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Combined assessment of coronary artery calcium and myocardial perfusion by hybrid Rb-82 PET/CT imaging in the identification of obstructive coronary artery disease

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Introduction

Myocardial perfusion imaging (MPI) with positron emission tomography (PET)/computed tomography (CT) is an accurate noninvasive procedure for the management of patients with suspected and known coronary artery disease (CAD), allowing an accurate quantitative measurements of coronary artery calcium (CAC), myocardial blood flow (MBF) and myocardial perfusion in one examination [1-3]. PET is currently the most validated imaging technique for the absolute quantitative evaluation of MBF and coronary flow reserve (CFR). Despite the diagnosis of obstructive CAD by MPI procedures is typically achieved by quantitative assessment of myocardial ischemia, evaluated as relative hypoperfusion between stress and rest images, consistent data demonstrated that CFR provides additional diagnostic power in detecting CAD, especially in the assessment of multivessels disease [4,5]. A normal CFR has been demonstrated to have a high negative predictive value for excluding high-risk CAD on angiography [6]. As well, an abnormal CFR increases the probability to identify significant obstructive CAD. Considering that the use of CAC scanning before or combining it with PET-MPI could lead to a change in the clinical management of patients without known CAD [7], the full understanding in combining functional and anatomic data by PET/CT is of great clinical interest. Recently, a combination of regional ischemic total perfusion deficit (ITPD) along with regional and global CAC scores has been demonstrated to enhance the overall diagnostic accuracy of PET/CT in the detection of obstructive CAD [8]. However, no data are available on the role of regional CFR in combining functional and anatomic imaging. Thus, aim of the present investigation was to examine the full interaction between regional CAC score, myocardial ischemia and quantitative CFR in the identification of obstructive CAD.

Materials and method

Study population

We evaluated 388 consecutive patients with suspected or known CAD, referred to PET/CT MBF measurements between March 2014 and June 2016. Patients (n=134) have been excluded for: 1) prior myocardial revascularization procedures; (2) recurrent chest pain unresponsive to anti-ischemic medications; (3) recent acute coronary syndrome, stroke, or transient ischemic attack (past 3 months); (4) uncompensated congestive heart failure (New York Heart Association class III or IV) or recent admission for uncompensated heart failure (in the last 3 months); (5) pacemaker or prosthetic valve; (6) an absolute contraindication to dipyridamole, defined as ongoing wheezing, greater than first-degree atrioventricular block without a pacemaker, systolic blood pressure lower than 90 mm Hg, or recent (24 hours) use of dipyridamole or xanthines (eg, aminophylline and caffeine); (7) premenopausal women, unless it could be documented that they were not pregnant or lactating, and any patients unable to provide signed informed consent. Of the remaining 254 patients, 93 were referred to coronary angiography after 6 months by referring clinical physician and were considered for the analysis. For each patient the presence of coronary risk factors was noted. Hypertension was defined as a blood pressure ≥140/90 mmHg or the use of anti-hypertensive medication. Hypercholesterolemia was defined as total cholesterol level >6.2 mmol/L or treatment with cholesterol lowering medication. Patients were classified as having diabetes if they were receiving treatment with oral hypoglycemic drugs or insulin. A positive family history of CAD was defined by the presence of disease in first-degree relatives younger than 55 years in men or 65 years in women.

PET/CT imaging

As a routine preparation for 82Rb cardiac PET/CT, patients were asked to discontinue taking nitrates for 6 hours, calcium channel blockers and caffeine-containing beverages for 24 hours, and b-blockers for 48 hours before their appointment. Scans were acquired using a Discovery LS scanner (GE). Rest and stress cardiac PET/CT images were acquired as follows: following a CT scout acquisition (120 kVp, 10 mA) for proper patient positioning, a CT transmission scan was acquired (140 kVp, 80 mA) for subsequent attenuation correction and for CAC score measurements. Rest and stress CT transmission scans were acquired at end-expiration breath-hold, and patients were instructed to breathe normally during the PET acquisition. For both rest and stress images 1110 MBq of 82Rb were injected intravenously and a 6-minute dynamic PET study (12x8 seconds, 5x12 seconds, 1x30 seconds, 1x60 seconds and 1x60 seconds) was acquired. Pharmacologic stress was then administered using dipyridamole (0.142 mg/kg/min for 4 minutes). Both rest and stress dynamic images were reconstructed using attenuation-weighted ordered-subset expectation maximization (21 subsets and 2 iterations). CT-based attenuation, scatter, including decay and random corrections were applied to the reconstructed images. The heart rate, systemic blood pressure, and 12-lead ECG were recorded at baseline and throughout the infusion of dipyridamole. The rate pressure product was calculated as heart rate multiplied by systolic blood pressure.

CT data analysis

For CAC scoring measurements, rest CT axial reconstructions were transferred to a dedicated workstation (Vitrea Workstation, Toshiba Medical Systems, Tokyio, JAPAN) for post-processing and subsequent analysis. Coronary calcification was defined as a plaque with an area of 1.03 mm2 and a density $\geq$130 HU. The CAC score was calculated according to the method described by Agatston [9]. Experienced nuclear medicine physicians analyzed the CT, blinded to the PET results. CAC scores values were calculated separately for left anterior descending

(LAD), left circumflex (LCx), and right (RCA) coronary arteries. CAC score was also categorized into 2 groups, <300 and ≥300 [10].

Perfusion data analysis

Transaxial PET perfusion images were automatically reoriented into short-axis and vertical and horizontal long-axis slices using dedicated software (Emory Cardiac Toolbox, version 3.05, Emory University Medical Centre, Atlanta, GA). Myocardial perfusion was evaluating according to the 17-segment American Heart Association model [11]. Total perfusion defect (TPD) reflecting a combination of both severity and extent of myocardial defect was calculated using automated software (Cedars-Sinai Medical Center, Los Angeles, California) [12]. Per-vessel ischemic TPD (ITPD) was defined as stress TPD ─ rest TPD and computed separately for each vascular territory: left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA). IPTD values were categorized into three groups (0%; <5%; ≥5%) [8]. Absolute MBF (in mL·min-1·g-1) was computed from the dynamic rest and stress imaging series with commercially available software (FlowQuant, University of Ottawa Heart Institute) [13]. In addition, regional MBF was calculated for each of three vascular territories. Global and regional CFR was defined as the ratio of hyperemic to baseline MBF.

Invasive Coronary Angiography

Coronary angiography was performed using the standard Judkins method [14]. Experienced cardiologists visually interpreted all coronary angiograms. Presence of luminal diameter stenosis ≥75% in at least one of the three vascular territories (LAD, LCx and RCA) was considered as obstructive CAD [8].

Statistical Analysis

Continuous data are expressed as mean ± standard deviation and categorical data as percentage. A student two-sample t-test and chi-square test were used to compare the

differences in continuous and categorical variables, respectively. A P value <0.05 (two-sided) was considered statistically significant. Univariable receiver operating characteristic (ROC) curves, were constructed to obtain the best trade-off between sensitivity and specificity for different cutoff points of regional CFR in identifying obstructive CAD. Univariable and multivariable logistic regression analyses were used to evaluate the variables associated with obstructive CAD. The incremental value of different models was assessed: model 1 considered clinical data and CAC score, model 2 considered model 1 and ITPD categories and model 3 considered model 2 and CFR. Finally, the continuous net reclassification improvement (NRI), using the formula proposed by Pencina et al. [15], was used to evaluate CFR was additive upon clinical data, CAC score and regional ITPD in the prediction obstructive CAD. Statistical analysis was performed with Stata 12 software (StataCorp, College Station, Texas USA).

Results

Patient characteristics

Coronary angiography showed obstructive CAD in 36 (39%) patients and non-obstructive CAD in 57 (61%) patients. In particular, 23 (64%) patients had single vessels disease, 8 (22%) two vessels disease and 5 (14%) patients tree vessels disease. Baseline characteristics of patient population according to the presence of obstructive CAD are shown in Table 1. Patients with obstructive CAD were older with a higher prevalence of male gender.

Myocardial perfusion findings in per vessels analysis

Of the overall 279 vessels analyzed, obstructive CAD was observed in 54 (19%) vessels and non-obstructive CAD in 225 (81%) vessels. Coronary calcium and myocardial perfusion findings according to the presence of obstructive CAD in per-vessels analysis are illustrated in Table 2. During dipyridamole-induced hyperemia, baseline MBF increased significantly both in vessels with and without obstructive CAD (P<0.001 hyperemia vs baseline). As reported, the vessels with obstructive CAD showed a higher CAC score and a significantly lower baseline MBF, hyperemic MBF and CFR (P<0.005) and a higher ITPD (P<0.001) compared to vessels without obstructive CAD.

Prevalence of ITPD according to CAC score categories

ITPD was 0% in 174 (63%), <5% in 79 (28%) and ≥5% in 26 (9%) vessels. Of the 244 vessels with a CAC score <300, ITPD was 0% in 159 (65%), <5% in 63 (26%) and ≥5% in 22 (9%) vessels. In the 35 vessels with CAC score ≥300, ITPD was 0% in 15 (43%), <5% in 16 (46%) and ≥5% in 4 (11%) vessels (Figure 1). As observed, the prevalence of ITPD 0% was significantly higher in vessels with CAC score <300 as compared to vessels with a CAC score ≥300 (65% versus 43%, respectively, *P*<0.001). Differently, the prevalence of ITPD <5% was significantly higher in vessels with CAC score ≥300 as compared to those with CAC score

<300, (46% versus 26%, respectively, *P*<0.05), while no differences between the two groups were observed in the presence of ITPD ≥5%.

Relation between CAC score, regional ITPD and coronary vascular function

ROC analysis identified a CFR of 1.64 as the best cut-off value in identifying obstructive CAD (Figure 1). Reduced CFR was observed in 79 (28%) of the overall 244 vessels. The prevalence of reduced CFR according to CAC score and ITPD categories is depicted in Figure 2. The prevalence of reduced CFR is not significantly different between vessels with CAC score <300 and those with CAC score ≥300 in all ITPD categories. Moreover, the number of vessels with reduced CFR significantly increases with the increase of ITPD categories (24% 32% and 50%, respectively, *P*<0.05).

Prevalence of obstructive CAD across different CAC score, ITPD and CFR categories

The prevalence of obstructive CAD across different CAC score, ITPD and CFR categories is showed in Figure 3. As illustrated, in vessels with a CAC score<300 the prevalence of obstructive CAD was significantly higher in the presence of reduced CFR in both ITPD categories 0% and <5% (P <0.001 and P<0.05, respectively). On the contrary, in vessels with CAC score ≥300, the prevalence of obstructive CAD was comparable between the different ITPD and CFR categories.

Univariable and multivariable analyses

Univariable and multivariable logistic regression analyses in predicting obstructive CAD are reported in Table 3. At univariable analysis, age (*P*<0.001), male gender (P<0.01), a CAC score ≥ 300 (P<0.01), regional ITPD (P <0.001) and regional CFR<1.64 (P <0.001) were significant predictors of obstructive CAD. At multivariable analysis CAC score ≥300 (P <0.05), regional ITPD (P <0.001) and regional CFR <1.64 (P <0.001) resulted independent predictors of obstructive CAD. Incremental analysis results are reported in Figure 4. The

addition of regional ITPD to a model including clinical variables (age, male gender, diabetes, hypertension, dyslipidemia, smoking, family history) and a CAC score ≥300 increased the global chi-square value in predicting obstructive CAD from 29.91 to 72.72 (P <0.001). Moreover, the addition of regional CFR<1.64, to a model including clinical data, CAC score and regional ITPD, further significantly increased the global chi-square from 72.72 to 91.97 (P <0.001). The continuous NRI by adding regional CFR to clinical data was 0.682 (95% bootstrap confidence interval 0.274-1.045).

Discussion

To our knowledge, this is the first study examining the regional interaction between CAC score, myocardial ischemia and quantitative CFR in the identification of obstructive CAD on coronary angiography. From this study, it emerged that in patients with suspected CAD, the addition of regional CFR to clinical data, CAC score and ITPD could be helpful to identify the presence of obstructive CAD.

82Rb PET/CT imaging is being increasingly used for the evaluation of selected patients with known or suspected CAD [16]. The vast majority of PET-MPI studies are performed with PET/CT systems with which CAC scanning can be estimated with reasonable accuracy from the attenuation scans routinely performed for the PET [17]. Indeed, both CAC scoring and myocardial perfusion evaluation are used for risk stratification in patients with suspected CAD combining anatomic and functional data [18]. Schepis et al. [19] investigated the added value of the CAC score as an adjunct to MPI findings for the assessment of CAD in 77 patients at intermediate risk using single photon emission computed tomography (SPECT) imaging. Higher global CAC score values were observed in subjects with abnormal SPECT results and in patients with significant CAD (≥50% stenosis) at coronary angiography. However, considering that clinically CAD presents as a continuous spectrum of severity, absolute measures of MBF and CFR obtained by PET imaging besides the evaluation of myocardial ischemia can offer a unique advantage in assessing the extent of CAD. Previous studies evaluated the effects of coronary atherosclerosis morphology and extent on CFR [20-22]. Yoshinaga et al. [20]. evaluated regional MBF in segments with and without ischemia using [82]Rb PET in a small (n=12) cohort of patients with CAD. These authors found a significant inverse correlation between MBF and CFR measurements with significant diameter stenosis on coronary angiography in vessels with and without ischemia. Moreover, in a study of 73 patients, including 19 patients with 3-vessel CAD, Fiechter et al. [21]

demonstrated that a reduced CFR (<2.0), obtained by 13N-ammonia PET-CT imaging, was associated with a much higher positive predictive value for identifying extensive CAD on angiography. Naya et. al [22] evaluated the relationship between atherosclerosis plaque burden, morphology, and composition and regional CFR in 73 consecutive patients undergoing ^{82}Rb PET and coronary computed tomography angiography (CTA) for the evaluation of known or suspected CAD. They found that, on a per-patient analysis, global quantitative estimates of CFR were sensitive markers for the identification of patients with high-risk anatomic disease by CTA. In a more recent report, the same authors [6] evaluated how a preserved CFR could be helpful in excluding high risk CAD at coronary angiography in 180 patients. These authors identified the best cut-off for CFR for the detection of multivessels disease using ROC curve analysis (CFR <1.93), Their results showed that a normal CFR had a high negative predictive value for excluding high-risk CAD on angiography. Moreover, although an abnormal CFR increases the probability of significant obstructive CAD, the authors concluded that it cannot reliably distinguish significant from nonobstructive epicardial stenosis, diffuse atherosclerosis or microvascular dysfunction. More recently, Brodov and colleagues [8] in 152 consecutive patients without history of CAD showed how the combination of regional analysis of both CAC score and ITPD improves diagnostic accuracy of 82Rb PET-CT imaging in detecting CAD. However, despite the use of PET-CT in combining anatomic and functional information, no data has been presented on the possible role of regional CFR in the evaluation of ostructive CAD. In our study for the first time a combination of regional measures of CAC score, ITPD and CFR were considered in a relatively high cohort of patients with suspected CAD. From our analysis, a regional CFR <1.64 resulted the best cut-off value in order to identify the presence of severe CAD. As already showed by previous report [5,6], different severity threshold for CFR may be considered, according to the wide variability related to subclinical and clinical condition, different radionuclides, scanners, imaging protocols, stress agents and flow models.

Interestingly, on a per-vessels analysis, we found a higher prevalence of obstructive CAD in vessels with reduced CFR. In particular, the prevalence of severe CAD was significantly higher in vessels with low CAC score in the presence of a reduced CFR, both in non-ischemic vessels and in those with mild-moderate ischemia. Differently, no significant differences were appreciated in vessels with high CAC score values among all ITPD groups. This data should be potentially explained by the evidence that diffuse atherosclerosis or microvascular dysfunction could affect CFR measurements also in patients without significant stenosis. In particular, since high CAC score is associated with coronary vascular dysfunction and reduced CFR [23], in vessels with lower CAC score values a significant decrease in CFR may reflect the presence of non-calcified obstructive plaque. Our results support the additive value of regional measurements of ITPD and CFR in identifying obstructive CAD. At incremental analysis, the addition of regional ITPD to a model including clinical data and CAC score, improve the power of the model in predicting obstructive CAD. Moreover, in our study the addition of regional CFR to a model including clinical data, CAC score and regional ITPD further ìncrease the global chisquare in detecting severe CAD, with a continues NRI of 0.68.

Conclusion

The prevalence of obstructive CAD is higher in the presence of reduced CFR, in particular in patients with CAC score <300 and absent or mild-moderate ischemia. At per vessels analysis CAC score, ITPD and CFR result independent predictors of obstructive CAD. However, addition of regional CFR to a model including clinical data, CAC score and ITPD has an incremental value in the identification of obstructive CAD in patients with suspected CAD.

Table 1. Patients characteristics

	All (n=93)	Obstructive CAD (n=36)	Non-obstructive CAD (n=57)	*P* value
Age	59±11	63±10	57±12	.042
Male gender	73(78%)	33(92%)	40(70%)	.014
Diabetes	24(26%)	12(33%)	12(21%)	.187
Hypertension	84(90%)	32(89%)	52(91%)	.710
Dyslipidemia	72(77%)	29(80%)	43(75%)	.565
Smoking history	44(47%)	18(50%)	26(46%)	.680
Family history of CAD	52(56%)	18(50%)	34(60%)	.361
Angina	20(21%)	4(11%)	16(28%)	.053

Values are expressed as mean value±standard deviation or as number (percentage) ofsubjects

CAD coronary artery disease.

Table 2. Coronary calcium and myocardial perfusion findings in per-vessel analysis

	All (n=279)	Obstructive CAD (n=54)	Non-obstructive CAD (n=225)	*P* value
CAC score				
<300	244 (87%)	41 (76%)	203 (90%)	<.05
≥300	35 (13%)	13(24%)	22 (10%)	<.05
Baseline MBF	0.80±0.3	0.67±0.2	0.82±0.3	<.01
Hyperemic MBF	1.52±0.6	1.10±0.5*	1.63±0.6*	<.001
CFR	2.14±0.8	1.66±0.6	2.24±0.7	<.001
ITPD	1.54±3.7	5.1±6	0.7±1	<.001

Values are expressed as mean value±standard deviation, *P<0.001 versus baseline MBF

MBF myocardial blood flow;*CFR*coronary flow reserve; *ITPD* ischemic total perfusion defect

Table 3. Univariable and multivariable predictors of obstructive CAD

	Univariable analysis		Multivariable analysis	
	Odds Ratio (C.I. 95%)	*P* **value**	**Odds Ratio (C.I. 95%)**	*P* **value**
Age	1.055 (1.024-1.087)	<.001	1.016 (0.977-1.057)	.432
Male gender	5.768 (1.733-19.198)	<.01	1.7281 (0.455-6.559)	.421
Diabetes	1.583 (0832-3.012)	.161		
Hypertension	1.062 (0.383-2.945)	.908		
Dyslipidemia	0.705 (0.359-1.386)	.311		
Smoking history	0.951 (0.524-1.724)	.868		
Family history of CAD	0.619 (0.341-1.124)	.115		
CAC score ≥300	2.926 (1.364-6.277)	<.01	2.854 (1.084-7.513)	<.05
ITPD 0% (Reference group)				
ITPD <5%	5.087 (2.415-10.714)	<.001	4.068 (1.756-9.425)	<.005
ITPD ≥5%	27.865 (10.185-76.237)	<.001	24.469 (7.863-76.142)	<.001
CFR<1.64	6.115 (3.238-11.549)	<.001	5.583 (2.470-12.617)	<.001

CAD coronary artery disease; *CFR* coronary flow reserve; *ITPD* ischemic total perfusion

defect

Figure 1. Prevalence of ITPD categories (0%, <5% and ≥ 5%) in per vessels analysis according to CAC score categories <300 (A) and ≥ 300 (B)
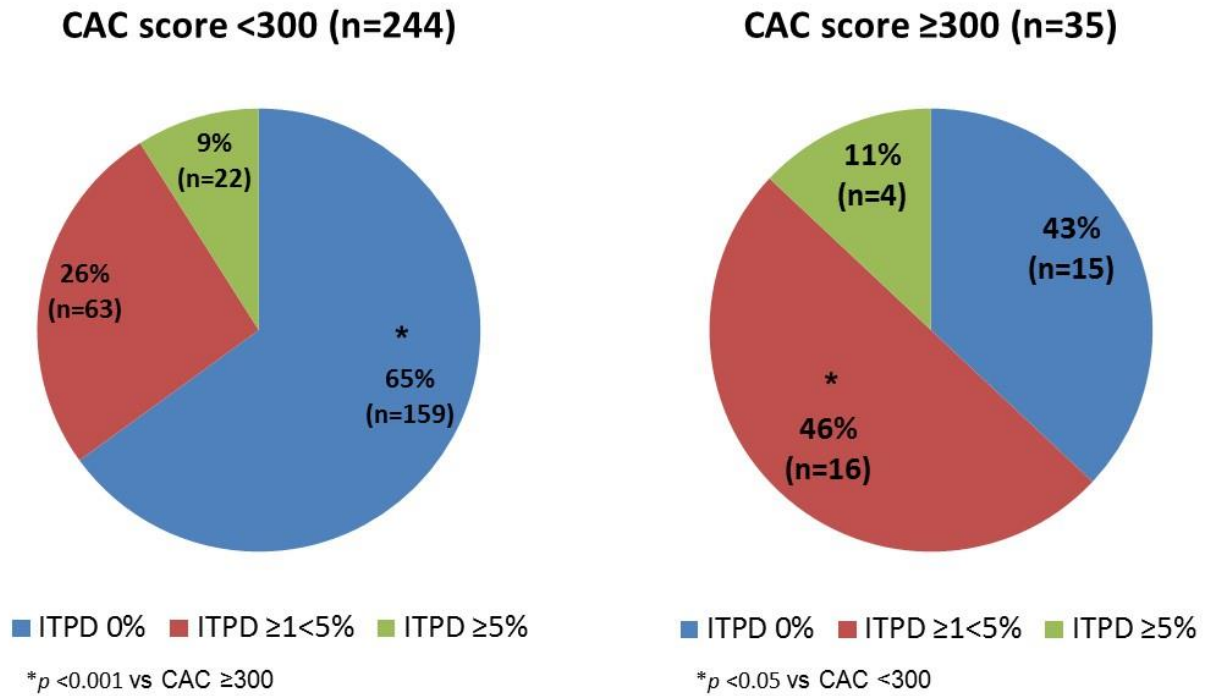

CAC score <300 (n=244)

9%
(n=22)

26%
(n=63)

*
65%
(n=159)

■ ITPD 0%   ■ ITPD ≥1<5%   ■ ITPD ≥5%

*p <0.001 vs CAC ≥300

CAC score ≥300 (n=35)

11%
(n=4)

43%
(n=15)

*
46%
(n=16)

■ ITPD 0%   ■ ITPD ≥1<5%   ■ ITPD ≥5%

*p <0.05 vs CAC <300

Figure 2: Univariate receiver operating characteristic (ROC) curve showing sensitivity (blue curve) and specificity (red curve) pairs for identification of patients with obstructive CAD by use regional CFR
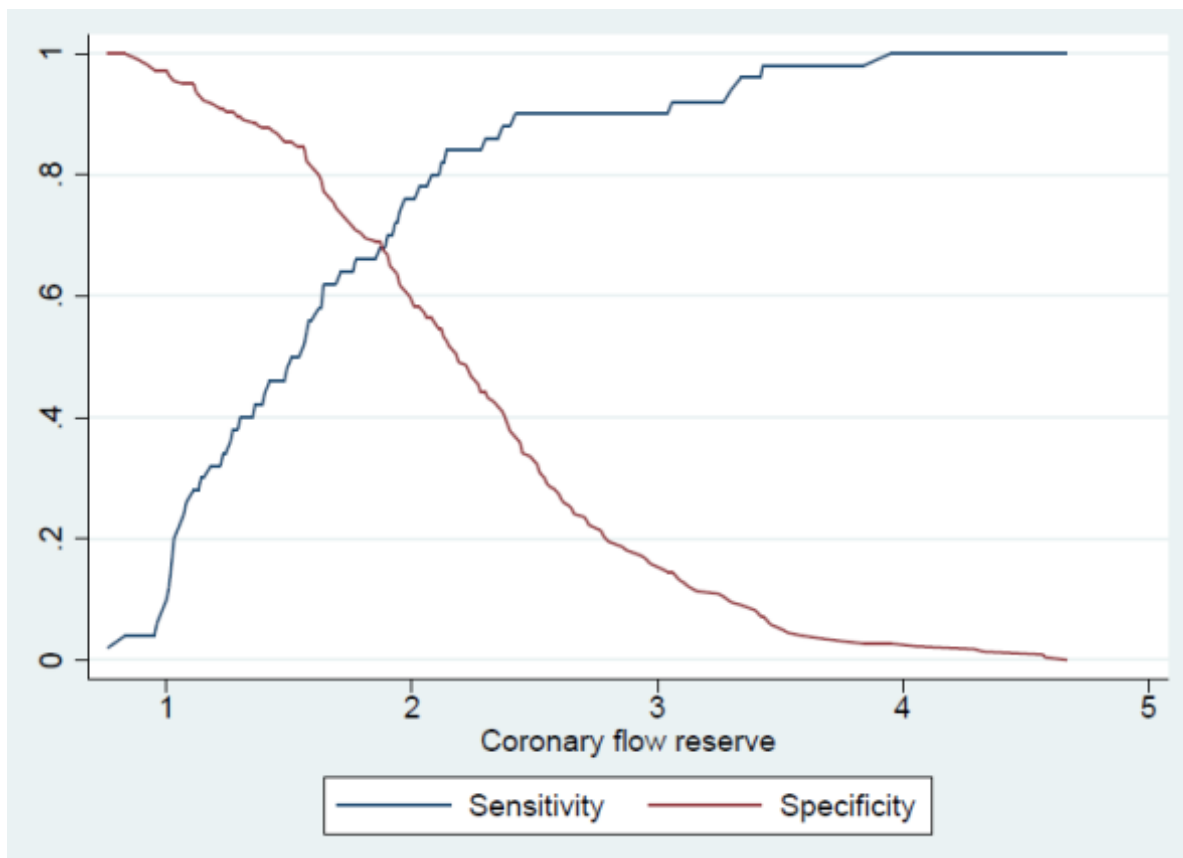
Figure 3. Prevalence of reduced CFR (<1.64) according to ITPD (0%; <5%, ≥5%) and CAC score (<300, ≥300) categories
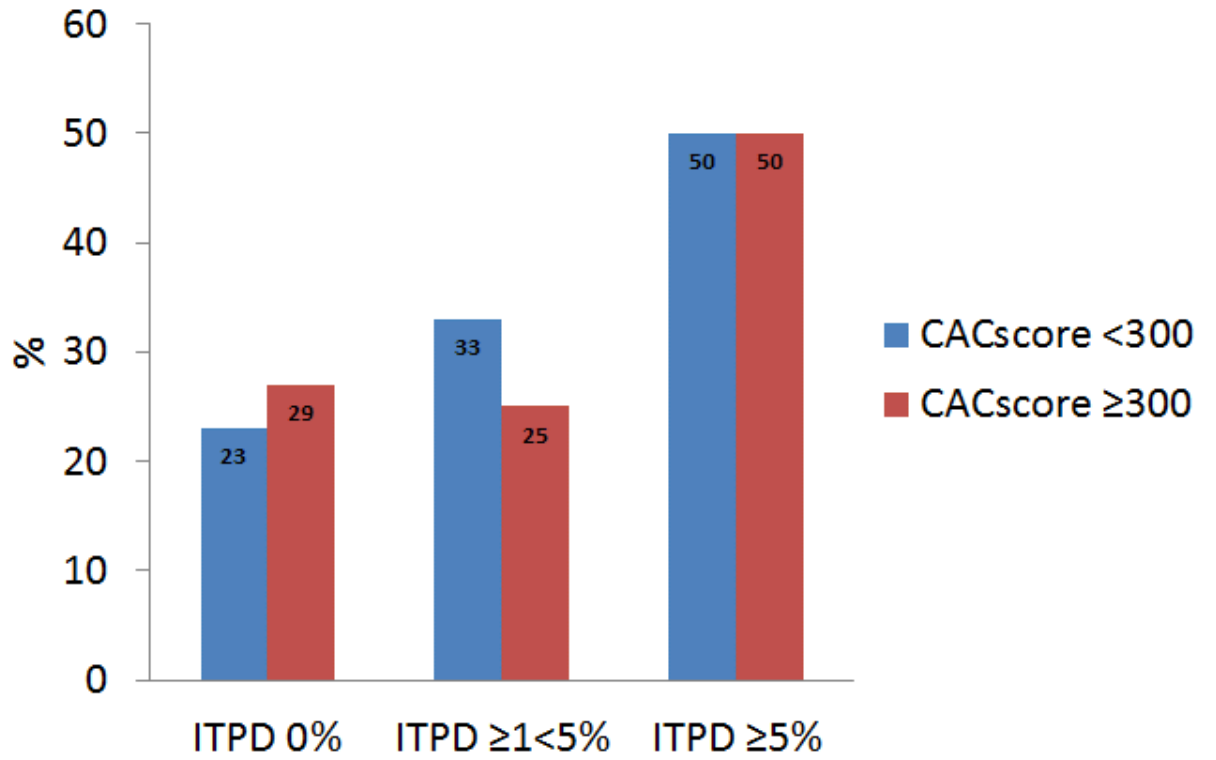
Figure 4. Prevalence of obstructive CAD across different CAC score (<300, ≥300), ITPD (0%; <5%, ≥5%) and CFR (≥1.64; <1.64) categories
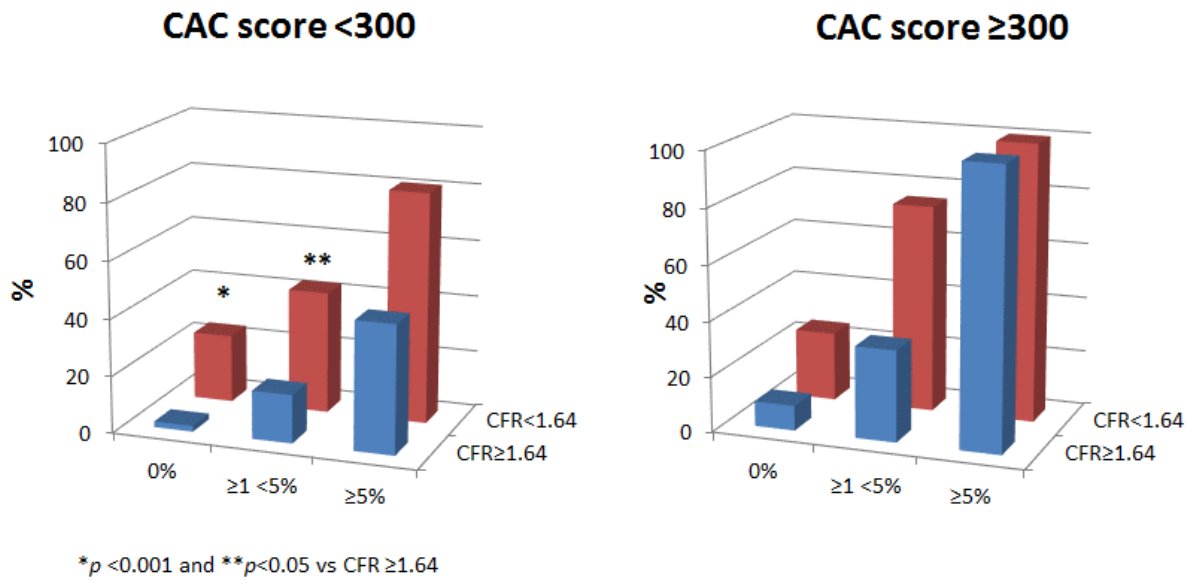

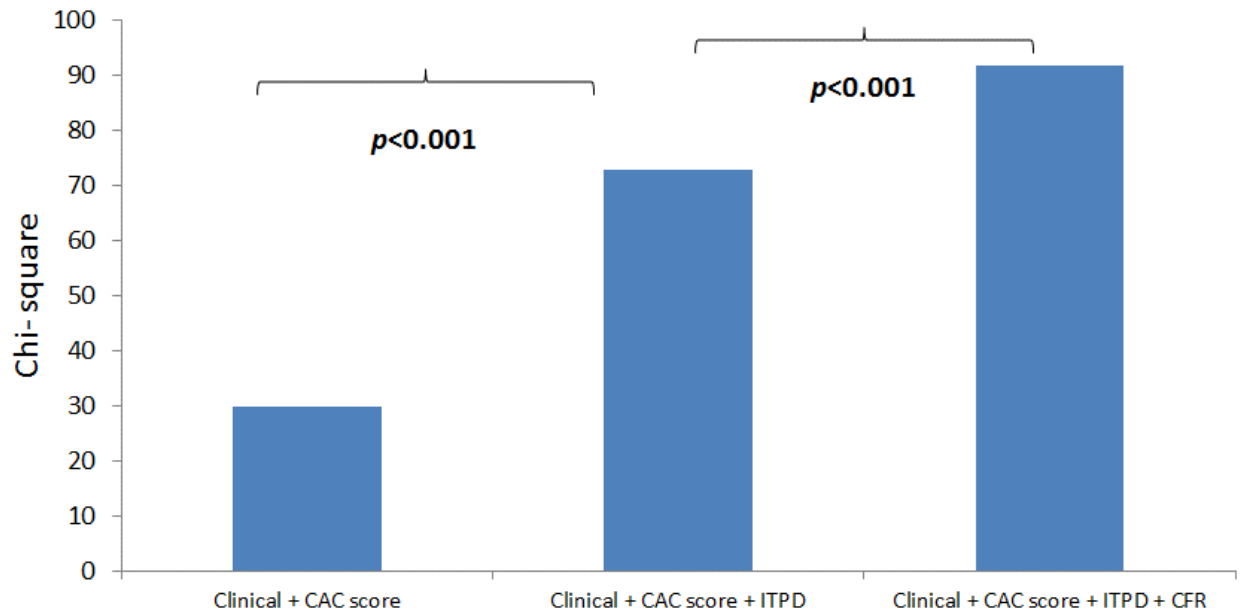
*p <0.001 and **p<0.05 vs CFR ≥1.64

Figure 5. Incremental value of regional CFR (<1.64) in predicting obstructive CAD

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