

Importance of plaque volume and composition for the prediction of myocardial ischaemia using sequential coronary computed tomography angiography/positron emission tomography imaging

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Aims

Coronary atherosclerosis with a large necrotic core has been postulated to reduce the vasodilatory capacity of vascular tissue. In the present analysis, we explored whether total plaque volume and necrotic core volume on coronary computed tomography angiography (CCTA) are independently associated with myocardial ischaemia on positron emission tomography (PET).

Methods and results

From a registry of symptomatic patients with suspected coronary artery disease and clinically indicated CCTA with sequential [¹⁵O]H₂O PET myocardial perfusion imaging, we quantitatively measured diameter stenosis, total and compositional plaque volumes on CCTA. Primary endpoint was myocardial ischaemia on PET, defined as an absolute stress myocardial blood flow ≤ 2.4 mL/g/min in ≥ 1 segment. Multivariable prediction models for myocardial ischaemia were consecutively created using logistic regression analysis (stenosis model: diameter stenosis $\geq 50\%$; plaque volume model: +total plaque volume; plaque composition model: +necrotic core volume). A total of 493 patients (mean age 63 ± 8 years, 54% men) underwent sequential CCTA/PET imaging. In 153 (31%) patients, myocardial ischaemia was detected on PET. Diameter stenosis $\geq 50\%$ ($P < 0.001$) and necrotic core volume ($P = 0.029$) were independently associated with myocardial ischaemia, while total plaque volume showed borderline significance ($P = 0.052$). The plaque composition model ($\chi^2 = 169$) provided incremental value for the prediction of ischaemia when compared with the stenosis model ($\chi^2 = 138$, $P < 0.001$) and plaque volume model ($\chi^2 = 164$, $P = 0.021$).

Conclusion

The volume of necrotic core on CCTA independently and incrementally predicts myocardial ischaemia on PET, beyond diameter stenosis alone.

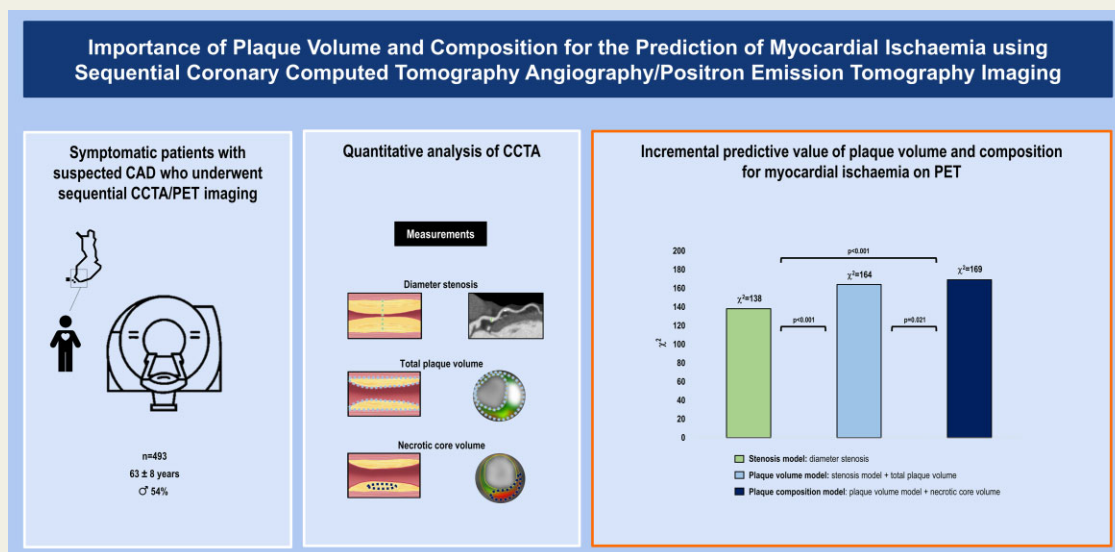
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Graphical Abstract



Importance of plaque volume and composition for myocardial ischaemia.

Schematic representation of the study design and patients (*left panel*), the quantitative analysis of CCTA (*middle panel*), and the incremental predictive value of plaque volume and composition for myocardial ischaemia on PET (*right panel*). Images are partly derived and adjusted from Puchner *et al.*, 'High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial', *Journal of the American College of Cardiology*, volume 64, page 687, copyright 2014, both with permission from Elsevier.

CAD, coronary artery disease; CCTA, coronary computed tomography angiography; PET, positron emission tomography.

Keywords

atherosclerosis • coronary artery disease • coronary computed tomography angiography • myocardial ischaemia • myocardial perfusion imaging • positron emission tomography

Introduction

Myocardial ischaemia occurs when the oxygen supply relative to the demand of the myocardium is insufficient, and this can be adequately assessed using non-invasive myocardial perfusion imaging or invasive fractional flow reserve.¹ Although the presence of myocardial ischaemia correlates with the degree of diameter stenosis from coronary plaques, the imperfect agreement between both has been well-established. Particularly in coronary plaques with moderate stenosis (40–70% luminal narrowing) a high variability in myocardial perfusion has been described, reporting ischaemia in one-third of plaques.^{2–4} These observations have underscored the importance of identifying novel factors beyond coronary artery stenosis that may affect downstream myocardial perfusion.¹ Recently, coronary computed tomography angiography (CCTA) has emerged as a non-invasive imaging modality that allows for the detailed volumetric measurement of different plaque components in coronary artery disease (CAD).^{5,6} Specifically, large volumes of vulnerable lipid-rich plaque—necrotic core—have been hypothesized to impair the vasodilatory response of vascular tissue, thereby inducing ischaemia.^{1,7,8} Hence, the present analysis sought to explore whether total plaque volume and necrotic core volume on CCTA are associated with myocardial ischaemia on positron emission tomography (PET), independent of diameter stenosis.

Methods

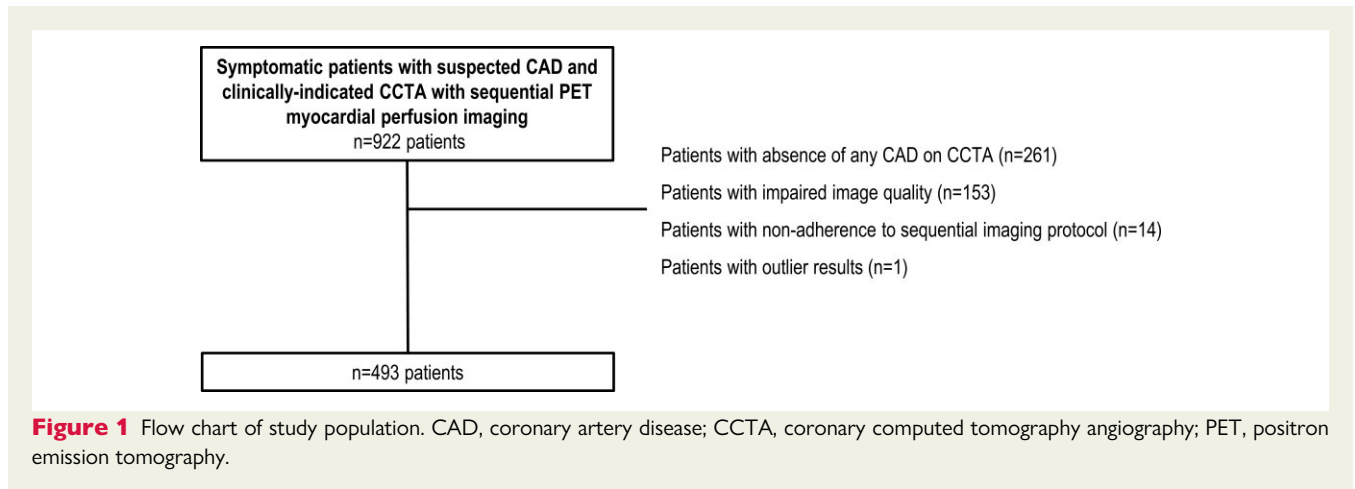
Study design and population

Consecutive symptomatic patients with suspected CAD and clinically indicated CCTA with sequential [¹⁵O]H₂O PET myocardial perfusion imaging were recruited at the Turku University Hospital, Turku, Finland between 2007 and 2011. The study design has been reported earlier.⁹ In brief, a total of 922 patients were referred for CCTA, and those with a suspected obstructive stenosis on CCTA underwent subsequent PET myocardial perfusion imaging to assess the presence of myocardial ischaemia. The study protocol was approved by the ethics committee of the Hospital District of South-West Finland, and the need for written informed consent was waived. The study was performed in compliance with the Declaration of Helsinki. For the current analysis, exclusion criteria were absence of any CAD on CCTA (n=261), impaired image quality (n=153), non-adherence to the sequential imaging protocol (n=14), and outlier results (n=1). Thus, 493 patients were included (*Figure 1*).

Sequential imaging protocol

Step 1: CCTA acquisition and image analysis

The CCTA was performed using a hybrid 64-detector row PET/CT scanner (GE Discovery VCT or GE D690; General Electric Medical Systems,



Waukesha, WI, USA). Intravenous low-osmolar iodine (48–155 mL; 320–400 mg/mL) was given as contrast agent.^{9,10} To reach target heart rates (<60/min), intravenous metoprolol (0–30 mg) was administered before acquisition. To reach maximal coronary vasodilatation, sublingual nitroglycerin (800 µg) or isosorbide dinitrate (1.25 mg) was administered. To minimize radiation dose, prospective electrocardiogram triggering was applied whenever possible. Scans were quantitatively analysed by an independent reader (blinded to clinical or other results) in accordance with the 17-segment American Heart Association model using semi-automated software (QAngio CT Research Edition version 1.3.6; Medis Medical Imaging Systems, Leiden, the Netherlands).⁵ All coronary segments ≥ 1.5 mm were analysed. Tissue ≥ 1 mm² within or adjacent to the lumen that could be distinguished from pericardial tissue, epicardial fat or lumen in >2 planes was defined as coronary plaque.¹¹ Coronary plaques were evaluated for diameter stenosis, total plaque volume, and compositional plaque volume. For diameter stenosis, the maximal (quantitative) plaque-based value was selected as the patient-level value. In addition to this, cross-sectional plaque burden, minimal luminal area, lesion length, and the remodelling index were measured for these maximal stenotic plaques.^{5,11,12} For total and compositional plaque volumes, all plaque-based values were summed to provide patient-level values. Compositional plaque volume was categorized according to Hounsfield units (HU) into calcified plaque (>350 HU), fibrous plaque (131–350 HU), fibrofatty plaque (76–130 HU), and necrotic core (≤ 75 HU).^{5,6}

Step 2: PET acquisition and image analysis

In patients with a suspected obstructive stenosis on initial CCTA evaluation, stress PET myocardial perfusion imaging was performed using the same PET/CT scanner.^{9,10} Intravenous [¹⁵O]H₂O (Radiowater Generator, Hidex Oy, Finland) was injected as radiotracer bolus over 15 seconds.¹⁰ Intravenous adenosine (140 µg/kg/min) infusion was started 2 minutes prior to the stress scan to reach maximal coronary vasodilatation and administered until the end of the scan. Stress scans were quantitatively analysed by an experienced reader (blinded to clinical or other results) in accordance with the 17-segment American Heart Association model using specialized software (Carimas version 1.1.0, Turku, Finland).^{13,14} Absolute stress myocardial blood flow was provided

for the individual myocardial segments and total left ventricular myocardium.

Primary endpoint

The primary endpoint was the presence of myocardial ischaemia on PET, defined as an absolute stress myocardial blood flow ≤ 2.4 mL/g/min in at least 1 of 17 segments.⁹ Patients without a suspected obstructive stenosis on initial CCTA evaluation did not undergo subsequent PET myocardial perfusion imaging (per study design) and were assumed non-ischaemic.

Statistical analysis

Continuous data are shown as mean \pm standard deviations or medians with interquartile ranges (IQR), dependent on distribution. Categorical data are shown as absolute numbers with percentages. Continuous data were compared with the independent sample *T* test or Mann–Whitney *U* test. Categorical data were compared with the χ^2 test. Uni- and multivariable logistic regression analyses were performed to assess the association between selected variables and myocardial ischaemia. The following models for the prediction of myocardial ischaemia were constructed: a stenosis model (diameter stenosis $\geq 50\%$), a plaque volume model (stenosis model + total plaque volume), and a plaque composition model (plaque volume model + necrotic core volume). Particular focus was given to necrotic core volume as plaque composition, considering its link with local vasodilatory dysfunction.^{1,7,8} All models were adjusted for important clinical variables as chosen by domain expertise (X.W., I.J.v.d.H., S.C.B.). Multicollinearity between variables was ruled out as calculated with the variance inflation factor (<3 for all). Measures of association were displayed as odds ratios with 95% confidence intervals (CIs). Area under the receiver-operating characteristic curves (AUCs) of the models were compared with the DeLong's test to evaluate discriminatory ability. χ^2 's of the models were compared with the likelihood ratio test to evaluate goodness of model fit. Effect modification of necrotic core volume on myocardial ischaemia by total plaque volume was tested with interaction terms. A two-sided *P*-value of <0.05 indicated statistical significance, and all statistical analyses were performed with R (version 4.1.1; R Development Core Team, Vienna,

Table 2 CCTA and PET results

	Total cohort n = 493	Ischaemia n = 153	No ischaemia n = 340	P-value
CCTA				
General				
Diameter stenosis (%)	39.8 ± 20.9	55.9 ± 21.3	32.6 ± 16.2	<0.001
<50%	356 (72)	61 (40)	295 (87)	<0.001
≥50%	137 (28)	92 (60)	45 (13)	<0.001
Total plaque volume (mm ³)	169.0 (81.4–353.2)	371.5 (197.8–739.4)	127.8 (65.0–230.8)	<0.001
Calcified volume (mm ³)	28.1 (4.3–95.9)	84.9 (24.1–224.1)	14.9 (2.4–51.3)	<0.001
Fibrous volume (mm ³)	85.1 (40.9–164.7)	165.5 (94.8–309.6)	62.0 (34.2–110.9)	<0.001
Fibrofatty volume (mm ³)	32.0 (16.5–61.2)	63.5 (37.2–109.9)	24.1 (13.8–42.8)	<0.001
Necrotic core volume (mm ³)	20.0 (9.4–39.1)	41.3 (22.7–66.8)	14.3 (6.6–27.0)	<0.001
Maximal stenotic plaque				
Cross-sectional plaque burden (%)	67.5 (54.3–83.7)	84.1 (69.1–95.0)	62.4 (50.6–73.5)	<0.001
Minimal luminal area (mm ²)	3.4 (1.7–5.7)	1.4 (0.5–2.6)	4.4 (2.7–6.7)	<0.001
Lesion length (mm)	9.6 (5.8–14.6)	13.5 (7.4–20.5)	8.5 (5.4–12.5)	<0.001
Remodelling index	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.849
PET myocardial perfusion imaging				
Global stress myocardial blood flow (mL/g/min)	–	2.3 ± 0.7 ^a	3.8 ± 0.9 ^b	<0.001

Values are presented as mean ± SD, median (IQR) or n (%).

CCTA, coronary computed tomography angiography; PET, positron emission tomography.

^aWithin this group, regional stress myocardial blood flow for the ischaemic and remote non-ischaemic myocardium was 1.8 ± 0.3 and 3.0 ± 0.4 mL/g/min, respectively. For the ischaemic and remote non-ischaemic myocardium, this was calculated as the mean of all segments classified as ischaemic or non-ischaemic (≤2.4 and >2.4 mL/g/min, respectively).

^bWithin this group, values were only available for those who underwent subsequent PET myocardial perfusion imaging.

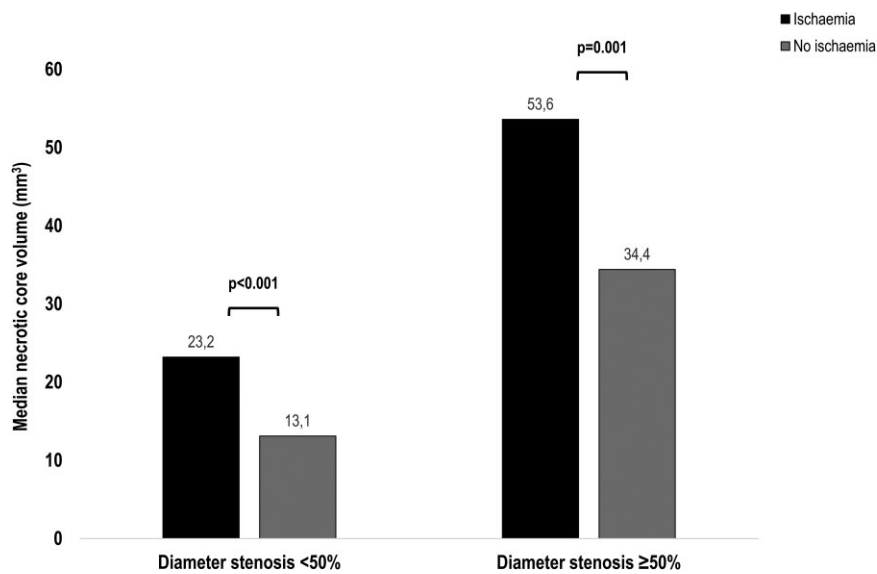


Figure 2 Necrotic core volumes according to obstructive status. Patients were categorized into 2 groups according to diameter stenosis: <50 and ≥50%. The black bars represent ischaemia-positive patients and the grey bars ischaemia-negative patients on PET myocardial perfusion imaging. Median necrotic core volumes (y-axis) are compared between groups. PET, positron emission tomography.

PET results

PET myocardial perfusion imaging results of the study population are depicted in Table 2. A median of 9 segments (IQR 4–15

segments) was affected in patients with myocardial ischaemia. Patients with myocardial ischaemia demonstrated a lower global stress myocardial blood flow when compared with patients

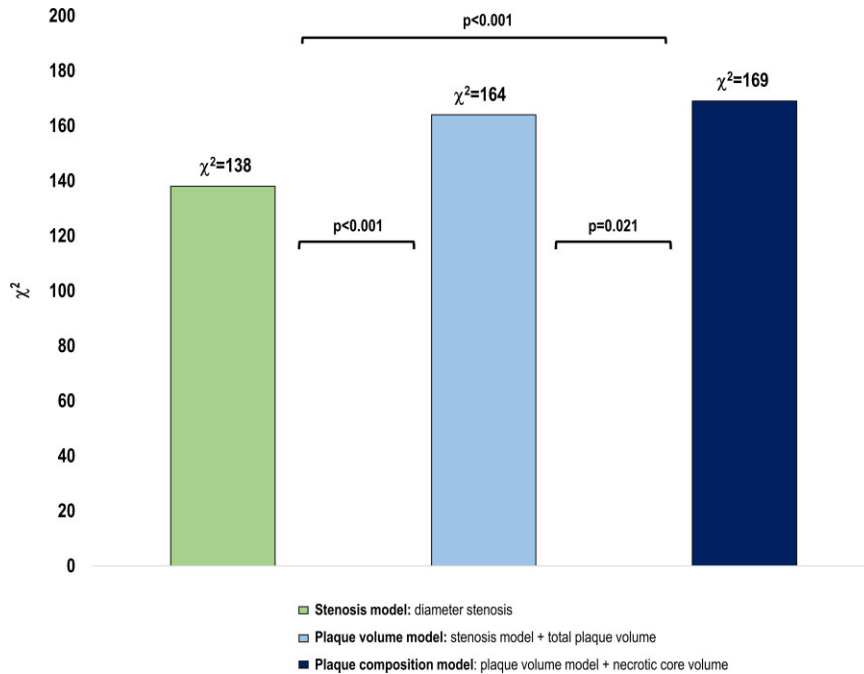


Figure 3 Incremental predictive value of total plaque volume and necrotic core volume. The left bar represents the stenosis model, the middle bar the plaque volume model, and the right bar the plaque composition model. χ^2 Values (y-axis) are compared between the models. All models are adjusted for age, sex, and >3 cardiac risk factors including hypertension, dyslipidaemia, diabetes mellitus, family history of CAD, and smoking current or former. CAD, coronary artery disease.

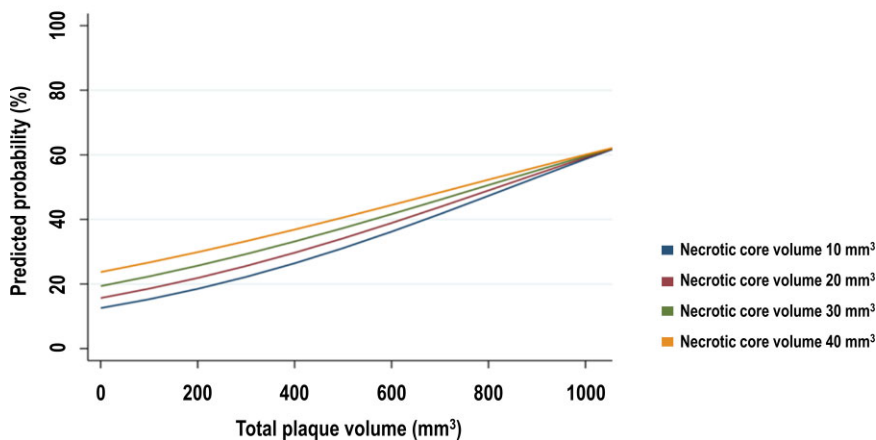


Figure 4 Interaction between total plaque volume and necrotic core volume. In order to show the interaction between total plaque volume and necrotic core volume, 4 values of necrotic core volume were chosen (10 mm³, 20 mm³, 30 mm³, 40 mm³). The differences between the slopes of the 4 groups reflect the interaction ($P=0.036$). A greater necrotic core volume was associated with an increased risk of myocardial ischaemia. However, this effect was more pronounced in patients with a smaller total plaque volume and decreased with increasing total plaque volume. Predicted probabilities are calculated from the plaque composition model.

emission computed tomography. In addition, other studies employing an invasive fractional flow reserve ≤ 0.80 as reference standard for myocardial ischaemia, comparably revealed stenosis severity as a strong and independent predictor of ischaemia.^{19–23}

Effect of vulnerable plaque on myocardial ischaemia

Although CCTA-derived stenosis has a well-established effect on myocardial ischaemia, discordances between the two have

