Pericardial fat volume as a predictor of atherosclerosis, stenosis severity and plaque composition in symptomatic and asymptomatic populations - a cardiac CT angiography study

ABSTRACT

Introduction: Coronary CT angiography (CCTA) can provide comprehensive information of the coronary arteries, including the identification of coronary plaques, determination of stenosis severity and morphological characterization of plaques with regard to the presence or absence of calcification – all of which have been linked to the pathogenesis of coronary artery disease (CAD). It is also possible to calculate the pericardial fat volume (PFV) using CCTA; however the relationship of PFV to CAD has been controversial. The aim of this study was to evaluate the relationship between PFV and these indicators of CAD in asymptomatic and symptomatic population-based cohorts.

Method and Results: The CCTA scans of asymptomatic (383) people and symptomatic (549) patients were examined. The symptomatic patients were part of the "Cardiac cT in the treatment of acute Chest pain" (CATCH) trial and were admitted on suspicion of acute coronary syndrome with a normal electrocardiogram and troponins. The asymptomatic cohort was taken randomly from the Copenhagen General Population Study. Measurements were made on the PFV, stenosis grading, plaque characteristics, and coronary artery calcium (CAC) scores. Relations between PFV and the indicators of CAD were assessed using logistic regression.

In the symptomatic population, 59% of the patients had atherosclerosis present, compared to 73% in the asymptomatic population. Symptomatic patients with atherosclerosis had a significantly higher mean PFV (142.96 mL) compared to those without (111.22 mL, $P<0.001$). A significant difference was also detected in the asymptomatic population (199.32 mL vs. 171.5 mL, $P=0.079$). When adjusting for age, gender, and BMI, a larger PFV was significantly associated with atherosclerosis in symptomatic patients ($P=0.044$), but not asymptomatic patients ($P=0.358$). PFV was not a predictor of significant coronary artery stenosis (≥70%) in either population, although in symptomatic patients, increased PFV was independently associated with the presence of noncalcified plaques ($P=0.032$). There was no relationship between PFV and CAC scores in symptomatic or asymptomatic populations ($P=0.403$ and $P=0.292$ respectively).

Conclusion: These findings support the hypothesis that PFV contributes to the presence of coronary atherosclerosis and also can indicate the presence of non-calcified plaques, but only for symptomatic patients. However, PFV cannot predict the degree of stenosis.

INTRODUCTION

Coronary atherosclerosis is an inflammatory disease marked by changes in coronary vasculature and is the principle cause of coronary artery disease (CAD). The diagnostic and risk stratification of CAD is a clinical challenge; usually, it manifests through chest pain caused by ischemia in the myocardium.[1]

Invasive angiography is the gold standard to diagnose cardiovascular pathologies because its high resolution allows accurate assessments of the degree of lumen stenosis; however, it is not possible to analyze plaque components.[2] A computerized tomography coronary angiogram (CCTA) is an easy modality for comprehensive information of the coronary arteries – specifically, assessment of plaques in earlier stages of CAD.[3,4,5,6] Recently, other clinical applications of CT have been explored. Ectopic fat depots have been linked to the pathogenesis of cardiovascular disease; thus, a relevant application of CT

imaging is to measure these fat deposits.[7] This is done by selecting the region within the sac and restricting the radiodensity of the pixels.[8]

Pericardial fat may have both a paracrine effect through releasing proatherogenic cytokines, vascular relaxing factors, and smooth muscle cell growth factors as well as a mechanical effect by its proximity to the myocardium.[9] Compared to other local visceral fat depots, pericardial fat has been shown to be a source of inflammatory cytokines which may be atherogenic by increasing vascular stiffness.[10] Pericardial fat volume (PFV) has been linked to risk factors of CAD, future adverse cardiovascular outcomes, presence of coronary arterial calcium (CAC), and biochemical markers of inflammation.[11,12] Epicardial fat volume (EPV), which is highly associated with PFV and body mass index[13], is also an independent predictor of high risk plaque features.[14] A study using the Framingham Heart Study population opposed this conclusion and found that though pericardial fat is correlated with cardiovascular magnetic resonance measures (LV mass, LV end-diastolic volume, and left atrial dimension), this correlation is not stronger than other fat stores or proxy measures of adiposity.[15]

The clinical relevance of PFV as a diagnostic tool for cardiovascular disease risk stratification is still questionable. The guidelines today indicate that further diagnostic evaluation is necessary for patients with symptoms that have a normal electrocardiogram and normal troponins.[16] An assessment for these patients (and possibly asymptomatic people, as well) could include using PFV. The current study explores the relationship between PFV and the pathogenesis of CAD – including its relationship to the grade of stenosis and the characteristics of the plaques – using the CCTA scans of asymptomatic and symptomatic patients. We hypothesize that a larger PFV will indicate a poorer prognosis in the development of CAD.

METHODS

Patient selection. The symptomatic population was selected from the CATCH trial. The asymptomatic population was randomly selected from an ongoing MDCT sub-study of the Copenhagen General Population Study.[17] Refer to "Figure 1" for inclusion and exclusion criteria for these studies. Refer to "Figure 2" for the characteristics of the study populations and "Figure 3" for the flow diagram.

Clinical data. Patients were asked questions through a structured interview and information from their medical record was used.

Figure 1: Inclusion and Exclusion Criteria of CATCH and the General Copenhagen Population Studies

	Symptomatic Population	Asymptomatic Population
Inclusion Criteria	▪ Age >18 years ▪ Hospitalized on suspicion of acute coronary syndrome ▪ Normal ECG's and troponins after 12h of observation	▪ Age >40 years
Exclusion Criteria	▪ Contrast allergy ▪ Renal dysfunction (S-Creatinin>130 $\frac{mg}{L}$) ▪ Geographical residence or mental/physical complications ▪ Former coronary artery bypass graft operation	▪ Contrast allergy ▪ Renal dysfunction ((S-Creatinin<100) ▪ BMI >35 ▪ Other heart rhythm than sinus ▪ Former coronary artery bypass graft operation ▪ History of known CAD

MDCT scan protocol. Patients were asked to not consume caffeine at least 18 hours prior to the scan to maintain a low heart rate. An intraveneous line (18 gauge) was inserted in an antecubital vein for contrast delivery. Patients with a heart rate >60 bpm were administered a beta-blocker (metoprolol, 50-150 mg) one hour before image acquisition with a 64-slice MDCT (Aquilion 64, Toshiba Medical systems, Tokyo, Japan) unless contraindicated. A non-contrast-enhanced, electrocardiogram-triggered calcium score was performed at 75% of the R-R interval. Then, a CCTA was performed with the following parameter settings: 64 x 0.5 mm detector collimation, 120 to 135 kV tube voltage, 380 to 450 mA tube current, 250 to 500 ms pantry rotation time (heart rate-dependent). The intraveneous contrast was infused with a flow rate of 5 ml/s with a biphasic injection protocol.

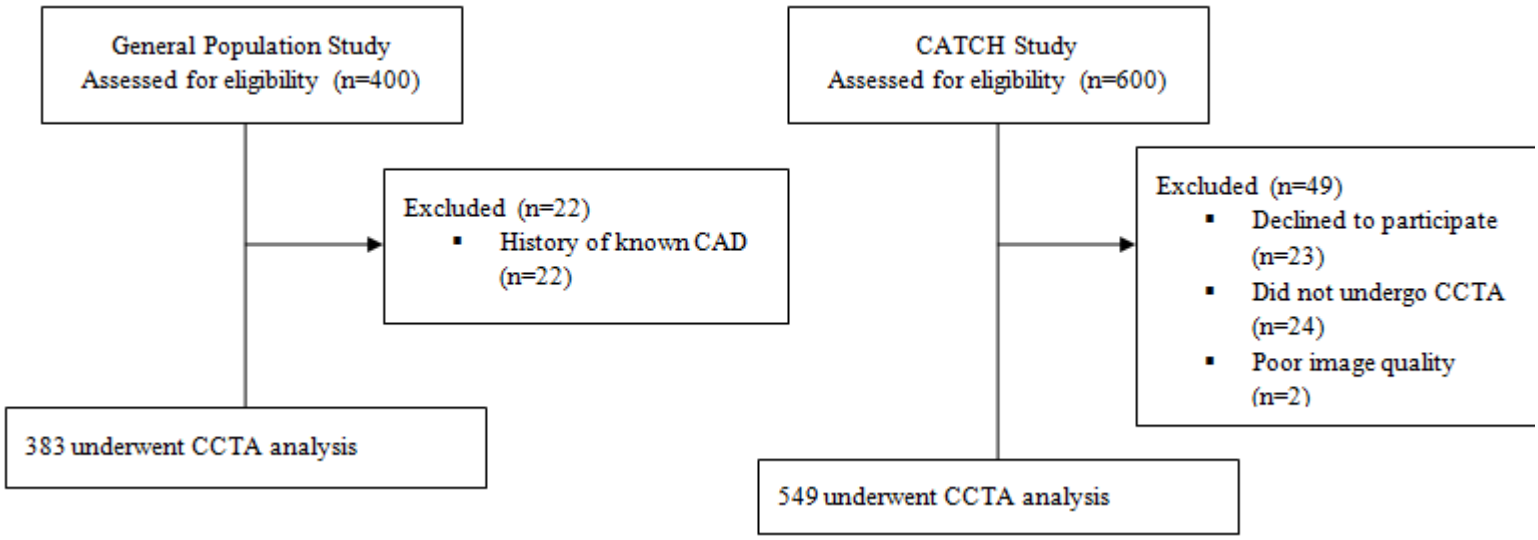
Figure 2. Population Cohort Characteristics

	Symptomatic N=549	Asymptomatic N=383	p-value
BMI, kg/m^2	28±5	25±4	<0.001
Age, years	56±12	61±13	<0.001
Gender, % male	58	51	<0.001
Risk Factors			
Smoking, %	63	54	<0.001
Hypertension, %	41	21	-
Lipid, %	38	-	-
Diabetes mellitus, %	11	4	-
Family History, %	25	-	-
Known CAD, %	14	-	0
Plaque characteristics			
Atherosclerosis Present	305 (59%)	294 (73%)	<0.001
>25% Stenosis	207 (30%)	139 (35%)	<0.001
>50% Stenosis	109 (21%)	72 (18%)	<0.001

Image analysis. Images were transferred to and analyzed with an external workstation (Vitrea 3.1 Vital Images Inc, USA). Segments were visually graded as normal appearing (0–24% of normal lumen), mild narrowing (25–49%), moderate narrowing (50–69%) and severe narrowing (≥70%). Significant or severe forms of stenosis were defined as ≥50 and ≥70%, respectively. The plaque morphology was determined using the artery segment with the greatest occlusion and grading the plaque as calcified, mixed but primarily calcified, mixed but primarily noncalcified, and noncalcified. Coronary calcium scoring was assessed using the Agatston score method for all plaques.[11]

Pericardial fat measurement. For each patient, the contrast CT image was selected. The pericardial sac was traced at different cross-sections of the heart using the "Sculpt" function under "Segment Anatomy," with the computer interpolating between the slices. The lowest boundary is where the vessel

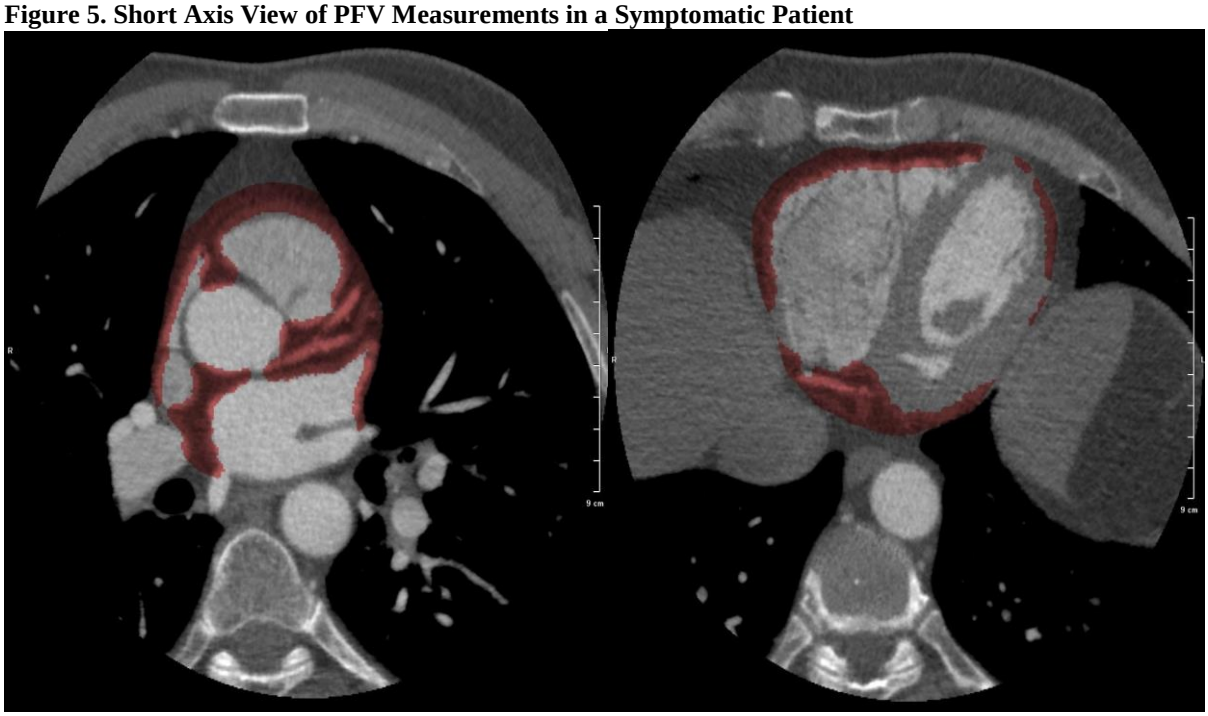
Figure 3. Flow Diagram



Post Descending Artery departs and the upper boundary is where the coronary artery Left Main departs. The coronary arteries and other visible vessels were marked with the "Vessel Probe" function and removed from the selected region. The Houndsfield units were limited to the range -190 and -30 and the volume of the region was measured using "Show Volume." Figure 5 shows the short-axial view of a symptomatic patient's heart at the lowest and uppermost part of the assessment with PFV highlighted in red.

Multivariate analysis. Categorical data was expressed as counts and percentages while continuous data was expressed as a mean and standard deviation.

Figure 5. Short Axis View of PFV Measurements in a Symptomatic Patient



RESULTS

Presence of atherosclerosis. The symptomatic and asymptomatic cohorts with atherosclerosis had a significantly higher median PFV (142.96 mL and 199.32 mL respectively) compared to those without (111.22 mL and 171.5 mL), with P<0.001. See Figure 6 for a box plot of this data.

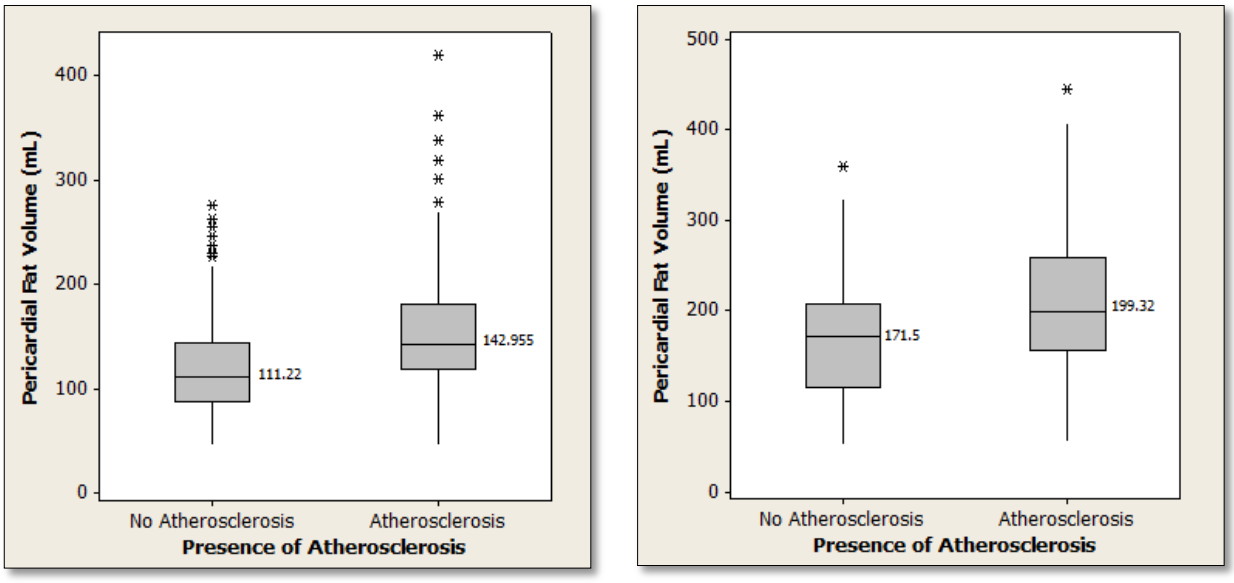
Using multivariate linear regression analysis when adjusting for age, gender, and BMI, a larger PFV was significantly associated with atherosclerosis in symptomatic patients (P=0.044). The odds ratio of this regression analysis was 1.01, meaning the odds of having atherosclerosis is greater in individuals with a large PFV than for those with a small PFV. The concordant percentage was 68.5%. For BMI, P=0.001. This association between PFV and atherosclerosis did not hold for the asymptomatic cohort (P=0.358). The BMI was not associated with atherosclerosis in the asymptomatic cohort, as well (P=0.419).

Stenosis grade. PFV was not a predictor in the symptomatic or asymptomatic populations of moderate (≥50%, P=0.158 and P=0.292 respectively), or severe (≥75%, P=0.087 and P=0.143) coronary artery stenosis.

Calcium scoring. PFV was not a predictor in the symptomatic or asymptomatic populations of CAC (P=0.403, P=0.292 respectively).

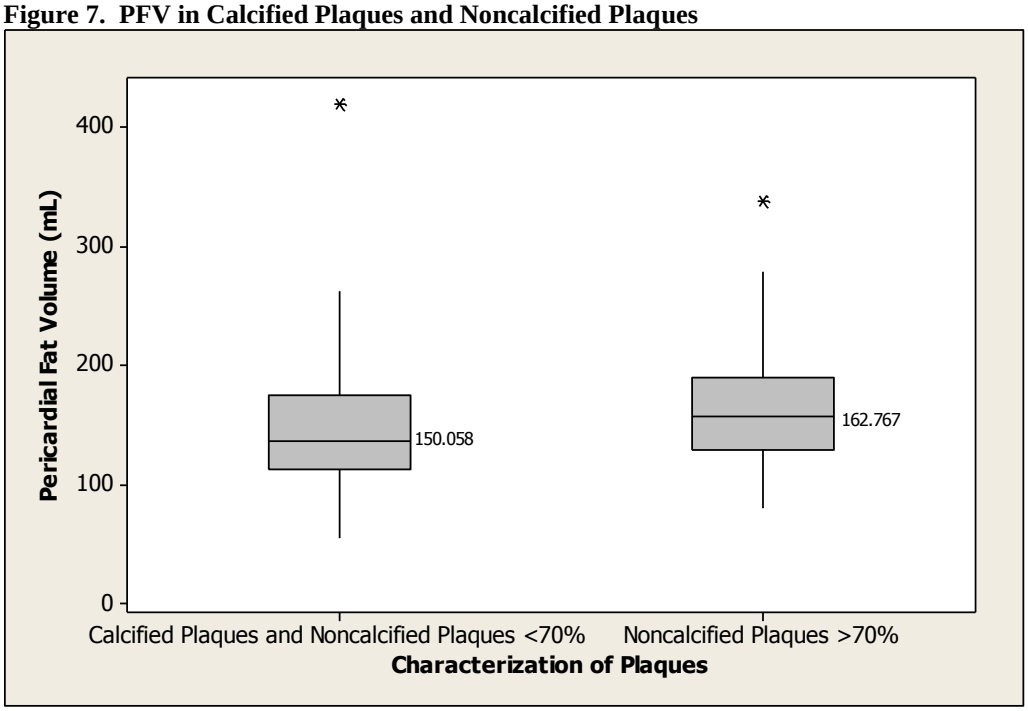
Morphology of plaques. The analysis was conducted on 113 symptomatic patients with plaque present. The median PFV in patients with noncalcified plaques with ≥70% occlusion (162.77 mL) was not significantly higher than the median PFV in patients with calcified plaques or with non-calcified plaques with <70% occlusion (150.06 mL), with P=0.349. This is shown in Figure 7. A larger PFV was significantly associated with the presence of noncalcified plaques with ≥70% occlusion (P=0.032). The odds ratio of this regression analysis was 1.03, meaning the odds of having a severe morphological characterization of the plaque for individuals with high PFV is greater than that for individuals with low

Figure 6. PFV in the Presence and Absence of Atherosclerosis (Left – Symptomatic, Right – Asymptomatic)



PFV. For BMI, P=0.682. There was no significant association with the presence of non-calcified plaques with ≥50% occlusion (P=0.397).

Figure 7. PFV in Calcified Plaques and Noncalcified Plaques



DISCUSSION

This study is the first to identify symptomatic patients and asymptomatic patients and characterize the strength of PFV as a predictor of CAD. We examined the association of PFV with the presence of atherosclerosis, the degree of stenosis, the CAC score, and the morphological characterization of present plaques. Increased PFV was associated with the presence of atherosclerosis and the presence of noncalcified plaques with ≥70% occlusion and independent of cardiovascular risk factors in symptomatic patients. Thus, PFV may play a role in determining an unfavorable cardiovascular risk profile. When adjusting for other cardiac risk factors – including smoking, family history, pretest risk, known coronary artery disease, hypertension, lipids, and angina – the association was attenuated. However, PFV cannot indicate the degree of stenosis or the CAC score.

The method of measuring the PFV in this study was similar to the work of other authors. The computerized measurement used is accurate to the physical anatomy – using cardiovascular magnetic resonance imaging of merino sheep hearts, the volume of the interpolated regions of adipose tissue were significantly correlated to the autopsy measures.[18] A popular method within literature is to select the region within the pericardial sac and restrict the pixels within it to a window of -195 to -45 Houndsfield units[19], though this limit has been modified appropriately between studies. One study chose to use the upper slice limit as the bifurcation of the pulmonary trunk and the lower limit as the last slice of the heart.[20]

In this study, an increased PFV was found to be associated with the presence of atherosclerosis in symptomatic – but not asymptomatic – individuals. It has been previously hypothesized that the close proximity of pericardial fat to the coronary arteries and the release of inflammatory cytokines from pericardial fat could contribute to atherosclerosis by increasing vascular stiffness.[21] The correlation between PFV and atherosclerosis has been investigated extensively among different populations. A previous study found that pericardial fat was more abundant in patients with coronary atherosclerosis plaques compared to those without, in both obese and non-obese patients.[22] This was also true in symptomatic patients.[23],[24],[25] Investigators in a study examining PFV in detecting coronary atherosclerotic lesions found PFV was significantly higher in patients with any coronary plaques as opposed to those without and also that PFV correlated with a larger number of coronary plaques.[26] Another study also showed that PFV was related to the presence of coronary artery plaques.[27] However, there is very little literature on asymptomatic people. A study by Miao et al. examined this population cohort and opposed our results. Using a population of 183 from the Multi_ethnic Study of Atherosclerosis (MESA), they found that symptomatic individuals display a similar correlation between pericardial fat and atherosclerosis.[28] However, this study used the eccentricity of the plaques (calculated by the ratio of maximal to minimal wall thickness) as an indicator of early-stage atherosclerosis. Eccentric lesions are also considered to be a less advanced disease compared to concentric lesions because of their larger lumen and smaller plaque, which reduce the burden on the artery. [29] Our study chose to define atherosclerosis as the presence of a plaque with ≥25% stenosis. This would suggest that pericardial fat could be related to the plaque features in asymptomatic patients as opposed to the presence of the plaque, as PFV is in symptomatic patients.

A previous study conducted by Nafakhi et al. has also suggested that pericardial fat is related to a significant coronary artery stenosis.[30] Our study did not find an association between PFV and stenosis with an occlusion ≥50% or ≥75% in either population cohort through multivariate analysis. The statistical analysis performed by Nafakhi et al grouped the 115 member population into ones with a PFV lower than the median and those with a PFV higher than the median and found a significant association observed between high PFV and significant coronary artery stenosis. Demographic differences between the groups could account for this association. Meanwhile, our analysis accounted for other other factors, including BMI, age, and gender. PFV appears to not be related to how occluded an artery is.

Plaques with a thin fibrous cap and a large necrotic core are especially prone to rupture and can attribute to acute thrombus formation compared to plaques that are predominately calcified.[31,32,33] The total amount of noncalcified plaque within a nonobstructive lesion has been associated with an increased risk in coronary events for NSTEMI patients, more so than the calcified and total plaque volume and other clinical variables.[34] We found that there is a relationship between a larger PFV and the presence of these more dangerous noncalcified plaques. However, the mean PFV was not significantly different between those with calcified plaques with≤100% and noncalcified plaques with <70% to noncalcified plaques with ≥70% occlusion. Results from several recent studies indicate that the epicardial fat volume (EFV) is associated strongly with the presence of plaque overall, but primarily with the presence of noncalcified plaque.[35] The observation that PFV was associated with dangerous plaque characteristics independent of coronary calcification is in agreement with a report by Ito et al. [36] However, investigators in another study found no significant difference between patients of a symptomatic with calcified, mixed, or noncalcified lesions.[37] Further inquiry needs to be performed in this field before being conclusive on the relevance of noncalcified plaques in the prognosis of CAD.

PFV was found to not be an indicator of CAC. One study examined the development of CAC and EFV within the span of 3-5 years for 1248 low-risk subjects with an initial CAC score of 0. One cohort of the population subsequently developed incident coronary calcium and the other cohort remained free of coronary calcium. The baseline EFV and the change in EFV were not related to the development of CAC.[38] Another study used a population-based study with 4,093 participants and found that those with a higher CAC score tended to have a higher EFV, suggesting that CAC and EFV may share some risk factors.[39] Because this study has shown PFV is not a predictor of CAC, but both PFV and CAC can predict atherosclerosis – it is possible that PFV may be linked to CAD in a mechanistic pathway different than coronary calcification, such as noncalcified plaque burden. Epicardial fat was associated with plaque burden in symptomatic patients with zero CAC, suggesting that EFV itself can be a useful marker of these dangerous noncalcified plaques while CAC can indicate another mechanism of CAD.[40] The prognostic value of PFV has been previously suggested to be used in conjunction with CAC, where a Cox regression model showed that EAT increased the predictive value of CAC score in patients with CAD.[41]

Pericardial fat was previously shown to be significantly higher in patients with coronary plaques and has also demonstrated that it was more highly associated with the development of coronary artery disease (CAD) than waist circumference.[42] PFV has also been shown to correlate with coronary atherosclerotic plaques, even the nonstenotic and noncalcified plaques, unlike waist circumference.[43] Throughout this study, PFV has demonstrated that it is a better measure of plaque morphology than BMI and can possibly characterize another pathway in the pathogenesis of CAD.

Limitations. The strength of this study was the large population size and the systematic method of measuring pericardial fat. Demographic differences between the populations may have resulted in a higher PFV in asymptomatic than symptomatic patients. However, multivariate analysis would account for these differences. The effects of confounding factors in a case-control study design can be further (stratified) by matching the populations. A greater percentage of the asymptomatic population had atherosclerosis present (73%) and ≥25% stenosis (35%) compared to the symptomatic population (59% and 30% respectively), suggesting that the asymptomatic population may was just as diseased – if not more – but without persisting symptoms.

CONCLUSION

Pericardial fat was associated with atherosclerosis and noncalcified plaques ≥70% in symptomatic patients and may be useful for risk stratification. Instead of being related to the amount of occlusion or the coronary artery calcium scoring, the PFV could instead measure other characteristics of the plaque, including its composition and morphology. PFV may affect another mechanism in the development of plaques in CAD – likely related to the volume of noncalcified lesions – than has previously been seen with stenosis grading and CAC scores. Further projects could look into the composition of plaques.

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