Clinical Significance of Cardiomegaly Caused by Cardiac Adiposity

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Enlarged cardiac silhouette on chest x-ray (CXR) in the absence of cardiopulmonary disease is often dismissed as "pseudocardiomegaly." We aimed to assess the impact of epicardial adipose tissue (EAT) on radiographic heart size and to determine the clinical significance of cardiomegaly caused by EAT. In total 112 patients (52 ± 13 years old, 53% women, body mass index 32 ± 8 kg/m^2) with structurally normal hearts by transthoracic echocardiography underwent cardiac computed tomography (CCT). EAT volume was measured by CCT and cardiothoracic ratio (CTR) and cardiac transverse and lateral horizontal transverse diameters were measured on posteroanterior and lateral view CXR. EAT volume (mean 122 ± 49 ml) correlated directly with age, body mass index, hypertension, hyperlipidemia (p <0.05 for all comparisons), transverse diameter (r = 0.50, p <0.001), CTR (r = 0.45, p <0.001), and lateral horizontal transverse diameter (r = 0.38, p <0.001). EAT volume was larger in those with increased (n = 22) compared to those with normal (n = 90) CTR (154 ± 54 vs 115 ± 54 ml, p = 0.0005). Patients with cardiomegaly were also older (58 ± 13 vs 50 ± 12 years old, p = 0.009) and more often had diabetes (32% vs 9%, p = 0.03), hypertension (86% vs 46%, p = 0.001), hyperlipidemia (68% vs 44%, p = 0.04), or obstructive coronary artery disease by CCT (32% vs 11%, p = 0.04). Coronary artery calcium score was also higher in those with cardiomegaly (median 56 [first tertile 0, third tertile 298] vs 0 [0, 55], p = 0.006). In conclusion, cardiomegaly on CXR can be caused by excessive EAT. This is associated with several coronary risk factors and with coronary calcification and stenosis. Cardiomegaly in this setting may be regarded as another noninvasive marker of coronary atherosclerosis. **(Am J Cardiol 2012;109:1374–1378)**

The epicardium in most residents in western societies contains adipose tissue.[1] At necropsy, epicardial adipose tissue (EAT) adds markedly to total cardiac weight.[2,3] This visceral depot has also been examined by noninvasive cardiac imaging techniques such as echocardiography,[4] cardiac computed tomography (CCT),[5] and cardiac magnetic resonance imaging.[6] These studies have established a close relation between EAT and atherosclerotic risk factors (obesity, hyperlipidemia, metabolic syndrome) and coronary calcium.[5] Some data have indicated that large deposits of EAT are associated with the presence of inducible myocardial ischemia[7] and adverse cardiac events[8] and that weight loss and aerobic exercise can lead to a decrease in the size of the EAT compartment.[9,10] Because chest x-ray (CXR) is the most commonly performed cardiac imaging procedure, we aimed to determine whether cardiomegaly in the absence of apparent cardiopulmonary abnormalities would provide an initial clue to the presence of cardiac adiposity and its associated heightened risk of coronary atherosclerosis.

Methods

The study population consisted of 112 adults from 356 consecutive admissions to the Geisinger Medical Center Chest Pain Decision Unit who underwent technically adequate posteroanterior and lateral view CXR, transthoracic echocardiography, and CCT during the same short stay (23-hour observation). They also fulfilled the following criteria: had normal cardiac size and function and no pericardial effusion by transthoracic echocardiography, had no pulmonary disease by CXR or CCT, and had high-quality, digitally acquired, and stored studies for review. Clinical information was available for all patients through the medical center's electronic health record system.

Posteroanterior and lateral CXRs were obtained using standard radiographic techniques with a patient positioned upright and at a distance of 6 feet from the camera. All CXRs were stored digitally and selected measurements including cardiothoracic ratio (CTR), transverse diameter, lateral horizontal transverse diameter, and percent retrosternal air space obliteration were made offline (Figure 1). Potential retrosternal air space was defined as the distance from the angle of Louis to the sternal-diaphragmatic angle on the lateral film. The following values were considered normal CXR measurements: <50% for CTR, ≤14.5 cm for transverse diameter, ≤11.6 cm for horizontal transverse diameter, and ≤33% for retrosternal air space obliteration.[11–14] All measurements were obtained independently of the results of other diagnostic studies.

Complete transthoracic 2-dimensional echocardiographic (in fundamental and harmonic modes) and Doppler ultrasound examinations at rest were performed using a broadband (S_3) transducer attached to an iE33 ultrasound system (Phillips Ultrasound, Andover, Massachusetts). Images were obtained and stored digitally. Parameters used for assessment of chamber sizes included 2-dimensional measurements of

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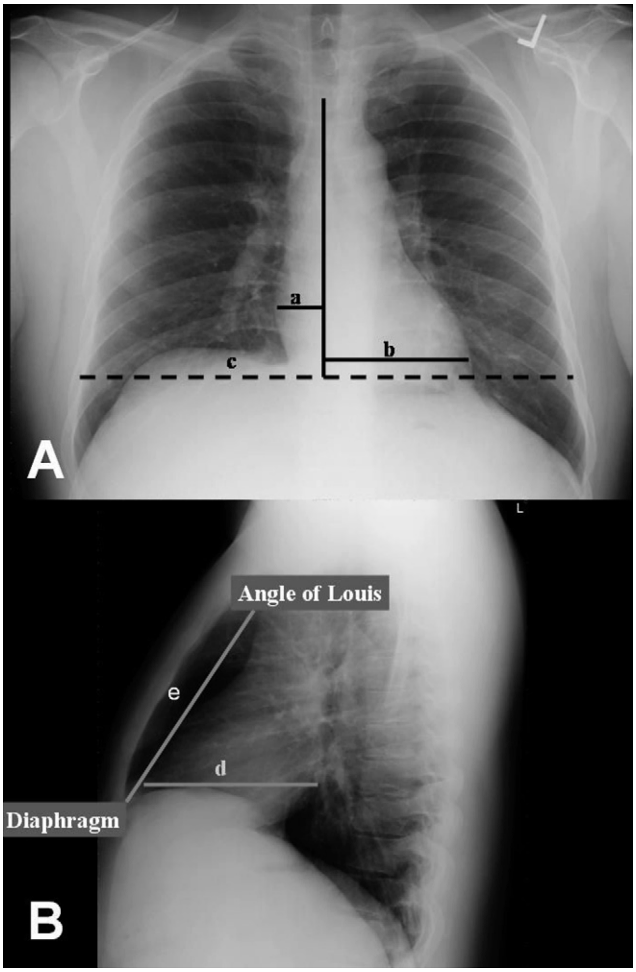

Figure 1. Posteroanterior *(A)* and lateral *(B)* views of the chest showing the technique used for measurement of heart size. Transverse diameter of the heart was defined as the sum of *a* (distance from midline to right heart border) and *b* (distance from midline to left heart border); cardiothoracic ratio was obtained by dividing the transverse diameter of the heart by the transverse diameter of the chest measured at the level of the diaphragm *(c)* and multiplying the result by 100. The lateral horizontal transverse diameter of the heart *(d)* and the retrosternal air space *(e)* were measured on the lateral view.

ventricular septal thickness, left ventricular internal dimension, and left ventricular posterior (inferolateral) wall thickness in diastole and left ventricular internal dimension in systole and left atrial anteroposterior diameter in the parasternal long-axis view. In addition, left atrial surface area and left ventricular end-diastolic and end-systolic volumes were measured in the apical 4-chamber view. Left ventricular mass was calculated by the standard cube formula and was indexed to body surface area. All echocardiographic measurements were made offline using a workstation by an expert blinded to the CXR and cardiac computed tomographic findings.

All patients were in sinus rhythm at the cardiac computed tomographic study that included calcium scoring and gated contrast coronary angiography using a 64-slice scanner (General Electric, Minneapolis, Minnesota). A steady heart rate <60 beats/min was achieved using β-blocking agents if necessary. Scanning started superiorly at the level of carina and extended 10 mm beyond the left ventricular apex. A semiautomated volumetric method was developed for quantification of EAT as previously described.[5] Briefly, using 2.5-mm-thick axial slices that were used for calcium scoring, the parietal pericardium was traced manually in every fourth slice starting from the aortic root to the apex. The number of slices that had to be traced manually ranged from 7 to 10 in each patient. The computer software then automatically interpolated and traced the parietal pericardium in all slices interposed between the manually traced slices. Total number of slices traced manually or automatically ranged from 28 to 40 in each patient. Two histograms were then generated to depict total cardiac and EAT volumes. Fat voxels were identified by threshold attenuation values from −30 to −250 HU. Intraobserver and interobserver variabilities for quantification of EAT volume were <5%.

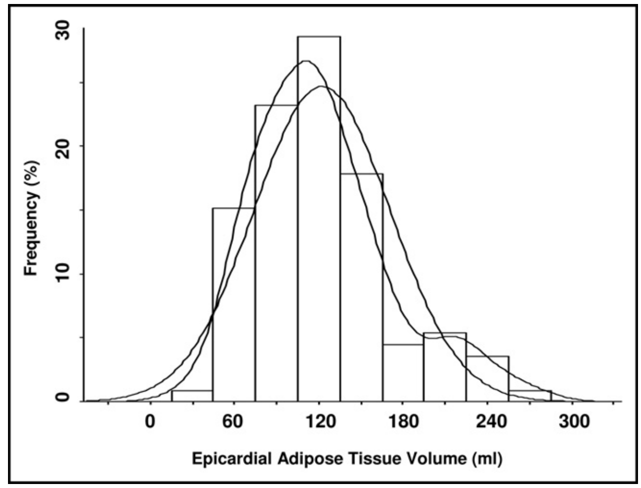

Figure 2. Histogram demonstrating the frequency distribution of epicardial adipose tissue volume as measured semiquantitatively by computerized tomography in 112 patients.

Results from normally distributed continuous data are presented as range (mean ± SD) and categorical data as number (percentage). Categorical data were analyzed by chi-square test and normally distributed continuous data by Student's *t* test. The relation between the known clinical, electrocardiographic, and CXR variables and EAT volume was examined using the Spearman correlation. Univariate regression analysis was used to identify predictors of cardiomegaly by CXR. Significant differences were defined as p values <0.05. The study was reviewed and approved by the Geisinger Medical Center institutional research review board.

Results

The age ranged of the 112 patients was 26 to 79 years (mean 52 ± 13) and 59 were women (53%). Average body weight, height, and body mass index were 93 ± 21 kg, 170 ± 10 cm, and 32 ± 8 kg/m^2, respectively. Diabetes mellitus, hypertension, and hypercholesterolemia were present in 15 (13%), 60 (54%), and 55 (49%), respectively, and 22 (20%) were smokers.

CTR ranged from 36% to 70% (mean 50 ± 7) and exceeded the upper normal limit in 22 patients (20%). Cor-

Table 1
Comparison of patients with normal or increased cardiac size as measured by cardiothoracic ratio on chest x-ray

	Normal CTR (n = 90)	Increased CTR (n = 22)	p Value
Age (years)	50 ± 12	58 ± 13	0.009
Body mass index (kg/m^2)	32.0 ± 8.0	32.7 ± 8.0	0.7
Diabetes mellitus	8 (9%)	7 (32%)	0.03
Hypertension*	41 (46%)	19 (86%)	0.001
Hyperlipidemia†	40 (44%)	15 (68%)	0.04
Obstructive coronary artery disease	10 (11%)	7 (32%)	0.04
Coronary artery calcium score	0 (0, 55)	56 (0, 298)	0.006
Sum of 12-lead electrocardiographic QRS voltage (mm)	128 (111, 138)	124 (101, 141)	0.6
Epicardial adipose tissue volume (ml)	115 ± 44	154 ± 54	0.0005

Values are presented as mean ± SD, number (percentage), or median (first tertile, third tertile).

* Blood pressure at rest >140/90 mm Hg or on medical therapy for hypertension.

† Total cholesterol >200 mg/dl or on medical therapy for hypercholesterolemia.

Table 2
Univariate correlates of epicardial adipose tissue volume

Variable	Correlation Coefficient (r)	p Value
Age (years)	0.27	0.004
Body mass index (kg/m^2)	0.37	0.0001
Chest x-ray measurements		
Transverse diameter (cm)	0.50	<0.001
Cardiothoracic ratio (%)	0.45	<0.001
Lateral horizontal transverse diameter (cm)	0.38	<0.001
Retrosternal air space obliteration (%)	0.14	0.1
Coronary artery calcium score	0.29	0.002
Sum of 12-lead electrocardiographic QRS voltage (mm)	−0.10	0.3

responding numbers for transverse and lateral horizontal transverse diameters were 10.3 to 21.2 cm (15.2 ± 2.3, 64 abnormal, 57%) and 7.6 to 18.3 cm (12.1 ± 1.9, 62 abnormal, 55%), respectively. Degree of retrosternal air space obliteration by cardiac shadow averaged 44.4% (first tertile 36.5, third tertile 58.5).

As measured on cardiac computed tomogram, EAT volume ranged from 25 to 274 ml (mean 122 ± 49). Distribution of EAT volume in the 112 patients is shown in Figure 2. Compared to 90 patients with normal CTR, the 22 patients with increased CTR were older and more often had diabetes, hypertension, hyperlipidemia, and obstructive coronary artery disease ($p < 0.05$ for all comparisons; Table 1). In addition, coronary calcium score and EAT volume were significantly increased in those with than without increased CTR (Table 1). There was no significant correlation between EAT volume and percent retrosternal air space obliteration by cardiovascular shadow. Table 2 lists univariate correlates of EAT volume. Overall, EAT volume directly correlated with age (r = 0.27, p = 0.004), body mass index (r = 0.37, p = 0.0001), and coronary calcium score (r = 0.29, p = 0.002). EAT volume also directly correlated with CXR measurements of cardiac size.

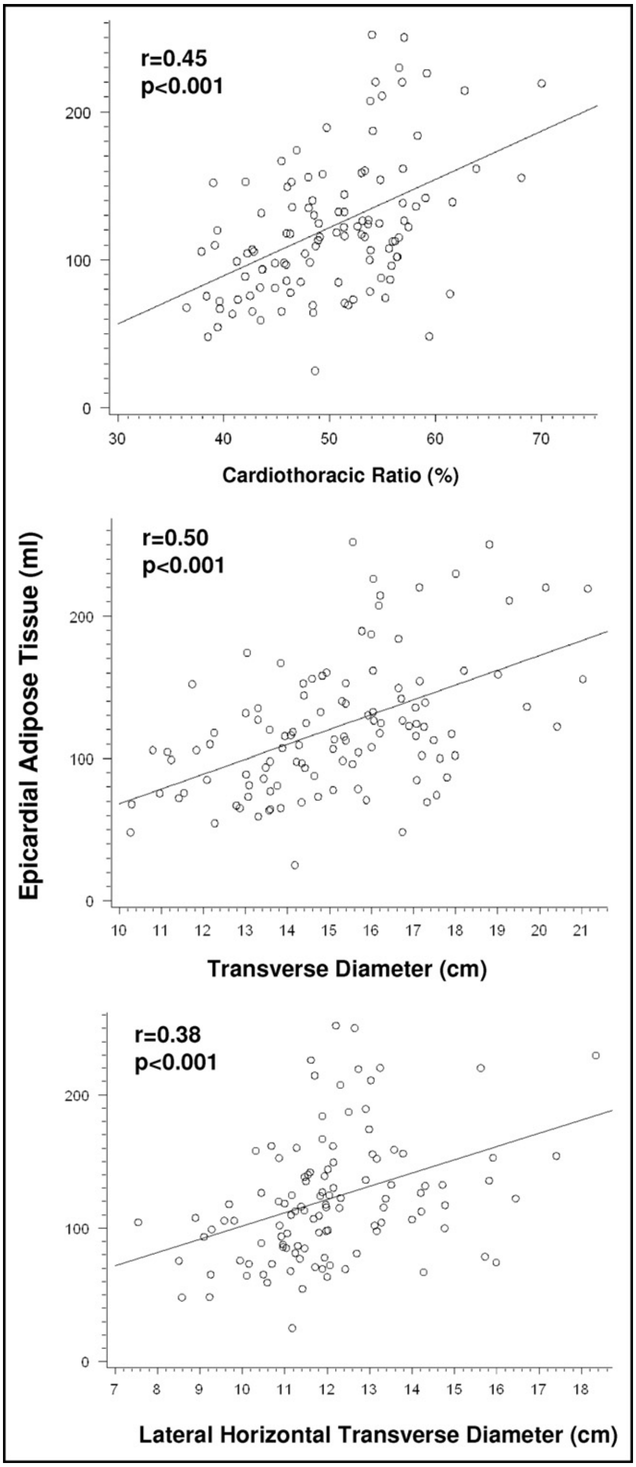

Figure 3. Simple regression analysis showing the incremental effect of epicardial adipose tissue volume on linear measurements of heart size on chest x-ray.

Correlation between EAT volume and cardiac size on CXR was found to be linear and predictable, as shown in Figure 3. On average, an increase of 1% in CTR or 1 mm in

Table 3
Impact of epicardial adipose tissue volume on unit increase in heart size as measured on chest x-ray

Heart Size	Incremental EAT Volume (ml) per Unit Increase in Heart Size	p Value
Transverse diameter (cm)	6.5	0.001
Cardiothoracic ratio (%)	1.8	0.009
Lateral horizontal transverse diameter (cm)	7.0	0.005

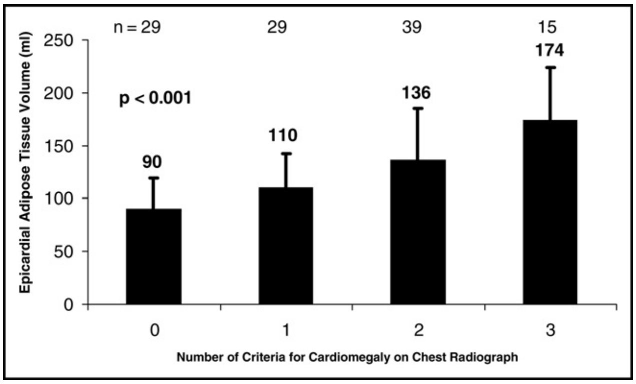

Figure 4. Bar graph demonstrating the direct relation of epicardial adipose tissue volume to number of chest x-ray criteria for cardiomegaly (cardiothoracic ratio, transverse diameter, and lateral horizontal transverse diameter).

transverse diameter or lateral horizontal transverse diameter was associated with an increase in EAT volume of 1.8, 6.5, and 7 ml, respectively (Table 3). EAT volume was directly proportional to the number of CXR criteria for cardiomegaly (0 = 90 ± 29 ml, 1 = 110 ± 32 ml, 2 = 136 ± 50 ml, 3 = 174 ± 50 ml, $p < 0.001$), as illustrated in Figure 4.

Discussion

This study provides objective evidence for the impact of EAT volume on CXR measurements of cardiac size. Thus, presence of large EAT volumes resulted in cardiomegaly on CXR in 20% of adults without cardiopulmonary disease or chest wall deformities. The findings further emphasize that cardiomegaly caused by EAT is directly related to several coronary artery risk factors and to computed tomographic evidence of coronary atherosclerosis manifested as hard (calcified) or soft plaques.

Since being proposed as a measurement of cardiac size on posteroanterior CXR,[15] an increased (≥50%) CTR has been regarded an indicator of organic heart disease when pericardial effusion and paracardiac pathology are excluded. The original cut-off value <50% was based on a study of nearly 500 CXRs and without any comparative evaluation.[15] A later study, however, showed that up to 25% of normal adults have CTR values >50%.[16] Similarly, a necropsy study showed that premortem CTR exceeded the upper limit of normal in 17% (20 of 118) of those with normal left ventricular mass.[17] These observations have been regarded simply as the expected limitations of CTR. However, longitudinal studies have frequently associated CTR with poor outcomes in those with underlying cardiac

Table 4
Comparison of prevalence of coronary atherosclerosis risk factors in patients in present study and United States adult population

Risk Factor	Present Study	United States Population
Diabetes mellitus	13%	11.3%[31]
Hypertension	54%	24–29%[32,33]
Hypercholesterolemia	49%	49%[34]
Smoking	20%	24.5%[35]

disease[18–22] and in the general adult population.[23,24] In the Framingham Study, cardiomegaly by CXR was a significant predictor of future congestive heart failure.[25] In other studies, all-cause or coronary artery disease mortality has been closely related to CTR values even at "normal" ranges (42% to 49%).[26–28] Our study provides a potential explanation for the apparent discrepancy between cardiomegaly as measured on CXR and by other imaging techniques.[29] Furthermore, it explains why increased CTR in the absence of cardiac chamber dilation may be associated with major adverse coronary events. It is important to note that in some of our patients CTR reached values as high as 70% despite normal cardiac chamber sizes by echocardiography. Extreme cardiomegaly in these cases was associated with excessive EAT volume.

Normally a small amount of fat can be found over the surface of the heart. This adipose tissue generally surrounds the epicardial coronary arteries in their courses over the surface of the heart and in the atrioventricular groove and interventricular sulcus. A variable amount of fat may also be seen over the anterior surface of the right ventricle and over its acute margin. Large quantities of fat may accumulate on the epicardial surface of the heart (cardiac adiposity) and result in an overall increase in cardiac size even in the presence of normal cardiac chamber sizes.[2] This visceral fat depot is metabolically active and secretes proinflammatory, prothrombotic, proatherogenic hormones and cytokines.[1] We previously reported that EAT, as measured semiquantitatively by CCT, is associated with many known risk factors for coronary artery disease and directly correlates with coronary artery calcium score and presence of obstructive coronary artery disease.[5] In the present study, we extend these observations to include the role of EAT in cardiomegaly as assessed by CXR and propose that the findings explain why cardiomegaly on CXR is a predictor of adverse cardiac outcomes, especially related to coronary artery events, even in patients with no significant cardiopulmonary abnormality.

We used the "standard" CXR measurements in this study to allow comparison of the findings with those of previous epidemiologic studies. However, data have been limited on these measurements other than that of the CTR and cut-off values used for transverse and lateral horizontal transverse diameters have been variable. Others have advocated the use of cardiac surface area or volume index[30] for assessment of heart size on CXR. However, these measurements are cumbersome, reproducibility has not been well studied, these measurements may not offer an advantage over the simple CTR for assessment of prognosis,[22] and data on their prognostic value have been limited. Although our patients presented with acute chest pain to a rural tertiary care center, comparison of their atherosclerotic risk factor profile to national estimates (Table 4) indicate that the findings may be applicable to the general adult population of the United States.[31–35]

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