The obesity epidemic and its metabolic consequences are a major focus of current cardiovascular research. Increased visceral adiposity is thought to be a marker of cardiovascular risk through production and regulation of atherogenic inflammatory cytokines. Total intrathoracic fat (ITF) is a combination of both epicardial adipose tissue (EAT) and thoracic fat (TF). Unlike TF, EAT has a common embryological origin with abdominal visceral fat. The latter is associated with both coronary artery disease (CAD) risk factors and atherosclerotic plaque. All of these fat volumes (v) (ie, ITFv, EATv, and TF volume) can be directly measured by noncontrast cardiac computed tomography (CT).

Clinical Perspective on p 66

The coronary artery calcium score (CACS) measured by CT is directly related to the extent of coronary atherosclerotic plaque burden. CACS severity is known to predict risk for cardiac events in asymptomatic and symptomatic individuals and beyond that provided by the Framingham risk score (FRS) or C-reactive protein. CACS can also risk stratify low to intermediate-risk patients with acute chest pain (ACP) of unclear cardiac pathogenesis who present to the emergency department for evaluation. There are preliminary data that fat volumes may add prognostic value in patients with CACS >400, CACS is most strongly correlated with outcome. (Circ Cardiovasc Imaging. 2013;6:58-66.)

Key Words: angina ■ atherosclerosis ■ coronary artery disease ■ coronary computed tomography ■ epicardial fat

Background—Noncontrast cardiac computed tomography allows calculation of coronary artery calcium score (CACS) and measurement of epicardial adipose tissue (EATv) and intrathoracic fat (ITFv) volumes. It is unclear whether fat volume information contributes to risk stratification.

Methods and Results—Cardiac computed tomography was performed in 760 consecutive patients with acute chest pain admitted thorough the emergency department. None had prior coronary artery disease. CACS was calculated using the Agatston method. EATv and ITFv were semiautomatically calculated. Median patient follow-up was 3.3 years. Mean patient age was 54.4±13.7 years and Framingham risk score 8.2±8.2. The 45 patients (5.9%) with major acute cardiac events (MACE) were older (64.8±13.9 versus 53.7±13.4 years), more frequently male (60% versus 40%), and had a higher median Framingham risk score (16 versus 4) and CACS (268 versus 0) versus those without events (all P<0.01). The MACE group had a higher median of EATv (154 versus 116 mL) and ITFv (330 versus 223 mL), and a higher prevalence of EATv >125 mL (67% versus 44%) and ITFv >250 mL (64% versus 42%) (all P<0.01). CACS, EATv, and ITFv were all independently associated with MACE. CACS was associated with MACE after adjustment for fat volumes (P<0.0001), whereas EATv and ITFv improved the risk model only in patients with CACS >400.

Conclusions—CACS and fat volumes are independently associated with MACE in acute chest pain patients and beyond that provided by clinical information alone. Although fat volumes may add prognostic value in patients with CACS >400, CACS is most strongly correlated with outcome. (Circ Cardiovasc Imaging. 2013;6:58-66.)

Does Quantifying Epicardial and Intrathoracic Fat With Noncontrast Computed Tomography Improve Risk Stratification Beyond Calcium Scoring Alone?

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Study Population

This was a substudy of an observational cohort trial evaluating the prognostic value of CACS in 1031 low to intermediate-risk patients with ACP. The original study cohort has been previously described in detail. Patients were excluded if they had prior CAD, ischemic ECG findings diagnostic of an acute coronary syndrome, an elevated initial
Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Included Patients n=760</th>
<th>Excluded Patients n=271</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>54.4±13.7</td>
<td>52.9±12.9</td>
<td>0.12</td>
</tr>
<tr>
<td>Female</td>
<td>450 (59.2)</td>
<td>168 (62.0)</td>
<td>0.43</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>30.6±7.3</td>
<td>30.5±6.9</td>
<td>0.85</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>36 (4.7)</td>
<td>16 (5.9)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hypertension</td>
<td>430 (56.6)</td>
<td>160 (59.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>Abnormal lipids</td>
<td>252 (33.2)</td>
<td>100 (36.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>112 (14.7)</td>
<td>40 (14.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Never</td>
<td>621 (81.7)</td>
<td>218 (80.4)</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>98 (12.9)</td>
<td>41 (15.1)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>41 (5.4)</td>
<td>12 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Mean FRS</td>
<td>8.2±8.2</td>
<td>8.0±8.1</td>
<td>0.66</td>
</tr>
<tr>
<td>Median FRS</td>
<td>4 (1–16)</td>
<td>4 (1–16)</td>
<td>0.56</td>
</tr>
<tr>
<td>CACS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>125±429</td>
<td>104±399</td>
<td>0.29</td>
</tr>
<tr>
<td>Median</td>
<td>0 (0–42)</td>
<td>0 (0–19)</td>
<td>0.14</td>
</tr>
<tr>
<td>≤25</td>
<td>450 (59.2)</td>
<td>175 (64.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>&gt;25</td>
<td>174 (22.9)</td>
<td>50 (18.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;100</td>
<td>71 (9.3)</td>
<td>28 (10.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;400</td>
<td>65 (8.6)</td>
<td>18 (6.6)</td>
<td></td>
</tr>
<tr>
<td>ITFv, mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>255±132</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>227 (163–321)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25</td>
<td>433 (57.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25</td>
<td>327 (43.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EATv, mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>127±61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>117 (83–159)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤125</td>
<td>415 (54.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;125</td>
<td>345 (45.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or median (interquartiles) for continuous variables and number (%) for categorical variables. BMI indicates body mass index; CACS, coronary artery calcium score; CAD, coronary artery disease; EATv, epicardial adipose tissue volume; FRS, Framingham risk score; and ITFv, intrathoracic fat volume.

troponin level, or hemodynamic instability. All patients underwent noncontrast CT after admission. The present study consisted of those 760 patients who had CT data available for calculation of both CACS and fat volumes. There were no significant differences in baseline characteristics (Table 1) between the 760 patients in the present study and the 271 who were excluded from analysis.

Calcium Scoring Procedure

Patients underwent CACS on a 16-slice multidetector CT scanner (Philips Precedence, Best, The Netherlands) without pretreatment with β-blockers. Images were acquired during a single breath hold using prospective electrocardiographic gating with imaging triggered at 75% of the R-R interval (collimation 8×2.5 mm, voltage 120 keV, current 75 mAs). Reconstructed axial images of 2.5 mm thickness were displayed for review, and the CACS was calculated as previously described.20 The computer software automatically defined the presence of calcified lesions as those >130 Hounsfield units and calculated the CACS, which was reviewed by a cardiologist. CACS results were categorized as normal (CACS = 0), mild (1–100), moderate (101–400), or severe (>400) calcification. The interpreting physician was blinded to both fat volume results and patient outcome.

Quantification of ITFv and EATv

EATv and ITFv were measured offline on a Philips Extended Brilliance Workspace Workstation, version 4.02.145 (Philips Healthcare, Cleveland, OH) on previously acquired noncontrast cardiac CT scans performed for measurement of CACS. A semiautomated volumetric method using the Volume software module was used to quantify the amount of ITF and EAT (Figure 1). Adipose tissue was defined by an attenuation coefficient between −40 and −200 Hounsfield units.21 Regions of interest for ITF measurements were defined semiautomatically by the program as any adipose tissue present in the thoracic cavity, excluding the posterior mediastinum, from the level of the pulmonary trunk bifurcation to the diaphragm. The anterior and posterior limits for ITF were the ribcage and descending aorta and esophagus, respectively. A similar method was used for EAT measurement where regions of interest were defined for any adipose tissue located within the pericardial sac from the level of the pulmonary trunk bifurcation to the visceral layer of the pericardium beyond the apex of the heart. In both measurements all automatically traced slices were reviewed and verified for accuracy. Necessary adjustment was made manually on both axial images and the 3-dimensional rendered fat shell. Because EAT is incorporated within the ITF measurement, we also calculated the extent of ITF volume by subtracting EAT from ITF. Abdominal visceral fat was not evaluated because CT imaging was limited to the chest.

One investigator quantified all fat measurements blinded to clinical, CACS, and patient outcome information. Fat measurements were performed by an investigator who was not trained in the measurement of CACS.

Intra- and interobserver reproducibility for quantification of ITFv and EATv were assessed from 20 randomly selected CT scans. The mean intraobserver difference was 0.4±7.8 mL for ITFv and 3.1±10.5 mL for EATv (Wilcoxon signed-rank nonparametric test: P=0.88 for ITFv and 0.36 for EATv) with corresponding Spearman correlation coefficients of 0.99 and 0.98 (both P<0.0001). The mean interobserver difference was 4.1±2.5 mL for ITFv and 2.6±3.8 mL for EATv (Mann–Whitney nonparametric test: P=0.75 for ITFv and 0.78 for EATv) with corresponding Spearman correlation coefficient of 0.99 and 0.98 (both P<0.0001).

Data Collection and Patient Follow-up

All clinical information was obtained on admission by research study personnel. All subjects had calculation of their FRS based on standard criteria.22 Serial cardiac biomarkers, ECG tracings, and the results of all cardiac procedures performed during hospitalization were collected by research personnel at the time of hospital discharge.

After hospital discharge, patients were prospectively contacted by phone at 1 week, 1 month and >6 months after admission, and then in November 2010 to identify those with a new cardiac event. Research personnel asked specific, scripted questions regarding subsequent visits to the emergency department or readmission to the hospital for evaluation of chest pain symptoms, myocardial infarction, cardiac catheterization, or coronary revascularization (angioplasty, stenting, or bypass procedures). One qualified and blinded physician investigator reviewed the medical records of all patients who reported subsequent hospitalizations or cardiac procedures after the index admission. Death was confirmed by either immediate family members or through the Social Security death index. The time from performance of cardiac CT to a new cardiac event or the final contact encounter in those without events was chosen for outcome analysis.

Cardiac Events

Major acute cardiac events (MACE) were defined as cardiac death, nonfatal myocardial infarction, and unstable angina pectoris.
Cardiac death was defined as death caused by myocardial infarction, congestive heart failure or arrhythmia, or any unknown causes of death not explained by a noncardiac pathogenesis. The diagnosis of myocardial infarction was defined as chest pain associated with typical ECG findings and a troponin I >0.10 ng/dL. Unstable angina was defined as follows: (1) new onset or worsening ACP at rest necessitating hospitalization, (2) normal troponin levels, and (3) significant (>70%) major epicardial CAD by invasive angiography with or without revascularization. In patients who had multiple events, MACE were counted only once. The median follow-up was 3.3 years.

Statistical Analysis
Baseline characteristics were summarized by MACE status and are presented as mean±SD for continuous variables, as medians and interquartiles for skewed continuous variables, and as numbers and percentages for categorical variables.

Kaplan–Meier estimates of MACE rates and overall survival were calculated in strata defined by the following: (1) CACS categories 0, 1 to 100, 101 to 400, and >400; and (2) EATv and ITFv dichotomized at 125 mL and 250 mL, respectively. The CT date was used as time 0. Two-sided log-rank tests were used to determine significance. Cox proportional hazards model was used to calculate unadjusted and adjusted hazard ratios and corresponding 95% CIs with respect to CACS, EATv, and ITFv. The baseline model included FRS and body mass index (BMI). Subsequent models were further adjusted for ITFv (dichotomized at 250 mL) and EATv (dichotomized at 125 mL) when evaluating CACS; and CACS (0 versus >0 and 400 versus <400) when evaluating ITFv or EATv. An identical analysis was also performed to define the relationships between CACS and TF volume. The proportionality assumption of Cox models was verified by including the time-dependent interaction of each covariate with survival time in the model. There was no evidence of violation of this assumption for any covariate. Global χ² statistic by likelihood ratio test was also used to determine whether addition of fat volume would improve MACE prediction accuracy beyond clinical and CACS variables. All analyses were performed with STATA version 11 (StataCorp. 2009; Stata Statistical Software; Release 11; College Station, TX; StataCorp LP). Statistical significance was defined as 2-tailed P<0.05 for all tests.

Results
Baseline Characteristics
The mean age for all patients was 54.4±13.7 years, with 59% female and 15% diabetic. In the 760 patients, 450 (59.2%) had CACS 0, 174 (22.9%) had CACS 1 to 100, 71 (9.3%) had CACS 101 to 400, and 65 (8.6%) had CACS >400. The mean ITFv was 255±132 mL, and 327 patients (43%) had an ITFv >250 mL. The mean EATv was 127±61 mL, and 345 patients (45.4%) had an EATv >125 mL (Table 1).

Cardiac Events
Forty-five patients (5.9%) had at least 1 MACE (6 cardiac deaths, 17 nonfatal myocardial infarctions, and 22 with unstable angina) during a median follow-up period of 3.3 (range 0–5.03) years.

Relationships Between BMI, CACS, and Fat Volume
Overall, there was a weak direct relationship among BMI, EATv, and ITFv and a weak inverse relationship between BMI and CACS (Figure 2).
Higher CACS severity was associated with significantly higher fat volumes. The mean EATv based on CACS severity was 113±53 mL for CACS 0; 142±65 mL for CACS 1 to 100; 149±70 mL for CACS 101 to 400; and 159±70 mL for CACS >400 (P<0.001). The mean ITFv was 222±107 mL for CACS 0; 293±138 mL for CACS 1 to 100; 297±150 mL for CACS 101 to 400; and 337±167 mL for CACS >400 (P<0.001). Despite these overall group relationships, a very poor correlation was observed between fat volumes and CACS in individual patients (Figure 3).

Cardiac Events Based on CACS and Fat Volume
The 45 patients with MACE had a significantly higher median CACS (268 versus 0, P<0.0001) and events increased with increasing CACS severity. Annual MACE rates in each of the CACS categories were as follows: 0.40% (CACS of 0); 2.38% (CACS 1–100); 6.51% (CACS 101–400); and 11.20% (CACS >400) (P<0.001 for trend). The unadjusted hazard ratio for development of MACE in patients with a CACS >0 was 11.95 (95% CI, 4.71–30.28; P<0.0001) (Table 2). Only 5 of 450 patients with a CACS of 0 had a subsequent cardiac event. Two patients had an isolated troponin elevation during their initial hospitalization but no event in follow-up and both had a normal gated stress myocardial perfusion study. Another patient had elective coronary revascularization performed 26 months after the index CACS study. The last 2 patients also had a normal gated stress myocardial perfusion study during the index hospitalization but died from unknown causes 12 and 36 months later.

The median EATv (154 mL versus 116 mL; P=0.006) and ITFv (330 mL versus 223 mL; P=0.001) were significantly larger in patients with events versus those without events, respectively. A significantly higher percentage of patients with MACE had a large EATv >125 mL (67% versus 44%; P=0.005) or ITFv >250 mL (64% versus 42%; P=0.003), respectively. Annual MACE rates were 3.23% versus 1.31% for EATv dichotomized at 125 mL (P=0.003) and 3.25 versus 1.35% for ITFv dichotomized at 250 mL (P=0.004) (Figure 4B). The unadjusted hazard ratios for log2(EATv) and log2(ITFv) were 2.02 (95% CI, 1.3–3.1; P=0.002) and 2.16 (95% CI, 1.43–3.27; P<0.0001), respectively (Table 2). The unadjusted hazard ratios for the fourth versus the first quartiles of EATv and ITFv were 3.62 (95% CI, 1.46–8.97; P=0.005) and 3.34 (95% CI, 1.43–7.80; P=0.005), respectively.

Cardiac Events Based on Combined CACS and Fat Volume Analysis
Overall risk stratification was improved by combining fat volume and CACS severity information (Figure 5). Annual MACE rates significantly increased with increasing CACS severity in both the low and high EATv and ITFv categories (P<0.0001 for each trend). Annual MACE rates also showed nonsignificant increases with higher fat volumes among most CACS categories. However, when individual fat volumes were plotted within each CACS category, no specific cutpoints for

Figure 2. Linear regression analysis showing significant but weak correlations between body mass index (BMI) and log2(EATv) (A), log2(ITFv) (B), and log(CACS) (C) results. BMI indicates body mass index; CACS, coronary artery calcium score; EATv, epicardial adipose tissue volume; and ITFv, intrathoracic fat volume.
EATv or ITFv were found that better defined patients with and without MACE beyond CACS alone (Figure 6).

**Multivariable Risk Analyses**

By multivariable analysis, CACS, EATv, and ITFv were independently associated with MACE, even after adjustment for FRS and BMI (Table 2, Model 1A and Table 3, Model 1B). However, fat volumes lost significance after adding CACS into the model (\(P=0.128\) for \(\log_2[EATv]\) and \(P=0.05\) for \(\log_2[ITFv]\)), whereas with CACS there remained a significant independent association with MACE after adjustment for either EATv or ITFv \((P<0.0001)\) (Table 2, Model 2A and Table 3, Model 2B). EATv and ITFv retained statistical significance only when the CACS was dichotomized at 400 (Table 3, Model 2B). These relationships were similar whether using continuous or specific cutpoints of fat volumes. Similar results were obtained when using TF volume in the above analysis.

Global \(\chi^2\) statistic by likelihood ratio test was used to further evaluate the relationship between CACS and fat volumes (Figure 7). As in the multivariable analysis, CACS, EATv, and ITFv all added significantly to the clinical model (FRS and BMI), but EATv and ITFv did not improve risk prediction once CACS was known (Figure 7A and 7B). Conversely, CACS improved risk prediction beyond the combined clinical and EATv or ITFv models (Figure 7A and 7B). The only model where EAT and ITF fat volumes significantly increased the global \(\chi^2\) values was when CACS was dichotomized at 400 (Figure 7C and 7D).

**Discussion**

Our study demonstrates the independent value of CACS and fat volumes for defining risk beyond clinical variables alone in a large cohort of patients admitted through the emergency department with ACP of uncertain cardiac pathogenesis. Our results confirm that CACS, as a marker of the presence and...
extreme of coronary atherosclerosis, is best at discriminating low from high-risk individuals. During a median follow-up of 3.3 years, the annual event rate was only 0.4% in patients with a CACS of 0 but increased to 11.2% in patients with a severe CACS (>400). Our study is currently the largest patient series evaluating the long-term risk implications of CACS among those with ACP and should thereby provide reassurance that a 0 CACS identifies a very low-risk population. Our event rates are consistent with those previously reported in patients with a CACS of 0 and no history of CAD.12–18 Although our results indicate that fat volumes identify populations at risk for cardiac events, these markers may only contribute minimal additional information once CACS is known.

**Visceral Fat and Coronary Atherosclerosis**

EAT has a common embryological origin within abdominal visceral fat and may be a more specific marker for CAD than ITF,23 and a better predictor of MACE.19 EAT is located within the pericardial sac and tracks the coronary arteries in the atrioventricular and interventricular grooves. Its close proximity to the epicardial coronary arteries has implicated EAT in the pathogenesis of coronary atherosclerosis through paracrine production of cytokines1,2 and leukocyte infiltration (ie, macrophages) around the heart.24 However, EAT may also provide cardioprotection through secreting cytokines, such as interleukin-4, transforming growth factor-β, and adiponectin.25 Postmortem studies report significantly higher levels of adiponectin in EAT isolated from subjects with normal coronary arteries versus those with severe CAD.25 Currently, it is unclear whether proatherogenic or cardioprotective EAT factors predominate and in which patients. Our results indicate that ITFv and EATv were very similar at defining risk populations at different CACS levels. Slightly better measurement than EAT.10

**CACS Versus Fat Burden**

CACS is known to add incremental prognostic value to traditional clinical risk factor analysis,26,27 C-reactive protein results,18 and the results of functional stress tests, such as myocardial perfusion imaging.28 Our study demonstrates that larger fat volumes define MACE better than clinical risk factors alone. The weak correlation we observed between fat burden and CACS raised the possibility that the former may provide independent and possibly additive value to CACS in risk assessment. Although fat burden was independently correlated with MACE in our study, CACS was much stronger

---

### Table 2. Multivariable Risk Analysis: CACS >0 (n=310) Vs CACS =0 (n=450)

<table>
<thead>
<tr>
<th>Model 1A: adjusted for FRS and BMI.</th>
<th>Model 2A: adjusted for FRS, BMI, and CACS (dichotomized at 0) for evaluation of ITF, TFv and EAT; or FRS, BMI and ITFv (dichotomized at 250 mL) for evaluation of CACS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>CACS &gt;0 vs CACS =0</td>
<td>11.95 (4.71–30.28)</td>
</tr>
<tr>
<td>Log2(ITFv)</td>
<td>2.16 (1.43–3.27)</td>
</tr>
<tr>
<td>Log2(TFv)</td>
<td>2.61 (1.60–4.30)</td>
</tr>
<tr>
<td>Log2(EATv)</td>
<td>2.02 (1.30–3.13)</td>
</tr>
<tr>
<td>ITFv &gt;250 mL vs ≤250 mL</td>
<td>2.39 (1.30–4.40)</td>
</tr>
<tr>
<td>EATv &gt;125 mL vs ≤125 mL</td>
<td>2.44 (1.31–4.54)</td>
</tr>
</tbody>
</table>

---

### Table 3. Multivariable Risk Analysis: CACS >400 (n=65) Vs CACS ≤400 (n=695)

<table>
<thead>
<tr>
<th>Model 1B: adjusted for FRS and BMI.</th>
<th>Model 2B: adjusted for FRS, BMI, and CACS (dichotomized at 400) for evaluation of ITF, TFv and EAT; or FRS, BMI, and ITFv (dichotomized at 250 mL) for evaluation of CACS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>CACS &gt;400 vs CACS ≤400</td>
<td>7.22 (3.95–13.21)</td>
</tr>
<tr>
<td>Log2(ITFv)</td>
<td>2.16 (1.43–3.27)</td>
</tr>
<tr>
<td>Log2(TFv)</td>
<td>2.61 (1.60–4.30)</td>
</tr>
<tr>
<td>Log2(EATv)</td>
<td>2.02 (1.30–3.13)</td>
</tr>
<tr>
<td>ITFv &gt;250 mL vs ≤250 mL</td>
<td>2.39 (1.30–4.40)</td>
</tr>
<tr>
<td>EATv &gt;125 mL vs ≤125 mL</td>
<td>2.44 (1.31–4.54)</td>
</tr>
</tbody>
</table>

---

*When adjusted for FRS, BMI, and EATv (dichotomized at 125 mL), hazard ratio=7.66, 95% CI (2.80–20.38), P<0.0001.

BMI indicates body mass index; CACS, coronary artery calcium score; EATv, epicardial adipose tissue volume; FRS, Framingham risk score; TFv, thoracic fat volume; and ITFv, total intrathoracic fat volume.
at defining risk with minimal additional contribution from the ITF or EAT results. In this regard, we could not identify a specific cutoff for fat volume, which would further discriminate low from high-risk patients within specific CACS categories.

Previous Studies

To the best of our knowledge, there is only 1 other study examining the clinical value of fat volume in relation to CACS for defining risk in patients without known CAD. In this registry study by Cheng et al, 58 patients with MACE were propensity matched to 174 same-sex, event-free control subjects based on age, risk factors, and CACS. As in our study, mean EATv and ITFv and the percentage of patients with large fat volumes (EATv >125 mL and ITFv >250 mL) were significantly greater in patients with, as compared to those without, events. EATv and ITFv were independently associated with MACE after correcting for age, traditional risk factors, and CACS. Both our study and that of Cheng et al showed a possible additional contribution from fat burden for defining outcome in patients with a severe (>400) CACS. Because patients with a severe CACS >400 already merit aggressive risk factor modification and clinical surveillance, the additional clinical value of fat burden remains unclear. Nonetheless, the similar results reported in these 2 studies are particularly striking considering the differences in study design and patient cohorts evaluated.

Limitations

Because CAD is a chronic disease that develops over decades, our follow-up duration may not have been long enough to fully capture the clinical significance of increased fat burden. However, despite this limitation, CACS still proved to be robust for defining risk as verified in other studies.

Our study had only 30% to 50% power to identify any additional value of fat volumes over CACS for defining risk. This power calculation was based on testing for an increase in developing MACE from 46% to 89% in a Cox proportional hazards model with a sample of 760 observations at a 0.05 significance level assuming an anticipated event rate of 5.92%.

Figure 5. Adjusted annualized MACE rates based on CACS, EATv, (A) and ITFv (B) results. Event rates increased with increasing CACS within each fat volume category (P<0.0001 for all trends). However, with larger fat volumes there was only a nonsignificant trend toward increasing event rates among most CACS categories. MACE indicates major acute cardiac events; CACS, coronary artery calcium score; EATv, epicardial adipose tissue volume; and ITFv, intrathoracic fat volume.

Figure 6. Scatterplot of EATv (A) and ITFv (B) within each CACS category stratified by MACE. No specific cutpoints for EATv or ITFv better defined patients at risk for MACE in any of the CACS categories. MACE, major acute cardiac events; CACS, coronary artery calcium score; EATv, epicardial adipose tissue volume; and ITFv, intrathoracic fat volume.
A sample size of ≥2500 patients would have been required to achieve 80% power to detect a 68% increase risk of developing MACE for those with ITFv >250 versus those with ITFv ≤250 at a 0.05 significance level, assuming the same anticipated event rate of 5.92%. All sample size and power calculations were generated using PASS 2008 (Kaysville, UT) for Cox proportional hazards models with a Type I error rate of α=0.05. Despite the sample size limitation, fat volumes did add to risk assessment in patients with severe (>400) CACS. Of note, CACS significantly improved risk stratification after adjusting for either ITF or EAT within the constraints of the current sample size.

Fat volumes vary widely across different patient populations and are dependent on overall BMI. A recent study defined a high EATv as 68.1 mL/m², which was the upper 95th percentile for a normal healthy population. This value corresponded to their previously reported nonindexed EATv cutoff of 125 mL. Optimal fat volume thresholds for predicting patient outcome require further refinement and confirmation.

Finally, we did not collect radiation dose information in our population. However, the dose associated with a CACS is only 2 to 3 mSv, similar to the average background environmental radiation received by general US population. In addition, fat volume information can be obtained from the same CACS scan without additional radiation exposure. Although other radiation free technique, such as echocardiography and cardiac magnetic resonance imaging, may be used to estimate fat burden, none of these techniques can provide information on the presence or extent of coronary atherosclerosis.

Conclusions

CACS and fat volumes are independently associated with MACE in low to intermediate-risk patients with ACP and improve risk stratification beyond that provided by clinical information alone. Although fat volumes may add value in patients with CACS >400, CACS remains the strongest overall marker for defining risk.

Sources of Funding

Investigator-initiated study; not otherwise funded.

Disclosures

None.

References


CLINICAL PERSPECTIVE

There is considerable interest as to whether epicardial and intrathoracic fat volumes contribute to the development of coronary artery disease and adversely affect patient outcome. Cardiac computed tomography allows for calculation of the coronary artery calcium score (CACS) as well as measurement of epicardial and intrathoracic fat volumes. We performed noncontrast cardiac computed tomography in 760 consecutive patients admitted through the emergency department with complaints of acute chest pain but without known coronary artery disease. Patients were followed for a median of 3.3 years to determine whether information on pericardial fat volume improved risk stratification for major adverse cardiac events. Mean patient age was 54.4±13.7 years, and Framingham risk score was 8.2±8.2. CACS and fat volumes were independently associated with major acute cardiac events and provided information incremental to clinical assessment. If accounted for CACS, fat volumes added prognostic value only in patients with a CACS >400. Our study is the largest consecutive patient series to date demonstrating that both CACS and pericardial fat volumes improve risk stratification in patients who present to the emergency department with acute chest pain.

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Circ Cardiovasc Imaging. 2013;6:58-66; originally published online November 27, 2012; doi: 10.1161/CIRCIMAGING.112.976316

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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