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# Correlation between pericardial, mediastinal, and intrathoracic fat volumes with the presence and severity of coronary artery disease, metabolic syndrome, and cardiac risk factors

**On Chen[1], Abhishek Sharma[2], Ijaz Ahmad[3], Naji Bourji[3], Konstantin Nestoiter[3], Pauline Hua[3], Betty Hua[3], Alexander Ivanov[3], James Yossef[3], Igor Klem[4], William M. Briggs[3], Terrence J. Sacchi[3], and John F. Heitner[3]***

[1]Department of Cardiology, Maimonides Medical Center, Brooklyn, NY, USA; [2]Department of Medicine, Maimonides Medical Center, Brooklyn, NY, USA; [3]Division of Cardiology, New York Methodist Hospital, Brooklyn, NY, USA; and [4]Duke Cardiovascular Magnetic Resonance Center, Durham, NC, USA

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**Aims** To investigate the association of pericardial, mediastinal, and intrathoracic fat volumes with the presence and severity of coronary artery disease (CAD), metabolic syndrome (MS), and cardiac risk factors (CRFs).

**Methods and results** Two hundred and sixteen consecutive patients who underwent cardiac magnetic resonance (CMR) imaging and had a coronary angiogram within 12 months of the CMR were studied. Fat volume was measured by drawing region of interest curves, from short-axis cine views from base to apex and from a four-chamber cine view. Pericardial fat, mediastinal fat, intrathoracic fat (addition of pericardial and mediastinal fat volumes), and fat ratio (pericardial fat/mediastinal fat) were analysed for their association with the presence and severity of CAD (determined based on the Duke CAD Jeopardy Score), MS, CRFs, and death or myocardial infarction on follow-up. Pericardial fat volume was significantly greater in patients with CAD when compared with those without CAD [38.3 $\pm$ 25.1 vs. 31.9 $\pm$ 21.4 $cm^3$ ($P = 0.04$)]. A correlation between the severity of CAD and fat volume was found for pericardial fat ($\beta = 1$, $P < 0.01$), mediastinal fat ($\beta = 1$, $P = 0.03$), intrathoracic fat ($\beta = 2$, $P = 0.01$), and fat ratio ($\beta = 0.005$, $P = 0.01$). These correlations persisted for all four thoracic fat measurements even after performing a stepwise linear regression analysis for relevant risk factors. Patients with MS had significantly greater mediastinal and intrathoracic fat volumes when compared with those without MS [126 $\pm$ 33.5 vs. 106 $\pm$ 30.1 $cm^3$ ($P < 0.01$) and 165 $\pm$ 54.9 vs. 140 $\pm$ 52 $cm^3$ ($P < 0.01$), respectively]. However, there was no significant difference in pericardial fat, mediastinal fat, intrathoracic fat, or fat ratio between patients with or without myocardial infarction during the follow-up [33.6 $\pm$ 22.1 vs. 35.7 $\pm$ 23.8 $cm^3$ ($P = 0.67$); 115 $\pm$ 26.2 vs. 114 $\pm$ 33.8 $cm^3$ ($P = 0.84$); 149 $\pm$ 44.7 vs. 150 $\pm$ 55.7 $cm^3$ ($P = 0.95$); and 0.27 $\pm$ 0.15 vs. 0.28 $\pm$ 0.14 ($P = 0.70$), respectively]. There was no significant difference in pericardial fat, mediastinal fat, intrathoracic fat, or fat ratio between patients who were alive compared with those who died during follow-up [36.6 $\pm$ 26.6 vs. 35.3 $\pm$ 23.2 $cm^3$ ($P = 0.76$); 114 $\pm$ 40.2 vs. 114 $\pm$ 31.4 $cm^3$ ($P = 0.95$); 150 $\pm$ 64.7 vs. 149 $\pm$ 52.5 $cm^3$ ($P = 0.92$); and 0.29 $\pm$ 0.15 vs. 0.28 $\pm$ 0.14 ($P = 0.85$), respectively].

**Conclusion** Our study confirms an association between pericardial fat volume with the presence and severity of CAD. Furthermore, an association between mediastinal and intrathoracic fat volumes with MS was found.

**Keywords** Pericardial fat • Mediastinal fat • Cardiac magnetic resonance • Coronary artery disease

* Corresponding author. Tel: +1 718 780 3000; fax: +1 718 780 7717. Email: john.heitner@gmail.com

# Introduction

Recent studies have shown that the distribution of fat is a stronger predictor of coronary artery disease (CAD) than the overall body fat quantity.[1–3] Abdominal visceral fat exerts a systemic effect on atherosclerosis by increasing the expression of inflammatory markers.[4,5] Strong correlation has been reported between abdominal visceral fat, CAD, and metabolic syndrome (MS).[4,5] Intrathoracic fat has also been shown to have a pro-inflammatory activity similar to that found in abdominal visceral fat.[3–8] The contribution of intrathoracic fat to the systemic effect on atherosclerosis might be limited, due to the smaller amount of fat when compared with abdominal fat. However, due to its close proximity to coronary arteries, it is hypothesized to have a local effect on the development of CAD.[1–8]

Intrathoracic fat consists of pericardial fat and mediastinal fat. Studies have reported an association between pericardial fat, CAD, and MS; and total intrathoracic fat with CAD.[5–10] However, the relationship between mediastinal fat, CAD, and MS is not clear. Furthermore, whether pericardial fat has a stronger association with CAD (due to its close proximity to the coronary arteries) than mediastinal fat is not yet known. We aim to investigate the association of pericardial, mediastinal, and intrathoracic fat volumes quantified by cardiac magnetic resonance (CMR) with the presence and severity of CAD, MS, cardiac risk factors (CRFs), and the development of death or myocardial infarction upon follow-up.

# Methods

## Population

Two hundred and twenty consecutive patients between 18 and 90 years old who underwent CMR and coronary angiography within 12 months at our institution from 2006 to 2009 were initially evaluated; four patients were excluded based on inadequate CMR image quality. The final study population consisted of 216 patients. At the time of CMR, IRB-approved consent was obtained from all participating patients. Blood was drawn for laboratory testing including a fasting lipid panel.

## Assessment of CAD

Conventional X-ray coronary angiography was performed using standard techniques in all 216 patients. Interpretation of angiography was performed by an experienced physician who was unaware of the patients' clinical information or CMR results in 189 cases; the remaining 27 cases were interpreted based on the clinicians report due to an inability to obtain angiography images from our archive system.

Significant CAD was defined as any stenosis of ≥75% on angiogram by visual assessment and severity of CAD was determined based on the Duke CAD Jeopardy Score. This scoring system is a quantitative system in which the coronary circulation is considered as six arterial segments: the left anterior descending artery, the diagonal branches, the first major septal perforator, the left circumflex artery, the circumflex marginal branch, and the posterior descending artery (*Figure 1*). In patients with a left dominant system, the right coronary artery is assigned no points. Each segment with luminal stenosis of ≥75% or a branch distal to a stenosis of ≥75% received a score of 2 points; thus, the maximal score is 12 points.[11] A site of prior stent was considered as significant stenosis and was scored appropriately. In patients with prior coronary artery bypass grafting, scoring was based on stenosis found in native vessels only.

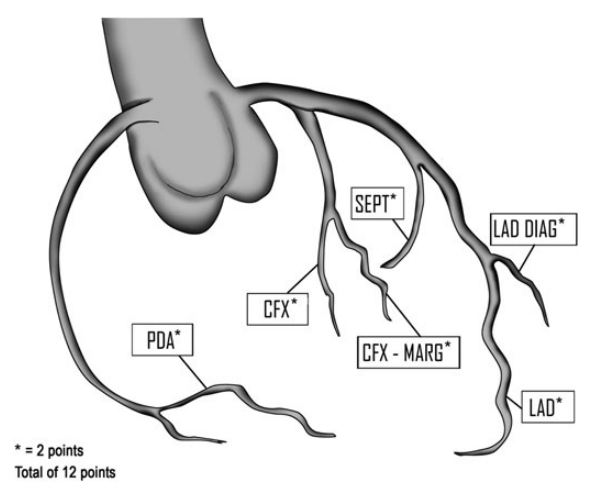


**Figure 1:** The Duke CAD Jeopardy Score—this scoring system divides the coronary circulation into six branches: the left anterior descending, diagonal, septal, circumflex, obtuse marginal and the right coronary artery or its posterior descending branch. A branch with luminal stenosis of ≥75% or a branch distal to a stenosis of ≥75% received a score of 2 points; thus, the maximal score is 12 points. CAD, coronary artery disease; LAD, left anterior descending artery; LAD DIAG, diagonal branch of the left anterior descending artery; SEPT, septal perforator; CFX, circumflex artery; CFX MARG, marginal branch of the circumflex artery; PDA, posterior descending artery.

## Cardiovascular magnetic resonance

Images were acquired using a 1.5-T clinical scanner (Siemens Sonata) using a six-channel phased-array receiver coil. Steady-state free precession cine images were acquired in multiple short-axis and three long-axis views during repeated breath holds (mean duration of 6–8 s). Typical imaging parameters were as follows: repetition time 3.0 ms, echo time 1.5 ms, flip angle: 60°, temporal resolution 35 ms, and voxel size 1.7 × 1.4 × 6 mm.

Pericardial fat was defined as the fat observed over the free wall of the right ventricle, apex, and the anterior region of the left ventricle (LV) within the parietal pericardium (*Figures 2* and *3*). Mediastinal fat was defined as the fat present within the thoracic cavity external to the parietal pericardium (*Figure 2* and *3*). Intrathoracic fat was defined as the combination of pericardial and mediastinal fat. Fat ratio was defined as the ratio between pericardial fat and mediastinal fat. Fat volume was measured from 6 to 8 consecutive cine views, obtained in the short-axis plane and covering the heart from base to apex. Fat surface area was measured by drawing the region of interest curves on each slice. Each slice measured 6 mm in thickness and a gap of 4 mm between slices was used, thus each slice represented a thickness of 1 cm (*Figure 3*). Fat surface area obtained on each slice was multiplied by 1 cm thickness and then summed to obtain the fat volume. Since the mediastinal fat was not fully represented by the short-axis views, mediastinal fat surface area was also measured from a single four-chamber view and multiplied by 1 cm, and this was added to the total mediastinal fat volume obtained from the short-axis views (*Figure 2*).

## Inter-reader reliability

Two different readers performed fat volume measurements. For the assessment of inter-reader reliability of fat measurements, the intraclass

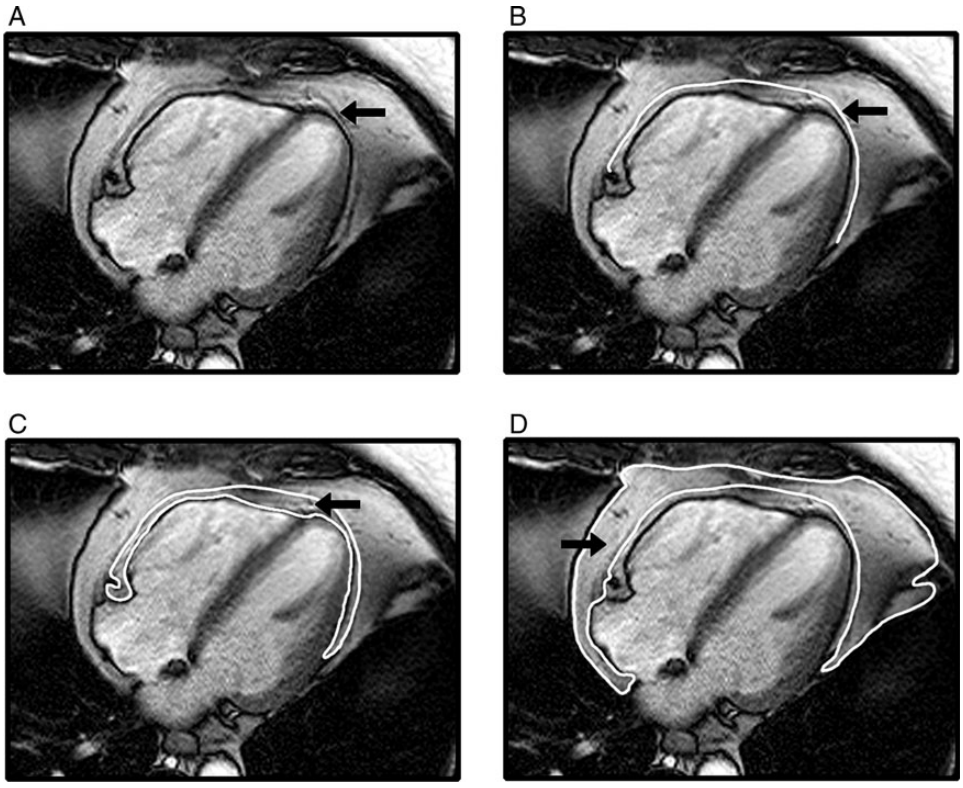


**Figure 2:** The assessment of fat surface area by CMR (long axis). (*A*) Four-chamber cine view, dark line representing the pericardium, (*B*) white line represents the pericardium, (*C*) pericardial fat, and (*D*) mediastinal fat.

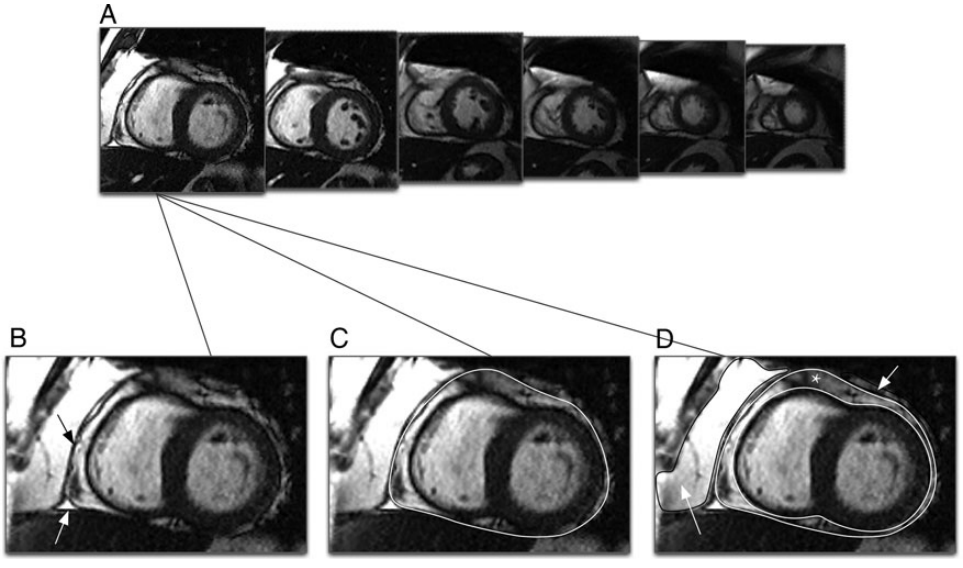


**Figure 3:** The assessment of fat surface area by CMR (short axis). (*A*) Six sections of short-axis (SA) cine views from base to apex, (*B*) SA view with black arrow pointing to the dark line representing the pericardium, the white arrow pointing to a small amount of fluid in the pericardium that is easily distinguished from fat. (*C*) The pericardium is traced in white, (*D*) white star indicates pericardial fat traced by white line, and the black arrow pointing to the mediastinal fat traced by black line. Pericardial and mediastinal fat surface areas were measured on each of the six SA sections.

correlation coefficient was calculated on a sample consisting of 20 patients that were measured independently by each of the two readers and blinded to the results of the other reader.

## Definition of terms

Data on CRFs were obtained from the medical history taken at the time of CMR. We included both modifiable and non-modifiable risk factors such as hypertension (HTN), diabetes mellitus (DM), hyperlipidaemia, renal disease, smoking, and family history of premature CAD defined as symptomatic CAD in a male first-degree relative before age 55, or a female first-degree relative before age 65.

MS was defined as the presence of at least three of the following five parameters: obesity (BMI $\geq$30 kg/m$^2$), serum triglycerides $\geq$150 mg/dL, HDL cholesterol $<$40 in males and $<$50 in females, HTN, and DM. HDL cholesterol and triglycerides levels were obtained from results of fasting samples taken on the day of CMR. HTN and DM were considered present in patients with a past medical history of these conditions, or receiving anti-hypertensive or anti-diabetic medication(s). Race was based on patients self-reporting. Myocardial infarction was defined as per universal definition of myocardial infarction (MI), taking into consideration symptoms, ECG, and cardiac enzymes.[12]

## Follow-up

All patients included in our study (Cohort study with cross-sectional and longitudinal analysis) were followed by phone using a standardized questionnaire. Medical records were reviewed to confirm myocardial infarction. Social security death index and chart review were utilized in patients who could not be contacted by phone.

## Statistical analysis

Data in text and tables are expressed as mean $\pm$ standard deviation (SD) for continuous variables or *n* (%) for categorical variables. The significant differences between continuous variables for patients with CAD and control group were determined by the use of the *T*-test and for categorical variables, the Pearson chi-square test was used.

The association between the presence of CAD with pericardial fat, mediastinal fat, intrathoracic fat, and fat ratio was determined with a *T*-test and also with logistic regression analysis that adjusted for the relevant covariates. All the other analyses with categorical independent variables used the *T*-test and the Pearson correlation analysis was used when comparing two continuous variables. For the correlation of severity of CAD and fat volume, a stepwise linear regression was used, $\beta$-coefficient represents the value by which fat volume increased for every increase in the CAD score. A linear regression was performed for the correlation of fat volume and CRFs with continuous variables; β-coefficient represents the change in fat volume for an increase of 1 unit in a risk factor. In addition, measurements of fat surface area were correlated with that of total fat volume. We have also assessed the effect of BMI and LV dysfunction on the relationship between pericardial, mediastinal, and intrathoracic fat volumes and CAD using chi-square analysis. We further performed a regression analysis controlling for left ventricular function and presence of CAD. All *P*-values are two-sided.

# Results

Baseline characteristics of patients with and without CAD are presented in *Table 1*. There were 120 (56%) patients with CAD by angiography. Patients with CAD were significantly older, predominantly male (66%), had a significantly greater prevalence of diabetes, HTN, hyperlipidaemia, history of heart failure, and a lower ejection fraction (EF). There was no significant difference between patients with and without CAD regarding BMI, presence of MS, family history of CAD, or smoking history.

## Reproducibility

The intraclass correlation coefficient was calculated to assess the inter-reader reliability for fat measurements; results were excellent for both mediastinal fat ($r = 0.94$, $P < 0.01$) and pericardial fat ($r = 0.87$, $P < 0.01$) measurements.

## CAD and fat

Pericardial fat volume was significantly greater in patients with CAD when compared with those without CAD [38.3 $\pm$ 25.1 vs. 31.9 $\pm$ 21.4 cm$^3$ ($P = 0.04$)]; this significance persisted ($P < 0.01$) after performing a stepwise logistic regression analysis including all statistically significant variables from *Table 1* (see Supplementary data online, *Table S1*). There was no statistically significant difference in mediastinal fat, intrathoracic fat, or fat ratio when comparing the two groups [117 $\pm$ 33 vs. 110.1 $\pm$ 32.4 cm$^3$ ($P = 0.14$); 155 $\pm$ 56.5 vs. 142 $\pm$ 51.1 cm$^3$ ($P = 0.07$); and 0.3 $\pm$ 0.15 vs. 0.27 $\pm$ 0.14 ($P = 0.11$), respectively]. A correlation between the severity of CAD and fat volume was found for pericardial fat ($\beta = 1$, $P < 0.01$), mediastinal fat ($\beta = 1$, $P = 0.03$), intrathoracic fat ($\beta = 2$, $P = 0.01$), and fat ratio ($\beta = 0.005$, $P = 0.01$). These correlations persisted with *P*-values of $<$0.001 for all four fat measurements after performing a stepwise linear regression analysis accounting for parameters from *Table 1* (see Supplementary data online, *Table S1*).

## MS and fat

There were 84 patients (39%) who met criteria for MS. Patients with MS had significantly greater mediastinal and intrathoracic fat volumes when compared with those without MS [126 $\pm$ 33.5 vs. 106 $\pm$ 30.1 cm$^3$ ($P < 0.01$) and 165 $\pm$ 54.9 vs. 140 $\pm$ 52 cm$^3$ ($P < 0.01$), respectively]. There were no statistically significant differences in pericardial fat volume or fat ratio between patients with and without MS [39 $\pm$ 24 vs. 33 $\pm$ 23 cm$^3$ ($P = 0.10$) and 0.29 $\pm$ 0.14 vs. 0.29 $\pm$ 0.15 cm$^3$ ($P = 0.94$), respectively].

## Subgroups of population and fat

We evaluated differences in pericardial fat, mediastinal fat, intrathoracic fat, and fat ratio in four subgroups of patients: Group A = CAD(−) and MS(−), Group B = CAD(+) and MS(+), Group C = CAD(+) and MS(−), Group D = CAD(−) and MS(+) (*Table 2*). Groups B, C, and D were compared with Group A that was considered to be a control group (*Table 2*). Pericardial fat, mediasinal fat, and intrathoracic fat were significantly greater in Group B when compared with Group A ($P = 0.02$, $P < 0.01$, and $P < 0.01$, respectively); no statistically significant difference was found in fat ratio between those two groups ($P = 0.29$). Mediastinal fat and intrathoracic fat were significantly greater in Group D when compared with Group A ($P < 0.01$ and $P < 0.01$, respectively); this was not true for pericardial fat and fat ratio ($P = 0.10$ and $P = 0.71$, respectively).

## Cardiac risk factors and fat

The results for the association between pericardial, mediastinal, intrathoracic fat volume, and fat ratio with the presence of CRFs are presented in *Table 3*. Patients with DM had higher mediastinal and intrathoracic fat volumes when compared with those without

**Table 1 Baseline characteristics of the study population**

| Characteristics | Entire group ($n$ = 216) | No CAD ($N$ = 96) | CAD[a] ($N$ = 120) | $P$-value |
|---|---|---|---|---|
| Age (years) | 64.5 ± 13.3 | 61.2 ± 15.6 | 67.1 ± 10.4 | 0.001 |
| Female gender | 95 (44%) | 53 (55.8%) | 42 (44.2%) | 0.003 |
| BMI | 28.6 ± 6.2 | 28.8 ± 7.3 | 28.4 ± 5.2 | 0.700 |
| Weight (kg) | 78.4 ± 17.9 | 78.3 ± 20.2 | 78.5 ± 15.9 | 0.936 |
| Race, $n$ (%) | | | | |
| Whites | 104 (48.1%) | 45 (46.9%) | 59 (49.2%) | 0.445 |
| Blacks | 70 (32.4%) | 35 (36.5%) | 35 (29.2%) | |
| Other | 42 (19.4%) | 16 (16.7%) | 26 (21.7%) | |
| Past medical history, $n$ (%) | | | | |
| MS | 84 (38.9%) | 33 (34.4%) | 51 (42.5%) | 0.224 |
| DM | 74 (34.3%) | 21 (21.9%) | 53 (44.2%) | <0.001 |
| HTN | 171 (79.2%) | 68 (70.8%) | 103 (85.8%) | 0.007 |
| Current smoker | 22 (10.2%) | 12 (12.5%) | 10 (8.3%) | 0.314 |
| Hyperlipidaemia | 128 (59.3%) | 41 (42.7%) | 87 (72.5%) | <0.001 |
| Family history of CAD | 47 (21.8%) | 18 (18.8%) | 29 (24.2%) | 0.338 |
| Peripheral arterial disease | 9 (4.1%) | 2 (2.1%) | 7 (5.8%) | 0.171 |
| CABG | 23 (10.6%) | 0 (0.0%) | 23 (19.2%) | <0.001 |
| PCI | 26 (12%) | 0 (0.0%) | 26 (21.7%) | <0.001 |
| Renal disease | 37 (17.1%) | 14 (14.6%) | 23 (19.2%) | 0.374 |
| Haemodialysis | 9 (4.1%) | 2 (2.1%) | 7 (5.8%) | 0.171 |
| Stroke | 10 (4.6%) | 5 (5.2%) | 5 (4.1%) | 0.717 |
| Angina | 27 (12.5%) | 1 (1.0%) | 26 (21.7%) | <0.001 |
| Atrial fibrillation/flutter | 25 (11.6%) | 10 (10.4%) | 15 (12.5%) | 0.634 |
| Valve disease | 60 (27.8%) | 29 (30.2%) | 31 (25.8%) | 0.476 |
| Syncope | 5 (2.3%) | 2 (2.1%) | 3 (2.5%) | 0.840 |
| CHF | 106 (49.1%) | 34 (35.4%) | 72 (60%) | 0.001 |
| CHF class, $n$ (%) | | | | |
| Class 0 | 112 (51.9%) | 63 (65.6%) | 49 (40.2%) | 0.001 |
| Class 1–2 | 57 (26.4%) | 19 (19.8%) | 38 (31.1%) | |
| Class 3–4 | 47 (21.9%) | 14 (14.6%) | 35 (28.7%) | |
| Medications, $n$ (%) | | | | |
| Beta blockers | 136 (63%) | 52 (54.2%) | 84 (70%) | 0.017 |
| Statins | 102 (47.2%) | 31 (32.3%) | 71 (59.2%) | <0.001 |
| ACE inhibitors | 102 (47.2%) | 38 (39.6%) | 64 (53.3%) | 0.044 |
| ARB | 25 (11.6%) | 9 (9.4%) | 16 (13.3%) | 0.366 |
| Calcium channel blockers | 45 (20.8%) | 21 (21.9%) | 24 (20%) | 0.736 |
| Plavix | 48 (22.2%) | 9 (9.4%) | 39 (32.5%) | <0.001 |
| Aspirin | 119 (55.1%) | 34 (35.4%) | 85 (70.8%) | <0.001 |
| Spironolactone | 4 (1.8%) | 2 (2.1%) | 2 (1.7%) | 0.821 |
| Diuretics | 71 (32.9%) | 30 (31.2%) | 41 (34.2%) | 0.650 |
| Nitrates | 16 (7.4%) | 4 (4.2%) | 12 (10%) | 0.104 |
| Coumadin | 19 (8.8%) | 10 (10.5%) | 9 (7.5%) | 0.438 |
| Blood tests | | | | |
| Total cholesterol (mg/dL)[b] | 174 ± 53.7 | 183 ± 58.8 | 166 ± 48.1 | 0.021 |
| Triglycerides (mg/dL)[b] | 138 ± 77.3 | 144.0 ± 83.8 | 134 ± 71.7 | 0.345 |
| HDL cholesterol (mg/dL)[b] | 49.5 ± 19.9 | 51.6 ± 20.3 | 48 ± 19.5 | 0.179 |
| LDL cholesterol (mg/dL)[b] | 99.9 ± 41.7 | 104 ± 41.7 | 96.9 ± 41.6 | 0.238 |
| C reactive protein (mg/L)[c] | 11.1 ± 25.3 | 9.2 ± 25.0 | 12.7 ± 25.6 | 0.347 |
| Pro-B-type natriuretic peptide (pg/mL)[d] | 4780 ± 19600 | 2190 ± 8750 | 6880 ± 25000 | 0.084 |

*Continued*

**Table 1** *Continued*

| Characteristics | Entire group ($n = 216$) | No CAD ($N = 96$) | CAD[a] ($N = 120$) | *P*-value |
|---|---|---|---|---|
| Ejection fraction (%) | 41.2 ± 13.2 | 47.2 ± 10.1 | 36.5 ± 13.6 | <0.001 |
| Time between CMR and angiogram (months) | 1.3 ± 2.7 | 1.8 ± 3 | 1.00 ± 2.3 | 0.031 |

Data are expressed as mean ± standard deviation (SD).
ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; CMR, cardiac magnetic resonance; CHF, congestive heart failure.
[a]CAD defined as stenosis ≥75%.
[b]Total cholesterol, LDL, HDL, and triglycerides were obtained in 217 patients.
[c]C-reactive protein was obtained in 202 patients.
[d]Pro-B-type natriuretic peptide was obtained in 212 patients. For logarithmic transformed values, regular values are shown and *P*-values are for the logarithmic transformed variables.

**Table 2 Subgroups by CAD, MS, and fat volume**

| | Group A CAD(−)/MS(−) ($n = 63$) | Group B CAD(+)/MS(+) ($n = 51$) | Group C CAD(+)/MS(−) ($n = 69$) | Group D CAD(−)/MS(+) ($n = 33$) | *P*-values groups: B vs. A | C vs. A | D vs. A |
|---|---|---|---|---|---|---|---|
| Pericardial fat | 29 ± 21 | 40 ± 25 | 37.1 ± 24.8 | 37 ± 21 | 0.002 | 0.051 | 0.104 |
| Mediastinal fat | 101 ± 28 | 125 ± 33 | 111 ± 31.4 | 127 ± 33 | <0.001 | 0.066 | <0.001 |
| Intrathoracic fat | 130 ± 47 | 165 ± 57 | 148 ± 55.2 | 164 ± 52 | <0.001 | 0.052 | 0.003 |
| Fat ratio | 0.27 ± 0.14 | 0.29 ± 0.14 | 0.3 ± 0.15 | 0.27 ± 0.13 | 0.286 | 0.13 | 0.713 |

Groups B, C, and D were compared with Group A (considered to be a control group). Data are expressed as mean ± standard deviation. Fat volume is expressed in $cm^3$.
Fat ratio, pericardial fat/mediastinal fat; CAD (+), presence of coronary artery disease; CAD (−), absence of coronary artery disease; MS(+), presence of metabolic syndrome; MS(−), absence of metabolic syndrome.

diabetes [122 ± 15 vs. 110 ± 31 $cm^3$ ($P < 0.01$) and 160 ± 57 vs. 144 ± 52 $cm^3$ ($P = 0.03$), respectively]. Although pericardial fat was greater in diabetics, there was no statistically significant difference, and there was no significant difference in fat ratio between the two groups. Patients with BMI ≥30 were found to have more pericardial, mediastinal, and intrathoracic fat volumes, but not fat ratio [42 ± 27 vs. 132 ± 21 $cm^3$ ($P < 0.01$); 138 ± 33 vs. 101 ± 24 $cm^3$ ($P < 0.01$); 180 ± 58 vs. 133 ± 44 $cm^3$ ($P < 0.01$); and 0.3 ± 0.1 vs. 0.3 ± 0.1 ($P = 0.54$), respectively].

For continuous variables, linear regression analysis was performed in order to correlate with fat volumes (see Supplementary data online, *Table S1*). While an increase in age was associated with a decrease in pericardial, mediastinal, and intrathoracic fat, significance was found only for the change in mediastinal fat ($\beta = -0.002$, $P = 0.99$; $\beta = -0.39$, $P = 0.02$; and $\beta = -0.39$, $P = 0.16$, respectively); there was no significant difference in fat ratio with advance in age. The increase in total cholesterol, LDL, and HDL cholesterol was associated with a decrease in fat volumes, but none of these findings reached statistical significance. Chi-square analysis showed that there is no interaction between CAD and BMI ($\chi^2 = 0.43$). However, an interaction was found between CAD and LV dysfunction (defined as EF <55) ($\chi^2 < 0.0001$). On regression analysis, we also found a statistically significant reduction in pericardial, mediastinal, and intrathoracic fat volumes and a non-significant reduction in fat ratio (−7, −11, −18 $cm^3$, and −0.02, respectively), in patients with an EF ≥55 when controlling for the presence of CAD.

## Race and fat

The results of the comparison of fat volume within the three race groups such as whites, blacks, and other races are presented in *Table 4*. When compared with other races, blacks had the least amount of pericardial, mediastinal, and intrathoracic fat volumes. Patients belonging to other races (non-black and non-whites) had more pericardial fat and fat ratio. Whites had more mediastinal fat and a higher intrathoracic fat.

## Follow-up

All patients were followed for a mean 12.5 ± 9.9 months. Twenty-five patients had a MI, 34 died, and 56 had a combined outcome defined as death or MI. There was no significant difference in pericardial fat, mediastinal fat, intrathoracic fat, or fat ratio between patients with or without MI during the follow-up [33.6 ± 22.1 vs. 35.7 ± 23.8 $cm^3$ ($P = 0.67$); 115 ± 26.2 vs. 114 ± 33.8 $cm^3$ ($P = 0.84$); 149 ± 44.7 vs. 150 ± 55.7 $cm^3$ ($P = 0.95$); and 0.27 ± 0.15 vs. 0.28 ± 0.14 ($P = 0.70$), respectively]. There was no significant difference in pericardial fat, mediastinal fat, intrathoracic fat, or fat ratio between patients who were alive compared with those who died during the follow-up [36.6 ± 26.6 vs. 35.3 ± 23.2 $cm^3$ ($P = 0.76$); 114 ± 40.2 vs. 114 ± 31.4 $cm^3$ ($P = 0.95$); 150 ± 64.7 vs. 149 ± 52.5 $cm^3$ ($P = 0.92$); and 0.29 ± 0.15 vs. 0.28 ± 0.14 ($P = 0.85$), respectively]. Furthermore, there was no significant difference in assessment of fat in patients who had a combined outcome when

**Table 3** Associations of cardiac risk factors with pericardial, mediastinal, intrathoracic fat, and fat ratio

| | HTN | | | DM | | | Hyperlipidaemia | | | Renal disease | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Presence ($n = 171$) | Absence ($n = 45$) | *P*-value | Presence ($n = 74$) | Absence ($n = 142$) | *P*-value | Presence ($n = 128$) | Absence ($n = 88$) | *P*-value | Presence ($n = 37$) | Absence ($n = 179$) | *P*-value |
| Pericardial fat[a] | 36 ± 24 | 32 ± 20 | 0.313 | 38 ± 25 | 34 ± 23 | 0.198 | 37 ± 24 | 34 ± 23 | 0.368 | 30 ± 23 | 37 ± 24 | 0.128 |
| Mediastinal fat[a] | 115 ± 34 | 108 ± 27 | 0.196 | 122 ± 35 | 110 ± 31 | 0.008 | 116 ± 33 | 110 ± 31 | 0.167 | 103 ± 32 | 116 ± 33 | 0.020 |
| Intrathoracic fat[a] | 152 ± 56 | 141 ± 45 | 0.223 | 160 ± 57 | 144 ± 52 | 0.032 | 153 ± 56 | 144 ± 52 | 0.220 | 133 ± 54 | 153 ± 54 | 0.039 |
| Fat ratio | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.607 | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.723 | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.821 | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.291 |
| | **Smoking** | | | **PAD** | | | **BMI** | | | **Statin use** | | |
| | Presence ($n = 22$) | Absence ($n = 194$) | *P*-value | Presence ($n = 9$) | Absence ($n = 207$) | *P*-value | BMI ≥30 ($n = 76$) | BMI<30 ($n = 140$) | *P*-value | Presence ($n = 47$) | Absence ($n = 171$) | *P*-value |
| Pericardial fat[a] | 32 ± 15 | 36 ± 25 | 0.407 | 35 ± 28 | 35 ± 24 | 0.997 | 42 ± 27 | 32 ± 21 | 0.003 | 38 ± 25 | 34 ± 23 | 0.217 |
| Mediastinal fat[a] | 108 ± 22 | 115 ± 34 | 0.343 | 111 ± 39 | 114 ± 33 | 0.776 | 138 ± 33 | 101 ± 24 | <0.001 | 116 ± 32 | 112 ± 34 | 0.632 |
| Intrathoracic fat[a] | 139 ± 34 | 150 ± 56 | 0.351 | 146 ± 66 | 149 ± 54 | 0.862 | 180 ± 58 | 133 ± 44 | <0.001 | 153 ± 55 | 146 ± 54 | 0.881 |
| Fat ratio | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.886 | 0.3 ± 0.2 | 0.3 ± 0.1 | 0.902 | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.536 | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.272 |

Data are expressed as mean ± standard deviation (SD).
Fat ratio, pericardial fat/mediastinal fat; DM, diabetes mellitus; HTN, hypertension; PAD, peripheral artery disease; BMI, body mass index; CAD, coronary artery disease.
[a]Fat surface area expressed in $cm^2$.

**Table 4 Associations of race and fat volume**

| Variable | Whites ($n = 104$) | Blacks ($n = 70$) | Other ($n = 42$) | *P*-value | | |
|---|---|---|---|---|---|---|
| | | | | Blacks vs. other | Whites vs. other | Whites vs. blacks |
| Pericardial fat ($cm^3$) | 38 ± 25 | 29 ± 20 | 39 ± 24 | 0.01 | 0.77 | 0.005 |
| Mediastinal fat ($cm^3$) | 118 ± 36 | 110 ± 27 | 110 ± 32 | 0.95 | 0.19 | 0.08 |
| Intrathoracic fat ($cm^3$) | 156 ± 59 | 138 ± 45 | 150 ± 54 | 0.26 | 0.51 | 0.02 |
| Fat ratio | 0.29 ± 0.14 | 0.24 ± 0.12 | 0.33 ± 0.14 | 0.001 | 0.15 | 0.01 |

Data are expressed as mean ± standard deviation (SD).
Fat ratio, pericardial fat/mediastinal fat; other, race other than white or black.

compared with those with no outcome during the follow-up [35.7 ± 24.9 vs. 35.4 ± 23.4 $cm^3$ ($P = 0.92$); 155 ± 35.5 vs. 114 ± 32 $cm^3$ ($P = 0.85$); 150 ± 58 vs. 149 ± 53.3 $cm^3$ ($P = 0.87$); and 0.28 ± 0.14 vs. 0.28 ± 0.14 ($P = 0.92$), respectively].

## Correlation of fat surface area and fat volume

The correlation between measurements of pericardial, mediastinal, and intrathoracic fat volumes with those of fat surface area measured from a single four-chamber cine view revealed a weak but statistically significant correlation between two ($\beta = 0.7$, $P = 0.02$; $\beta = 0.9$, $P < 0.01$; $\beta = 1$, $P < 0.01$, respectively).

# Discussion

The main finding of our study was the presence of significantly higher pericardial fat volume in patients with CAD when compared with those without CAD. This association remains statistically significant even after performing a stepwise logistic regression analysis for age, smoking, diabetes, peripheral artery disease, BMI, HTN, hyperlipidaemia, and renal disease (*Table 3* and see Supplementary data online, *Table S1*). Though, the mediastinal and intrathoracic fat volumes were higher among patients with MS; the difference in the mediastinal and intrathoracic fat did not achieve significance for patients with and without CAD. Furthermore, a correlation was noted between the severity of CAD and fat volume for pericardial fat, mediastinal fat, intrathoracic fat, and fat ratio.

Our results are in consensus with several previous studies reporting an association between CAD or surrogate markers for CAD and pericardial fat.[1,5,6,10,11,13–15] Pericardial fat volume has been shown to be more closely associated with early development of CAD compared with BMI and waist circumference among patients with suspected CAD.[16] This could be due to the high content of inflammatory factors and proximity to the coronary arteries. However, any intrathoracic fat volume correlated with the severity of CAD, which is similar to the relationship between CAD and other risk factors such as obesity that correlate with the overall burden of disease. In a study by Jeong *et al.*,[6] an association was found between the severity of CAD in patients with prior angiography and pericardial fat as assessed by echocardiography. In a study of 1267 patients, there was no association of mediastinal fat volume, as assessed by multidetector computed tomography (MDCT), and a composite outcome of cardiovascular diseases; however, there was an association with pericardial fat, but this association did not persist after adjustment for cardiovascular risk factors.[3] Similarly, two other studies have reported no significant association between pericardial fat measured by MDCT and CAD.[17,18] Several studies have reported a lack of association between pericardial fat and CAD. These studies suffer from lack of standardization, most were case control studies that are more sensitive to confounding bias than a cohort study such as ours. Furthermore these studies have used surrogate outcomes for the assessment of CAD, in our study CAD was assessed by coronary angiography which is considered the gold standard.[17–20] In contrast to previous studies which used MDCT and Single-photon emission computed tomography as the reference standard,[21,22] the use of X-ray coronary angiography and highly reproducible CMR for the measurement of fat volume reduces the possibility of a type I error. We used a cohort study design, which is less prone to the effect of confounding factors than previously reported case–control study designs. CMR has a distinct advantage, as it does not use radiation to precisely characterize soft tissue. Furthermore, the high-target acquisition and spatial resolution of CMR lead to an excellent reproducibility in calculations and a marked reduction in sample size.

Increased pericardial fat might contribute to the progression of CAD by functioning as an inflammatory tissue and facilitating chronic inflammation in epicardial coronary arteries.

Pericardial fat has been shown to have higher concentration of inflammatory cell and increased inflammatory gene expression and protein secretion when compared with subcutaneous fat.[23,24]

Though small in amount, it covers up to 80% of cardiac surface area and directly delivers pro-inflammatory cytokines IL-6, TNF-α, or TLR4 to the myocardium.[3,25] Pericardial adipose tissue has been shown to be rich in adipocytokine–chemerin, which regulates immune response and lipid metabolism. Pericardial chemerin levels have been strongly correlated with CAD severity.[26] An increase in the amount of pericardial fat has also been shown to be associated with a decrease in concentration of adiponectin, which exerts an anti-inflammatory effect via inhibition of NF-κB activity.[27] Macrophage and cytokine/adipocytokine signal imbalance and polarization of M1/M2 macrophages towards a pro-inflammatory state have been observed in pericardial adipose tissue of CAD patients.[28,29] Recently, several studies have shown that pericardial fat could alter vascular homeostasis and induce endothelial dysfunction, vascular inflammation, and plaque progression via an 'outside-to-inside' signalling

mechanism.[21,22,30] Our results also show an association between pericardial fat and CAD, suggesting its importance as a mediator of systemic CAD risk factors. Mediastinal fat is larger in amount, but unlikely to have the similar paracrine effect on local coronary inflammation as pericardial fat. This could be partly due to distinct biochemical nature, blood supply, and drainage of mediastinal fat.[3,23] Hence, pericardial fat might act as a local stimulator for coronary atherosclerotic lesion, while mediastinal fat may be a marker of MS and CAD.

A potential limitation of our study is related to the measurement of fat by CMR. Since standard imaging includes small gaps between slices, certain assumptions have to be made when calculating fat volume; however, these gaps are small and unlikely to be significant. Furthermore, we used short-axis views to measure mediastinal fat, and this likely underestimated the amount of mediastinal fat volume as the apex is under-represented; for this reason, we added the mediastinal fat volume of a single four-chamber view. Another limitation of this study is a potential selection bias in that all patients had to have both a CMR and a coronary angiography to be enrolled. This may have led to a heterogeneous population, which might not reflect the general population with CAD. There was no significant correlation with intrathoracic fat and major adverse cardiac events. This study was not powered for clinical endpoint and thus any conclusion should be tempered due to small sample size and duration of follow-up. Despite a high accuracy to evaluate pericardial, mediastinal, and intrathoracic adipose tissue, quantification of fat volume with CMR is time consuming and might limit its widespread application. However, our results show a statistically significant correlation between fat volume and fat surface area, which is relatively quick and easy to calculate.

# Conclusion

Our study confirms an association between pericardial fat volume with the presence and severity of CAD. Furthermore, an association between mediastinal and intrathoracic fat volumes with MS was found.

# Supplementary material

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

**Conflict of interest:** None of the authors have any financial arrangement with any company that might constitute a conflict of interest with respect to this manuscript.

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**IMAGE FOCUS**

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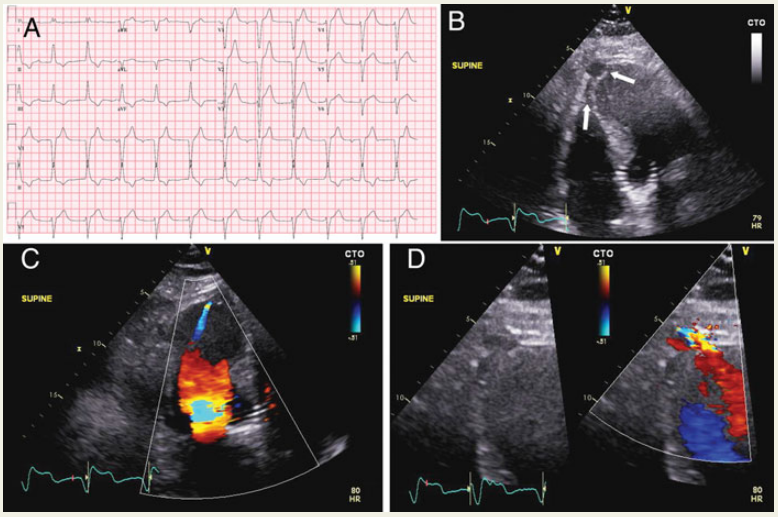
# Iatrogenic ventricular septal defect after dual-chamber pacemaker implantation

**Fausto Pizzino[1], Giampiero Vizzari[1], Tanvir Bajwa[2], Indrajit Choudhuri[2], and Bijoy K. Khandheria[2]***

[1]Clinical and Experimental Department of Medicine and Pharmacology, University of Messina, Azienda Ospedaliera Universitaria 'Policlinico G. Martino', Via Consolare Valeria 1, Messina 98125, Italy and [2]Aurora Cardiovascular Services, Aurora Sinai/Aurora St Luke's Medical Centers, University of Wisconsin School of Medicine and Public Health, 2801 W. Kinnickinnic River Parkway, #840, Milwaukee, WI 53215, USA

* Corresponding author. Tel: +1 414 649 3909; Fax: +1 414 649 3551. Email: publishing22@aurora.org




A 70-year-old obese man with pulmonary arterial hypertension, diabetes mellitus, dyslipidaemia and a history of coronary artery disease treated with four bypass grafts was referred to our centre for chest pain associated with lightheadedness and dyspnoea after usual activity. Two-dimensional echocardiography revealed left ventricular hypertrophy and severe aortic stenosis (mean gradient: 58 mmHg) with calcified leaflets and aortic root. Transcatheter aortic valve replacement (TAVR) was recommended. A temporary pacemaker was placed prior to the intervention, which was completed without complications. However, 5 days after TAVR, a third-degree atrioventricular block persisted (*Panel A*). Therefore, a dual-chamber permanent pacemaker was implanted. After 2 days, follow-up transthoracic echocardiography revealed the presence of a small ventricular defect in the apical portion of the septum (*Panel B, arrows*), likely secondary to the traumatic effect of the pacemaker's ventricular lead. Flow through the defect was directed towards the left ventricle in diastole (*Panel C*) and towards the right ventricle in systole (*Panel D*). This finding is unexpected; probably, a little pouch was formed in the apical portion of the right ventricle (*Panel* B) partially isolated from the main chamber and during diastole the pressure in the pouch was higher than in the left ventricle, causing the bidirectional flow. The shunt rate was not significant; pulmonary pressure was 28 mmHg, while left ventricle function was normal and the aortic mean gradient decreased to 11 mmHg. Pacemaker function was not compromised so the patient was discharged.

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.