Excess epicardial fat volume in post- menopausal women is associated with increased cardiovascular structural and functional abnormalities

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Abstract

Epicardial fat volume (EFV) has been associated with an increase in cardiovascular structural and functional abnormalities (CVSFA). The purpose of the study is to assess whether a stepwise excess increase in EFV is associated with a proportional increase in CVSFA. We screened 276 asymptomatic individuals, ages 50 to 89, for cardiovascular disease (CVD) risk using the Rasmussen Risk Score (RRS) and a CT scan for the coronary artery calcium score (CACS) and EFV determination. The RRS scoring system consists of 10 tests; 7 of which are vascular and 3 are cardiac. Additional tests included fasting blood sugar, fasting lipid profile, CRP, Pro-BNP, waist circumference, and BMI. Of the 276 total subjects that were asymptomatic of cardiac symptoms, 144 were post-menopausal women (52.2%). These 144 female subjects were further divided into 5 groups based on their EFV: Group 1 (31 subjects) with an EFV <69 cm^3, Group 2 (45 subjects) with an EFV between 70 cm^3 and 94 cm^3, Group 3 (21 subjects) with an EFV between 95 cm^3 and 119 cm^3, Group 4 (33 subjects) with an EFV between 120 cm^3 and 144 cm^3, and Group 5 (14 subjects) with an EFV of 145 cm^3 and greater. The statistical analysis used to determine statistical significance of the study results included ANOVA, T-Test and Chi-Square analysis. Based on our data, excess epicardial fat volume is associated with earlier structural and functional abnormalities in comparison to normal epicardial fat volume levels.

Background

Epicardial fat is defined as the adipose tissue which directly overlies the heart. It can cover up to 80% of the myocardium and account for up to 20% of the heart's mass [1,2]. Epicardial fat is directly vascularized by branches of the coronary arteries, and lacks a fascial layer separation from the myocardium, implying a close and strong interaction with both tissue structures [1]. The physiologic function of epicardial fat is complex and not yet completely understood, but can be generally distinguished by various mechanical, metabolic, thermogenic, and endocrine/paracrine functions [1,3]. Additionally, there is growing evidence that human epicardial fat produces bioactive cytokines which are both locally and systemically involved in the regulation of endothelial function. In menopausal women with endothelial dysfunction, menopausal transition is associated with increased carotid arterial stiffness and epicardial fat thickness, independent of age [2].

Epicardial fat volume (EFV), also referred to as epicardial adipose tissue (EAT), has been recently reported to be a novel cardiovascular risk marker [1,4,5]. Early detection of excess EFV (i.e.,> 69 ± 20 in females and males) has been found to correlate with early detection of cardiovascular structural and functional abnormalities among subjects with various comorbidities, such as type 2 diabetes and obesity, which mandates treatment through lifestyle modifications and aggressive medical therapy [4]. Epicardial fat belongs to the category of perivascular adipose tissue which also includes the fat surrounding the renal arteries. Epicardial adipose tissue differs from abdominal visceral adipose tissue mainly in its mRNA. Epicardial adipocytes are also smaller than that of abdominal visceral adipocytes [3,6]. It has been reported that many obese and/or diabetic individuals have increased EFV, which has been

associated with many risk factors contributing to coronary artery disease (CAD) [5,7-9]. Additionally, studies have found an association between excess EFV and metabolic syndrome [10,11]. EFV has also been correlated with other independent cardiac biomarkers, such as high levels of C-reactive protein, BNP, and microalbuminuria, along with cardiovascular risk factors (i.e., hypertension, dyslipidemia, and hyperglycemia) [12]. It has also been associated with cardiovascular structural and functional abnormalities, such as an abnormal rise in blood pressure post-mild protocol exercise, carotid intima-media thickness (CIMT), and left ventricular hypertrophy [13,14]. Under normal physiological conditions, epicardial fat is known to produce anti-inflammatory and anti-atherosclerotic cytokines, such as adiponectin and adrenomedullin, for cardioprotective function including increased free fatty acid oxidation, nitric oxide synthesis, and vasodilation [15,16]. A decrease in nitric oxide availability and vasodilator imbalance has been linked to the development of microvascular disease-based angina. Accordingly, it is time to focus on epicardial fat pathophysiology as an important risk marker for cardiovascular disease (CVD).

Women usually reach menopause between the ages of 40 and 60. Although there has not been sufficient data that menopausal women

tend to gain weight, it has been found that postmenopausal women have a greater amount of abdominal visceral fat in comparison to premenopausal women. EFV has been shown to be greater after menopause and may be regulated due to endogenous estrogen [8,17]. The increase in EFV after menopause has been correlated with the acceleration of atherosclerosis. Hormone therapy may have positive results in slowing down the deposition of epicardial fat [13]. This study aims to assess whether an Excess EFV in post-menopausal women leads to higher levels of vascular and cardiac abnormalities.

Methods

We screened 276 asymptomatic individuals, ages between 50-89, for cardiovascular disease (CVD) risk using the Rasmussen Risk Score (RRS) [8], CT scan for coronary calcium scores and epicardial fat volume determination. The RRS consists of 10 tests: 7 of these tests are vascular and 3 are cardiac. The vascular components are large (C1) and peripheral (C2) artery stiffness, blood pressure (BP) at rest and post-mild protocol exercise (PME) consisting of a 3-minute walk at 7% elevation and a speed of 2.5 mph. Abnormal BP-PME is defined as a systolic rise of >30 mmHg compared to systolic BP at rest [19,20]. Large (C1) arterial stiffness refers to conducting arteries which store blood ejected from the heart during systole and expel blood to the peripheral tissues during diastole. Peripheral (C2) arteries refer to resistance muscular arteries which can alter vascular smooth muscle tone, allowing them to modulate the velocity of pressure wave [21]. Normotension, elevated BP, and hypertension are defined according to the current ACC/AHA guidelines [22]. Other vascular assessments include Carotid Intima Media Thickness (CIMT), abdominal aorta ultrasound, retinal photography, and microalbuminuria. The 3 cardiac components are Pro-BNP, ECG, and left ventricle ultrasound (LVUS). All EKG abnormalities are considered, but some of these abnormalities include atrial fibrillation, bundle branch block, atrial flutter, etc. The LVUS looks for abnormalities in LV ejection fraction and mass. Additional tests are waist circumference, BMI, fasting blood sugar, fasting lipid profile, and hs-CRP [20]. Each of the 10 tests that make up the RRS is scored as Normal, Borderline, or Abnormal. A normal score = 0, a borderline score = 1, and an abnormal score = 2. After adding up the scores from all 10 tests, a subject can get a score between 0 through 20. A score of between 0-2 indicates low risk of CVD, and a score between 3-5 indicates intermediate risk of CVD, and a score ≥ 6 indicates strong risk of CVD. The RRS has been a previously peer-reviewed risk score [19,20]. Of the 276 total subjects that were asymptomatic of cardiac symptoms, which includes chest pain and other pre-existing cardiac conditions, 144 post-menopausal women (52.2%) underwent cardiac CT for coronary artery calcium scoring (CACS) and EFV determination using the Siemens Somatom Definition Dual-source CT scanner 64x2. Quantifying the EFV is done using a non-contrast 3mm sequenced scan with cardiac gating and post processing on Siemens VIA workstation. The coronary calcium artery is quantified using the Agatston method. The epicardium fat volume was quantified using Hounsfield method. These 144 female subjects were further divided into 5 groups based on their EFV: Group 1 (31 subjects) with an EFV <69 cm³, Group 2 (45 subjects) with an EFV between 70 cm³ and 94 cm³, Group 3 (21 subjects) with an EFV between 95 cm³ and 119 cm³, Group 4 (33 subjects) with an EFV between 120 cm³ and 144 cm³, and Group 5 (14 subjects) with an EFV of 145 cm³ and greater. The first group were chosen based on what was considered normal EFV (69 ± 20 in females) [23] and each subsequent group is an increase of 24 cm³ of EFV. The statistical analysis used to determine statistical significance of the study results included ANOVA, T-Test and Chi-Square analysis. A P-value <0.05 was considered statistically significant.

Results

The baseline characteristics of the groups included individuals who were asymptomatic of cardiac issues such as chest pain, myocardial infarctions, and strokes. All the groups consisted of post-menopausal women who were mostly of the Caucasian race. As noted in Tables 1, 2 and 3 a significant p-value was determined between the average RRS (0.022), abnormal C1 percentage (< 0.0001), abnormal C2 percentage (< 0.0001), abnormal CIMT percentage (0.00032), average triglyceride levels (0.0011), average microalbumin level (0.0447), average blood sugar level (0.0030), and average HDL level (0.0000393) to their corresponding levels of EFV. The data also reveals that excess epicardial fat (groups 3,4, and 5) is associated with earlier structural and functional abnormalities in comparison to normal epicardial fat volume (groups 1 and 2) such as abnormal endothelial function, CIMT, triglyceride levels, microalbumin levels, blood sugar levels, and HDL levels.

Discussion

Several methods of measuring cardiac fat volumes are feasible, such as total intrathoracic fat volume and epicardial adipose tissue and thoracic fat (i.e., ITFv, EATv, and TF volume) which can be measured directly by non-contrast cardiac computed tomography [24]. Some studies have utilized echocardiography as a way for quantifying EFV [2,25] but it is more accurately done using computed tomography. Given the high spatial resolution of CT and that adipose tissue has distinct attenuation values, EFV is readily identified allowing for accurate volumetric measurement [6]. Fat attenuation and volume can also be reliably measured from pre-contrast calcium scans, with volume quantification showing particularly strong correlation [26]. It is one of the more reliable and reproducible methods for estimating the extent of epicardial fat volume with high spatial resolution [27].

According to the present study normal EFV (Group 1 and 2) is associated with minimal cardiovascular structural and functional abnormalities. Upon reviewing the data, groups 1 and 2 do not have as many structural and functional cardiovascular abnormalities in comparison to the excess epicardial fat volume groups. Excess EFV (Group 3,4 and 5) is associated with statistically significant cardiovascular structural and functional abnormalities, as well as CVD biomarkers, such as: C2 abnormalities, abnormal rise in systolic BP, CRP, BNP, and microalbuminuria. As noted in Tables 1, 2 and 3, a significant p-value was determined between the average RRS, abnormal C1 percentage, abnormal C2 percentage, abnormal CIMT percentage, average triglyceride levels, average microalbumin level, and average HDL level to their corresponding levels of EFV. Studies have found an association between excess EFV and metabolic syndrome [10,11]. EFV has also been correlated with other independent cardiac biomarkers, such as high levels of C-reactive protein, BNP, and microalbuminuria, along with cardiovascular risk factors (i.e., hypertension, dyslipidemia, and hyperglycemia) [12]. The data also reveals that excess epicardial fat (groups 3,4, and 5) is associated with more early cardiovascular diseases risk markers in post-menopausal women.

Normal EFV is associated with minimal cardiovascular structural and functional changes, while excess EFV is associated with statistically significant cardiovascular structural and functional abnormalities, as well as the presence of CVD biomarkers, such as: C2 abnormalities, abnormal rise in systolic BP, CRP, and microalbuminuria. These microvascular changes have been observed and reported on in previous publications over the last decade [19]. EFV appears to be a significant factor involved in microvascular disease due to its ability to secrete several cytokines, referred to as adipokines. These cytokines play an

Table 1. EFV and structural & functional abnormalities

EFV (cm³)	Average RRS	Average Resting BP (mmHg)	Average CAC	Abnormal C1	Abnormal C2	Abnormal CIMT
<69	6	137/77	133.74	52%	65%	42%
70-94	5	137/75	210.01	40%	56%	42%
95 -119	5	141/78	681.24	24%	38%	29%
120-144	8	140/77	442.39	27%	54%	55%
>145	7	133/81	347.04	28%	14%	57%
p-values	0.022	0.6815	0.289	< 0.0001	< 0.0001	0.00032

The average RRS, average resting BP, average CAC, abnormal macrovascular (C1) percentage, abnormal microvascular (C2) percentage, and abnormal CIMT percentages for the separate groups of EFV are presented in the table. Corresponding p-values provided for statistical significance.

Table 2. EFV and biomarkers

EFV (cm³)	Average BNP (pg/mL)	Average CRP (mg/dL)	Average Microalbuminuria (mg/mmol)
<69	106.94	0.2955	0.2393
70-94	145.27	0.3016	0.2759
95 -119	78.33	0.1947	0.2409
120-144	124.97	0.3112	0.4347
>145	57.57	0.6143	0.5179
p-values	0.3347	0.3325	0.0447

The average CRP, average BNP, and average microalbuminuria level for the separate groups of EFV are presented in the table. Corresponding p-values provided for statistical significance.

Table 3. EFV and Lipid Profile & Blood-Sugar. The average low-density lipoprotein (LDL), average high-density lipoprotein (HDL), average triglyceride levels, average non-HDL, and average blood sugar for the separate groups EFV are presented in the table. Corresponding p-values provided for statistical significance

| EFV (cm³)	Average LDL (mg/dL)	Average HDL (mg/dL)	Average Triglyceride (mg/dL)	Average non-HDL (mg/dL)	Average Blood Sugar (mg/dL)
<69	108.06	68.4	127	130.74	81.84
70-94	103.09	63.4	93	121.73	84.49
95 -119	84.30	61.3	105	105.38	94.90
120-144	91.91	51.09	158	120.06	91.73
>145	96.93	45.93	164	129.71	108.93
p-values	0.1473	0.0000393	0.0011	0.2265	0.0030

important role in development of cardiovascular diseases due their pro-inflammatory properties [28]. Consequently, an increased number of macrophages, T-lymphocytes, and mast cells in epicardial fat tissue has been shown in patients with coronary artery disease by several researchers [28,29]. However, the effect of epicardial fat volume on the manifestation and progression of cardiovascular disease (CVD) and microvascular disease still needs to be more sufficiently and extensively explored Figure 1.

Many studies have correlated the regression of epicardial fat with weight loss and weight management, as well as routine exercise [28]. Secondly, consider using statin to reduce LDL levels below 70 mg/dL and utilizing a semaglutide for the reduction of EFV. Weekly administration of either GLP-1 receptor agonists semaglutide or dulaglutide causes a rapid, substantial, and dose-dependent reduction in EAT thickness [30]. Hopefully, these findings will be a stimulus to other investigators to better understand the role of excess epicardial fat volume in the genesis of cardiovascular disease and stimulate therapeutic interventions to prevent future cardiovascular complications.

Conclusions

Based on our data, we feel that excess EFV appears to be a significant marker for early cardiovascular structural and functional abnormalities. Accordingly, we urge all healthcare professionals that it is time to focus on early and accurate assessment of EFV which is probably the culprit for many CVD risk factors.

The majority of the female subjects in our study were of the white race, meaning that this study will need to be expanded upon with a
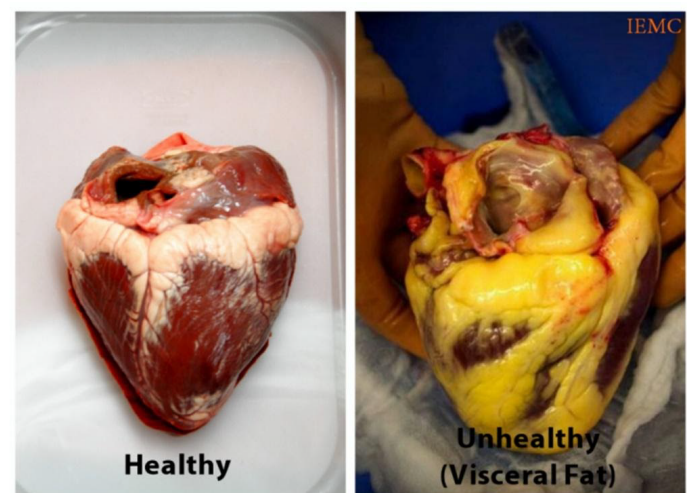
Figure 1. Healthy Heart vs. Unhealthy Heart with excess EFV

cohort of more racial diversity to further support the impact of excess EFV on cardiovascular health. Hopefully, studies in the near future will have a greater number of subjects and will be able to duplicate and confirm our findings.

Declarations

Ethics approval and consent to participate: This study was approved by the Sarasota Memorial Hospital Institutional Review Board

(IRB) and individual patient written consent was obtained, which was a further approved by the IRB. Committee reference numbers: 08-CARD-16 and 10-CARD-26.

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