

Effects of Age and Aerobic Fitness on Myocardial Lipid Content

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Background—Aging and sedentary lifestyles lead to cardiac atrophy, ventricular stiffening, and impaired diastolic function. Both conditions are marked by increased adiposity, which can lead to ectopic fat deposition in nonadipocyte tissues including the myocardium. The effect of excess intramyocardial fat on cardiac function in nonobese individuals is unknown.

Methods and Results—Cardiac lipid content was measured by magnetic resonance spectroscopy in 153 healthy nonobese subjects with varying fitness levels quantified by peak oxygen uptake during treadmill exercise. Cardiac function (echo and left ventricular [LV] filling pressures [right heart catheterization]) were measured under varying preloads. LV stiffness was calculated from a curve fit of the diastolic portion of the pressure–volume curve. The strongest clinical predictors of lipid content were body mass index ($\beta=+0.03; 95\%$ confidence interval, 0.001–0.06) and peak oxygen uptake ($\beta=−0.02; 95\%$ confidence interval, $−0.03$ to $−0.009; R^2=0.14; P<0.001$). Subjects in the highest quintile had smaller LV end-diastolic volumes (68±13 versus 58±12 mL/m$^2$; $P<0.01$) and decreased peak early mitral annular and increased peak late mitral inflow velocities. There were no differences in LV stiffness, but a leftward shift in the pressure–volume curve suggested a less distensible ventricle with increasing myocardial lipid levels. After adjusting for age, fitness, and body mass index, echocardiographic and morphometric differences among groups were attenuated and no longer significant.

Conclusions—Body mass index and fitness levels are the strongest predictors of myocardial lipid content in nonobese humans. Cardiac lipid content is associated with decreased ventricular distensibility, and it may provide a causal mechanism linking changes in LV function related to age and fitness. (Circ Cardiovasc Imaging. 2013;6:1048-1055.)

Key Words: aging ■ exercise ■ ventricular remodeling

Aging and inactivity are associated with significant changes in cardiovascular physiology. Previous studies by our group have shown that aged heart becomes smaller, stiffer, and less distensible.1,2 Extreme inactivity also recapitulates a similar cardiac phenotype as observed during spaceflight or prolonged bed rest.3,4 In contrast, habitual exercise training results in above average measures of peak VO$_2$ adjusted for age and sex, larger stroke volume, increased cardiac mass, and improved measures of ventricular compliance.5,6

Clinical Perspective on p 1055

A common relationship shared between aging and sedentariness is changes in body composition. As individuals age or become sedentary, percentage body fat increases with a concomitant decrease in lean body mass.7 Excess adiposity and metabolic derangements may directly affect the cardiovascular system via accumulation of intramyocardial triglycerides, leading to lipotoxicity. Typically associated with obesity-related diseases, the accumulation of ectopic fats in nonadipocyte tissues can lead to organ dysfunction via buildup of toxic fatty acid metabolic intermediaries.8

Although the abnormalities associated with lipid accumulation in hepatic, pancreatic, and connective tissues have been well documented, the effects of cardiac steatosis on cardiac structure and function are still in the early stages of clinical investigation, supported by a growing body of animal models of myocardial fatty acid accumulation showing significant decline in cardiac function.9-13 Small clinical studies in humans have suggested an association between lipid content and abnormal diastolic function, myocardial strain, and increased left ventricular (LV) mass in patients with diabetes mellitus and who are obese.14-18

In older and unfit individuals, cardiac steatosis may be a causal link contributing to the development of diastolic...
abnormalities, and it forms the basis for our current study investigating the effects of a sedentary lifestyle and aging on cardiac structure and function. We hypothesized that the accumulation of myocardial triglycerides increases with age and sedentariness, and it would be associated with ventricular stiffening and impairments in diastolic function in nonobese and nondiabetic individuals.

**Methods**

**Study Recruitment**

Study subjects were recruited from the Dallas Heart Study, a population-based cohort of ~60,000 individuals, enriched by a random sampling of employees of Texas Health Resources, a large healthcare provider in the Dallas-Fort Worth metroplex, as previously described. Subjects were also recruited prospectively from the Aerobic Center Longitudinal Database at the Cooper Clinic in Dallas, a cohort of individuals with extensively recorded exercise histories for 25 years. All study procedures were approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center at Dallas and Texas Health Resources. After providing informed consent, all subjects underwent testing as outlined below. Volunteers were excluded if they had a history of cardiovascular disease (eg, stroke, myocardial infarction, atrial fibrillation), diabetes mellitus, chronic smokers and if they had a history of cardiovascular disease (eg, stroke, myocardial infarction, atrial fibrillation), diabetes mellitus, chronic obstructive pulmonary disease (COPD), and body mass index (BMI) ≥30 kg/m². All subjects underwent a screening maximal exercise test. Volunteers were excluded if they had an evidence of coronary ischemia by ECG and echocardiography. Of 353 subjects, 162 were predominantly whites (>90%). Of the remaining 191 subjects, 162 were predominantly whites (>90%).

**Body Composition and Physical Activity Level**

Body composition was determined by body density using underwater weights as described previously. Subjects were also given activity monitors (Acticical, Phillips; RT3; and Stayhealthy) that reported total daily activity as METS (metabolic equivalent of task) for 7 days. Total time spent sedentary and active (by METS) were reported in minutes per day. A threshold of 4 METS was used to quantify minutes per day spent in fitness-related activities.

**Exercise Testing**

A modified Astrand–Saltin incremental treadmill protocol was used to determine peak exercise capacity. Measures of ventilatory gas exchange were made by use of the Douglas bag technique. Maximum oxygen uptake was defined as the highest oxygen uptake measured from ≥8.9 Douglas bag. To normalize for differences in sex and age, predicted peak VO₂ values were calculated adjusting for age and sex, as previously reported.

**Cardiac MRI**

All subjects underwent cardiac MRI to assess cardiac morphometric parameters in addition to myocardial triglyceride content. Subjects did not undergo MRI if they had cochlear implants or were claustrophobic. Images were obtained using a 1.5-tesla Gyroscan INTERA whole-body system (Philips Medical Systems, Best, The Netherlands) equipped with spectroscopy and cardiac packages. LV end-diastolic volumes (EDVs) and mass were measured as previously reported using a steady-state–free precision imaging sequence. Tissue triglyceride content was measured using 1H nuclear MR spectroscopy and quantified as a percentage of water content in a region of interest located in the midventricular septum. During acquisition of spectroscopic data, patients breathed freely. The spectroscopic signal was acquired with cardiac triggering at end systole and respiratory gating at end expiration. A Point-RESolved Spectroscopy (PRESS) sequence was used for spatial localization, and the interpulse delay was defined by the length of a respiratory cycle. NUTS software (Acorn NMR, Fremont, CA) was used to process data. The areas under the signals from water and methylenes of fatty acids in triglycerides were quantified by a line-fitting procedure, and the values were corrected for spin–spin relaxation.

**Intracardiac Pressure–Volume Measurements**

Right heart catheterizations were performed via an antecubital vein approach as described previously. A 6Fr Swan-Ganz catheter (Edwards Lifesciences) was placed under sterile conditions into the pulmonary artery using fluoroscopic guidance. Subjects were then placed in a lower body negative pressure chamber to decrease LV preload. Recordings of right atrial pressure, pulmonary capillary wedge pressure (PCWP), and LVEDVs using 3-dimensional (3D) echocardiography were made at baseline after 20 minutes of supine rest and again after 5 minutes of each lower body negative pressure of −15 mm Hg followed by −30 mm Hg. In addition, cardiac echocardiography as described below was also performed during each condition. Study participants were then subjected to 2 loading conditions to increase PCWP with rapid normal saline infusion at 15 and 30 mL/kg at flow rates of ≈200 mL/min. Pressure and echocardiographic measurements were made after each infusion. Cardiac output and stroke volume were calculated using a modified acetylene gas rebreathing technique. The diastolic portion of the pressure–volume (PV) curve was constructed using PCWP and corresponding LVEDVs under the experimental unloading and loading conditions. The ventricular stiffness constant was calculated by an exponential curve fit of the end-diastolic PV relationship, as previously described.

**Echocardiography**

Echocardiographic images were acquired on an iE33 machine (Philips) and measured offline using Xcelera cardiovascular image management system (Philips). Images were obtained under baseline, lower body negative pressure, and saline loading conditions. Tissue Doppler images were obtained in the apical 4-chamber view by placing a 2-mm sample volume on the septal and lateral mitral annulus. Mitral inflow velocities were also measured in the 4-chamber view by placing a 2-mm pulsed wave sample volume at the tips of the mitral leaflet during valve opening. Propagation velocity (Vp) was obtained by color M-mode imaging with a sampling area extending from the mid portion of the left atrium to the apex and measuring the slope of the early diastolic aliasing velocity. Isovolumic relaxation time was measured as the time between aortic valve closure and mitral valve opening by placing a 4-mm sample within the LV outflow tract from a 5-chamber view. LV volumes under different loading conditions were determined by offline 3D reconstruction (QLab, version 9.0; Philips).

**Statistical Analysis**

Statistical analysis was performed using commercially available software (SPSS, SigmaPlot version 12.0). All reported variables are presented as mean with SD. After dividing the subjects into quintiles by cardiac lipid content, the distribution of majority of variables was skewed. A nonparametric Jonckheere–Terpstra test was therefore used to determine the effect of increasing ranked quintiles of lipid content on measured variables. Pearson correlation of clinical variables with cardiac lipid was performed, and multiple linear regression modeling was then used to determine the clinical variables that best predicted myocardial lipid content. Regression analysis was also performed on echocardiographic and MRI variables. A 2-way repeated-measures ANOVA was used to identify the differences in pressure and volume parameters under varying loading conditions between the lowest and highest quintiles of cardiac lipid content. To adjust the cardiac lipid quintile comparisons for age and fitness-related differences in cardiac function, hemodynamic, echocardiographic, and morphometric parameters were modeled using age, sex, and peak VO₂ as covariates in ANCOVA models. Data transformations were used to
meet parametric analysis assumptions as necessary. A \( P \) value <0.05 was considered statistically significant.

## Results

### Baseline Characteristics

Cardiac lipid content was available in 153 of 162 enrolled subjects who had no contraindications to MRI. In the 9 volunteers who did not have lipid measures, 5 had technically limited scans because of motion artifact or excessive heart rate variability, 2 had contaminated signal from epicardial fat, and 2 had levels below detection limits. The mean age of all subjects was 62 years, ranging from 26 to 86 years with an interquartile range of 61 and 69 years. Subjects were stratified by lipid content into quintiles. Lipid content ranged from 0.31±0.10% in the lowest quintile to 1.61±0.62% in the highest quintile (Table 1; Figure 1). Subjects in the highest quintiles had larger BMI compared with those in the lowest quintile in addition to higher body fat composition. There were no differences in HgbA1c% or age between groups. As comparison, myocardial \(^1\)H nuclear MR spectroscopy from a previously published study by our group showed a range for triglycerides of 0.46±0.30% in lean (BMI<25 kg/m²) individuals to 1.06±0.62% in subjects with type 2 diabetes mellitus. \(^3\)

### Clinical Predictors of Cardiac Steatosis

In general, fitness and daily activity levels decreased with increasing quintiles of cardiac lipid content. Subjects in the highest quintile had the lowest measured peak \( V_\text{o2} \) (Figure 2). The distribution of peak \( V_\text{o2} \) was large and likely driven by differences in age, body weight, and fitness levels across all subjects. To adjust for the wide distribution and to distinguish whether the relationship between cardiac lipid content and fitness was because of age- and sex-related differences, peak \( V_\text{o2} \) was calculated as a percentage of age- and sex-predicted \( V_\text{o2} \) scaled to ideal body weight. There was a trend toward higher percent predicted peak \( V_\text{o2} \) for subjects with the lowest cardiac lipid content (Jonckheere–Terpstra test, \( P=0.06 \)). There was also an association between increasing lipid content and daily activity level. Subjects in the lower quintiles were more likely to spend additional minutes per day engaged in activities >4 METS (Table 1). There was no difference in the amount of time spent sedentary between groups.

Simple linear regression of clinical characteristics and cardiac lipid content across all 153 subjects showed an association among BMI, body fat, peak \( V_\text{o2} \), % of predicted peak \( V_\text{o2} \), and minutes per day spent in activities >4 METS (Table 1 in the online-only Data Supplement). In our multiple regression models, peak \( V_\text{o2} \) and BMI were significant variables in predicting lipid content (\( \beta=−0.02 \); 95% confidence interval, −0.03 to −0.009 and \( \beta=+0.03 \); 95% confidence interval, 0.001–0.06, respectively; \( R^2=0.14 \); \( P<0.001 \)). To better understand the association between peak \( V_\text{o2} \) and cardiac lipid content and to account for confounding factors (age, sex, and BMI) that influence peak \( V_\text{o2} \) which may not have been fully adjusted for, the multiple regression model was rerun using percent predicted peak \( V_\text{o2} \) instead of measured peak \( V_\text{o2} \). In this model, percent-predicted \( V_\text{o2} \) (\( \beta=−0.47 \); 95% confidence interval, −0.82 to −0.12) and age (\( \beta=0.013 \); 95% confidence interval, 0.005–0.021) were the most significant variables (\( R^2=0.15 \); \( P<0.001 \)) that predicted cardiac lipid content, suggesting that even relative fitness, when adjusted for sex- and age-expected values, remained determinative of intramyocardial lipids.

### Effects of Cardiac Lipid Content on Cardiac Structure and Function

MRI was used to assess baseline cardiac structure and function. With increasing quintiles of cardiac lipid, LV end-diastolic and stroke volumes indexed to BSA decreased, whereas LV ejection fraction slightly increased (Table 2). There was no correlation to BSA-indexed LV mass (Jonckheere–Terpstra, \( P=0.07 \)) or end-systolic volumes.

### Hemodynamic and Echocardiographic Parameters

There was no correlation between cardiac lipid content and ventricular stiffness derived from the end-diastolic portion of the PV curve. Stiffness constants derived from PV curves drawn using group-averaged values for indexed EDV and PCWP were similar between subjects with low and high cardiac lipids (Figure 3). Interestingly, the PV curve for the highest

<table>
<thead>
<tr>
<th>Q1 (30)</th>
<th>Q2 (30)</th>
<th>Q3 (30)</th>
<th>Q4 (32)</th>
<th>Q5 (31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid, %‡</td>
<td>0.31±0.10</td>
<td>0.56±0.07</td>
<td>0.76±0.06</td>
<td>1.04±0.10</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.8±14.3</td>
<td>60.9±12.4</td>
<td>59.4±12.0</td>
<td>62.6±10.5</td>
</tr>
<tr>
<td>% Women</td>
<td>43</td>
<td>37</td>
<td>60</td>
<td>53</td>
</tr>
<tr>
<td>Peak ( V_\text{o2} ) mL/kg per minute‡</td>
<td>31.7±7.8</td>
<td>29.8±7.1</td>
<td>27.8±7.2</td>
<td>27.5±7.7</td>
</tr>
<tr>
<td>Predicted ( V_\text{o2} ), %</td>
<td>130±47</td>
<td>117±31</td>
<td>110±39</td>
<td>111±30</td>
</tr>
<tr>
<td>BMI, kg/m²‡</td>
<td>23.1±2.8</td>
<td>24.7±2.8</td>
<td>24.6±3.1</td>
<td>24.7±3.3</td>
</tr>
<tr>
<td>Body fat, %†</td>
<td>28.6±8.1</td>
<td>28.1±7.0</td>
<td>29.7±9.0</td>
<td>31.6±8.1</td>
</tr>
<tr>
<td>HgbA1c, %</td>
<td>5.3±0.3</td>
<td>5.3±0.3</td>
<td>5.2±0.4</td>
<td>5.5±0.3</td>
</tr>
<tr>
<td>Minutes per day &gt;4 METS†</td>
<td>29±27</td>
<td>24±19</td>
<td>16±15</td>
<td>16±26</td>
</tr>
<tr>
<td>Minutes per day sedentary</td>
<td>1142±115</td>
<td>1196±148</td>
<td>1179±97</td>
<td>1183±73</td>
</tr>
</tbody>
</table>

BM indicates body mass index; and METS, metabolic equivalent of task. 
*\( P<0.05 \); †\( P<0.01 \); and ‡\( P<0.001 \) (Jonckheere–Terpstra trend across increasing quintiles).
quintile (Q5) was shifted leftward, suggesting decreased LV distensibility similar to changes seen with healthy aging or decreased fitness. Although indexed EDVs were significantly lower under each of the loading conditions with increasing cardiac lipids (P<0.01 for lipid quintile effect; 2-way repeated-measures ANOVA), there were no differences in PCWP across quintiles (Table II in the online-only Data Supplement). There was a slight increase in right atrial pressure across all preload conditions with increasing lipid content (Jonckheere–Terpstra test, P<0.05), suggestive of a differential effect of myocardial steatosis on right and left ventricular hemodynamic function.

Under baseline conditions, subjects with the highest level of cardiac lipid content had lower peak early mitral annular velocity (tissue Doppler E’ lateral wall velocity) and higher late diastolic mitral inflow (A wave), in addition to lower E/A ratios compared with those with lower levels (Table 2). There were no differences in measures of ventricular relaxation as assessed by isovolumic relaxation time or mitral inflow propagation velocity. The association between decreasing peak early mitral annular velocity and cardiac lipid content remained consistent with increasing ventricular loading conditions. Similarly, the association between increasing late diastolic mitral inflow and cardiac lipid content also persisted across loading conditions (Table 3).

To determine the independent effects of cardiac lipid content on echocardiographic and morphometric parameters, ANCOVA analysis using cardiac lipid quintiles and defined covariates of age, BMI, and peak VO2 was performed. Once adjusted for these covariates, many of the observed relationships were attenuated, and they were no longer statistically significant. Nearly all the interactions were highly nonsignificant (much greater than P=0.25), and they did not contribute meaningful information to the model. Therefore, our final model does not include interaction terms. There were no differences by ANCOVA among quintiles with regard to mitral annular tissue Doppler, mitral inflow velocities, or filling pressures. Indexed EDV was also no longer significantly different across lipid quintiles, suggesting that the differences in distensibility seen in Figure 3 were likely reflective of the differences in age and peak fitness levels among the groups.

Discussion
The primary findings of this current study are (1) myocardial steatosis can vary greatly across metabolically healthy individuals and can approach or exceed levels previously reported in patients with diabetes mellitus and metabolic syndrome; (2) clinical predictors of cardiac steatosis included BMI and peak VO2; however, these associations ceded to age after adjusting peak VO2 for age and sex; and (3) myocardial steatosis was associated with decreased ventricular distensibility and markers of early diastolic dysfunction.

Adiposity and the Heart
Myocardial steatosis is a compelling means of bridging the connection between metabolic disorders and associated abnormalities in diastolic function, which in turn could form the basis for the increased incidence of heart failure observed in patients with obesity-related disorders. Although frequently associated with comorbid conditions of coronary artery disease, hypertension and renal dysfunction, patients with diabetes mellitus and who are obese are twice as likely to develop heart failure compared with...
lean controls even after adjusting for baseline differences in covariates. Advances in nuclear magnetic resonance spectroscopy have opened insight into changes in myocardial composition in patients with metabolic disorders independent of ischemia and ventricular hypertrophy. This concept of metabolic remodeling has focused primarily on the presence of intracardiac triglyceride accumulation as a surrogate marker of a lipotoxic heart. Whether myocardial triglycerides are direct mediators of abnormal cardiac function or represent a biomarker of altered cardiac metabolism remains a key question. The presence of intramyocardial fat has been correlated previously with decreased ventricular strain rates, increased LV mass, and decreased early peak mitral inflow velocity in small studies of individuals with diabetes mellitus and individuals who are obese, suggesting that cardiac lipid content has adverse effects on myocardial structure, leading to diastolic dysfunction and raising the possibility of a therapeutic target to reverse diastolic abnormalities.

However the confounding impact of diabetes mellitus and obesity on measures of cardiac function can be difficult to distinguish from the independent effects of intracardiac triglycerides. Diabetes mellitus is known to cause alterations in myocardial calcium signaling and endothelial dysfunction, factors that are difficult to assess clinically. Measuring the effects of cardiac steatosis on myocardial structure and function in metabolically healthy individuals reduces potential confounders, and it may help to elucidate a clearer causal correlation. The findings of our study provide insight into the changes in ventricular function with increasing levels of cardiac lipid content and suggest a plausible causal mechanism, linking the effects of aging, aerobic fitness, and total body adiposity on cardiac function.

### Fitness, Aging, and Adiposity

To date, no studies have analyzed the impact of physical activity on cardiac steatosis. Previous studies have shown that metabolic syndrome, visceral adiposity, and impaired glucose tolerance are important clinical predictors of myocardial steatosis. The accumulation of triglycerides in metabolically active tissues, particularly muscle, further decreases the response to insulin-mediated glucose uptake. In contrast, metabolic changes associated with increasing fitness are essentially the antithesis of changes that occur in

### Table 2. MRI-Derived LV Morphometric and Echocardiographic Parameters by Lipid Quintile

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %*</td>
<td>67±6</td>
<td>69±7</td>
<td>69±7</td>
<td>70±6</td>
<td>71±6</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>123±29</td>
<td>116±32</td>
<td>112±28</td>
<td>108±26</td>
<td>109±28</td>
</tr>
<tr>
<td>LVEDVi, mL/m²†</td>
<td>68±13</td>
<td>62±15</td>
<td>62±12</td>
<td>60±11</td>
<td>58±12</td>
</tr>
<tr>
<td>LVSVi, mL/m²*</td>
<td>82±20</td>
<td>79±21</td>
<td>76±18</td>
<td>75±19</td>
<td>76±19</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>57±12</td>
<td>56±13</td>
<td>52±9</td>
<td>53±11</td>
<td>52±11</td>
</tr>
<tr>
<td>TDI E’ lateral, cm/s†</td>
<td>11.4±2.7</td>
<td>10.9±2.4</td>
<td>11.2±2.3</td>
<td>10.5±2.8</td>
<td>9.2±2.4</td>
</tr>
<tr>
<td>TDI A’ lateral, cm/s</td>
<td>8.7±2.0</td>
<td>9.5±2.5</td>
<td>8.7±2.4</td>
<td>9.7±2.7</td>
<td>9.3±2.4</td>
</tr>
<tr>
<td>TDI S’ lateral, cm/s</td>
<td>9.2±1.7</td>
<td>9.3±1.8</td>
<td>9.0±1.4</td>
<td>9.6±2.4</td>
<td>8.5±1.5</td>
</tr>
<tr>
<td>E wave, cm/s</td>
<td>67±15</td>
<td>65±14</td>
<td>74±17</td>
<td>65±13</td>
<td>67±15</td>
</tr>
<tr>
<td>A wave, cm/s‡</td>
<td>59±20</td>
<td>58±19</td>
<td>62±22</td>
<td>67±19</td>
<td>69±15</td>
</tr>
<tr>
<td>E/A ratio†</td>
<td>1.25±0.46</td>
<td>1.23±0.51</td>
<td>1.32±0.57</td>
<td>1.01±0.30</td>
<td>1.01±0.30</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>115±27</td>
<td>124±27</td>
<td>110±20</td>
<td>110±22</td>
<td>116±21</td>
</tr>
<tr>
<td>Vp, cm/s</td>
<td>46±12</td>
<td>45±11</td>
<td>45±10</td>
<td>43±8</td>
<td>44±8</td>
</tr>
</tbody>
</table>

A indicates peak late mitral inflow velocity; E, peak early mitral inflow velocity; IVRT, isovolumic relaxation time; LVEDV, left ventricular end-diastolic volumes; LVEDVi, LVEDV indexed to BSA; LVF, LV ejection fraction; LVEF, LV mass BSA indexed; LVSV, LV stroke volume; LVSVi, LVSV BSA indexed; TDI A’ lateral, A’ lateral wall velocity; TDI E’ lateral, tissue Doppler E’ lateral wall velocity; TDI S’ lateral, S’ lateral wall velocity; and Vp, mitral inflow propagation velocity. 

*P<0.05; †P<0.01; and ‡P<0.001 (Jonckheere–Terpstra trend across increasing quintiles).
metabolic syndrome and include improved insulin sensitivity and decreased total body adiposity. Individuals with better fitness would be expected to have improved markers of metabolic health, but because of the colinearity of many variables associated with peak \( \text{VO}_{2} \), it is difficult to distinguish the independent effects of 1 clinical factor compared with others. Individuals with high aerobic fitness are more likely to be younger, and they have low BMI and body fat percentage. In a regression model, the correlation between aerobic fitness (peak \( \text{VO}_{2} \)) and myocardial triglycerides was more strongly associated than BMI or body fat percentage, suggesting that peak \( \text{VO}_{2} \) was likely the primary driving factor.

Age also was an important factor in the development of cardiac steatosis. Even after scaling for age- and sex-predicted \( \text{VO}_{2} \), age remained significantly associated with cardiac lipid content. Both low aerobic fitness and advanced age can be associated with impaired insulin sensitivity, and although not directly measured in our study, these associations may mirror similar metabolic changes and development of cardiac steatosis seen in subjects who are obese or subjects with diabetes mellitus. As individuals age or become more sedentary, the heart is likely not spared from the metabolic milieu of increased body adiposity and BMI. The accumulation of myocardial fat with aging, decreasing aerobic fitness, and increasing BMI, thus, may represent a metabolic change in organ function, eventually leading to the development of increased ventricular diastolic stiffening or prolonged myocardial relaxation times.

### Adiposity and Cardiac Function

Myocardial lipid accumulation was associated with premature markers of abnormal diastolic function. Subjects with the highest quintiles of cardiac lipid content were more likely to have abnormalities in early diastolic myocardial relaxation, lower E/A mitral inflow ratios, smaller indexed EDV, and decreased LV distensibility. These observations were consistent with expected changes in cardiac function based on clinical predictors of intramyocardial triglyceride accumulation (poor aerobic fitness, advanced age). After adjusting for covariates of age, peak \( \text{VO}_{2} \), and BMI, the association between myocardial fat and diastolic function was attenuated. Although aging and low cardiovascular fitness share similar diastolic phenotypes, the causal connection leading to diastolic abnormalities shared between these 2 discrete conditions is unknown. The accumulation of cardiac lipid could provide a plausible mechanism for the increased observation of diastolic dysfunction in older or unfit individuals, and it may have deleterious consequences beyond acting just as a biomarker for impaired total body metabolic homeostasis. Preclinical work has shown that lipotoxicity leads to increased production of reactive oxygen species and apoptosis. Prolonged or accelerated accumulation of toxic metabolites could be a key mediator in the decline in diastolic function with age and poor fitness. Although our study did not show an increase in LV stiffness using invasive measures with lipid accumulation, subtle changes in diastolic function may be the precursors, leading to the development of more significant diastolic abnormalities and symptoms of heart failure.

Several questions remain about the consequences of excess cardiac fat content in individuals with concomitant metabolic and cardiac comorbidities. Because the prevalence of diabetes mellitus and obesity continues to rise, there is a greater need to better characterize the consequences of excess adiposity on cardiovascular physiology. Patients with diabetes mellitus or ventricular hypertrophy may accumulate myocardial lipids at an earlier age and develop the metabolic phenotype of an older and sedentary heart. Whether these metabolic changes are pathological remains unanswered, and other studies have even raised the possibility of a beneficial effect of obesity in heart failure, a concept termed the obesity paradox. Future studies may help to answer these questions by the use of agents to lower myocardial triglyceride content in conjunction with a comprehensive assessment of myocardial function. In addition, long-term prospective studies of cardiac fat content and the development of diastolic abnormalities and heart failure may also be helpful in establishing a causal connection.

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**Table 3. Correlation and \( \beta \)-Coefficients for Cardiac Lipid Content on Select Echocardiographic Parameters Across Varying Left Ventricular Preload Conditions**

<table>
<thead>
<tr>
<th>Echo Variable</th>
<th>Loading Condition</th>
<th>( r )</th>
<th>( \beta ) (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDI E’ lateral</td>
<td>−30 mm Hg LBNP</td>
<td>−0.08</td>
<td>−0.019 (−0.056 to 0.018)</td>
<td>0.32</td>
</tr>
<tr>
<td>TDI A’ lateral</td>
<td>−30 mm Hg LBNP</td>
<td>−0.003</td>
<td>−0.0006 (−0.037 to 0.036)</td>
<td>0.976</td>
</tr>
<tr>
<td>E wave</td>
<td>−30 mm Hg LBNP</td>
<td>0.01</td>
<td>0.0001 (−0.007 to 0.009)</td>
<td>0.863</td>
</tr>
<tr>
<td>A wave</td>
<td>−30 mm Hg LBNP</td>
<td>0.017</td>
<td>0.006 (0.0001 to 0.012)</td>
<td>0.045</td>
</tr>
</tbody>
</table>

**Footnotes:**

- A indicates peak late mitral inflow velocity; CI, confidence interval; E, peak early mitral inflow velocity; LBNP, lower body negative pressure; NS, normal saline rapid infusion; TDI A’ lateral, A’ lateral wall velocity; and TDI E’ lateral, tissue Doppler E’ lateral wall velocity.

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Sarma et al  Age, Fitness, and Myocardial Lipid Content 1053
Limitations
Our study is limited by incomplete characterization of the metabolic profile of participants. Both visceral fat and insulin sensitivity have been correlated previously to myocardial triglyceride content, but they were not measured in our current study.\textsuperscript{2,20} Fasting glucose was also unavailable. The majority of our subjects were elderly with only 25% of participants <60 years. This may have underestimated the association between age and cardiac lipid content, given that younger subjects tended to have lower cardiac lipid content.

Overall, we think that our study provides further insight to the cardiac metabolic adaptations that develop with aging and sedentariness. Our findings suggest that lipid content in a healthy population is more widely distributed than those previously reported, and the accumulation of myocardial lipids is associated with low aerobic fitness, increased BMI, and advanced age. Decreased ventricular distensibility and early markers of diastolic abnormalities were seen with increasing levels of myocardial triglyceride, suggesting that myocardial fatty acid metabolism may be a viable therapeutic target in improving cardiac function in diabetic or obese patients.

Sources of Funding
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Disclosures
None.

References
Aging and sedentary lifestyles lead to cardiac atrophy, ventricular stiffening, and impaired diastolic function. Both conditions are marked by an increase in total body adiposity, which can lead to ectopic fat deposition in nonadipocyte tissues including the myocardium. Numerous preclinical studies have shown a causal correlation between excessive myocardial lipid content and cardiac dysfunction. The consequences of excess intramyocardial lipid accumulation in healthy (nonhypertensive, nondiabetic, and nonobese) individuals is unknown. We measured the myocardial fat content in 153 healthy nonobese individuals of varying ages and fitness levels to determine the effects of age and sedentary lifestyles on myocardial metabolism and function. There was a large range in myocardial triglyceride content among individuals and in some approached levels previously reported in those with diabetes mellitus. The strongest predictors of high myocardial fat were increased body mass index and low aerobic fitness (peak $V_o_2$). Individuals with high lipid content were also more likely to have markers of abnormal diastolic function and decreased left ventricular distensibility. Our findings suggest that sedentary aging is associated with declines in cardiac function, which may be in part mediated by changes in myocardial metabolism. Therapies, either pharmacological or lifestyle-based, to limit or reduce intracardiac lipid accumulation may potentially reverse age-related development of diastolic abnormalities even in healthy and nonobese individuals.
Effects of Age and Aerobic Fitness on Myocardial Lipid Content
Satyam Sarma, Graeme Carrick-Ranson, Naoki Fujimoto, Beverley Adams-Huet, Paul S. Bhella, Jeffrey L. Hastings, Keri M. Shafer, Shigeki Shibata, Kara Boyd, Dean Palmer, Edward W. Szczepaniak, Lidia S. Szczepaniak and Benjamin D. Levine

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Supplemental Table 1. Univariate correlation between factors across increasing quintiles of cardiac lipid content

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>R</th>
<th>Beta (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.137</td>
<td>0.006 (0.004)</td>
<td>0.092</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.063</td>
<td>-0.067 (0.086)</td>
<td>0.442</td>
</tr>
<tr>
<td>BMI</td>
<td>0.250</td>
<td>0.046 (0.015)</td>
<td>0.002</td>
</tr>
<tr>
<td>Body Fat%</td>
<td>0.260</td>
<td>0.017 (0.005)</td>
<td>0.001</td>
</tr>
<tr>
<td>HgbA1c</td>
<td>0.047</td>
<td>0.081 (0.147)</td>
<td>0.584</td>
</tr>
<tr>
<td>Peak VO2</td>
<td>-0.331</td>
<td>-0.023 (0.005)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>%Predicted peak VO2</td>
<td>-0.211</td>
<td>-0.030 (0.012)</td>
<td>0.009</td>
</tr>
<tr>
<td>Minutes/day &gt; 4 METS</td>
<td>-0.230</td>
<td>-0.006 (0.002)</td>
<td>0.013</td>
</tr>
<tr>
<td>Minutes/day sedentary</td>
<td>0.036</td>
<td>&lt;0.001</td>
<td>0.703</td>
</tr>
</tbody>
</table>
Supplemental Table 2. Intracardiac filling pressures under varying left ventricular pre-load conditions (all values in mmHg)

<table>
<thead>
<tr>
<th>Quintile</th>
<th>PCWP -30 LBNP</th>
<th>PCWP BL</th>
<th>PCWP +30 NS</th>
<th>CVP * -30 LBNP</th>
<th>CVP * BL</th>
<th>CVP * +30 NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.7 ± 1.9</td>
<td>9.2 ± 2.3</td>
<td>19.0 ± 3.4</td>
<td>2.2 ± 1.5</td>
<td>5.6 ± 1.9</td>
<td>12.8 ± 2.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0 ± 1.3</td>
<td>8.6 ± 1.6</td>
<td>19.0 ± 3.1</td>
<td>2.4 ± 1.1</td>
<td>5.6 ± 1.3</td>
<td>12.6 ± 1.9</td>
</tr>
<tr>
<td>3</td>
<td>4.3 ± 1.5</td>
<td>9.6 ± 2.0</td>
<td>19.5 ± 2.8</td>
<td>2.7 ± 1.0</td>
<td>6.6 ± 1.5</td>
<td>13.8 ± 2.2</td>
</tr>
<tr>
<td>4</td>
<td>4.1 ± 1.6</td>
<td>9.0 ± 1.9</td>
<td>19.3 ± 3.0</td>
<td>3.1 ± 1.8</td>
<td>6.1 ± 2.0</td>
<td>13.5 ± 2.3</td>
</tr>
<tr>
<td>5</td>
<td>4.6 ± 1.4</td>
<td>9.0 ± 1.6</td>
<td>19.8 ± 2.7</td>
<td>3.2 ± 2.0</td>
<td>6.2 ± 1.6</td>
<td>13.6 ± 2.3</td>
</tr>
</tbody>
</table>

-30 LBNP: lower body negative pressure of -30 mmHg; BL: baseline; +30 NS: 30 ml/kg normal saline rapid infusion. *p < 0.05 (Jonckheere-Terpstra trend across increasing quintiles)