Pericardial Adipose Tissue Determined by Dual Source CT Is a Risk Factor for Coronary Atherosclerosis

Martin Greif, Alexander Becker, Franz von Ziegler, Corinna Lebherz, Michael Lehrke, Uli Brödl, Janine Tittus, Klaus Parhofer, Christoph Becker, Maximilian Reiser, Andreas Knez, Alexander W. Leber

Objectives—Pericardial fat as a visceral fat depot may be involved in the pathogenesis of coronary atherosclerosis. To gain evidence for that concept we sought to investigate the relation of pericardial fat volumes to risk factors, serum adiponectin levels, inflammatory biomarkers, and the quantity and morphology of coronary atherosclerosis.

Methods and Results—Using Dual source CT angiography pericardial fat volume and coronary atherosclerosis were assessed simultaneously. Plaques were classified as calcified, mixed, and noncalcified, and the number of affected segments served as quantitative score. Patients with atherosclerotic lesions had significant larger PAT volumes (226 cm$^3$±92 cm$^3$) than patients without atherosclerosis (134 cm$^3$±56 cm$^3$; $P<0.001$). No association was found between BMI and coronary atherosclerosis. PAT volumes $>$300 cm$^3$ were the strongest independent risk factor for coronary atherosclerosis (odds ratio 4.1; CI 3.63 to 4.33) also significantly stronger compared to the Framingham score. We furthermore demonstrated that elevated PAT volumes are significantly associated with low adiponectin levels, low HDL levels, elevated TNF-$
\alpha$ levels, and hsCRP.

Conclusion—In the present study we demonstrated that elevated PAT volumes are associated with coronary atherosclerosis, hypoadiponectinemia, and inflammation and represent the strongest risk factor for the presence of atherosclerosis and may be important for risk stratification and monitoring. (Arterioscler Thromb Vasc Biol. 2009;29:00-00.)

Key Words: 

There is growing evidence that regional visceral fat distribution may contribute to an unfavorable metabolic and cardiovascular risk profile. In patients with obesity, insulin resistance, diabetes, and hyperlipidemia visceral fat hypertrophies and transforms into a multifunctional organ that produces and secretes multiple endocrine and paracrine factors promoting inflammation, neovascularization, and oxidative stress, features that also characterize atherosclerosis. Pericardial fat as a local visceral fat depot with close proximity to coronary arteries may serve as a source of inflammatory cytokines and cells that may locally enhance systemic proatherogenic effects via outside to inside signaling. Thus it may be a specific parameter indicating an unfavorable cardio-metabolic state and may be used for risk stratification. To date, however, only little attention has focused on this regional fat depot located around the heart and its relation to cardiovascular risk factors, and the quantity and composition of coronary atherosclerosis is not well studied yet.

Multi-slice CT is a noninvasive tool that allows to reliably assess both obstructive and nonobstructive subclinical coronary artery disease in an earlier stage than invasive angiography. Based on density measurements, plaques can be further characterized in noncalcified, mixed, and calcified plaques. By using the same scan data this tool furthermore allows to quantify the exact pericardial fat volume. We thus sought to assess the relation of pericardial fat volume to cardiovascular risk factors, levels of inflammatory cytokines, adiponectin, and to the extent and the phenotype of coronary atherosclerosis.

Methods

For detailed methods, please see the supplemental materials (available online at http://atvb.ahajournals.org).

Patients

From March 2006 until August 2007 we included 286 consecutive patients who underwent dual-source multi-slice CT coronary angiography with an intermediate pretest likelihood for coronary artery disease. Further patient characteristics are given in Table 1.

Dual-Source CT

CT coronary angiography was performed using a Siemens Definition scanner (Siemens Medical Solutions), which uses 2 X-ray sources for image generation.

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Table 1. Baseline Characteristics

| Age, years | 61±12 |
| Male, %    | 67    |
| BMI, kg/m² | 27±4  |

Risk factors

| Smoking, % | 12    |
| Arterial hypertension, % | 43    |
| Hypercholesterolemia, % | 54    |
| Diabetes mellitus, % | 5     |
| No risk factors, % | 16    |

Plaque characteristics

| No plaques, % | 22    |
| Only noncalcified plaques, % | 16    |
| Mixed plaques, % | 41    |
| Only calcified plaques, % | 21    |

PAT volume

| PAT volume <100 cm³, % | 12    |
| PAT volume 100–200 cm³, % | 43    |
| PAT volume 200–300 cm³, % | 28    |
| PAT volume >300 cm³, % | 17    |

Adiponectin (ng/ml) 6255±4544

HDL, mg/dl 51±12

LDL, mg/dl 122±38

hs CRP, mg/dl 0.84±1.6

TNF alpha, pg/ml 6.8±3.7

IL 6, pg/ml 7.4±7

Table 2. Correlation of PAT Volume and Atherosclerotic Plaque Score in Different BMI Ranges

<table>
<thead>
<tr>
<th>BMI &lt;25</th>
<th>BMI 25 to 29</th>
<th>BMI &gt;29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation coefficient</td>
<td>r = 0.36</td>
<td>r = 0.34</td>
</tr>
<tr>
<td>P value</td>
<td>P = 0.0005</td>
<td>P = 0.0005</td>
</tr>
</tbody>
</table>

Spearman correlation coefficient.

 Coronary Analysis

Atherosclerotic plaques were classified as calcified, mixed, or noncalcified as described previously by our group. Based on the number of diseased segments a plaque score for each patient was calculated.10

Following the publications of Stary et al, Mautner et al, and most recently Bamberg et al, we defined existence of exclusively noncalcified plaques in a patient as early stage atherosclerosis.11–14

Peri- and Epicardial Fat Assessment Protocol

The pericardial fat volume was measured in cm³ using the Volume Analysis software tool of our cardiac workstation (Siemens, Leonardo). We defined pericardial fat as epicardial fat plus paracardial fat.

In a subset of 120 patients both epi- and pericardial fat volume was determined. Our analysis revealed an excellent correlation (Pearson correlation coefficient r = 0.97 between those two fat depots and an equal correlation of both fat depots with the number of atherosclerotic plaques r = 0.40 versus 0.41). Because epicardial fat volume was less reproducible (interobserver variability 15%) compared to PAT volume (8%), only the latter was used for further analysis. In our study, the acquisition of an additional data set was not necessary to determine PAT volume; the data set of coronary CTA could be used.

Results

DSCT angiography could be performed in all 286 patients. Adequate image quality for evaluation of coronary plaques could be obtained in 264 patients. The remaining 22 patients with insufficient image quality because of motion artifacts (n = 17) or insufficient opacification were excluded from the study. In all 264 study patients, PAT volume could be determined.

Morphology of Coronary Plaques

In 56 of 264 (21%) patients coronary plaques could be excluded, 42 (16%) patients showed only noncalcified plaques, 110 (42%) patients revealed a mixture of all plaque types, and 56 (21%) patients exclusively calcified plaques.

Relation of PAT Volume to Age, Gender, Risk Factors, and Coronary Plaques

We found a significant increase of PAT volume with age in both men and women from 148±77 cm³ in patients under 40 years to 252±118 cm³ for patients above 70 years (P < 0.05).

In all age groups women showed a significantly lower PAT volume compared to men. Patients with cardiovascular risk factors showed a significantly higher PAT volume compared to patients without cardiovascular risk factors (222±110 cm³ versus 187±71 cm³, P < 0.05). We also found an increase of PAT volume with an increasing number of risk factors: from 187±71 cm³ in patients without any risk factors up to 226±119 cm³ in patients with 3 or more risk factors (P < 0.05). PAT volume correlated with BMI (r = 0.45, P < 0.0001) and with the number of diseased coronary segments (r = 0.44, P < 0.0001). The correlation of PAT volume and number of plaques remained statistically significant even after adjusting for BMI (Table 2). There was no correlation between the presence or the number of atherosclerotic segments and BMI (r = 0.12, P = 0.13).

Patients with any coronary plaque showed a significant higher PAT volume compared to patients without coronary plaques (226±97 cm³ compared to 134±56 cm³, P < 0.01). This difference was persistent independent of patients age (Figure 1). A significant difference in PAT volume between patients with noncalcified, calcified, or a mixture of all plaque types could not be observed, although patients with exclusively noncalcified plaques had a significantly lower plaque burden (Table 3). All plaque types revealed a similar and significant correlation to PAT-volume (Table 3).

The relative risk for the presence of coronary plaques in dependence of PAT-Volume and risk factors is given in Table 4a and 4b. The area under the ROC curve to discriminate patients with atherosclerotic plaques from those without plaque was significantly higher for PAT volume compared to the Framingham score (0.82 versus 0.64, P < 0.02, Figure 2).

Relation of PAT Volume to Serum Lipids, Inflammation, and Adiponectin

Using the spearman correlation coefficient a significant correlation between PAT volume, Adiponectin (inverse correlation), HDL (inverse correlation), TNF-α, and hsCRP correlation coefficient, HDL (inverse correlation), TNF-α, and hsCRP.
could be observed (Table 4c). No correlation was found between PAT volume and IL 6 and LDL.

**Discussion**

The results of the present study demonstrate that PAT volume is strongly associated with the presence and extent of coronary atherosclerosis. This relation is independent of body mass index. Compared to all traditional risk factors including the Framingham Score, PAT volumes $>300$ cm$^3$ represented the strongest predictor for the presence of coronary atherosclerosis. We further found a significant association of PAT volumes to hypoadiponectinemia and systemic inflammation. Patients revealing only noncalcified plaques already reveal significantly elevated PAT volumes, indicating that PAT volume accumulation may precede plaque calcification and the development of mature atherosclerotic plaques in general. Thus PAT volume quantification may be used in addition to calcium scoring to identify patients with coronary artery disease even in the absence of coronary calcium.

**Measurements of PAT Volume**

It is widely accepted that the amount of visceral fat is an important cardiovascular risk factor. Because quantification of visceral abdominal fat is difficult, waist circumference is clinically used as a surrogate marker. Waist circumference, however, could be confounded by large amounts of subcutaneous fat, and a number of studies have demonstrated that waist circumference reflects both subcutaneous and visceral fat amount with only moderate correlations to intraabdominal fat.$^{15}$ Thus efforts are made to develop better measures of visceral adiposity.$^{16}$ In the context of coronary artery disease, PAT is attributable to its location of particular interest. Thus peri- and epicardial fat was quantified in recent studies by different imaging tools. Iacobellis et al have shown using echocardiography that the thickness of epicardial fat anteriorly to the right ventricle is highly correlated to the amount of visceral adipose tissue determined by MRI.$^{16}$ They further demonstrated that epicardial fat thickness correlated well
with PAT volume determined by MRI. In two additional studies using CT, PAT volume was highly correlated to visceral abdominal fat.9,17

By echocardiography the thickness of PAT anterior to the right ventricle is generally used as a surrogate marker for the entire PAT volume. Iacobellis et al have shown that these measurements correlate well with PAT volume measurements by MRI.15 The advantage of echocardiography is the fact that it can be easily performed and is less demanding compared to MRI and CT. The disadvantage is the inability to determine the exact PAT volume, as the distribution of PAT around the heart is variable, single measurements of fat-thickness at one location only may significantly under- or overestimate the real PAT volume. Multi-slice CT allows to visualize coronary arteries in a detailed manner and allows to detect and characterize atherosclerotic plaques even in subclinical stages. Because of the submillimeter resolution it is the most accurate tool to quantify PAT volume. Therefore it offers the unique opportunity to simultaneously assess both the presence and the extent of coronary atherosclerosis and the magnitude of PAT volume. MSCT exams are, however, associated with radiation exposure. In our study a protocol was used for CT coronary angiography with an average dose of 9.4 msv.

Table 3. Plaque Phenotype and Its Relationship to PAT Volume and Age

<table>
<thead>
<tr>
<th></th>
<th>No Plaques</th>
<th>Noncalcified</th>
<th>Mixture of All Plaques</th>
<th>Calcified Plaques</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>56</td>
<td>42</td>
<td>110</td>
<td>56</td>
</tr>
<tr>
<td>Age</td>
<td>52±14</td>
<td>59±11</td>
<td>65±8*</td>
<td>65±9*</td>
</tr>
<tr>
<td>PAT, cm³</td>
<td>133±56</td>
<td>222±77*</td>
<td>223±94*</td>
<td>223±91*</td>
</tr>
<tr>
<td>Segment score, range</td>
<td>0</td>
<td>1–9</td>
<td>1–15</td>
<td>2–26</td>
</tr>
</tbody>
</table>

Mean 2.5±1.8 Mean 3.5±3.2 Mean 8.5±5.3

Correlation to PAT-volume r

<table>
<thead>
<tr>
<th></th>
<th>No Plaques</th>
<th>Noncalcified</th>
<th>Mixture of All Plaques</th>
<th>Calcified Plaques</th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td>0.23</td>
<td>0.24</td>
<td>0.27</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Mean age of patient groups depending on coronary artery plaque phenotype compared to patients with only noncalcified plaque.

Mean PAT volume of patient groups depending on coronary artery plaque morphology compared to patients without coronary artery plaque. Segment Score=Amount of diseased segments; *P<0.05.

Table 4. Relative Risk for Coronary Atherosclerosis in Dependence of Risk Factors and PAT Volume

<table>
<thead>
<tr>
<th></th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>1.6</td>
<td>(1.38–1.81)*</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>1.8</td>
<td>(1.59–2.27)*</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2.5</td>
<td>(2.11–3.02)*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.0</td>
<td>(2.60–3.61)*</td>
</tr>
<tr>
<td>Framingham score</td>
<td>2.8</td>
<td>(2.42–3.50)*</td>
</tr>
<tr>
<td>PAT volume&gt;300 cm³</td>
<td>4.1</td>
<td>(3.63–4.33)*</td>
</tr>
</tbody>
</table>

Multivariable Cox proportional hazards model predicting the relative risk for coronary atherosclerosis in dependence of cardiovascular risk factors, Framingham score (10 unit increase) and pericardial fat volume >300 cm³. *P<0.05 compared to the patient group without cardiovascular risk factors. Corrected for age and sex.

b. Univariable Cox Proportional Hazards Model Predicting the Relative Risk for Coronary Atherosclerosis in Dependence of Pericardial Fat Volume

<table>
<thead>
<tr>
<th>PAT Volume</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>100–200 cm³ PAT</td>
<td>1.89</td>
<td>(1.61–2.11)*</td>
</tr>
<tr>
<td>200–300 cm³ PAT</td>
<td>3.22</td>
<td>(2.88–4.49)*</td>
</tr>
<tr>
<td>Over 300 cm³ PAT</td>
<td>3.76</td>
<td>(3.45–4.68)*</td>
</tr>
</tbody>
</table>

*Significant difference (P<0.05) compared to patients with a pericardial fat volume under 100 cm³.

Corrected for age, sex, and conventional cardiovascular risk factors.

c: Spearman Correlation of PAT and Serum Markers

<table>
<thead>
<tr>
<th></th>
<th>Adiponectin</th>
<th>HDL</th>
<th>LDL</th>
<th>Hs CRP</th>
<th>TNF-alpha</th>
<th>IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation coefficient r</td>
<td>−0.238</td>
<td>−0.252</td>
<td>0.112</td>
<td>0.122</td>
<td>0.18</td>
<td>0.12</td>
</tr>
<tr>
<td>P value</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.06</td>
<td>0.04</td>
<td>0.002</td>
<td>0.11</td>
</tr>
</tbody>
</table>

P value <0.05 indicates a significant correlation.

Figure 2. ROC curve analysis to demonstrate the discriminatory power of PAT in the diagnosis of coronary plaques. A cut-off value of 300 cm³ determined a specificity to detect any plaque of 95%. Accuracy values are given for different thresholds.
PAT Volume and Its Relation to Cardiovascular Risk Factors
Recent studies have demonstrated that epicardial and PAT volume is related to cardiovascular risk factors indicating the metabolic syndrome. Iacobellis et al demonstrated an independent and significant relation of epicardial fat thickness assessed by echocardiography to fasting insulin levels and diastolic blood pressure. In addition to these findings we now demonstrated that PAT volume increases with the number of risk factors. In the multivariate analysis it is significantly correlated to hypertension, diabetes, age, and hypercholesterolemia, and thus it reflects the clustering effect of multiple risk factors in the individual patient and is a good indicator for the metabolic syndrome.

PAT Volume and Its Relation to Coronary Atherosclerosis
So far there are only a few studies investigating the association of PAT volume and coronary atherosclerosis, although there is striking evidence that visceral fat is adversely related to cardiovascular risk. In a recent study by Jeong et al., PAT volume was the best predictor for angiographic disease severity compared to waist circumference or visceral abdominal fat volume. Ahn et al have demonstrated that patients with significant obstructive coronary artery disease have significantly more epicardial fat determined by echocardiography than patients with non significant coronary artery disease. These results are in line with the observations of our present study. Patients with evidence for any coronary plaques substantially. The ROC analysis revealed that 95% of patients with PAT volumes >300 cm³ had detectable coronary atherosclerosis. Compared to traditional risk factors PAT volumes >300 cm³ represent the strongest independent risk factor for the presence of coronary plaques (odds ratio 4.1). Interestingly, we found absolutely no association between BMI and presence or extent of coronary atherosclerosis, so that this parameter seems to be not useful in predicting coronary artery disease.

Association of PAT Volume and Plaque Composition
In addition to plaque burden we examined for the first time the association of plaque composition and PAT volume. Prior studies using MSCT have demonstrated that the number of noncalcified plaques is associated with unstable coronary artery disease, and it was suggested that these lesions may indicate an elevated disease activity. Bamberg et al recently demonstrated that noncalcified plaques on MSCT are a feature of early stage atherosclerosis and that their number decreases with age whereas the number of calcified lesions increases. Unfortunately CT does not yet allow an accurate and reliable further classification of noncalcified lesions in fibrous and lipid-rich vulnerable lesions, so that we only classified in calcified, mixed, and noncalcified lesions. We found no difference of PAT-Volumes between patients with only noncalcified, mixed, or only calcified lesions. All types of plaques individually and independently correlated significantly with PAT-volume with similar correlation coefficients. However, patients with exclusively noncalcified plaques were significantly younger and had a significantly lower plaque burden than patients with calcified lesions. These findings indicate that PAT-Volume accumulation is already present before plaque calcification occurs and it may also precede development of atherosclerosis in general. This speculation is supported by a study of Lear et al who observed that abdominal visceral fat accumulation was more strongly associated with carotid intimal thickening than to plaque number and plaque area. They hypothesized that visceral adipose tissue–derived proatherogenic factors are responsible for early endothelial dysfunction and predisposition for atherosclerosis. Thus it may be used additionally to calcium scoring as a parameter indicating an increased cardiovascular risk, and it may indicate an elevated disease activity even in patients with lower plaque burden. However, whether these cross sectional observations will translate into a higher rate of complications in prospective trials has to be proven.

Pathophysiological Considerations
Visceral fat is able to produce large amounts of proinflammatory cytokines like TNF-α, IL-6, free fatty acids, or plasminogen activator inhibitor-1 (PAI-1). All of them are also involved in atherosclerosis and thrombosis. Adiponectin is a hormone that is exclusively synthesized by adipocytes and has antiatherosclerotic properties. The release of adiponectin is reduced by TNF-α in states like obesity and insulin resistance. We assume that the correlation of PAT volume and systemic inflammation and hypoadiponectinemia, observed in our study, is driven by the fact that PAT volume is a surrogate marker for the entire visceral fat burden. Nevertheless, because of its location around the coronary vessels, evidence suggests that PAT locally enhances systemic atherogenic effects, accelerating initiation and progression of coronary atherosclerosis. In patients undergoing bypass surgery it could be demonstrated that PAT reveals a pathological adipokine and cytokine profile as well as a large number of inflammatory cells, which could not be observed in subcutaneous fat. The exact mechanism on how cyto- and chemokines originating from pericardial adipocytes enter the vessel wall and accelerate and initiate atherosclerosis is not clear yet. These inflammatory mediators may exert their effect through diffusion and direct adventitial contact. In a porcine model adventitial treatment with proinflammatory factors resulted in early stage atherosclerosis and migration of inflammatory cells into the vessel wall. Another mechanism may be a direct communication of the vasa vasorum with epicardial adipocytes. The concept of this kind of local signaling is supported by some interesting observations in...
human studies: (1) There is a closer correlation and association of PAT to coronary atherosclerosis than of abdominal visceral fat to coronary atherosclerosis.17 (2) In the human myocardial bridge where visceral fat around the coronary vessels is totally absent, no atherosclerotic plaque development can be observed. (3) By using intravascular ultrasound it could be demonstrated that plaques develop most frequently with a pericardial spatial orientation suggesting a permissive role of pericardial fat.26 (4) In coronary arteries that on autopsy revealed plaques with large necrotic cores more macrophages in periadventitial fat could be observed than in vessels with lipidcore plaques,4,27,28

**Limitations and Clinical Perspectives**

The findings of our study identify PAT volume as a strong and independent risk factor for coronary artery disease. By using CT this local fat depot can be easily quantified even on native CA scoring scans with an acceptable radiation exposure. Future prospective trials, however, are needed to prove the incremental prognostic impact of this parameter over CA scoring and traditional risk factors. As we have found some evidence that pathological PAT accumulation may precede the development of atherosclerotic plaque and indicates a proatherogenic state, this fat depot may be an attractive target for antiatherosclerotic therapies, and future research should also address the effect of different drugs and weight modifying strategies on PAT volume.

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**Disclosures**

Alexander Leber is an employee for Siemens AG Healthcare.

**References**


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Supplemental Material

MATERIAL and METHODS

Patients:

From march 2006 until august 2007 we included 286 consecutive patients who underwent dual-source multi-slice CT-coronary angiography for exclusion of coronary artery stenosis due to typical and atypical chest pain with an intermediate pretest likelihood for coronary artery disease. None of the patients had prior known coronary artery disease. Of the 286 patients that were assessed, 193 were male. Mean age of the study population was 61 ± 12 years (range 20 - 87). 156 patients were less than or equal to and 130 patients were over the age of 65 years.

Further patient characteristics are given in table I.

Risk factors:

For all patients we evaluated conventional cardiovascular risk factors by personal interview and screening of medical records. In addition arterial blood pressure, LDL-cholesterol level, HDL cholesterol level, triglyceride level and blood glucose level were determined in the fasting state. Diabetes was defined as a fasting glucose level > 120mg/dl or treatment with a glucose lowering agent, Hypercholesterolemia was defined as a total Cholesterol level > 200mg/dl or treatment with a lipid lowering medication. Hypertension was defined as a systolic blood pressure > 140mmHg or a diastolic value > 90mmHg.

Serum Markers:

Blood samples were stored at -70°C until analysis. Serum levels of adiponectin (µg/ml), TNF-alpha and Interleukin 6, were determined with a commercial enzyme-linked immunosorbent assay (R&D, Wiesbaden, Germany). Plasma LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglycerides were measured by routine enzymatic methods. Determination of
high sensitivity C-reactive protein (hsCRP) levels was performed at the Department of Clinical Chemistry (Campus Grosshadern, University of Munich, Germany).

**Dual-source CT:**

CT-coronary angiography was performed using a Siemens Definition scanner (Siemens Medical Solutions, Forchheim Germany) that uses two X-ray sources for image generation. With two tubes and two detectors mounted at orthogonal orientation in the gantry, the transmission data required for the reconstruction of one slab can be acquired in half the time needed by a conventional MSCT-system. A gantry rotation time of 0.33 s thus results in a temporal resolution of 82.5 ms. Tube voltage for CT-angiography was 120 kV for both tubes in patients with a bodyweight >80 kg and 100 kv for those with a weight < 80kg. Current was 560 mAs with modulation, and full current between 30-50%-80% of the cardiac cycle, gantry rotation time 0.33 s, and pitch 0.2-0.44 adapted to the HR. Per rotation 64 slices were generated with a collimation of 0.6 mm, leading to an isotropic voxel resolution of approximately 0.6 mm edge length and 0.2 mm³ volume. Before the scan, nitroglycerine was administered sublingually. A bodyweight- adapted volume of contrast agent (1.25 cm²/kg bodyweight; Ultravist 370, Schering, Berlin, Germany) was injected continuously at a calculated rate to achieve constant injection duration of 20 s. The scan was started with a delay of 5 s after the density in the aortic root exceeded a density value of 100 HU (bolus tracking). A saline flush (100 cm³ at 5 cm³/s) was applied to maintain a compact bolus. Axial images were reconstructed with 0.75 mm slice thickness and 0.5 mm increment using a medium sharp convolution kernel (B26f) and retrospective ECG gating. The reconstructions were performed in 10% steps over the entire R-R cycle using a single-segment algorithm that utilizes a quarter segment of projection data from both detectors.
Dual source-CT image analysis

Coronary analysis:

In the first step all reconstructed data sets were evaluated at different ECG-phases for diagnostic image quality and the optimal data set was then chosen for analysis. The DSCT datasets were evaluated by two independent investigators using a dedicated cardiac workstation (Siemens, Leonardo Circulation).

Atherosclerotic plaque were classified as calcified, mixed or noncalcified as described previously by our group. Calcified plaques were defined as lesions with a Hounsfield Unit value above 130. Noncalcified plaques were defined as structures clearly assignable to the vessel wall (in at least two views) with densities less then the lumen contrast. Plaques in which <50% of the plaque area was occupied by calcium were classified as mixed. The coronary tree was segmented according to the suggestions of the AHA into a 15-segment model. Each segment was further divided in a proximal and a distal segment. Each segment was then classified as containing calcified, noncalcified, mixed or no plaque. Based on the number of diseased segments a plaque score for each patient was calculated.

Peri- and Epicardial fat assessment protocol:

CT measurements of PAT volume were made with a dual-source multi-slice CT System. The same images used for the analysis of atherosclerotic plaque were used to measure pericardial adipose tissue volumes. There was no impact on PAT volume measurement by cardiac contrast enhancement. The pericardial fat volume was measured in cm³ using the Volume Analysis software tool of our cardiac workstation (Siemens, Leonardo).

We defined pericardial fat as epicardial fat plus paracardial fat. Epicardial fat was defined as any adipose tissue located within the pericardium. Paracardial fat was defined as any adipose tissue situated on the external surface of the parietal pericardium. Our upper cut off point in the axial slices was the bifurcation of the pulmonary artery. Inferiorly, the
analysis volume was segmented from the intrabdominal adipose tissue. The anterior border was defined by the chest wall and the posterior extend by the oesophagus and the aorta descendens. The region of interest containing the heart and the surrounding adipose tissue was assessed by manually tracing in the axial slices. The observer had simultaneously access to the coronal images.

After the segmentation of the heart and surrounding adipose tissue from the remainder of the thorax, a threshold of -250 to -30 CT units (ie, Hounsfield units) was applied to isolate the adipose tissue (fat-) containing voxels. The adipose tissue voxels were then summed to achieve adipose tissue volume in cm³. (s. figure 1) In a subset of 120 patients both epi- and pericardial fat volume was determined. Our analysis revealed an excellent correlation (Pearson correlation coefficient $r= 0.97$ between those two fat depots and an equal correlation of both fat depots with the number of atherosclerotic plaque $r= 0.40$ vs. 0.41). Because epicardial fat volume was less reproducible (introobserver variability 15%) compared to PAT volume (8%) only the latter was used for further analysis. In our study, the acquisition of an additional data set was not necessary to determine PAT volume; the data set of coronary CTA could be used. The radiation dose for CT-angiography in this study was on average 9.4 msv.

**Statistical analysis:**

Statistical analyses were performed using the SPSS software package (version 10.0, SPSS Inc. Chicago, Illinois). All values are expressed as mean score ± standard deviation except where indicated. Due to the non normality of the distribution of the PAT volume statisticall analysis were performed on the natural log transformed PAT volume scores = ln (1 + PAT volume score). To compare score values in different risk groups we used the Wilcoxon signed rank test for unpaired data. A p-value under 0.05 was considered to indicate statistical significance. We performed univariate Cox regression analysis to calculate hazard ratio and 95 percent confidence interval of coronary plaque in dependence of cardiovascular risk
factors (patients without cardiovascular risk factors served as the reference group), age, sex, and PAT volume (patients with PAT volume below 100 cm³ served as the reference group). To demonstrate the discriminatory power of PAT volume in the diagnosis of coronary plaques the area under the receiver-operating characteristic (ROC) curve was determined. All figures are given as mean standard ± deviation.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>193</td>
</tr>
<tr>
<td>Female</td>
<td>93</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 +/−12 (range 20-87)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>131</td>
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<tr>
<td>Diabetes</td>
<td>18</td>
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<tr>
<td>Smokers</td>
<td>32</td>
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<tr>
<td>Family history of premature coronary artery</td>
<td>59</td>
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<tr>
<td>Hypercholesterolaemia</td>
<td>170</td>
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<tr>
<td>No risk factors</td>
<td>55</td>
</tr>
<tr>
<td>Epicardial fat (cm³)</td>
<td>206 +/−97 (range 47-754)</td>
</tr>
</tbody>
</table>

Baseline characteristics of 286 individuals included in the study