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REVIEW

Imaging cardiac fat

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Ectopic fat deposition has been associated with lipotoxicity and derangement in local and systemic metabolism, insulin resistance, cardiac dysfunction, atherosclerosis, local, and systemic inflammation. The mechanisms and potentially detrimental effects of such an accumulation should be fully investigated in order to establish preventive strategies. The aim of this review is to provide an overview of current knowledge regarding imaging techniques to measure cardiac fat deposition and its potential clinical relevance, if any.

Keywords Pericardial fat • Imaging biomarkers • Cardiovascular risk • Echocardiography

Introduction

Risk profiling remains a challenge in clinical cardiology. There is a need to define individual vs. population risk assessment obtained with conventional risk factors. Cardiac fat may play a role in this setting once its multifaceted action as an endocrine organ is thoroughly established and investigated. Nowadays, cardiac fat can be imaged with several modalities offering a quantitative assessment. However, when, how and why to measure cardiac fat remains a challenging clinical question that should be addressed in properly designed studies. Imaging techniques can play a role, not only as surrogate biomarkers, but also to assess cardiac fat modulation with therapeutic interventions.

Methods for quantification of cardiac fat

There is no consensus regarding the upper limit of normality for cardiac fat, either epicardial adipose tissue (EAT) or pericardial adipose tissue (PAT), and the reported volumes are highly variable among different patient populations, with some reporting a range of 4–52% of the total heart mass at autopsy[1] and no significant change with age, whereas others document a trend towards an increase or decrease in the amount of tissue found in older patients.[1] Ultrasound, cardiac tomography (CT), and cardiac magnetic resonance (CMR)[1–4] have been used to quantify cardiac fat. Currently, there is no consensus on the 'gold standard' for an *in vivo* quantification of EAT and PAT.

Echocardiography

Ultrasound is the most widely available technique for estimating the amount of cardiac fat; it is also the fastest and the least expensive. However, echocardiography cannot directly quantify the volume of cardiac fat, although it has been shown to be correlated with volume assessed at CMR.[5] Moreover, it is sometimes difficult to distinguish between EAT and PAT by echocardiography and it is likely that in many instances, PAT rather than EAT thickness is reported. In fact, ultrasound tends to overestimate the EAT volume and to underestimate the PAT volume when compared with MRI.[5] This indicates that pericardial and epicardial fat in echocardiography can be lumped together, given the fact that the pericardium itself and its borders cannot always be clearly visualized. To standardize ultrasound measurements, Iacobellis and Willens[2] proposed measuring EAT (*Figure 1*) in the parasternal long-axis view at end-systole, placing the caliper at the level of the free wall of the right ventricle and averaging the measurement during three cardiac cycles, and in the mid-ventricular parasternal short-axis view on the right ventricular free wall along the mid-line of the ultrasound beam perpendicular to the interventricular septum at mid-chordal and tip of the papillary muscle level.[2]

Cardiac tomography

CT provides a true volumetric visualization and quantification of EAT and PAT.[6–9] In comparison with other imaging modalities, however, CT may provide a more accurate evaluation of fat tissue due to its higher spatial resolution compared with ultrasound and MRI.

CT offers the advantages of submillimeter collimation, high temporal and spatial resolution, and 3D views of the heart and its epicardial surface. Based on the reconstructed cross-sectional images, area[8,10,11] or preferably volumetric measurements can be performed.[6,7,12] Hence, EAT and PAT can be separately quantified in CT images (*Figure 2*). Fox *et al.*[13] proposed the following methodology:

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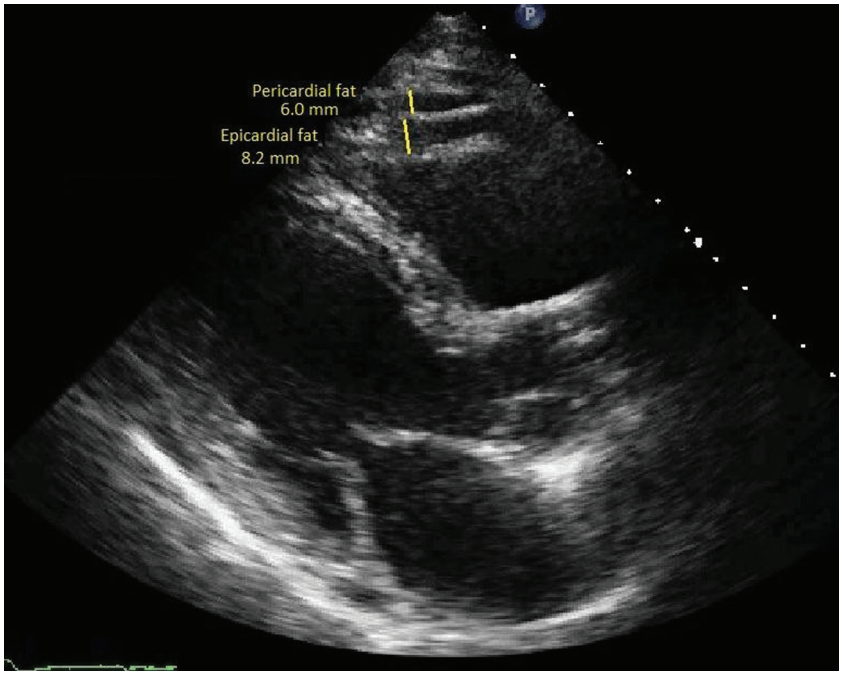

Figure 1 Echocardiographic images of the heart. EAT can be seen as a hyperechoic or hypoechoic region over the right ventricular free wall depending on the amount of tissue present. EAT and PAT can be separated in two different layers as shown in figure.

the heart is imaged on average with 48 contiguous 2.5 mm slices with a prospectively ECG-triggered scanning protocol. There is no need to use contrast to assess pericardial fat. The method uses a pre-processing step to remove all other structures apart from the heart, using a region growing segmentation strategy. Then, an experienced user is required to scroll through the slices between upper and lower heart limit and, if the pericardium is visible, he is required to place from 5 to 7 control points. Catmull-Rom cubic spline functions are then automatically generated to obtain a smooth closed pericardial contour. Identification of the fat inside the contour is finally achieved by thresholding.[14] The total thoracic fat volume included adipose tissue located in the pericardium and in the thorax from the level of the right pulmonary artery to the diaphragm and the chest wall to the descending aorta (*Figure 2*).[13]

Magnetic resonance

For MRI acquisition of the heart a standardized protocol is used. Cardiac coil and ECG triggering is used for the sequences; during the acquisition time, patients are in breath-hold (10–12 s). Cardiac adipose tissue scans are obtained by fast-spin echo T1-weighted sequences with oblique axial orientation, for a correct study of horizontal long axes of the heart, in diastole[5] (TE 42 ms; Echo Train Length 23; Bandwidth 62.50; slice thickness 8 mm; slice gap 0 mm; FOV 38 cm; matrix 288 × 224; Phase FOV 0.75; NEX 1; Trigger delay = minimum[5] mm-thick section with 0 mm intersection gap, field of view, and a 256 × 256 matrix). Epicardial fat is defined as any adipose tissue located within the pericardial sac (*Figure 3*).[5,6] The analysis of fat volumes is often manual and time-consuming. Images are also acquired in the short-axis view that covers the heart from the apex of the ventricles to the top of the atria. For each slice, area is quantified and volume is calculated by multiplying each area by the thickness, i.e. 8 mm, with no gap between images. Weight of cardiac fat can be obtained by multiplying the volume (cm^3) by 0.92, which corresponds to cardiac fat density in gram per kilogram.[6] We have recently demonstrated that fat volume is highly correlated with the fat area ($r^2 = 0.87$, $P < 0.0001$) measured in a four-chamber view, the average fat area was 2656 mm^2; the average fat volume was 234 cm^3, corresponding to the total cardiac fat mass of 215 g (EAT + PAT).[6] This was confirmed in an animal-based model that studied MRI images of cardiac fat and found a strongly positive correlation with an *ex vivo* pericardial adipose mass at necropsy,[9] validating it as an adequate technique for measuring fatty tissue around the heart. Unfortunately, due to the technical difficulty entailed in dissecting EAT from the myocardium, this observation could only be made on total pericardial fatty tissue and not on each one of its components as a different compartment.

Association of cardiac fat with cardiovascular risk factors

A growing body of evidence shows that epicardial fat may play a relevant role as a biomarker for cardiovascular risk assessment.[1,15–17] PAT and EAT amounts increase with the body mass index (BMI)[6,7] and decrease after weight loss and lifestyle interventions.[18,19] PAT and EAT are strongly correlated to each other, while the correlation with intra-abdominal visceral adipose tissue (VAT), waist circumference, and BMI is greater for PAT than

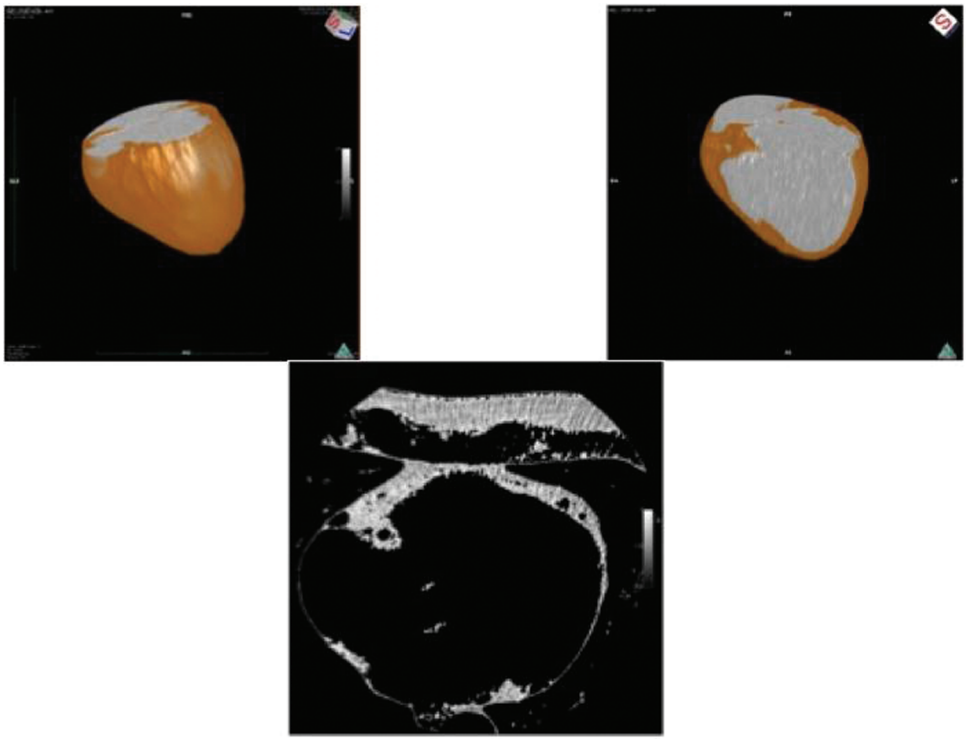

Figure 2 CT image of the heart. Epicardial fat volume represented in 3D as a result of semiautomatic computation (upper left and right panel) and total thoracic fat (lower central panel).

EAT.[6,20] It has been shown that fat accumulation is proportional to the degree of obesity, with body fat ranging from 14 to 33 kg, visceral fat from 0.8 to 1.8 kg and cardiac fat from 134 to 236 g. In male subjects with primary untreated hypertension, blood pressure increased proportionally to the amount of visceral and total cardiac fat, while epicardial and subcutaneous fat were similar to that of healthy subjects.[7] Nelson *et al.*[16] found a weak correlation between the Framingham risk score and EAT thickness >5 mm at echo.

Multiple metabolic risk factors, such as blood pressure, low-density lipoprotein cholesterol, glucose, and high-density lipoprotein cholesterol, were found to be associated with PAT in a subgroup of patients from the Framingham Heart study.[1] Regarding classic anthropometric measures, both PAT and EAT measured with echo have been found to correlate with waist circumference and visceral adiposity.[5,6,17] In a recent study of obese men, following an exercise training programme [(12 weeks) 60–70% of the maximal heart rate; 60 min/day, 3 days/week], epicardial fat thickness significantly decreased.[21]

Association of cardiac fat with other imaging biomarkers of cardiovascular disease

A significant positive correlation was observed between pericardial fat and carotid intima media thickness (CCA-IMT).[22] In an unadjusted sex-specific linear regression analysis, there was a significant association between pericardial fat and CCA-IMT in both women and men, an association that persisted after further adjusting for age and ethnicity. In the general population, pericardial fat is associated with carotid IMT, an association that may not be independent from markers of overall adiposity or common atherosclerosis risk factors.[22] Pericardial fat measured by computed tomography assessed in 5770 participants in the MESA study was correlated with carotid distensibility; higher pericardial fat is associated with higher carotid stiffness, independent of traditional cardiovascular disease (CVD) risk factors and obesity.[23] Epicardial fat tissue thickness is correlated negatively with flow mediated dilatation and positively with age, diastolic blood pressure, hsCRP, fibrinogen, HOMA-IR, and lipid parameters. Multiple regression analyses showed epicardial fat tissue thickness to be an independent factor influencing endothelial function in patients with metabolic syndrome.[24]

Correlation with severity and outcome of cardiovascular disease

Several studies have linked cardiac fat accumulation to the presence and severity of coronary artery disease (CAD).

The MESA study was able to determine an association between PAT and CAD after correcting for known risk factors in a community-based population with a prospective study design. It

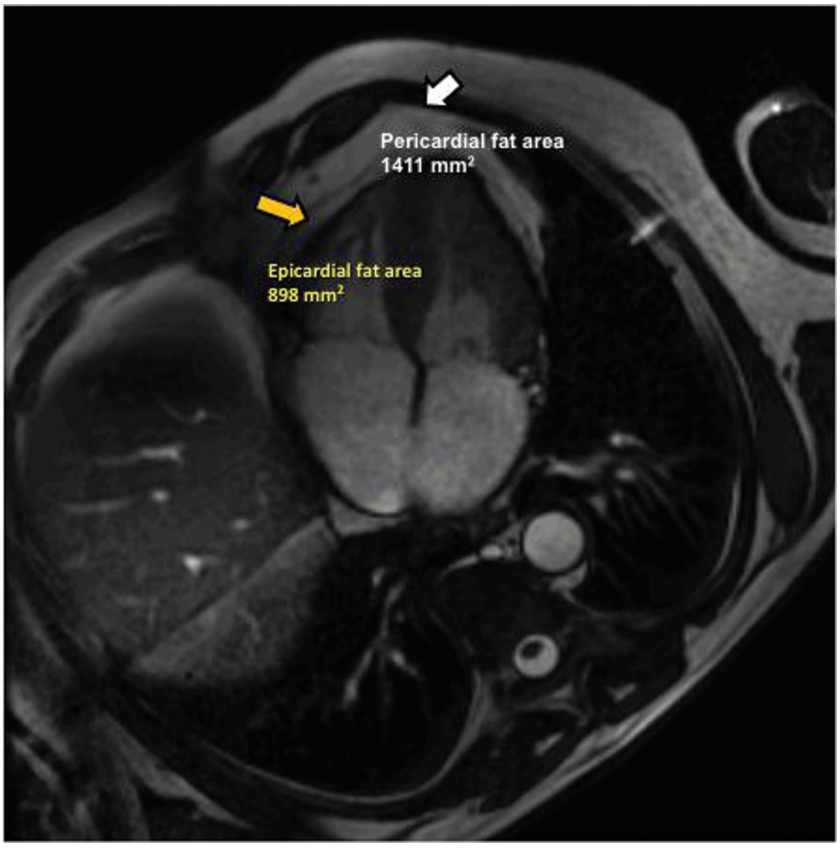

Figure 3 CMR image: the four-chamber view of the heart of a subject with high total cardiac fat. Adipose tissue surrounding the entire heart can be visualized and measured to achieve a complete assessment of epicardial, pericardial, and intra-thoracic fat.

also found a positive correlation between PAT and waist circumference; however, there was no association with the BMI.[22] Others have also measured pericoronary fat when measuring EAT,[25] and there is evidence that, in patients with the BMI <27, the two measurements correlate well with the extent of CAD and calcium score.

Sade *et al.*[26] studied microvascular dysfunction in women with angina and normal coronary arteries, and documented PAT to be an independent predictor with a cut-off value of >0.45 cm, whereas traditional risk factors were not predictive of microvascular dysfunction.

In a study of obese and non-obese Japanese men, pericardial fat measured by CT scan was a significant variable for the presence of CAD and its severity based on coronary angiography; it also correlated well with age, triglycerides, and systolic blood pressure in non-obese patients.[15] Tonbul *et al.*[27] studied a patient population with end-stage renal disease (ESRD) and found a statistically significant relationship between the EAT and CAC score in ESRD patients, which was even higher in diabetic than in non-diabetic ESRD patients.

Using a cardiac 64 multi-slice CT protocol, Harada *et al.*[12] described significantly larger EAT volumes in patients with acute coronary syndrome (ACS) than those with normal coronary arteries. PAT has also been documented to correlate well with multiple measures of metabolic risk factors and CAC in a community-based setting when measured with CT[1] even after adjusting for several possible confounders. When indexed by the body surface area, the EAT volume was a strong independent determinant of the presence of total coronary occlusions and was associated with advanced age, male sex, degree of metabolic alterations, atheromatosis, and the history of ACS.[27] EAT thickness over the free right ventricle wall measured using transthoracic echo has also been positively correlated with CAD severity and was found to independently predict significant coronary artery stenosis.[28,29] In a sample of 1000 subjects in the Framingham Heart Study[13] undergoing contemporaneous CMR and CT examinations, the pericardial fat volume was associated with LV mass, LVEDV, and LA size in women and with the LV mass and the LA size in men. These associations persist after multivariable adjustment but not after accounting for body weight or VAT, with the exception of the LA size in men. These findings do not suggest that pericardial fat is a better correlate of cardiac structure and function than VAT or other more easily conducted anthropometric measures of adiposity. Based on these results, it is likely that systemic effects of generalized adiposity may overwhelm the local effects of pericardial fat. From the Framingham Heart Study Offspring cohort,

abdominal and chest multidetector computed tomography to quantify volumes of pericardial fat, intra-thoracic fat, and VAT was performed.[30] The analysis of 1267 participants demonstrated that pericardial fat and VAT, but not intra-thoracic fat, were significantly associated with prevalent CVD in age-/sex-adjusted models and after adjustment for the BMI and waist circumference. After multivariable adjustment, associations were attenuated. Only pericardial fat was associated with prevalent myocardial infarction after adjusting for conventional measures of adiposity. Iozzo *et al.*[31] showed that CAD is accompanied by augmented fat depots surrounding the heart, which are negatively related to coronary flow hyperaemia. Among fat depots, intra-pericardial fat was the only independent predictor of the hyperaemic myocardial blood flow, supporting the hypothesis of a direct paracrine/vasocrine effect.[31] Janik *et al.*[32] investigated the association between EAT and myocardial perfusion and showed that EAT volume assessed by CT was an independent predictor of ischaemia on PET, and outperformed CAC score in a CAD naive population at intermediate pre-test probability of disease. Similar results were obtained with SPECT, showing that pericardial fat was significantly correlated with myocardial ischaemia in patients without known CAD.[33]

A few studies showing the impact on the progression of CAD and outcome are available. In a series of 375 consecutive asymptomatic subjects with an intermediate risk of developing CAD, who underwent serial non-contrast CT at least 3–5 years apart, epicardial fat volume increase $\geq$15% and hypertension were independent predictors of the number of new calcified plaques on follow-up.[34]

In a dual-cohort study, the upper threshold of the epicardial fat volume from non-contrast-enhanced cardiac computed tomography in a healthy population was obtained and applied in a separate population assessed for major adverse cardiovascular events. The epicardial fat volume exceeding the newly defined upper normal threshold (median, range, and 25 and 75th percentiles of the non-normally distributed EFV indexed on the body surface were 33.3, 10.8–96.6, and 24.5 and 45.5 cm^3/m^2. The 95th percentile definition of the upper normal limit of EFVi was 68.1 cm^3/m^2) was significantly and independently associated with major adverse cardiac events and tended to predict them better when added to the combination of the Framingham risk score and the coronary calcium score.[35] A recent study[36] evaluated the relationship between pericardial fat volume, thoracic fat volume, and subsequent adverse cardiovascular outcome, in a case–control study, based on 4-year post-non-contrast CT follow-up in asymptomatic patients without established CAD. An increased pericardial fat volume was independently related to spontaneous hard events.

Conclusions

There is still a long way to go before obtaining a complete description of how cardiac fat in all its components affects the myocardium and the coronary arteries, and what can be done to modulate its mechanical, metabolic, and endocrine activities in different clinical contexts.[37,38] However, current literature appears to support this link, and future uses for this fatty tissue depot are already being postulated from an experimental standpoint. Cardiac fat appears to be an endocrine organ able to modulate cardiac and vascular function due to its proximity to these structures. Its potential clinical uses range from risk profiling in metabolic and CVDs to outcome and follow-up studies and the assessment of therapeutic interventions through pharmacological and dietary modulation. Moreover, it is important to understand the relationship of cardiac fat and all its components with the distribution of visceral fat to other organs and vascular districts. Of the available imaging techniques, if one were to be used as a large-scale screening method, the most likely candidate would be cardiac fat thickness measured by echo given its affordability, availability, and shorter testing time. Areas of uncertainty to be covered are standardization of measurement, fat depot to be measured, site of fat accumulation, function, and altered conditions. The use of epicardial fat as an imaging biomarker is still in the promising phase of the health technology assessment pathway and more studies are needed for it to become an established imaging biomarker. Unfortunately, available evidence was not built in appropriately designed studies to assess the role of cardiac fat and most of the information that we have is a surrogate one coming from studies aimed at assessing other risk factors.

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Conflict of interest: none declared

References

1. Rosito GA, Massaro JM, Hoffmann U, Ruberg FL, Mahabadi AA, Vasan RS Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation* 2008;**117**:605–13.
2. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. *J Am Soc Echocardiogr* 2009;**22**:311–9.
3. Iacobellis G. Imaging of visceral adipose tissue: an emerging diagnostic tool and therapeutic target. *Curr Drug Targets Cardiovasc Hematol Dis* 2005;**5**:345–53.
4. Sarin S, Wenger C, Marwaha A, Qureshi A, Go BD, Woomert CA *et al.* Clinical significance of epicardial fat measured using cardiac multislice computed tomography. *Am J Cardiol* 2008;**102**:767–71.
5. Sicari R, Sironi AM, Petz R, Frassi F, Chubuchny V, De Marchi D *et al.* Pericardial rather than epicardial fat is a cardiometabolic risk marker: an MRI vs. echo study. *J Am Soc Echocardiogr* 2011;**24**:1156–62.
6. Sironi AM, Petz R, De Marchi D, Buzzigoli E, Ciociaro D, Positano V *et al.* Impact of increased visceral and cardiac fat on cardiometabolic risk and disease. *Diabet Med* 2012;**29**:622–7.
7. Sironi AM, Gastaldelli A, Mari A, Ciociaro D, Positano V, Buzzigoli E *et al.* Visceral fat in hypertension: influence on insulin resistance and beta-cell function. *Hypertension* 2004;**44**:127–33.
8. Saremi F, Mekhail S, Sefidbakht S, Thonar B, Malik S, Sarlaty T. Quantification of epicardial adipose tissue: correlation of surface area and volume measurements. *Acad Radiol* 2011;**18**:977–83.
9. Nelson MR, Mookadam F, Thota V, Emani U, Al Harthi M, Lester SJ *et al.* Epicardial fat: an additional measurement for subclinical atherosclerosis and cardiovascular risk stratification? *J Am Soc Echocardiogr* 2011;**24**:339–45.
10. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. *Am Heart J* 2007;**153**:907–17.
11. Pracon R, Kruk M, Kepka C, Pregowski J, Opolski MP, Dzielinska Z *et al.* Epicardial adipose tissue radiodensity is independently related to coronary atherosclerosis. *Circ J* 2011;**75**:391–7.
12. Harada K, Amano T, Uetani T, Tokuda Y, Kitagawa K, Shimbo Y *et al.* Cardiac 64-multislice computed tomography reveals increased epicardial fat volume in patients with acute coronary syndrome. *Am J Cardiol* 2011;**108**:1119–23.

13. Fox CS, Gona P, Hoffmann U, Porter SA, Salton CJ, Massaro JM *et al.* Pericardial fat, intrathoracic fat, and measures of left ventricular structure and function: the Framingham Heart Study. *Circulation* 2009;**119**:1586–91.
14. Coppini G, Favilla R, Marraccini P, Moroni D, Pieri G. Quantification of epicardial fat by cardiac CT Imaging. *Open Med Inform J* 2010;**4**:126–35.
15. Taguchi R, Takasu J, Itani Y, Yamamoto R, Yokoyama K, Watanabe S *et al.* Pericardial fat accumulation in men as a risk factor for coronary artery disease. *Atherosclerosis* 2001;**157**:203–9.
16. Nelson AJ, Worthley MI, Psaltis PJ, Carbone A, Dundon BK, Duncan RF *et al.* Validation of cardiovascular magnetic resonance assessment of pericardial adipose tissue volume. *J Cardiovasc Magn Res* 2009;**11**:15.
17. Wang TD, Lee WJ, Shih FY, Huang CH, Chang YC, Chen WJ *et al.* Relations of epicardial adipose tissue measured by multidetector computed tomography to components of the metabolic syndrome are region specific and independent of anthropometric indexes and intraabdominal visceral fat. *J Clin Endocrinol Metab* 2009;**94**:662–9.
18. Rabkin SW. Epicardial fat: properties, function and relationship to obesity. *Obes Rev* 2007;**8**:253–61.
19. Willens HJ, Byers P, Chirinos JA, Labrador E, Hare JM, De Marchena E. Effects of weight loss after bariatric surgery on epicardial fat measured using echocardiography. *Am J Cardiol* 2007;**99**:1242–5.
20. Sacks HS, Fain JN, Holman B, Cheema P, Chary A, Parks F *et al.* Uncoupling protein-1 and related messenger ribonucleic acids in human epicardial and other adipose tissues: epicardial fat functioning as brown fat. *J Clin Endocrinol Metab* 2009;**94**:3611–5.
21. Kim MK, Tomita T, Kim MJ, Sasai H, Maeda S, Tanaka K. Aerobic exercise training reduces epicardial fat in obese men. *J Appl Physiol* 2009;**106**:5–11.
22. Soliman EZ, Ding J, Hsu FC, Carr JJ, Polak JF, Goff DC Jr. Association between carotid intima-media thickness and pericardial fat in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Stroke Cerebrovasc Dis* 2010;**19**:58–65.
23. Brinkley TE, Hsu FC, Carr JJ, Hundley WG, Bluemke DA, Polak JF *et al.* Pericardial fat is associated with carotid stiffness in the Multi-Ethnic Study of Atherosclerosis. *Nutr Metab Cardiovasc Dis* 2011;**21**:332–8.
24. Aydin H, Toprak A, Deyneli O, Yazici D, Tarçin O, Sancak S *et al.* Epicardial fat tissue thickness correlates with endothelial dysfunction and other cardiovascular risk factors in patients with metabolic syndrome. *Metab Syndr Relat Disord* 2010;**8**:229–34.
25. Gorter PM, de Vos AM, van der Graaf Y, Stella PR, Doevendans PA, Meijs MF. Relation of epicardial and pericoronary fat to coronary atherosclerosis and coronary artery calcium in patients undergoing coronary angiography. *Am J Cardiol* 2008;**102**:380–5.
26. Sade LE, Eroglu S, Bozbas H, Özbic S, Hayran M, Haberal A *et al.* Relation between epicardial fat thickness and coronary flow reserve in women with chest pain and angiographically normal coronary arteries. *Atherosclerosis* 2009;**204**:580–5.
27. Tonbul HZ, Turkmen K, Kayıkcıoglu H, Ozbek O, Kayrak M, Biyik Z. Epicardial adipose tissue and coronary artery calcification in diabetic and nondiabetic end-stage renal disease patients. *Ren Fail* 2011;**33**:770–5.
28. Ueno K, Anzai T, Jinzaki M, Yamada M, Jo Y, Maekawa Y *et al.* Increased epicardial fat volume quantified by 64-multidetector computed tomography is associated with coronary atherosclerosis and totally occlusive lesions. *Circ J* 2009;**73**:1927–33.
29. Jeong JW, Jeong MH, Yun KH, Oh SK, Park EM, Kim YK *et al.* Echocardiographic epicardial fat thickness and coronary artery disease. *Circ J* 2007;**71**:536–9.
30. Mahabadi AA, Massaro JM, Rosito GA, Levy D, Murabito JM, Wolf PA *et al.* Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. *Eur Heart J* 2009;**30**:850–6.
31. Bucci M, Joutsiniemi E, Saraste A, Kajander S, Ukkonen H, Saraste M *et al.* Intrapericardial, but not extrapericardial, fat is an independent predictor of impaired hyperemic coronary perfusion in coronary artery disease. *Arterioscler Thromb Vasc Biol* 2011;**31**:211–8.
32. Janik M, Hartlage G, Alexopoulos N, Mirzoyev Z, McLean DS, Arepalli CD *et al.* Epicardial adipose tissue volume and coronary artery calcium to predict myocardial ischemia on positron emission tomography-computed tomography studies. *J Nucl Cardiol* 2010;**17**:841–7.
33. Tamarappoo B, Dey D, Shmilovich H, Nakazato R, Gransar H, Cheng VY *et al.* Increased pericardial fat volume measured from noncontrast CT predicts myocardial ischemia by SPECT. *JACC Cardiovasc Imaging* 2010;**3**:1104–12.
34. Nakanishi R, Rajani R, Cheng VY, Gransar H, Nakazato R, Shmilovich H *et al.* Increase in epicardial fat volume is associated with greater coronary artery calcification progression in subjects at intermediate risk by coronary calcium score: a serial study using non-contrast cardiac CT. *Atherosclerosis* 2011;**218**:363–8.
35. Shmilovich H, Dey D, Cheng VY, Rajani R, Nakazato R, Otaki Y *et al.* Threshold for the upper normal limit of indexed epicardial fat volume: derivation in a healthy population and validation in an outcome-based study. *Am J Cardiol* 2011;**108**:1680–5.
36. Cheng VY, Dey D, Tamarappoo B, Nakazato R, Gransar H, Miranda-Peats R *et al.* Pericardial fat burden on ECG-gated noncontrast CT in asymptomatic patients who subsequently experience adverse cardiovascular events. *JACC Cardiovasc Imaging* 2010;**3**:352–60.
37. Gastaldelli A, Basta G. Ectopic fat and cardiovascular disease: what is the link? *Nutr Metab Cardiovasc Dis* 2010;**20**:481–90.
38. Gastaldelli A, Morales MA, Marraccini P, Sicari R. The role of cardiac fat in insulin resistance. *Curr Opin Clin Nutr Metab Care* 2012;**15**:523–8.