded from analysis. The TAG_{320} value was defined as the linear regression coefficient between intraluminal radiologic attenuation (in Hounsfield units) and length from the ostium (in millimeters). TAG_{320} was performed for arteries that had stenosis or occlusion (10). A retrospectively determined TAG_{320} cut-off (determined from the dataset with a sensitivity of >50% and optimized for the sum of sensitivity and specificity of FFR ≤0.8) was obtained to indicate significant stenosis. For combined TAG_{320} and CT coronary angiography assessment, vessels were classified as nonsignificant if there was a stenosis less than 50% found by using CT coronary angiography. Vessels were classified as hemodynamically significant if there was stenosis 50% or greater found by using CT coronary angiography and if TAG_{320} was significant.

Invasive Angiography and FFR

Invasive coronary angiography was performed according to standard practice. Measurement of FFR (Pressure Wire; St Jude Medical, Minneapolis, Minn) was performed during invasive coronary angiography in at least one vessel with diameter of 2 mm or greater and stenosis of 30% or greater. The vessel chosen was at the discretion of the interventionist. Tracings were evaluated at an FFR core laboratory (Harrington Heart and Vascular Institute, University Hospitals, Cleveland, Ohio) to assess achievement of steady-state maximal hyperemia, pressure drift, and other artifacts that could compromise FFR interpretation. Segments that showed angiographic total occlusion were assigned an FFR value of 0.50.

Statistical Analysis

Categorical variables are presented as frequencies and percentages, with continuous variables as mean ± standard deviation or median with interquartile range. Comparisons of continuous variables were performed by using the Kruskal-Wallis test. Per-vessel sensitivity, specificity, positive predictive value, and negative predictive values of CT coronary angiography, TAG_{320}, FFR_{CT}, CT coronary angiography with TAG_{320}, and CT coronary angiography with FFR_{CT} were calculated with 95% confidence intervals. The discriminatory ability of both TAG_{320} with CT coronary angiography and FFR_{CT} (≤0.80) for the identification of hemodynamically significant stenosis was evaluated on a per-vessel basis by the area under the receiver operating characteristic (ROC) curve (AUC). Invasive FFR of 0.80 or less was the reference standard. Comparisons were performed by using the DeLong method (11), and Bonferroni adjustment was made for multiple comparisons. The

Figure 1

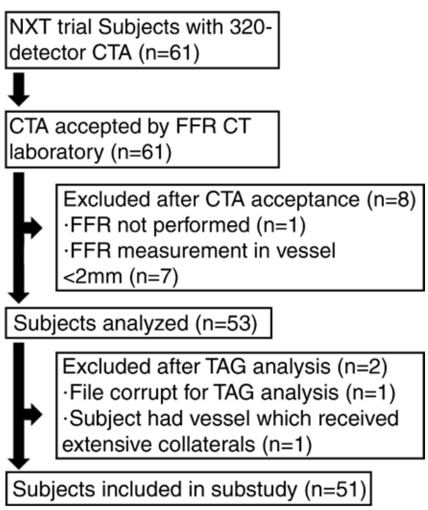


Figure 1: Flow chart shows study enrollment. *CTA* = CT angiography.

category-free net reclassification index was used to determine whether TAG_{320} and FFR_{CT} improve vessel classification to be hemodynamically significant compared with CT coronary angiography alone (12).

Statistical analysis was performed by using statistical software (SPSS version 18, SPSS, Chicago, Ill; and Stata version 13.1, Stata Corp, College Station, Tex). A *P* value of less than .05 was considered to indicate statistical significance.

Results

Sixty-one consecutive patients who were suspected of having coronary artery disease underwent 320–detector row CT coronary angiography and invasive coronary angiography with FFR measurement in Monash Medical Centre (n = 40), Kyoto Hospital (n = 18), and Keio Hospital (n = 3) between September 2012 and August 2013 (Fig 1). Eight patients were excluded by the FFR core laboratory because of FFR measurement in a vessel less than 2 mm (n = 7) or because FFR was not performed (n = 1). Two patients were excluded because of inability to perform TAG (in one patient the vessel was deemed to be too small by using CT to perform TAG and in one patient the vessel found to have severe stenosis with collateral supply). Finally, 82 vessels were analyzed from 51 patients.

Mean age was 62.2 years ± 10.4, and 74.5% (38 of 51) were men. Of the 82 coronary arteries, 34 were left anterior descending arteries, 23 were left circumflex arteries, and 25 were right coronary arteries. There were five occluded vessels in five patients in which FFR_{CT} and FFR values were assigned. Baseline patient and vessel characteristics are listed in Table E1 (online) and Table 1. CT scan parameters are listed in Table 2. There were 24 (29.3%) vessels with FFR of 0.80 or less.

Relationship of TAG_{320} and FFR_{CT} with FFR

The median TAG_{320} was significantly lower in vessels with hemodynamically significant stenoses compared with vessels without hemodynamically significant stenosis, −17.2 HU per 10 mm (interquartile range, −20.0 to −6.40) versus −8.86 HU per 10 mm (interquartile range, −13.2 to −3.83) (P = .002). Median FFR_{CT} was also significantly lower in vessels with hemodynamically significant stenosis compared with vessels without ischemia, 0.68 (interquartile range, 0.50–0.75) versus 0.87 (interquartile range, 0.81–0.93) ($P < .001$).

Figure 2 illustrates the correlation between TAG_{320}, FFR_{CT}, and invasive FFR. By using TAG_{320}, a modest yet statistically significant correlation with invasive FFR was demonstrated (Spearman

Table 1

Patient and Vessel Characteristics according to CT Angiography, TAG_{320}, FFR_{CT}, Invasive Coronary Angiography, and FFR

Characteristic	Result
CT angiography diagnostic findings (maximum stenosis severity distribution at patient level)	
Patients with coronary CT angiography maximum stenosis >50%	66.7 (34/51)
Patients with coronary CT angiography maximum stenosis >70%	60.0 (26/51)
Patients with intermediate-range stenosis (30%–70%)	35.3 (18/51)
Patients with FFR_{CT} ≤0.80	54.9 (28/51)
Vessels with FFR_{CT} ≤0.80	41.5 (34/82)
Patients with TAG_{320} less than −15.37	39.2 (20/51)
Vessels with TAG_{320} less than −15.37	26.8 (22/82)
Calcium score (Agaston Units)*	384.2 ± 522.3 (19)
Median score	195
Range	0–2213.0
Agatston score ≥400	31.6 (6/19)
Patients with QCA maximum stenosis >50%	41.2 (21/51)
Patients with QCA maximum stenosis >70%	13.7 (7/51)
Patients with FFR ≤0.80	41.2 (21/51)
Vessels with FFR ≤0.80	29.3 (24/82)
Patients with FFR ≤0.80 in at least one vessel	5.9 (3/51)

Note.—Except where indicated, data are percentages. Data in parentheses are numerator and denominator. There were 51 patients and 82 vessels. QCA = quantitative coronary angiography.

* Data are mean no. ± standard deviation. Data in parentheses are number of patients.

Table 2

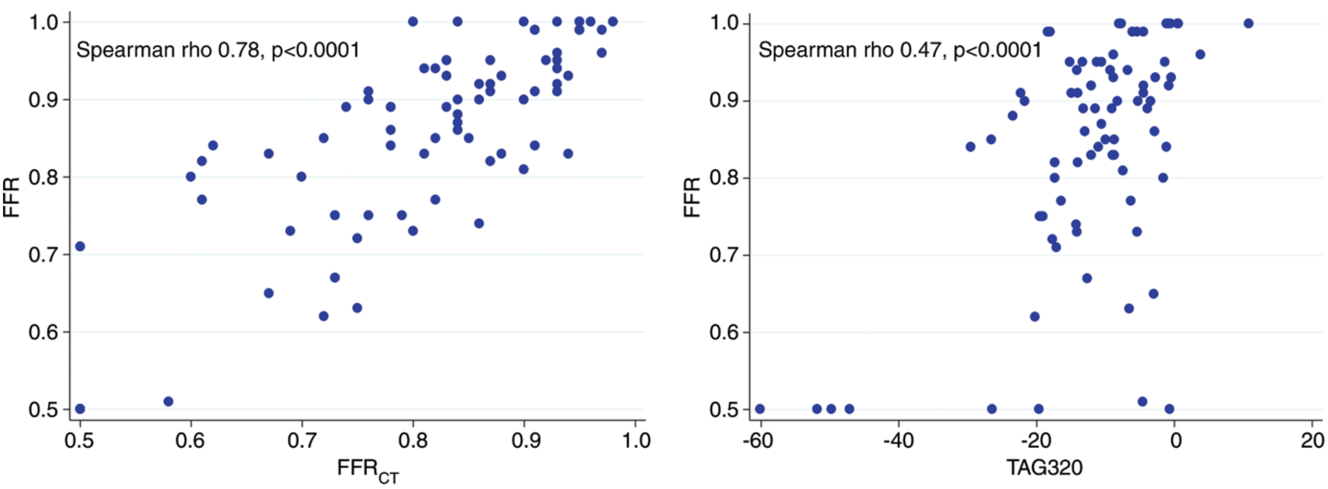
Coronary CT Angiography Acquisition Characteristics

CT Scan Acquisition Characteristic	Result
Heart rate before CT angiography	66.3 ± 11.8
No. of patients	51
Median heart rate (beats per min)	63.0
Nitrates administered	51 (100)
β Blockers administered	32 (62.7)
Prospective scan	33 (64.7)
Retrospective scan	18 (35.3)
Radiation calculated from dose-length product	
Retrospective scan (mSv)*	12.7 ± 4.8
No. of patients	18
Median (mSv)	12.3
Prospective scan*	3.3 ± 3.8
No. of patients	33
Median	2.1
Kilovolts administered	
100 kV	15 (29.4)
120 kV	34 (66.7)
135 kV	2 (3.9)
Milliampere-seconds administered (mAs)*	451.27 ± 193.14
Range	225–900
Single-beat acquisition	51 (100)
Multiple-beat acquisition	0 (0)

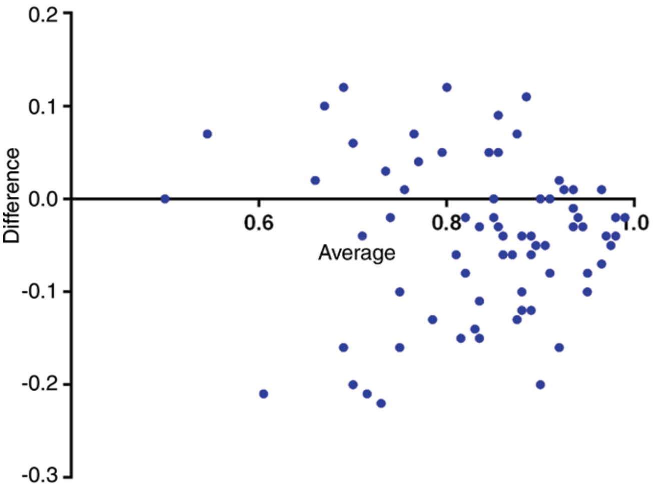
Note.—Unless otherwise indicated, data are number of patients. Data in parentheses are percentages.

* Data are mean ± standard deviation.

Figure 2



a. b.



c.

Figure 2: Scatterplots show correlation of **(a)** FFR_{CT} and **(b)** TAG_{320} with FFR. FFR_{CT} exhibited a stronger correlation with invasive FFR compared with TAG_{320} (Spearman ρ, 0.78 vs 0.47, respectively). **(c)** On Bland-Altman analysis of FFR_{CT} and FFR, there was good agreement, with a bias of −0.04 ± 0.08 (95% confidence interval: −0.19, 0.11).

ρ = 0.47; $P < .001$). FFR_{CT} demonstrated a strong and statistically significant correlation with invasive FFR (Spearman ρ = 0.78; $P < .001$). A sensitivity analysis was performed in which the relationship between invasive FFR as the outcome of interest and both TAG_{320} and FFR_{CT} as predictor variables were examined by using linear mixed effects models; participant identity was included as a clustering variable to account for the fact that in some participant multiple vessels were analyzed. For TAG_{320} and FFR_{CT}, the respective coefficients were 0.00708 (95% confidence interval: 0.00493, 0.00924; $P < .001$) and 0.921 (95% confidence interval: 0.796, 1.05; $P < .001$). With Bland-Altman analysis, there was good agreement between FFR_{CT} and FFR, with a bias of −0.04 ± 0.08 (95% confidence interval: −0.19, 0.11).

Diagnostic Performance of CT Coronary Angiography, TAG_{320}, and FFR_{CT}

The diagnostic performance of CT coronary angiography, TAG_{320}, FFR_{CT}, TAG_{320} with CT coronary angiography, and FFR_{CT} with CT coronary angiography for diagnosis of hemodynamically significant stenoses is summarized in Table 3 and Figures 2 and 3. Examples of correlation are given in Figures 4 and 5. The ROC curve analysis for CT coronary angiography alone showed an AUC of 0.68 (P = .007). The sensitivity, specificity, positive predictive value, and negative predictive value were 79%, 59%, 44%, and 87%, respectively.

A TAG_{320} cut-off value of −15.37 HU per 10 mm was found to be optimal and yielded 14 true-positive and 50 true-negative findings and eight false-positive and 10 false-negative findings. The sensitivity, specificity, positive predictive value, and negative predictive value of TAG_{320} were 58%, 86%, 64%, and 83%, respectively. The ROC curve analysis for TAG_{320} demonstrated an AUC of 0.72 (P = .002), which was not found to be superior to the AUC of CT coronary angiography (0.72 vs 0.68; P = .67). The net reclassification index for TAG_{320} when compared with CT coronary angiography was 0.89 ± 0.24 (standard error; $P < .001$). When CT coronary angiography findings were combined with TAG_{320}, the AUC was 0.72, and sensitivity, specificity, positive predictive value, and negative predictive value were 45.8%, 98.3%, 91.7%, and 81.4%, respectively. There was modest but not statistically significant difference in AUC when CT coronary angiography with TAG was compared with CT coronary angiography alone (0.72 vs 0.69; P = .59).

Table 3

Per-Vessel Diagnostic Performance

Parameter	CT Angiography (≥50% Stenosis)	QCA (≥50% Stenosis)	TAG_{320} (≥15.37)	FFR_{CT} (≤0.80)	CT Angiography with TAG_{320}	CT Angiography with FFR_{CT}
True-positive finding	19	14	14	22	11	17
True-negative finding	34	48	50	46	57	49
False-positive finding	24	10	8	12	1	9
False-negative finding	5	10	10	2	13	7
Accuracy	64.6	75.6	78.0	82.9	82.9	80.5
Sensitivity	79.2 (57.3, 92.1)	58.3 (36.9, 77.2)	58.3 (36.9, 77.2)	91.7 (71.5, 98.5)	45.8 (26.2, 66.8)	70.8 (48.8, 86.6)
Specificity	58.6 (45.0, 71.1)	82.7 (70.1, 91.0)	86.2 (74.1, 93.4)	79.3 (66.3, 88.4)	98.3 (89.5, 99.9)	84.5 (72.1, 92.2)
Positive predictive value	44.2 (29.4, 60.0)	58.3 (36.9, 77.2)	63.6 (40.8, 82.0)	64.7 (46.5, 79.7)	91.7 (59.8, 99.6)	65.4 (44.4, 82.1)
Negative predictive value	87.2 (71.8, 95.2)	82.8 (70.1, 91.0)	83.3 (71.0, 91.3)	95.8 (84.6, 99.3)	81.4 (70.0, 89.4)	87.5 (75.3, 94.4)
AUC	0.69	0.75	0.72	0.93	0.72	0.78

Note.—There were 82 vessels used. Data in parentheses are 95% confidence intervals. QCA = quantitative coronary angiography.

Figure 3

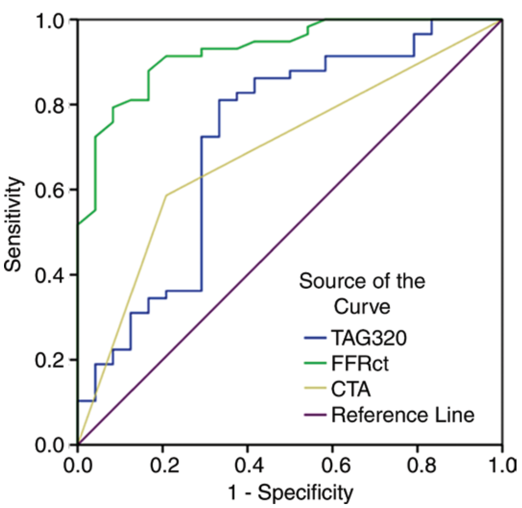


Figure 3: AUCs of CT angiography *(CTA)*, TAG_{320}, and FFR_{CT}, with a reference line for comparison.

By using a FFR_{CT} threshold of 0.80 or less, the ROC curve analysis for FFR_{CT} demonstrated an AUC of 0.93 (P < .001), which was significantly superior to both CT coronary angiography (P = .008) and TAG_{320} (P = .003). This resulted in 22 true-positive findings, 46 true-negative findings, 12 false-positive findings, and two false-negative findings. Sensitivity, specificity, positive predictive value, and negative predictive value of FFR_{CT} were 92%, 79%, 65%, and 96%, respectively. The net reclassification index for FFR_{CT} compared with CT coronary angiography was 1.42 ± 0.24 (P < .001).The AUC for FFR_{CT} with CT coronary angiography was 0.78, with a sensitivity, specificity, positive predictive value, and negative predictive value of 71%, 85%, 65%, and 88%, respectively.

Interobserver Variability and Time Taken for TAG_{320} Analysis

The medium per-vessel time required for TAG_{320} analysis was 200 seconds (interquartile range, 118–276). Assessment of interobserver variability of TAG_{320} demonstrated an intraclass coefficient 0.985 (95% confidence interval: 0.961, 0.994). On the basis of Bland-Altman analysis, there was a mean variability of −0.06 ± 1.18, and the 95% limit of agreement was 2.37 to −2.25.

Discussion

This study demonstrates that FFR_{CT} derived from wide–detector row CT has superior correlation with invasive FFR compared with TAG_{320}, and that diagnostic performance of FFR_{CT} is superior to TAG_{320} and CT coronary angiography alone for the diagnosis of hemodynamically significant stenoses determined by invasive FFR in stable patients suspected of having coronary artery disease. FFR_{CT} also demonstrated a net reclassification index superior to TAG_{320} when both were compared with CT coronary angiography alone.

The diagnostic performance of TAG was reported (3,13,14) to differ when applied to CT images acquired by scanners with varied longitudinal coverage. Previous work (13,14) demonstrated that the diagnostic accuracy of TAG derived from 64– and 256–detector row CT coronary angiography acquisitions was not significantly different from CT coronary angiography alone and inferior to FFR_{CT}, while the results based on single center studies by using 320–detector row CT coronary angiography to date showed the most

Figure 4

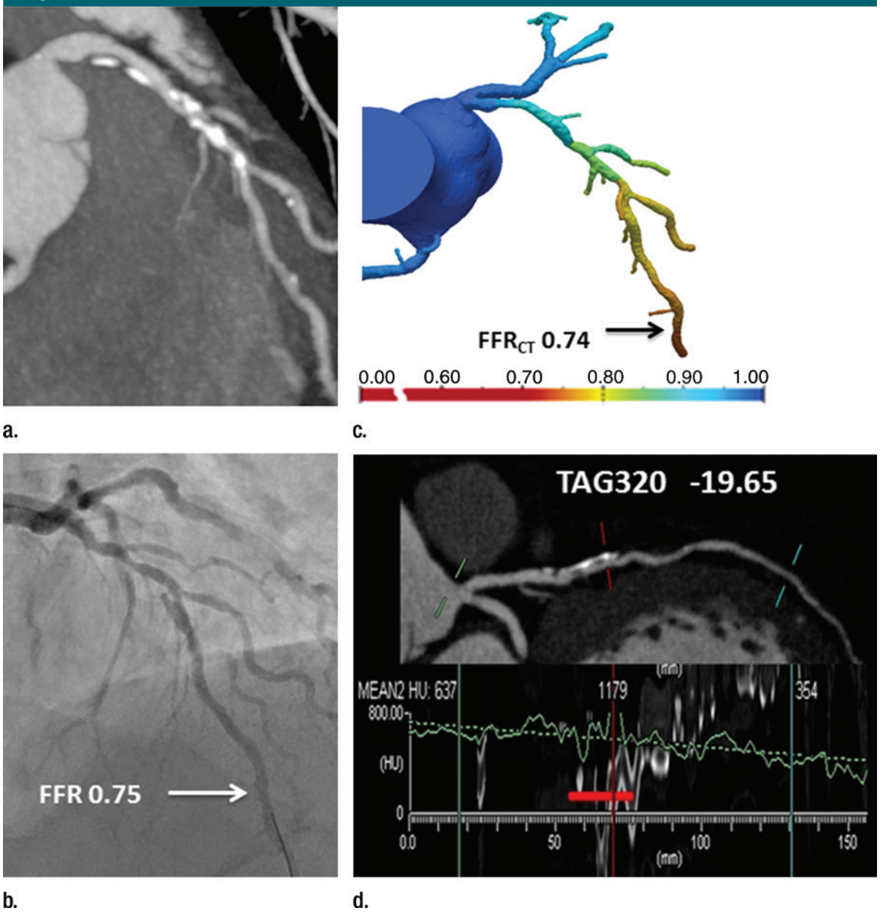


Figure 4: Case example demonstrating correlation of FFR_{CT} and TAG_{320} with invasive FFR. On **(a)** CT angiography, there was a stenosis greater than 70% in the proximal and mid left anterior descending artery, which was **(b)** 50% on invasive coronary angiography with FFR of 0.75 (arrow). The **(c)** FFR_{CT} was 0.74 (arrow), and **(d)** TAG_{320} was −19.65.

promise. Wong et al (3) reported in a retrospective single-center cohort of 54 patients, including 78 vessels, that TAG_{320} detected FFR of 0.80 or less with a per-vessel sensitivity of 77%, specificity of 74%, and AUC of 0.81. The accuracy of the technique further improved when added to CT coronary angiography alone with a AUC of 0.88 (3), and the combined approach was shown to have comparable accuracy to combined rest CT coronary angiography and stress CT myocardial perfusion imaging (15). The superior results derived from TAG_{320} may be related to the ability of the 320–detector row CT scanner to image the entire heart volume in a single gantry rotation, hence enabling near-isophasic, single-beat imaging of the entire coronary tree. Comparison of the diagnostic performance of FFR_{CT} derived from wide–detector row CT and TAG_{320}, to our knowledge, has not been reported thus far.

This study compares the diagnostic performance of TAG_{320} with FFR_{CT} derived from wide–detector row CT in a cohort of patients recruited from multiple international centers. Our results demonstrate that the overall accuracy of both FFR_{CT} and TAG_{320} is higher than CT coronary angiography alone (TAG_{320}, 78%; FFR_{CT}, 83%; CT coronary angiography, 65%). While the overall accuracy reported for TAG_{320} and FFR_{CT} are similar, comparison of AUC and net reclassification indexes in this study indicate that the diagnostic performance of FFR_{CT} is superior to TAG_{320}.

The superior diagnostic performance may relate to the superior correlation of FFR_{CT} with invasive FFR versus that observed for TAG_{320}, which may relate to the way in which each technique is derived. FFR_{CT} permits the computation of pressure, flow, and FFR along the entire coronary tree. Assumptions are made for conditions of maximal hyperemia and minimal microvascular resistance, which mimics invasive FFR (5). However, TAG_{320} has been postulated to be a surrogate of resting coronary blood flow, based on in vitro observations (16) and in vivo studies which demonstrated its relationship with resting Thrombolysis in Myocardial Infarction (known as TIMI) grade flow and stenosis severity on invasive angiography (10,17,18). In the absence of maximal hyperaemia, TAG_{320} may be influenced by both epicardial and microvascular resistance and hence a linear relationship between flow and pressure cannot be assumed.

Three large multicenter observations trials have thus far evaluated the performance of FFR_{CT} compared with invasive FFR (4,6,7). The most recent NXT study demonstrated a per-vessel sensitivity, specificity, positive predictive value, and negative predictive value of 84%, 86%, 61%, and 95%, respectively, by using images acquired with CT scanners that had varied longitudinal coverage, including 64–, 128–, 256– and 320–detector row CT (4). The results derived from this subset of NXT patients demonstrate consistent per-vessel diagnostic performance of FFR_{CT} evaluated by using wide–detector row CT, reported in the entire NXT cohort, which suggests that the diagnostic performance FFR_{CT} may not be affected by the longitudinal coverage of CT scanners.

Comparable with the findings of the previous single center studies evaluating TAG_{320} (3,15), our results demonstrate that TAG_{320} has a higher accuracy than CT coronary angiography alone, which are driven by improvements in specificity and positive predictive value.

Figure 5

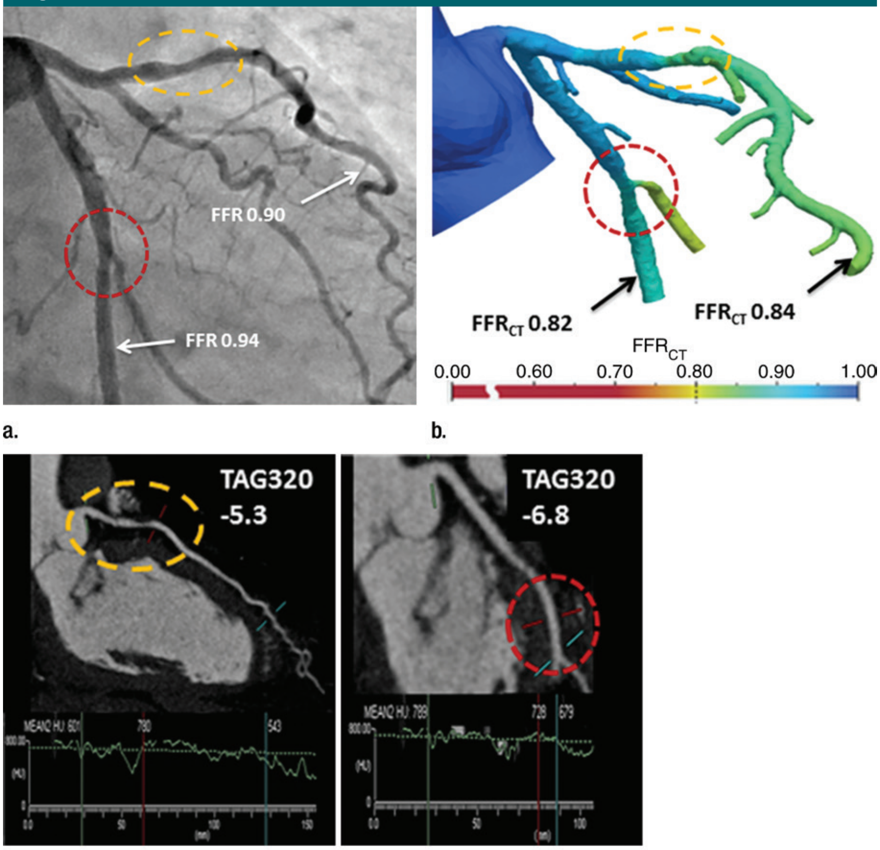


Figure 5: Case example that demonstrates correlation of FFR_{CT} and TAG_{320} with invasive FFR. **(a)** On invasive coronary angiography, there was a 50% stenosis in the proximal left anterior descending artery (yellow circle). FFR was 0.90 in the distal left anterior descending. In the mid left circumflex artery (arrow), there was a 25% stenosis (red circle). The FFR was 0.94 (arrows). The corresponding FFR_{CT} was 0.84 and 0.82 (arrows in **b**); and the TAG_{320} was −5.3 and −6.8, respectively (**c**). The dashed regions represent the lesion.

However, the sensitivity of TAG_{320} in this study was 58%, which is lower than reported in two previous studies (the previous studies had sensitivities of 77% and 71%) (3,15).

The observed lower sensitivity of TAG_{320} may relate to the technique by which TAG_{320} was performed in this study. Earlier studies reported the use of a manual technique in which the Hounsfield units were sampled along a vessel's centerline at 5-mm intervals. TAG_{320} was determined in this study by using a semiautomated method in which Hounsfield units are sampled at 1-mm intervals and the most distal point of the vessel in which Hounsfield units were sampled was guided by automated luminal contouring. As a result, the number of vessels in which TAG can be evaluated significantly increased; for example, only two of 84 vessels were excluded compared with 30 of 127 vessels in a previous study (15). However, algorithmic errors in luminal contouring may result in premature cessation in Hounsfield unit sampling in the distal vessel, which can result in an overestimation of TAG to be less negative and potentially associated with a larger number of false-negative results.

Previous studies suggested that the presence of stenosis greater than 50% on CT coronary angiography images may be an important gatekeeper to defer invasive angiography and revascularization. This is on the basis of the observation that the presence of stenosis greater than 50% may have high sensitivity and negative predictive value for FFR of 0.80 or less (2,19). The specificity and positive predictive value for FFR of 0.80 or less is limited; therefore, in practice, patients who have been identified with stenoses severity of 50% or greater on CT coronary angiography often require noninvasive functional testing to assess for burden of ischemia before referral for invasive angiography and revascularization. For this reason, the diagnostic performance of TAG_{320} and FFR_{CT} when they are applied in the presence of a CT coronary angiography stenosis of greater than 50% was evaluated. The sensitivity and negative predictive value of CT coronary angiography alone for FFR of 0.8 or less in this cohort was comparatively lower (79% and 86%, respectively) than reported in previous work. This may explain the lack of significant difference between the diagnostic performance of CT coronary angiography and CT coronary angiography with TAG_{320} or CT coronary angiography with FFR_{CT}. Indeed, the AUC for TAG_{320} with CT coronary angiography was equivalent to TAG alone (AUC, 0.72), and FFR_{CT} with CT coronary angiography was inferior to FFR_{CT} alone (0.93 vs 0.78, respectively).

This study had limitations. It is a multicenter, retrospective analysis of a prospectively enrolled cohort. Therefore, the relatively small number of study patients may not provide definite evidence for the superior diagnostic performance of FFR_{CT} compared with TAG. Moreover, patients who underwent clinically indicated invasive coronary angiography and FFR as well as CT coronary angiography were enrolled in this study. Therefore, the ability to assess the diagnostic performance of FFR_{CT} and TAG in all-comer consecutive patients undergoing CT coronary angiography is not possible. Finally, opacification of coronary artery lumen and luminal contrast attenuation with CT coronary angiography can be influenced by contrast iodine concentration, contrast agent infusion rate, volume of contrast agent, timing of image acquisition,

and cardiac output. Differences in contrast agent administration protocols of each center may affect the overall diagnostic performance of TAG_{320} in this multicenter study.

On the basis of the results acquired by using wide–detector row CT in our cohort of patients, noninvasive FFR derived from typically acquired CT coronary angiography images (ie, FFR_{CT}) provides better diagnostic performance to detect and exclude hemodynamically significant coronary artery lesions compared with gradient of transluminal radiologic attenuation (ie, TAG_{320}) or visual stenosis grade on CT coronary angiography.

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