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Determination of Pericardial Adipose Tissue Increases the Prognostic Accuracy of Coronary Artery Calcification for Future Cardiovascular Events

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Key Words
Cardiovascular risk · Coronary calcification · Multislice CT · Pericardial adipose tissue

Abstract
Objectives: Pericardial adipose tissue (PAT) is associated with coronary artery plaque accumulation and the incidence of coronary heart disease. We evaluated the possible incremental prognostic value of PAT for future cardiovascular events. ***Methods:*** 145 patients (94 males, age 60 ± 10 years) with stable coronary artery disease underwent coronary artery calcification (CAC) scanning in a multislice CT scanner, and the volume of pericardial fat was measured. Mean observation time was 5.4 years. ***Results:*** 34 patients experienced a severe cardiac event. They had a significantly higher CAC score (1,708 ± 2,269 vs. 538 ± 1,150, $p < 0.01$), and the CAC score was highly correlated with the relative risk of a future cardiac event: 2.4 (1.8–3.7; $p = 0.01$) for scores >400, 3.5 (1.9–5.4; $p = 0.007$) for scores >800 and 5.9 (3.7–7.8; $p = 0.005$) for scores >1,600. When additionally a PAT volume >200 cm^3 was determined, there was a significant increase in the event rate and relative risk. We calculated a relative risk of 2.9 (1.9–4.2; $p = 0.01$) for scores >400, 4.0 (2.1–5.0; $p = 0.006$) for scores >800 and 7.1 (4.1–10.2; $p = 0.005$) for scores >1,600. ***Conclusions:*** The additional determination of PAT increases the predictive power of CAC for future cardiovascular events. PAT might therefore be used as a further parameter for risk stratification.

Introduction

Coronary artery disease (CAD) is still the leading cause of death in western industrialized countries. A more effective and patient-centered prophylaxis is needed to decrease CAD-associated morbidity and mortality. To establish an effective individual prophylaxis of future cardiovascular events, reliable risk stratification is crucial.

Coronary artery calcification (CAC) has shown to be a highly specific marker of coronary atherosclerosis and its extent is directly related to the atherosclerotic plaque burden [1]. Several clinical studies identified CAC as a valuable predictor for the risk of subsequent cardiovascular events in the context of patient screening and in study groups with cardiovascular risk factors [2–5]. Various

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studies indicate that CAC has a significantly higher diagnostic accuracy in predicting cardiovascular events and offers the possibility of a more individual risk assessment compared to conventional risk stratification scores (i.e. Framingham and UK Prospective Diabetes Study risk scores [6–8]).

Visceral adipose tissue plays an important role in the development of the metabolic syndrome and is an important risk factor for CAD [9, 10]. Pericardial adipose tissue (PAT) is a local visceral fat depot. Due to its close proximity to the coronary arteries, it may serve as a source of inflammatory cytokines and cells that locally enhance systemic pro-atherogenic effects via outside-to-inside signaling [11, 12]. PAT may therefore be a parameter indicating an unfavorable cardiometabolic state and may be used for risk stratification. In a previous study, we demonstrated that elevated PAT volumes are associated with coronary atherosclerosis and an increased number of diseased coronary segments [13]. It is still unclear whether PAT possesses a predictive value for future cardiovascular events similar to CAC.

Both parameters, CAC and PAT, can be easily assessed non-invasively by multi-slice CT without the administration of contrast agents. PAT volume and CAC score can be determined by analyzing the same data set, thus we sought to evaluate the incremental prognostic value of PAT and CAC over CAC alone for predicting the occurrence of cardiac events and long-term survival of patients with stable CAD.

Table 1. Baseline characteristics of the study patients

Males	94 (65)
Females	51 (35)
Age, years (range)	60 ± 10 (29–87)
Hypertension	108 (74)
Diabetes	25 (17)
Smokers	64 (44)
Family history of premature CAD	49 (38)
Hypercholesterolemia	90 (62)
Risk factors	
None	8 (0.5)
One	27 (19)
Two	67 (46)
Three	36 (25)
Four	7 (0.5)
Risk factors per patient, n	2.2 ± 1.1
Pericardial fat, cm^3 (range)	240 ± 110 (72–789)
Coronary artery calcium score (range)	847 ± 1,555 (0–9,586)
CAD history	
One-vessel disease	46 (33)
Two-vessel disease	69 (45.5)
Three-vessel disease	30 (21)
Therapy	
Acetylsalicylic acid	139 (95)
Clopidogrel	44 (30)
Statin	119 (82)
ACEI	122 (84)
Angiotensin inhibitor	17 (12)
β-Blocker	115 (79)

Data are means ± SD or numbers (%). ACEI = Angiotensin-converting enzyme inhibitor.

Patients and Methods

Patients

Patients with stable CAD (n = 145, 94 males, age 60 ± 10 years), defined by the criterion of at least one coronary artery stenosis (>50% in coronary angiography) and/or prior myocardial infarction (MI; 29 patients; 22%) underwent CAC scanning between January 2000 and April 2006. Of 145 patients, 95 where symptomatic at baseline, and 47 had prior stent implantation. Patients were recruited during their follow-up visits according to routine protocols or in the event that new symptoms appeared. All patients gave written informed consent to undergo multislice CT for CAC scanning according to a protocol that was approved by the local clinical institutional review board. Patients and treating physicians were unaware of CAC results, so that an influence of clinical treatment could be excluded.

Patients with acute coronary syndrome, advanced ischemic cardiomyopathy, defined as reduced left ventricular ejection fraction (<35%) and patients who had undergone coronary artery bypass grafting were excluded.

Further patient characteristics are shown in table 1.

Risk Factors

The diagnosis of diabetes mellitus was confirmed in all patients by glucose determination in the fasting state as described by the definition of the World Health Organization [14]. In every patient, arterial blood pressure (three times after 10 min of rest), and levels of LDL and HDL cholesterol, and triglycerides were determined in the fasting state in our hospital. Arterial hypertension was defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg. Family history was defined as coronary heart disease in male first-degree relatives <55 years and coronary heart disease in female first-degree relatives <65 years. Smoking was defined as current smoking or a lifetime history of having smoked within the last 5 years.

Coronary Artery Calcium Scanning

CAC scanning was performed using a Siemens multislice CT scanner (Somatom Sensation 4 or 16; Siemens Medical Solutions, Forchheim, Germany) in the high-resolution mode. ECG-triggered scans of 100-ms duration were acquired at 80% of the R-R interval during one end-inspiratory breath-holding period. A total of 40.3-mm-thick slices were obtained covering the whole heart. Coronary calcifications were automatically defined as lesions with a density >130 HU in >4 adjacent pixels. For quantifi-

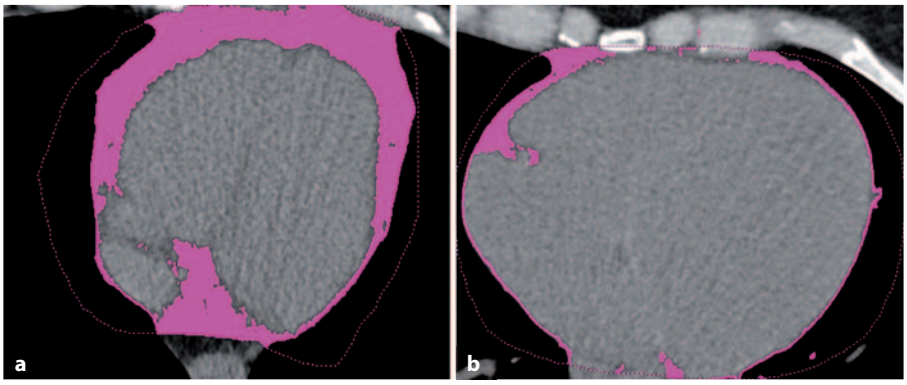

Fig. 1. a Patient with a PAT volume >200 cm^2 and a CAC score >400 cm^3 who suffered a severe cardiac event during the follow-up. **b** Patient with a PAT volume <100 cm^2 and a CAC score <400 without any severe cardiac event during the follow-up.

cation of coronary calcium, the Agatston score was calculated, which constitutes the product of the surface area of the lesion and a weighting factor ranging from 1 to 4. The weighting factor was based on the peak density of the lesion [15]. Coronary segments with stents were excluded from quantifications.

Pericardial Fat Assessment Protocol

CT measurements of pericardial fat were performed as described by our group previously [11]. The same images used for the analysis of CAC scores were also used to measure PAT. The volume of pericardial fat was measured in cubic centimeters using the volume analysis software tool of our cardiac workstation (Leonardo; Siemens Medical Solutions, Forchheim, Germany).

Pericardial fat was defined 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. The superior cutoff point in the axial slices was the bifurcation of the pulmonary artery. Inferiorly, the volume analyzed was segmented up to the intraabdominal adipose tissue. The anterior border was defined by the anterior chest wall and the posterior border by the esophagus and the descending aorta. The region of interest containing the heart and the surrounding adipose tissue was assessed by manual tracing of the axial slices. The observer had simultaneous 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 HU was applied to isolate the adipose tissue (fat)-containing voxels. The adipose tissue voxels were then summed to obtain adipose tissue volume (in cm^3; fig. 1). PAT measurements were performed by two independent investigators who were unaware of CAC scores.

Patient Outcomes

Patient outcomes were recorded by telephone interviews by an investigator blinded to the patients' test results. Patients were followed for the occurrence of severe cardiac events, defined as either cardiac death (CD), confirmed by a review of death certificates and hospital charts or physician s' records, or MI, defined by typical ECG findings, myocardial enzyme elevations and typical symptoms. Coronary revascularization was confirmed by a review of hospital charts or physician's records. The decision to perform coronary revascularization was made on the basis of clinical angiographic findings of stenosis >50% or the occurrence of symptoms in conjunction with significant SPECT myocardial perfusion imaging under stress conditions. Patients with non-CD were excluded from the study.

Statistical Analysis

Categorical variables are presented with absolute and relative frequencies; continuous variables are presented as means ± SD. For between-group comparisons, unpaired Student's t tests were used for parametric data, and Mann-Whitney tests for nonparametric data. Where appropriate, a Pearson 2 or Fisher's exact test was performed to determine significant differences.

The end of follow-up was defined as either the date of a severe cardiac event or the end of the study period. For univariate analysis of time-to-event data, Kaplan-Meier survival curves, including log rank tests, were constructed. Non-CD were treated as right-censored data points in the Kaplan-Meier plots. The multivariate Cox proportional hazard model was used to obtain hazard ratio estimates and 95% confidence intervals for CAC score and PAT adjusted for sex, age and coronary risk factors, including hypertension, hypercholesterolemia and diabetes. Annualized event rates were calculated on the basis of events per patient per year. Statistical software (SAS, version 9.1; SAS Institute, Cary, N.C., USA) was used to perform the analyses. Values of $p < 0.05$ were considered statistically significant.

Results

PAT Volume and CAC Scores

CAC scanning could be performed and adequate image quality for evaluation of CAC could be obtained in all 145 patients. The PAT volume could be determined in all 145 study patients. There was no significant difference in mean age between men (58.3 ± 10.1 years) and women (61.3 ± 10.3 years). Image analysis for PAT as well as for CAC was performed by two experienced investigators (M.G. and A.B.). Interobserver variability was assessed

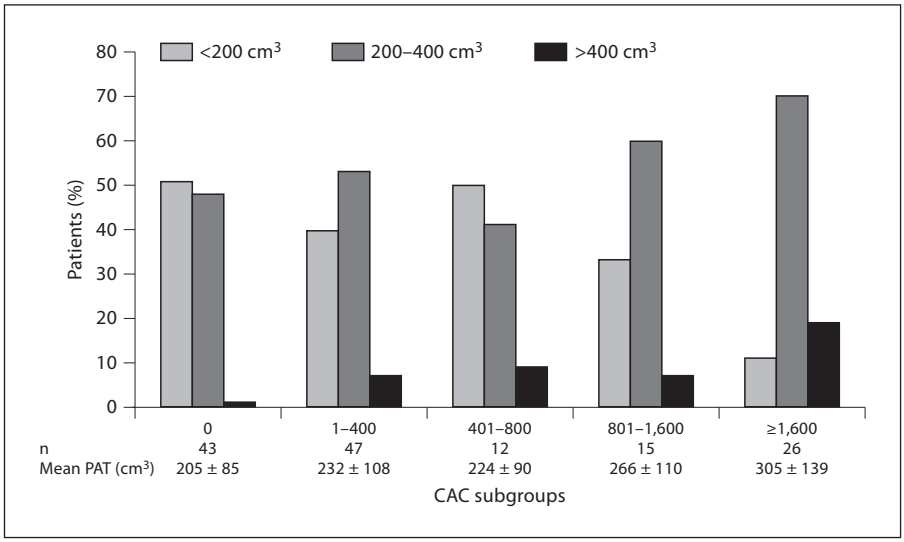

Fig. 2. Bar graphs show the distribution of PAT volumes in different CAC subgroups. Data below bars are numbers of patients and mean PAT volumes of different CAC subgroups.

using Bland/Altman analysis. Interobserver variability of PAT volume and CAC measurements was low with 6 and 4%, respectively.

Mean CAC score was 847 ± 1,555 (males 1,152 ± 1,709 and females 692 ± 1,381). Patients with cardiovascular events showed a significantly higher CAC score compared to event-free patients (1,708 ± 2,269 vs. 538 ± 1,150, $p < 0.001$).

Mean PAT volume was 240 ± 110 cm^3. Figure 2 shows the distribution of PAT volume in the different CAC subgroups. In patients with CAC scores >1,600, the fraction of patients with a PAT volume <200 cm^3 was significantly lower compared to patients with CAC scores ≤400. The percentage of patients with a PAT volume >400 cm^3 increased from 1% for patients with a CAC score of 0, to 20% for patients with a CAC score >1,600. However, the range of PAT volumes in the different CAC score subgroups showed no significant difference: in all CAC subgroups, patients with PAT volumes <200 but also >400 cm^3 could be found.

Outcome, Events and Survival Analysis

The median follow-up time was 5.4 years (range 3–8 years). Two patients were excluded from the analysis due to death of non-cardiac cause. Ten patients (6.9%) suffered a severe cardiac event (4 CD and 6 MI) and in 22 patients (15.3%) a coronary revascularization had to be performed. In total, 32 of 143 patients (22.3%) had severe cardiac events or underwent coronary revascularization during the follow-up period. Event rates of the different subgroups are shown in table 2.

Table 2. Frequency of severe cardiac events during the long-term follow-up

Group	Patients n (%)	Severe cardiac events, n (%)
All patients	143	32
CAC score		
0–400	90 (62.9)	10 (31.2)
401–800	12 (8.3)	6 (18.7)
901–1,600	15 (10.4)	5 (15.6)
>1,600	26 (18.1)	11 (34.3)
PAT volume, cm^3		
0–200	55 (38.4)	8 (25)
200–400	77 (53.8)	24 (75)
400–600	10 (6.9)	0
>600	1 (0.6)	0
CAC score with PAT <200 cm^3		
0–400	41 (28.6)	2 (6.2)
401–800	6 (4.1)	3 (9.3)
801–1,600	5 (3.4)	1 (3.1)
>1,600	3 (2)	2 (6.2)
CAC score with PAT >200 cm^3		
0–400	49 (34.2)	8 (25)
401–800	6 (4.1)	3 (9.3)
801–1,600	10 (6.9)	5 (15.6)
>1,600	23 (16)	8 (25)

Traditional cardiovascular risk factors such as age >65 years, hypertension, hypercholesterolemia or diabetes mellitus could not be identified as significant risk factors for future cardiovascular events (table 3). The Cox proportional hazard model, which was adjusted for age, sex

Table 3. Analysis of patient characteristics and imaging scores as predictors of clinical outcome

Variable	Severe cardiac events, univariate analysis		Severe cardiac events, multivariate analysis	
	hazard ratio	p value	hazard ratio	p value
Hypertension	1.1 (0.8–1.3)	NS		
Hypercholesterolemia	1.3 (0.8–1.6)	NS		
Diabetes	1.6 (1.1–1.8)	NS		
Age >65 years	1.1 (0.7–1.3)	NS		
CAC score >400	2.6 (2.0–3.3)	0.02		
PAT volume >200	2.1 (1.6–3.0)	0.017		
CAC score >400			2.4 (1.8–3.7)	0.01
CAC score >800			3.5 (1.9–5.4)	0.007
CAC score >1,600			5.9 (3.7–7.8)	0.005
PAT volume >200			2.1 (1.4–3.2)	0.01
PAT volume >400			2.2 (1.5–3.4)	0.01
PAT volume >600			2.5 (1.6–3.9)	0.009
CAC score >400 and PAT >200			2.9 (1.9–4.2)	0.009
CAC score >400 and PAT >400			3.0 (1.9–4.5)	0.009
CAC score >400 and PAT >600			3.0 (1.9–4.9)	0.009
CAC score >400 and PAT >200			2.9 (1.9–4.2)	0.01
CAC score >800 and PAT >200			4.0 (2.1–5.0)	0.006
CAC score >1,600 and PAT >200			7.1 (4.1–10.2)	0.005

Data in parentheses are 95% confidence intervals. NS = Not significant. PAT in cm^3.

and coronary risk factors, was used to identify CAC score and PAT volume as the only independent predictors for future severe cardiovascular events in this high-risk patient population, in both uni- and multivariate analyses. In univariate analysis, CAC score >400 (odds ratio 2.6; p = 0.02) and PAT >200 cm^3 (odds ratio 2.1; p = 0.017) were identified as risk factors for future cardiovascular events in our study group. The odds ratio for future severe cardiovascular events for a CAC score >400 in the multivariate analysis was 2.4 (1.8–3.7; p = 0.01) and increased in parallel with the CAC score: 3.5 (1.9–5.4; p = 0.007) for CAC scores >800 and 5.9 (3.7–7.8; p = 0.005) for CAC scores >1,600.

The risk for future cardiovascular events in the multivariate analysis for patients with PAT volume >200 cm^3 was 2.1 (1.4–3.2; p = 0.01). In contrast to the CAC score, where a further increase in risk with higher CAC scores was demonstrated, the risk for future cardiovascular events did not further increase with increasing PAT volumes (2.2 for PAT scores >400 cm^3 and 2.5 for PAT scores >600 cm^3).

The CAC score was the most important risk factor for future cardiovascular events and the risk increased in parallel with the CAC scores. Nevertheless, a PAT volume >200 cm^3 as a concomitant risk factor offered incremental prognostic value over the CAC score alone. When used in combination with an elevated CAC score, we calculated a further increased risk for future events (2.4 vs. 2.9 for CAC scores >400, 3.5 vs. 4.0 for CAC scores >800 and 5.9 vs. 7.1 for CAC scores >1,600; table 3).

Kaplan-Meier survival curves showed an increased risk of cardiovascular events for patients with a CAC score >400 in comparison to patients with a score <400 (fig. 3a). In the subgroup of patients with a score >400 and a PAT volume >200 cm^3, there was a significantly higher risk of cardiovascular events compared to those with a PAT volume <200 cm^3 (fig. 3b).

Discussion

The aim of this pilot study was to evaluate if PAT increases the prognostic value of CAC for future cardiovascular events.

Our study population consisted of patients with known CAD, therefore the clinical impact of an intensified risk stratification by PAT determination is limited. On the other hand, we managed to archive an adequate

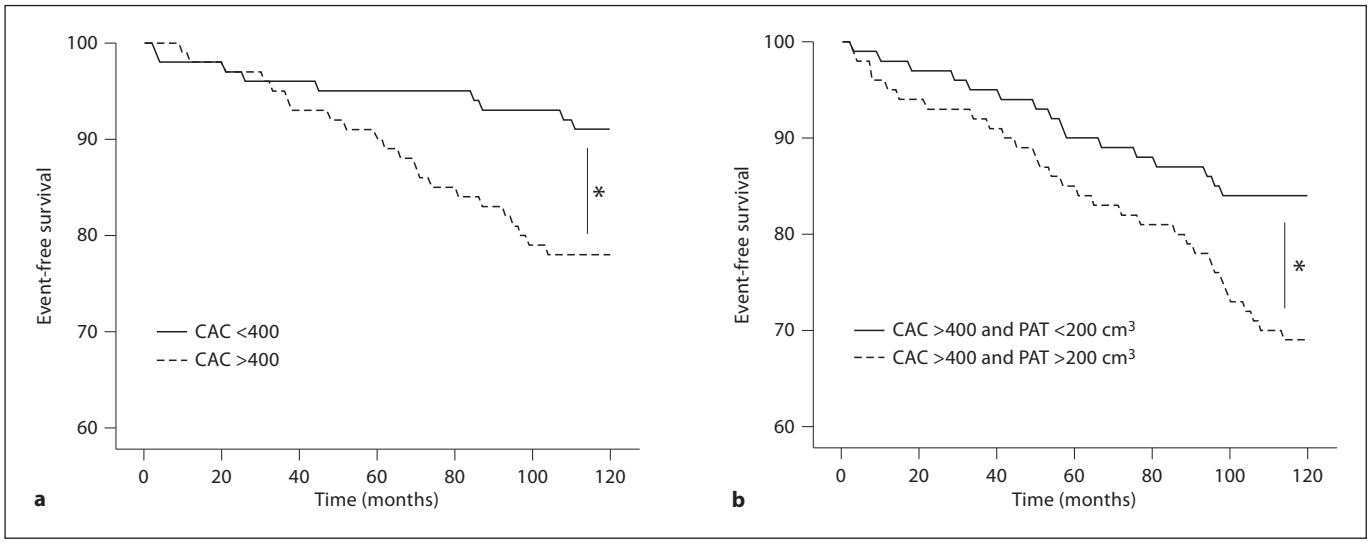

Fig. 3. Kaplan-Meier survival (freedom of severe cardiac events, e.g. CD, nonfatal MI and percutaneous coronary intervention) curves as functions of CAC score (**a**; $p < 0.05$) and CAC score and PAT volume (**b**; * $p < 0.05$).

event rate to evaluate the predictive value of PAT. The event rate in our study cohort (22.3%) is comparable to the event rate in other studies investigating patients with known CAD and a high risk for future cardiovascular events [16].

CAC is a well-established risk marker for future cardiovascular events. In this study, patients with cardiovascular events also had a significantly higher CAC score compared to those without events. CAC was the strongest risk factor for future cardiovascular events compared to classic cardiovascular risk factors such as hypercholesterolemia, hypertension, diabetes, smoking or a family history of CAD. These findings are consistent with those of several other studies that have shown that CAC is superior to classic cardiovascular risk factors or other risk scores like the Framingham risk score or the ATB III score, not only in asymptomatic patients but also in patients with known CAD [7, 8, 17–19]. The risk for future cardiovascular events increased continuously with the amount of CAC [5, 20]. The relative risk increased from 2.4 for patients with scores from 400 to 800 to 3.5 for scores from 801 to 1,600 and 5.9 for scores >1,600. Additionally, we found a high negative predictive power of up to 100%. This was also shown in several other studies [4, 6, 21]. Correspondingly, the proportion of patients with an event-free survival was significantly higher in patients with scores <400 (fig. 3a). The conventional cardiovascular risk factors age, hypercholesterolemia, hypertension or diabetes did not help to stratify the cardiovascular risk within this high-risk population (table 3).

Being a visceral fat depot, PAT produces a large amount of proinflammatory chemokines like TNF-α, IL-6, free fatty acids or plasminogen activator inhibitor-1, which are involved in atherosclerosis and thrombosis. Adiponectin, which has anti-atherosclerotic properties, shows an inverse correlation with PAT [12]. Several studies demonstrated that PAT is related to cardiovascular risk factors as well as to the metabolic syndrome. Furthermore, PAT is related to CAD [22, 23]. In addition, we recently demonstrated that PAT reflects the extent of coronary atherosclerosis and the individual plaque burden. The PAT volume correlated with the relative risk of CAD and the number of atherosclerotic lesions [13]. Due to these findings, we hypothesize that elevated PAT indicates an unfavorable metabolic status and might be used as an additional risk factor for future cardiovascular events. Similar findings were reported in patients without known CAD by Ding et al. [24] and Cheng et al. [25].

As indicated by the low interobserver variability, PAT volume could be determined very reliably. The determination of PAT volume itself can be performed easily using the same data set acquired for CAC screening without additional radiation exposure.

In our patient population, PAT volume increased with increasing CAC score (fig. 2). Nevertheless, patients with a PAT volume >400 cm^3 and patients with a PAT volume

<200 cm^3 could be found in all CAC subgroups. This indicates that PAT can be considered an independent risk factor that might offer additional information to risk stratification.

Corresponding results were found in the analysis of cardiovascular events: a PAT volume >200 cm^3 was associated with an increased relative risk (2.1; p = 0.01) independent of concomitant risk factors; a further increase in the relative risk for patients with higher PAT volumes could not be observed. These finding comply with the results of Ding et al. [24], who recently demonstrated an association between PAT and the incidence of coronary heart disease.

Using PAT volume >200 cm^3 and CAC score as a combined risk factor, we could increase the predictive power in comparison to CAC alone. PAT volume >200 cm^3 determined in addition to the CAC score significantly increased the relative risk for future cardiovascular events: 2.9 for scores of 400–800, 4.0 for scores of 801–1,600 and 7.1 for scores >1,601. Thus, the additional determination of PAT increased the predictive power of CAC for future cardiovascular events. The combination of these two parameters may provide improved risk stratification.

Limitations

The study population was relatively small and consisted of patients with known cardiovascular diseases and with a high risk for future cardiovascular events. Our study population cannot be considered as an unselected population and our results may not be applicable to asymptomatic patients without known obstructive CAD. Because of our small study population we cannot exclude that small but significant associations between PAT, CAC, cardiovascular risk factors and CAD may have not been detected. To achieve a sufficient event rate for our pilot study, we concentrated on this high-risk population. This also explains why conventional risks factors could not be used for further risk stratification in this population. The data of our pilot work have to be confirmed by larger studies in asymptomatic patients.

Although the CAC score combined with PAT volume offers the possibility of improved risk stratification, the clinical benefit is limited in the study population, as all patients are already eligible for secondary prevention. Again, the clinical relevance has to be evaluated in a larger asymptomatic population.

Due to the fact that vascular segments with stents were excluded from analysis, we may have slightly underestimated the CAC score in these patients. However, as the segments with stents represent only a small portion of the whole coronary system, this possible consequent underestimation of the CAC score should be minimal.

Conclusions

The findings of our study identify PAT as a risk marker for future cardiovascular events in addition to CAC. By using the data of a CT data set for CAC screening, this local fat depot can be easily quantified with a high reproducibility. However, future prospective trials are needed to confirm the supportive power of this parameter. In addition, it remains to be evaluated whether the identified patients at risk can profit from a prophylactic medical treatment.

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