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Atherosclerotic Plaque Characteristics by CT Angiography Identify Coronary Lesions That Cause Ischemia: a Direct Comparison to Fractional Flow Reserve

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Abstract

Objective—We evaluated the association between atherosclerotic plaque characteristics (APCs) by coronary CT angiography (CT) and lesion ischemia by fractional flow reserve (FFR).

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Background—FFR is the gold standard for determining lesion ischemia. While APCs by CT—including aggregate plaque volume % (%APV), positive remodeling (PR), low attenuation plaque (LAP) and spotty calcification (SC)—are associated with future coronary syndromes, their relationship to lesion ischemia is unclear.

Methods—252 patients (17 centers, 5 countries) [mean age 63 years, 71% males] underwent CT, with FFR performed for 407 coronary lesions. CT was interpreted for < and >50% stenosis, with the latter considered obstructive. APCs by CT were defined as: (1) PR, lesion diameter/reference diameter >1.10; (2) LAP, any voxel <30 HU; and (3) SC, nodular calcified plaque <3 mm. Odds ratios (OR) and net reclassification improvement (NRI) of APCs for lesion ischemia, defined by FFR <0.8, were analyzed.

Results—By FFR, ischemia was present in 151 lesions (37%). %APV was associated with a 10% increased risk of ischemia per 5% additional APV. PR, LAP and SC were associated with ischemia, with a 3-5 times higher prevalence than in non-ischemic lesions. In multivariable analyses, a stepwise increased risk of ischemia was observed for 1 [OR 4.5, p<0.001)] and ≥2 (OR 13.2, p<0.001) APCs. These findings were APC-dependent, with PR (OR 5.4, p<0.001) and LAP (OR 2.2, p=0.028) associated with ischemia, but not SC. When examined by stenosis severity, PR remained a predictor of ischemia for all lesions, while %APV and LAP were associated with ischemia for only >50% but not for <50% stenosis.

Conclusions—%APV and APCs by CT improve identification of coronary lesions that cause ischemia. PR is associated with all ischemia-causing lesions, while %APV and LAP are only associated with ischemia-causing lesions >50%.

Keywords

coronary plaque; fractional flow reserve; coronary computed tomography angiography; myocardial ischemia; coronary artery disease

INTRODUCTION

Fractional flow reserve (FFR) enables physiologic assessment of coronary lesions at the time of invasive coronary angiography (ICA), and is the gold standard for identification of lesions that cause ischemia (1). Prior studies have demonstrated the importance of FFR, with identification of ischemia-causing lesions associated with worsened survival, and with FFR-guided revascularization enhancing event-free survival (2). Use of FFR has established stenosis severity as an unreliable indicator of ischemia, with approximately half of high-grade stenoses manifesting no ischemia. Conversely, a significant proportion of non-obstructive lesions cause ischemia by FFR (3), emphasizing the importance of other factors beyond stenosis as critical to lesion-specific ischemia.

By invasive and pathologic studies, high-risk anatomic plaque features have been established as fundamental to the processes of acute coronary syndromes (ACS) and sudden cardiac death (4). For these lesions, several common characteristics are shared, including plaque burden, thin-cap fibroatheroma, positive arterial remodeling, necrotic cores, spotty calcifications, and macrophage infiltration (5). Prior invasive data have observed the majority of plaques implicated in ACS to be non-obstructive in anatomic stenosis severity—

with high-grade stenoses comprising less than 1/3 of culprit lesions—and have emphasized the need for improved methods beyond stenosis for identification of high-risk plaques (6). To date, the precise relationship of these plaque features to coronary lesion-specific ischemia remains unstudied.

Recently, coronary CT angiography (CT) has emerged as a non-invasive method for accurate detection and exclusion of high-grade coronary stenoses, when compared to an ICA reference standard. In addition to luminal diameter narrowing, CT also enables assessment of several coronary atherosclerotic plaque characteristics with high accuracy; including aggregate plaque volume (APV), positive arterial remodeling (PR); low attenuation plaque (LAP) as a marker for necrotic lipid laden intra-plaque core; and spotty intra-plaque calcification (SC) (7). Similar to invasive studies by intravascular ultrasound (IVUS), these CT characteristics have been associated with culprit lesions in retrospective and prospective cohorts (8,9).

Yet, the physiologic mechanisms underlying these findings remain ill-defined. To this end, whether APCs by CT are associated with specific coronary lesions that cause ischemia remains unknown. In a prospective international multicenter study, we thus examined the relationship between APCs by CT and lesion-specific ischemia by FFR.

METHODS

Study population

We studied 252 consecutive stable patients (178 men and 74 women, mean age: 62.9 ± 8.7 years) and 407 coronary lesions from the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) study [NCT01233518], which was performed prospectively at 17 centers in 5 countries (Belgium [n=1], Canada [n=1], Latvia [n=1], South Korea [n=2], and United States [n = 12]) (10). Enrolled patients were adults with suspected CAD who underwent clinically indicated invasive coronary angiography after CT within 60 days with no intervening coronary event. Exclusion criteria included: prior coronary artery bypass graft surgery; prior percutaneous coronary intervention with suspected in-stent restenosis based upon CT findings; contraindication to adenosine; suspicion of or recent acute coronary syndrome; complex congenital heart disease; prior pacemaker or defibrillator; prosthetic heart valve; significant arrhythmia; serum creatinine level greater than 1.5 mg/dL; allergy to iodinated contrast; pregnant state; body mass index greater than 35 (calculated as weight in kilograms divided by height in meters squared); evidence of active clinical instability or life-threatening disease; or inability to adhere to study procedures. In this study, 33 patients were excluded [non-evaluable CT scans, n=31; unresolvable integration of FFR wire transducer location by ICA to corresponding location on CT, n=2].

ICA and FFR measurements

Selective ICA was performed by standard protocol in accordance with societal guidelines, with a minimum of 2 projections obtained per vessel distribution and with angles of projection optimized based on the cardiac position. ICAs were evaluated by quantitative

coronary angiographic (QCA) stenosis severity using a blinded angiographic core laboratory (University of British Columbia, Vancouver, Canada) using commercially available software (Discovery Quinton). FFR was performed at the time of ICA (PressureWire Certus, St Jude Medical Systems; ComboWire, Volcano Corp). Investigators performed FFR in vessels deemed clinically indicated for evaluation, demonstrating an ICA stenosis between 30% and 90%. After administration of nitroglycerin, a pressure-monitoring guide wire was advanced distal to a stenosis. Hyperemia was induced by administration of intravenous or intracoronary adenosine at a rate of 140μg/kg per minute. Fractional flow reserve was calculated by dividing the mean distal coronary pressure by the mean aortic pressure during hyperemia. FFR at a threshold of 0.80 or less was considered hemodynamically significant and causal of ischemia.

CT performance, image reconstruction and evaluation

CT was performed using 64–detector row or higher scanners with prospective or retrospective electrocardiographic gating in accordance with the Society of Cardiovascular Computed Tomography guidelines. Approximately 80-100cc of intravenous contrast, followed by 50–80 ml of saline, was administered at a rate of 5 ml/s via a power injector through an antecubital vein. Scanning parameters included heart-rate-dependent pitch (0.2 to 0.45), 330 ms gantry rotation time, 100 kVp or 120 kVp tube voltage, and 350-800 mA tube current. Estimated radiation dose for CTs ranged between 2-10 mSv.

CTs were reconstructed using the following parameters: 0.5-0.75-mm slice thickness, 0.3-mm slice increment, 160-250 mm field of view, 512 x 512 matrix, and a standard kernel. Optimal phase reconstruction was assessed by comparison of different phases, if available, and the phase with the least amount of coronary artery motion was chosen for analysis. Multiple phases were utilized for image interpretation if minimal coronary artery motion differed among the various arteries. All CTs were interpreted in an intention-to-diagnose fashion.

Independent level III-experienced readers blinded to clinical, ICA, and FFR results analyzed all of the CTs. CT analysis was performed on dedicated 3D workstations (Ziosoft, Redwood City, CA; Advantage AW Workstation, GE Healthcare, Milwaukee, WI). CTs were evaluated by an array of post-processing techniques, including axial, multiplanar reformat, maximum-intensity projection, and short-axis cross-sectional views. In each coronary artery segment, coronary atherosclerosis was defined as tissue structures ≥1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself.

Coronary arteries and branches were categorized into 1 of 4 vascular territories: left main artery (LM), left anterior descending artery (LAD), left circumflex artery (LCx) and right coronary artery (RCA); diagonal branches, obtuse marginal branches and posterolateral branches were considered as part of the LAD, LCx and RCA system, respectively. The posterior descending artery was considered as part of the RCA or LCx system, depending upon the coronary artery dominance.

Qualitative coronary atherosclerotic plaque characteristics (APCs)—including PR, LAP and SC—were evaluated for coronary lesions directly interrogated by FFR. Stenosis severity was graded in accordance with societal guidelines, and categorized as 0%, 1-29%, 30-49%, 50-69% and ≥70% . A remodeling index (RI) was defined as a maximal lesion vessel diameter divided by proximal reference vessel diameter, with positive remodeling (PR) defined as a RI ≥ 1.1. LAP was defined as any voxel <30 Hounsfield units within a coronary plaque. SC was defined by an intra-lesion calcific plaque <3 mm in length that comprised <90° of the lesion circumference.

Quantitative coronary atherosclerotic plaque analysis was performed using semiautomated plaque analysis software (QAngio CT Research Edition v2.02; Medis medical imaging systems, Leiden, The Netherlands), which has been previously validated for accuracy . Lesion length, lumen area stenosis (AS), plaque volume, and percent aggregate plaque volume (%APV) were measured. As we have previously described, aggregate plaque volume was measured from the coronary artery ostium to the distal end of the lesion. %APV was defined as the aggregate plaque volume divided by the total vessel volume (11).

Direct comparison of FFR to APCs was performed at the precise location of the wire transducer at the time of FFR. To maintain blinding, an Integration Core Laboratory (Minneapolis Heart Institute, MN) was used. The Integration Core Laboratory identified the location on CT that corresponded to the point where the FFR was measured. The location was communicated to the CT imagers by an arrow on a 3D volume rendered CT image of the coronary arteries.

Statistical methods

Continuous variables were compared by use of an unpaired t-test for normally distributed variables or by the Mann-Whitney U test for non-normally distributed variables. Categorical variables were examined by Pearson's chi-square or Fisher's exact test, as appropriate. Demographics of the study sample are reported as mean ± SD for continuous variables, and by counts with proportions for categorical variables. FFR measurements were recorded on a continuous scale and dichotomized at a threshold of 0.80, with values ≤0.80 considered hemodynamically significant and causal of ischemia. High-grade stenosis by CT was dichotomized at the 50% threshold, with a stenosis ≥50% considered obstructive.

Global chi-square analyses utilized logistic regression and a likelihood ratios test. In order to account for the correlation of coronary artery segments within patients in an unbalanced design, a random effects model using a maximum likelihood logit model for panel data was applied, wherein the binary outcome value of FFR ≤0.80 was modeled using a binomial distribution and a logit link function, with the individual patient serving as the random component. Univariable and multivariable odds ratio (OR) estimates with 95% confidence intervals (95% CI) utilizing a random effects model were employed to evaluate predictors of ischemia . Further, a category-free net reclassification improvement (NRI) of APCs was obtained using the resultant predicted probabilities of the random effects logit models predicting ischemia where model 1 consisted of CT stenosis ≥50% or <50%, and model 2 comprised model 1 plus any individual APC (e.g., PR, LAP or SC) . Area under the receiver operating characteristic curve (AUC) models were employed to evaluate the discrimination

of ischemia using the method proposed by DeLong et al. Category-free NRIs were calculated using a SAS macro. Statistical tests were 2-tailed, with a significance level set at $p < 0.05$.

RESULTS

Baseline characteristics of the study population are listed in **Table 1**. Of 407 lesions, the mean FFR value was 0.82 ± 0.13. Overall, 215 (53%) lesions were found to be obstructive (CT stenosis ≥ 50%), while 192 (47%) lesions were non-obstructive.

Relationship of APCs characteristics by CT to lesion-specific ischemia by FFR

As compared to non-ischemia causing lesions, coronary artery lesions that caused ischemia, consisted of a higher stenosis, longer lesion length; larger plaque volume; higher %APV; and higher rates of PR, LAP and SC (**Table 2**). These findings were observed for both >50% and <50% stenosis. As compared to lesions that did not cause ischemia, those that did were associated with a 11-, 13- and 4-fold higher prevalence of PR, LAP and SC, respectively (**Table 3**). Likewise, increasing numbers of APCs were observed within ischemic lesions compared with non-ischemic lesions, with 1 and >2 APCs associated with a 7- and 20-fold higher odds of lesion-ischemia. Other quantitative measures of plaque burden—including lumen area stenosis, lesion length, plaque volume and %APV—were also associated with lesion ischemia.

In multivariable analyses, obstructive stenosis, lesion length, PR and LAP were associated with ischemia, but SC was not **[Table 3 (Model 1)]**. Independent of lumen area stenosis and lesion length, the presence of or more than 2 APCs was associated with 13-fold increased odds of ischemia **[Table 3 (Model 2)].** When considering either specific APCs or number of APCs, %APV was an independent predictor of lesion-specific ischemia independent of obstructive stenosis severity, and provided incremental discriminatory power when added to APCs and CT stenosis **[Table 3 (Models 3 and 4) and Figure 1].**

Relationship of APCs to lesion-specific ischemia stratified by coronary artery stenosis severity

Table 2 describes FFR and APC prevalence for ischemic versus non-ischemic lesions, stratified by obstructive versus non-obstructive stenoses. For ≥50% and <50% stenoses, ischemia was observed in 119 of 215 (55%) and 32 of 192 (17%) lesions, respectively. PR, LAP, SC and increasing numbers of intra-plaque APCs were associated with ischemia for both >50% and <50% stenotic coronary lesions. In multivariable analyses, lumen area stenosis (per 5%), lesion length, PR and % APV were associated with ischemia for both >50% and <50% stenotic lesions, while LAP and %APV (per 5%) were associated with ischemia only for lesions >50% stenosis. SC was not associated with ischemia for both >50% and <50% stenotic lesions **(Table 4)**. Compared with the base model of AS alone, the AUC displayed further discriminatory value towards prediction of ischemia by invasive FFR when %APV and subsequently, APCs, were added **(Figure 2)**.

Net reclassification improvement of ischemic lesions

Individual APCs were associated with improved reclassification of lesions that cause ischemia for PR (NRI 0.97, 95% CI 0.80-1.15, p <0.001), LAP (NRI 0.92, 95% CI 0.74-1.09, p <0.001), and SC (NRI 0.35, 95% CI 0.19-0.51, p=0.0006). Similarly, an increasing number of APCs enabled effective reclassification of ischemic lesions for CT stenoses ≥50% for 1 APC (NRI 0.79, 95% CI 0.61-0.97, p <0.001) and ≥2 APCs (NRI 0.79, 95% CI 0.61-0.97, p <0.001). These findings remained robust when QCA substituted CT for determining stenosis severity. An example of a non-obstructive yet ischemia-causing coronary artery lesion possessing PR, LAP and SC is depicted in **Figure 3**. An example of an obstructive non-ischemia-causing coronary artery lesion that does not possess PR, LAP or SC is depicted in **Figure 4**.

DISCUSSION

We identified an independent association between quantitative and qualitative measures of atherosclerosis—by %APV and APCs—and ischemia-causing coronary lesions confirmed by FFR. We observed higher %APV, longer lesion length and increasing prevalence of APCs within ischemic lesions of higher stenosis severity, a finding that was more pronounced for lesions of higher angiographic stenosis. Furthermore, we observed a strong relationship between APC number and type—particularly for PR—and lesion-specific ischemia even amongst non-obstructive lesions that do not meet conventional thresholds of angiographically severe. Importantly, the absence of APCs identified lesions with a considerably lower prevalence of ischemia, even for highly stenotic coronary lesions. To our knowledge, these data represent the first to examine the quantitative as well as qualitative relationship of APCs by CT for precise identification of coronary lesions that do versus do not cause ischemia.

The relationship observed between stenosis and ischemia in the present study is in accordance with prior published reports. In the multicenter FAME trial, 20% of lesions ≥70% did not cause ischemia, a rate that is paralleled in the present study (1). Distinct from FAME, we also interrogated lesions that were <50% stenosis, and observed a 17% rate of ischemia (3). Given the relationship of ischemic lesions by FFR to future adverse events and the improved event-free survival for revascularization based upon FFR guidance, these data suggest the need for alternative factors beyond stenosis alone for enhancing the diagnosis of ischemic lesions (1,12,13).

We identified a distinct relationship between specific APCs and ischemia, independent of stenosis severity. Specifically, PR was associated with higher rates of ischemic lesions in both obstructive and non-obstructive stenoses. It is that this finding represents a point in the development of an atheroma wherein the lesion-specific burden exceeds a certain threshold that results in compensatory remodeling. Yet prior post-mortem studies where PR has demonstrated a correlation to luminal stenosis than plaque size, and our study both corroborate as well as advance these findings. Indeed, PR was a better predictor of ischemia in lesions of >50% and <50% stenosis, while plaque size (as measured by %APV and lesion length) were only predictive of ischemia in >50% stenosis. Interestingly, both in our study as well as the prior post-mortem study, the relationships between luminal stenosis and PR in

the arterial system were highly heterogeneous, suggesting a mechanism that cannot be fully deciphered by morphologic evaluation alone.

We also identified a relationship between LAP—a CT surrogate for necrotic lipid core—and lesion-specific ischemia (14). This relationship—similar to %APV and lesion length—was present only for lesions >50%. While it is tempting to conjecture that these lesions represent atheromas in a more advanced stage of their development, only future serial evaluation studies will be able to determine this. However, the presence of necrotic core has been related to endothelial dysfunction, which depresses coronary vasodilation and accentuates myocardial hypoperfusion (15-17). At the phenotypic level, the size of a lipid cores by intravascular methods has been associated with reduced myocardial blood flow, and our study results reinforce these findings.

We observed SC to allow reclassification but not prediction of ischemic lesions. These findings may be considered discordant with prior studies (18), which observed SC to be associated with ACS. This lack of prediction of ischemia by SC may be explained by a multitude of reasons. First, while these calcifications are small, the microcalcifications associated with pathologically-confirmed high risk plaque are beyond the detection of CT imaging. Thus, SC may represent a later stage in the evolution of an atheroma that proceeds ischemia production. Also, the presence of SC may reflect a form of “pseudo-disease,” wherein this feature may track with other morphologic characteristics (such as PR or LAP) but does not cause ischemia. In our study, quantitative metrics of atherosclerotic burden—using lesion length and %APV—were useful to discriminate lesions that caused ischemia, albeit restricted to lesions >50%. These findings confirm prior FFR and CT studies that have documented the importance of diffuse disease identification for diagnosis of ischemia. De Bruyne related abnormal coronary resistance and reduced hyperemic in arteries with diffuse atherosclerosis, a finding corroborated by our group in non-stenotic lesions. It is notable to mention that APCs embedded within any specific plaque represent that lesion alone, without consideration of the amount of myocardium that is subtended by this vessel. Future studies addressing the relationship between APCs and perfusion may be helpful to further elucidate the clinical utility of APCs.

Finally, the relationship of plaque burden and APCs is dose-dependent. And while it remains possible that collinearity exists amongst some of these variables, the co-existence of these features together likely represent an atheroma that is at higher risk of producing ischemia, and potentially of future events.

To date, the preponderance of studies evaluating APCs by CT have been related to ACS rather than to ischemia (8,9,19,20). These studies suggest a correlation between APCs and ACS, with APCs by CT—particularly PR and LAP—associated with future acute rather than stable events. In a prospective evaluation of 1059 patients undergoing CT, Motoyama associated plaques with PR and LAP with future ACS (9). The incremental value of APCs beyond stenosis was further confirmed by Kristensen et al., who observed in 312 patients presenting with ACS that increased non-calcified plaque within non-obstructive lesions was associated with an increased risk of recurrent adverse cardiac events, although the degree of PR or LAP was not specifically examined (21).

At present, interpretation of CT is based primarily on stenosis, a method advocated by societal guidance documents (22). Our study results reinforce a notion that stenosis is insufficient for the identification of specific coronary lesions that are implicated in the cause of ischemia (3) and, given the ability of %APV and APCs to independently improve discrimination of ischemia-causing coronary lesions—coupled with their association with incident ACS risk—consideration should be given to include these features in clinical reporting. Recently, other physiologic measures of CAD by CT have emerged, including fractional flow reserve derived from CT (FFR_{CT}) (23). Whether APCs augment the prediction of lesion-specific ischemia in a manner incremental to FFR_{CT} remains unknown, but future study of this concept is needed.

Study limitations

This study is not without limitations. While prior studies have observed CT APCs to be concordant with IVUS for measures of arterial remodeling, necrotic cores, and spotty calcifications, CT is limited in resolution, and the accuracy of CT measures may have affected study results. Due to spatial resolution, CT cannot identify TCFA, a feature vital to the coronary disease process. While it is unknown whether TCFA is directly associated with lesion ischemia, APCs by CT in this study are associated with TCFA when compared to optical coherence tomography, and may help explain our study findings (24). Further, the vessels interrogated by FFR were limited to those deemed clinically indicated. Thus, a potential bias of selection cannot be disencumbered from the present study, and all results presented herein should be considered hypothesis-generating. In addition, it is possible that the presence of atherosclerosis in other coronary vessels may have influenced the presence of ischemia in the FFR-interrogated vessel, and this premise could not be adequately tested.

CONCLUSIONS

Independent and incremental to stenosis severity, plaque burden and APCs by CT improve identification, discrimination and reclassification of coronary artery lesions that cause ischemia.

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Abbreviations list

ACS	acute coronary syndrome
APC	atherosclerotic plaque characteristics
CI	confidence interval
CT	coronary computed tomographic angiography
FFR	fractional flow reserve
ICA	invasive coronary angiography

IVUS	intravascular ultrasound
NRI	net reclassification improvement
OR	odds ratio
QCA	quantitative coronary angiographic
TCFA	thin cap fibroatheroma

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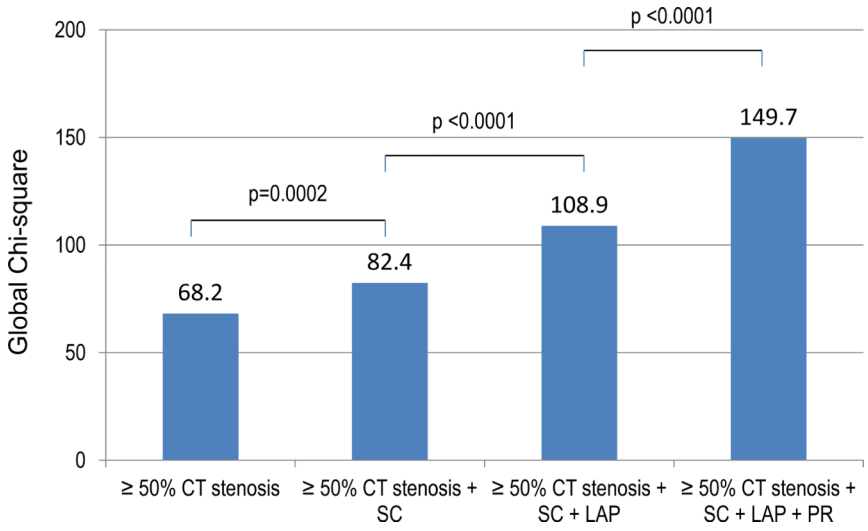

Figure 1. Global chi-square values

Incremental risk prediction beyond CT stenosis ≥50% when adding spotty calcification (SC); SC and low attenuation plaque (LAP); and SC, PR and positive arterial remodeling (PR).

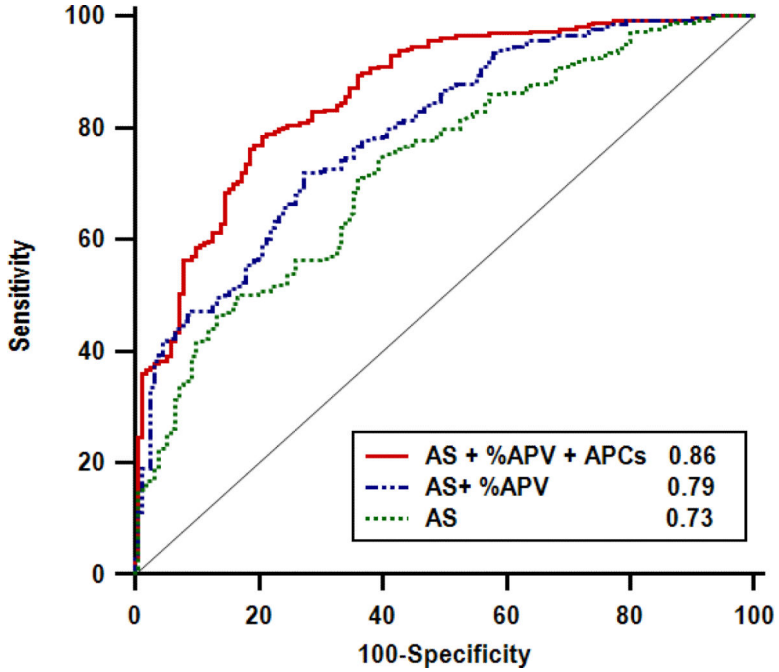

Figure 2. AUC for detecting FFR

AUC values gradually improving up to 0.79 (AS+%APV, p<0.001), and 0.86 (AS+%APV +APCs, p<0.001) respectively when %APV and APCs combined serially into AS. AUC = Area under the receiver operating curves, FFR = fractional flow reserve, AS = lumen area stenosis (%), %APV = percent aggregate plaque volume, APCs = atherosclerotic plaque characteristics.

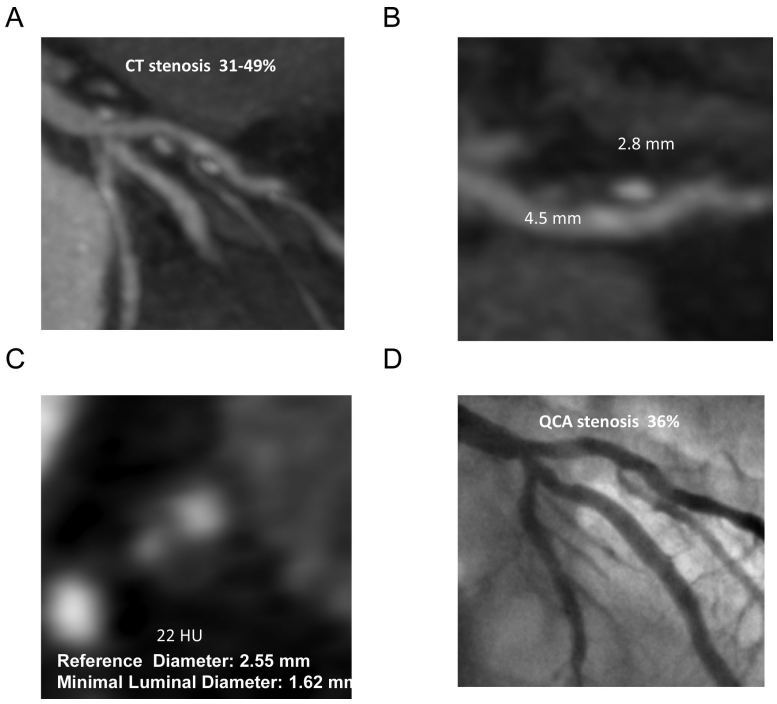

Figure 3. Non-obstructive coronary stenosis causing ischemia

(A) Arterial segment demonstrating no luminal compromise but significant atherosclerosis. (B) Multiplanar reformat demonstrating positive remodeling and spotty calcification. (C) CT cross section demonstrating low attenuation plaque [22 Hounsfield Units (HU)]. (D) Corresponding invasive angiogram demonstrating a 36% stenosis in the left anterior descending artery. The FFR value was 0.76 indicating ischemia. FFR = fractional flow reserve, QCA = quantitative coronary angiography.

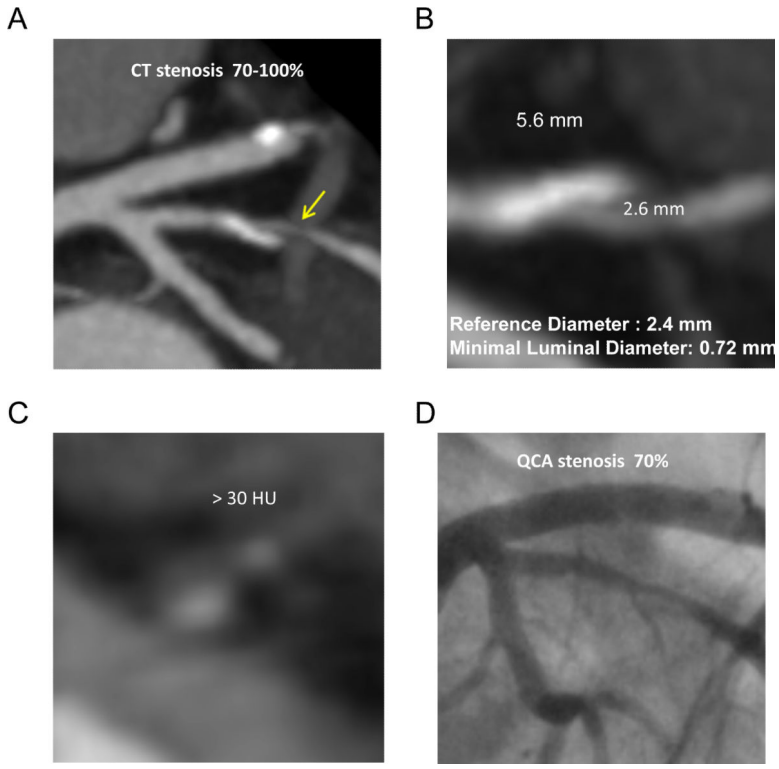

Figure 4. Obstructive coronary stenosis does not cause ischemia

(A) Arterial segment demonstrating significant luminal compromise. (B) Multiplanar reformat demonstrating no positive remodeling (remodeling index 1.08) and no spotty calcification. (C) CT cross section demonstrating no low attenuation plaque (>30 HU). (D) Corresponding invasive angiogram demonstrating a 70% stenosis in obtuse marginal branch of the circumflex artery. The FFR value was 0.89 indicating no ischemia. Abbreviations as in Figure 3.

Table 1

Baseline Characteristics of the Study Population

Characteristics	Number (%) of Patients
Age, mean ± SD	62.9 ± 8.7
Male gender	178 (71)
BMI, mean ± SD	26.8 ± 3.8
Race	
Caucasian	169 (67)
Other	83 (33)
Diabetes mellitus	53 (21)
Hypertension	179 (71)
Hyperlipidemia	201 (80)
Family history of coronary artery disease	50 (20)
Current smoker	44 (18)
Prior myocardial infarction	15 (6)
Prior PCI	16 (6)

BMI = body mass index, PCI = percutaneous coronary intervention.

Table 2

Lesion Characteristics

	Overall			Obstructive CT stenosis (≥50%) [n=215]			Non-obstructive CT stenosis (<50%) [n= 192]		
	FFR ≤ 0.8 Ischemic Group (n=151)	**FFR > 0.8 Non-ischemic Group (n=256)**	**P Value**	**FFR ≤ 0.8 Ischemic Group (n=119)**	**FFR > 0.8 Non-ischemic Group (n=96)**	**P Value**	**FFR ≤ 0.8 Ischemic Group (n=32)**	**FFR > 0.8 Non-ischemic Group (n=160)**	**P Value**
FFR	0.69 ± 0.11	0.90 ± 0.05	<0.0001	0.68±0.11	0.88±0.05	<0.0001	0.74±0.10	0.91±0.05	<0.0001
QCA stenosis (%)	57.1 ± 12.4	40.8 ± 13.8	<0.0001	59.2±11.2	48.1±12.3	<0.0001	49.4±13.6	36.5±12.9	<0.0001
Lesion length (mm)	30.1 ± 12.3	22.0 ± 10.8	< 0.001	30.8 ± 12.9	24.4 ± 11.8	< 0.001	27.3 ± 9.7	20.5 ± 9.9	< 0.001
Plaque volume (mm^3)	324.7 ± 210.4	206.0 ± 147.7	< 0.001	344.1 ± 220.1	244.7 ± 158.0	< 0.001	252.3 ± 151.5	182.7 ± 136.4	0.005
%APV	59.5± 11.4	52.6± 16.8	< 0.001	59.5 ± 8.2	55.1 ± 20.5	< 0.001	59.5 ± 19.2	51.1 ± 14.0	< 0.001
Reference vessel diameter (mm)	3.1 ± 0.9	3.1 ± 0.6	0.9	3.2±0.9	3.1±0.6	0.50	2.9±0.5	3.0±0.6	0.12
PR	121 (80%)	72 (28%)	< 0.001	97 (82%)	39 (41%)	<0.001	24 (75%)	33 (21%)	<0.001
LAP	66 (44%)	24 (9%)	< 0.001	58 (49%)	16 (17%)	<0.001	8 (25%)	8 (5%)	<0.001
SC	42 (28%)	26 (10%)	< 0.001	33 (28%)	13 (14%)	0.01	9 (28%)	13 (8%)	0.001
0 APC's	25 (17%)	173 (68%)	<0.001	18 (15%)	50 (52%)	<0.001	7 (22%)	123 (77%)	<0.001
1 APC	48 (32%)	52 (20%)	0.009	37 (31%)	29 (30%)	0.89	11 (34%)	23 (14%)	0.007
2 APCs	53 (35%)	23 (9%)	<0.001	41 (35%)	12 (13%)	<0.001	12 (38%)	11 (7%)	<0.001
3 APCs (overall p)	25 (17%)	8 (3%)	<0.001 (<0.001)	23 (19%)	5 (5%)	0.002 (<0.001)	2 (6%)	3 (2%)	0.16 (<0.001)

PR = positive remodeling; LAP = low attenuation plaque; SC = spotty calcification; APC = atherosclerotic plaque characteristic; %APV = percent aggregate plaque volume.

Table 3

Univariable and multivariable analysis of APCs for Ischemia detection

Univariable		
Variables	**OR (95% CI)**	**P Value**
CT stenosis ≥50%	8.7 (4.2-18.1)	<0.001
Lumen area stenosis (per 5%)	1.4 (1.2-1.5)	<0.001
Lesion length (mm)	1.1 (1.04-1.09)	<0.001
Plaque volume (per 10mm^3)	1.04 (0.03-1.06)	<0.001
% APV (per 5%)	1.3 (1.1-1.5)	<0.001
PR	10.5 (5.9-18.8)	<0.001
LAP	12.9 (5.4-30.9)	<0.001
SC	3.9 (2.0-7.4)	<0.001
0 APC's	1.0 (reference)	-
1 APC	6.9 (3.6-13.3)	<0.001
≥2 APCs	19.7 (9.1-42.5)	<0.001

Multivariable		
Variables	**OR (95% CI)**	**P Value**
*** Model 1**		
Lumen area stenosis (per 5%)	1.2 (1.1-1.4)	<0.001
Lesion length	1.03 (1.01-1.06)	0.008
PR	5.4 (3.0-10.0)	<0.001
LAP	2.2 (1.1-4.5)	0.028
SC	1.6 (0.8-3.1)	0.177
*** Model 2**		
Lumen area stenosis (per 5%)	1.2 (1.1-1.4)	<0.001
Lesion length	1.03 (1.01-1.06)	0.004
0 APC's	1.0 (reference)	-
1 APC	4.5 (2.3-8.8)	<0.001
≥2 APCs	13.2 (6.1-28.7)	<0.001
*** Model 3**		
Lumen area stenosis (per 5%)	1.3 (1.1-1.4)	<0.001
% APV (per 5%)	1.1 (0.99-1.2)	0.09
PR	5.8 (3.3-10.2)	<0.001
LAP	2.1 (1.1-4.0)	0.02
SC	1.5 (0.8-2.9)	0.22
*** Model 4**		
Lumen area stenosis (per 5%)	1.3 (1.1-1.4)	<0.001
% APV (per 5%)	1.1 (0.99-1.2)	0.095
0 APC's	1.0 (reference)	-

Multivariable		
Variables	**OR (95% CI)**	**P Value**
1 APC	4.9 (2.5-9.4)	<0.001
≥2 APCs	13.4 (6.1-29.3)	<0.001

OR = odds ratio; CI, confidence interval; other abbreviations as in Table 2.

Table 4

Multivariate analysis of APCs in obstructive lesions (≥50%) and non-obstructive lesions (<50%) for Ischemia detection

Obstructive lesions (≥50%)			**Non-Obstructive lesions (<50%)**		
Variables	**OR (95% CI)**	**P Value**	**Variables**	**OR (95% CI)**	**P Value**
*** Model 1**			*** Model 3**		
Lumen area stenosis (per 5%)	1.1 (0.99-1.3)	0.07	Lumen area stenosis (per 5%)	1.3 (1.06-1.6)	0.01
Lesion length	1.03 (1.01-1.06)	0.01	Lesion length	1.02 (0.97-1.07)	0.44
PR	3.6 (1.8-7.2)	<0.001	PR	10.5 (3.1-36.4)	<0.001
LAP	2.5 (1.2-5.3)	0.018	LAP	1.3 (0.3-5.6)	0.74
SC	1.4 (0.6-3.2)	0.42	SC	1.8 (0.5-7.3)	0.40
*** Model 2**			*** Model 4**		
Lumen area stenosis (per 5%)	1.14 (1.001-1.3)	0.049	Lumen area stenosis (per 5%)	1.3 (1.02-1.6)	0.03
% APV (per 5%)	1.04 (1.01-1.06)	0.007	% APV (per 5%)	1.02 (0.97-1.08)	0.39
0 APC	1.0 (reference)	-	0 APC	0 APCference))	
1 APC	2.6 (1.2-5.6)	0.01	1 APC	8.6 (2.4-31.8)	0.001
> 2 APCs	9.0 (4.1-19.7)	<0.001	≥2 APCs	21.6 (3.1-152.2)	0.002

Abbreviations as in Table 2.