Diastolic function is strongly and independently associated with cardiorespiratory fitness in central obesity


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Turzyniecka M, Wild SH, Krentz AJ, Chipperfield AJ, Clough GF, Byrne CD. Diastolic function is strongly and independently associated with cardiorespiratory fitness in central obesity. J Appl Physiol 108: 1568–1574, 2010. First published March 25, 2010; doi:10.1152/japplphysiol.00023.2010.—Cardiorespiratory fitness [maximal O2 consumption (V˙O2max)] is an independent risk factor for type 2 diabetes; but in individuals at risk, factors influencing V˙O2max are poorly understood. We tested the hypothesis that V˙O2max is associated with diastolic function [subendocardial viability ratio (SEVR), %], as diastolic function influences myocardial perfusion. We studied 47 men and women with central obesity without diabetes. We measured fitness (V˙O2max) by treadmill testing and diastolic function (SEVR%) by pulse-wave analysis. We measured other factors influencing this relationship: insulin sensitivity [whole body glucose uptake-to-insulin concentration ratio (M/I)] by hyperinsulinemic euglycemic clamp, fatness by MR imaging and dual-energy X-ray absorptiometry, physical activity energy expenditure (metabolic equivalents of tasks) by the Sensewear Pro2 device, and muscle microvascular exchange capacity (capillary filtration coefficient) by venous plethysmography. Mean age of the subjects was 51 ± 9 (SD) yr. V˙O2max was associated with SEVR% (r = 0.50, P = 0.001), fatness (r = −0.39, P = 0.008), and HbA1c (r = −0.35, P = 0.018), but not with whole body glucose uptake-to-insulin concentration ratio, metabolic equivalents of tasks, or capillary filtration coefficient. In regression modeling with age, sex, fatness, and SEVR% as explanatory variables, only age, sex, and SEVR% were independently associated with V˙O2max (SEVR% – standardized B coefficient = 0.37, 95% confidence interval = 0.003–0.18, P = 0.007). This model identified 46% of the variance in V˙O2max (R2 = 0.46, P = 0.0001). There was a strong, independent association between V˙O2max and a measure of diastolic function in sedentary individuals with central obesity.

myocardial perfusion; wave reflection; arterial stiffness; insulin sensitivity; physical activity

A LOW LEVEL OF CARDIORESPIRATORY fitness is a risk factor for type 2 diabetes (8, 36, 48) and cardiovascular morbidity and all-cause mortality (53), but the determinants of fitness in middle-aged, obese individuals at risk of cardiovascular disease and type 2 diabetes are poorly understood. The relative impacts of physical activity energy expenditure (PAEE), insulin sensitivity, skeletal muscle microvascular function, and cardiac function on maximal O2 consumption (V˙O2max) are uncertain, and there is a need to understand how much of the variance in V˙O2max can be explained by each of these factors. A better understanding of the key factors that regulate V˙O2max would provide better insight into how to improve this important risk factor for cardiovascular disease and type 2 diabetes. In a recent detailed systematic review of 36 publications, Fogelholm illustrated the importance of understanding the nature of the relationship between obesity and low levels of fitness in understanding the impact of both factors on diabetes incidence and cardiovascular mortality (18). Fogelholm reported the relationships between physical activity, fitness, and obesity as exposures and type 2 diabetes, cardiovascular morbidity, cardiovascular risk factors, and overall mortality as outcomes. The risk of all-cause and cardiovascular mortality was lower in individuals with high body mass index and good aerobic fitness than in those with normal body mass index and low fitness, illustrating the importance of understanding the factors contributing to high fitness-induced cardiovascular protection in obese individuals at risk of cardiovascular disease and type 2 diabetes.

Exercise is the most important physiological stimulus for increasing myocardial O2 demand, and physical activity and fitness explain much of the association between obesity, metabolic syndrome, and all-cause and cardiovascular mortality (30, 32, 33, 52). Structured exercise prescription often forms the basis of strategies to improve fitness, but the threshold intensity needed to improve V˙O2max should equate to 30–45% of the O2 uptake reserve, corresponding to ~60–70% of the highest heart rate achieved during peak exercise testing (21). Understandably, this intensity of exercise is difficult to achieve in middle-aged obese individuals at risk of type 2 diabetes, and other methods of improving V˙O2max are urgently needed.

V˙O2max is determined by convective O2 delivery, which is a product of cardiac function and skeletal muscle O2 diffusing capacity, which is affected by skeletal muscle functional capillary surface area (4). Insulin-mediated whole body glucose uptake, skeletal muscle microvascular function, whole body and visceral fatness, and levels and intensity of PAEE may therefore impact on V˙O2max. We aimed to examine relationships between fitness (V˙O2max) and measurements of insulin sensitivity [ratio of whole body glucose uptake to insulin concentration (M/I)], fatness (total, truncal, and visceral), PAEE [metabolic equivalents of tasks (METS)], skeletal muscle microvascular function [microvascular exchange capacity, i.e., capillary filtration coefficient (Kr)], and diastolic function [subendocardial viability ratio (SEVR), %] to elucidate the factors that were independently associated with V˙O2max and determine the proportion of the variance in V˙O2max that could be explained by these factors. We tested the hypothesis that V˙O2max is independently associated with diastolic function (as myocardial perfusion occurs during diastole), taking care to control for potential confounders in this relationship (such as physical activity levels, insulin sensitivity, skeletal muscle microvascular function, and visceral and total fat mass).
METHODS

Subjects and methods. The study was approved by the Southampton General Hospital Research Ethics Committee (LREC05/Q1704/38) and conducted in accordance with the Declaration of Helsinki. All participants (n = 47) were unpaid volunteers and gave informed consent. White Northern European subjects aged 18–75 yr were invited to participate in the study. Volunteers were eligible for the main study if they had central obesity by International Diabetes Federation waist circumference criteria and if their estimated cardiovascular risk was <20% over 10 yr on the basis of the equation derived from the Framingham Heart Study (3). Exclusion criteria were known or previously undiagnosed diabetes, renal, liver, or uncontrolled thyroid disease, blood pressure >160/100 mmHg, and treatment with lipid-modifying drugs, antihypertensive medication, corticosteroid therapy, and hormone replacement therapy. An oral glucose tolerance test was performed with a 75-g glucose load. HbA1c was measured by a Diabetes Control and Complications Trial-aligned high-pressure liquid chromatography assay using a cation-exchange cartridge on a Bio-Rad Variant II Turbo (Bio-Rad Laboratories, Irvine, CA).

Cardiorespiratory fitness and PAEE. Cardiorespiratory fitness measured in terms of V02max was determined using a maximal treadmill test and the Cortex Metalyzer, and physical activity [PAEE and metabolic equivalents of tasks (METS)] was assessed using an activity monitor (Sensewear Pro2 armband) (39). The Sensewear Pro2 armband contains accelerometers that sense movement in two planes, a galvanic skin sensor, a temperature sensor, and a near-patient temperature sensor. Subjects wore the activity monitor for 7–10 days to gain a reliable estimate of mean PAEE for each individual during a typical week, and mean METS were estimated for a 24-h period while the device was worn.

Body composition and visceral fat estimation. Body composition, fat mass, and lean body mass were measured by dual-energy X-ray absorptiometry (DEXA) using a Delfia W 4500 instrument (Hologic, Bedford, MA; coefficient of variation = 0.68%) and a standard visual method to divide images into trunk, limb, and head. Abdominal MR imaging was undertaken to measure visceral fat (28). We acquired five noncontiguous slices extending from 5 cm below to 15 cm above L5–Ls to obtain more detailed information about visceral fat than a single slice would demonstrate (49). Axial scans were taken with subjects in the supine position. Subjects were scanned on a 1.5-T Symphony MR scanner (software release 4VA15A, Siemens, Erlangen, Germany). A gradient-echo 2-dimensional FLASH (fast low-angle shot) sequence (TR = 111 ms, TE = 4.18 ms, flip angle = 70°, slice width = 10 mm, slice spacing = 50 mm) was used to obtain T1-weighted images.

MR images were analyzed using a proprietary software package (Mimics, Materialise) to identify regions of subcutaneous and visceral fat within the cross-sectional abdominal MR images. By examining the histogram of pixel values in each image, we set a threshold level for fat pixels. By using a seed-growing technique, where neighboring pixels of similar values (i.e., within the identified threshold) are selected, we could separate fat tissue from other tissue in the image. The areas of subcutaneous and visceral fat were calculated and selected, we could separate fat tissue from other tissue in the image. For fat pixels. By using a seed-growing technique, where neighboring pixels of similar values (i.e., within the identified threshold) are selected, we could separate fat tissue from other tissue in the image.

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Pulse-wave analysis-derived measures of wave reflection and diastolic function. Pulse-wave analysis (PWA) was undertaken by a single observer by radial artery planar tonometry (Sphygmocor, Version 7, Atcor, Sydney, Australia) to obtain measures of wave reflection [augmentation index at 75 beats/min heart rate (Alx@HR75)], which is a measure of arterial stiffness and peripheral arteriolar resistance, and measures of diastolic function/myocardial perfusion (SEVR%) and ejection duration (%), which is closely related to SEVR%. Data were obtained from 42 subjects. Waveforms were processed using specialized software to calculate an averaged radial artery waveform and to derive a corresponding central aortic pressure waveform using a previously validated generalized transfer function (11, 43). PWA has been validated as a noninvasive technique for estimating diastolic cardiac function, and myocardial perfusion relative to the left ventricular workload can be estimated by the SEVR (6, 7, 26). As the invasive nature of cardiac catheterization restricts its use in research on healthy volunteers, arterial tonometry has gained popularity in research studies (1). The waveform at the radial artery is easily and reproducibly measured at the wrist, and this noninvasive technique allows the estimation of diastolic function (SEVR%) and wave reflection as a proxy for arterial stiffness (Alx@HR75). Although SEVR% does not take into account the left ventricular end-diastolic pressure, SEVR% is a good estimate of the subendocardial viability index (derived from cardiac catheterization) in individuals without evidence of ischemic heart disease in whom the left ventricular end-diastolic pressure is normal (9, 10). SEVR% is not related to aortic pulse pressure but, rather, solely to the diastolic time systolic time in middle-aged individuals and is, therefore, a measure of diastolic function (9).

Skeletal muscle microvascular exchange capacity. A measure of skeletal muscle microvascular function was assessed using a Filtrass plethysmographic system equipped with a passive inductive transducer with an accuracy of ±5 μm (Compumedics dwl, Singen, Germany) and a small pressure-step venous congestion protocol. Fluid filtration rate (ml·min⁻¹·100 ml⁻¹) was measured from the slope of limb volume change in response to each pressure step (4 min, 10-mmHg steps to 60 mmHg around the thigh) plotted against cuff pressure to give a measure of skeletal muscle exchange capacity (Kf) (24, 50).

Measurement of insulin sensitivity by hyperinsulinemic euglycemic clamp. A hyperinsulinemic euglycemic clamp was undertaken to assess whole body glucose uptake during the steady state of the clamp (final 30 min of the clamp) with an insulin infusion rate of 1.5 mU·kg⁻¹·min⁻¹ (5). M/I (mg·kg⁻¹·min⁻¹·mlU⁻¹·l⁻¹) was estimated by dividing whole body glucose uptake by the mean insulin concentration during the last 30 min of the clamp as an index of whole body insulin sensitivity.

Statistical analyses. All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS, Chicago, IL). Student’s t-test was used to compare mean values of normally distributed data. Pearson’s correlation coefficients (r) are presented for univariate regression analyses of normally distributed data. V02max was categorized into tertiles to facilitate data presentation and interpretation. One-way ANOVA was undertaken to examine differences between tertiles of V02max and to examine linear trends across tertiles. Multivariate linear regression models were developed to describe factors that were independently associated with V02max or SEVR% as the dependent (outcome) variable. R² (coefficient of determination), the squared multiple correlation coefficient, indicates the percentage of the variance in the outcome variable that can be explained or accounted for by the explanatory variables. Factors that were entered into the regression model as explanatory variables were chosen from the results of univariate analyses. P < 0.05 was considered statistically significant for all analyses. Data are expressed as mean ± SD unless otherwise stated.

RESULTS

Baseline characteristics. Mean age of the 47 men and women with central obesity without diabetes was 51 ± 9 (SD) yr. Table 1 shows the baseline characteristics for all subjects. V02max was 26.1 ± 9.0 and 19.1 ± 6.6 (SD) ml·min⁻¹·kg⁻¹ for men and women, respectively (P = 0.005).

Univariate associations with V02max. We analyzed univariate associations with V02max. V02max was associated with HbA1c and total and truncal fat, but not with M/I (P = 0.11; Table 2). The measures of diastolic function (SEVR%) and
wave reflection (Alx@HR75) were associated with \( \dot{V}O_{2\text{max}} \) (\( r = 0.50, P = 0.001 \) for SEVR%; \( r = -0.46, P = 0.002 \) for Alx@HR75). Table 3 shows the distribution of each measure by tertile of \( \dot{V}O_{2\text{max}} \), with results of tests for differences between groups and for linear trends across groups. Visceral fat, total fat, Alx@HR75, and SEVR% showed statistically significant linear trends across \( \dot{V}O_{2\text{max}} \) tertiles. The scatter plots of the relationships between \( \dot{V}O_{2\text{max}} \) and SEVR% and \( \dot{V}O_{2\text{max}} \) and Alx@HR75 were examined to investigate the relationship between SEVR%, Alx@HR75, and \( \dot{V}O_{2\text{max}} \) (Fig. 1). These plots show strong associations between both \( \dot{V}O_{2\text{max}} \) and SEVR% (\( r = 0.50, P = 0.001 \)) and \( \dot{V}O_{2\text{max}} \) and Alx@HR75 (\( r = 0.46, P = 0.002 \)).

### Multiple regression analyses investigating factors independently associated with \( \dot{V}O_{2\text{max}} \)
To explore factors that were independently associated with \( \dot{V}O_{2\text{max}} \) and to estimate how much of the variance in \( \dot{V}O_{2\text{max}} \) could be explained, we undertook multiple linear regression with \( \dot{V}O_{2\text{max}} \) as the outcome. Factors that were associated with \( \dot{V}O_{2\text{max}} \) in univariate analysis were selected for inclusion in the models as explanatory factors. A regression model with age, sex, and truncal (or visceral) fat as explanatory variables was associated with 29% of the variance in \( \dot{V}O_{2\text{max}} \) (\( R^2 = 0.29, P = 0.001 \)). In regression modeling with \( \dot{V}O_{2\text{max}} \) as the outcome and age, sex, truncal fat, and SEVR% as explanatory variables, SEVR% was independently associated with \( \dot{V}O_{2\text{max}} \) (standardized B coefficient = 0.37, 95% confidence interval = 0.003–0.18, \( P = 0.007 \)). The explanatory variables in this model identified 46% of the variance in \( \dot{V}O_{2\text{max}} \) (\( R^2 = 0.46, P = 0.0001 \); Table 4). Replacement of truncal fat with any other measure of visceral fat (from MR imaging assessment) or total body fat or lean mass (from DEXA assessment) did not affect the independent association between SEVR% and \( \dot{V}O_{2\text{max}} \) (data not shown).

As HbA1c (a measure of hyperglycemia) was associated with \( \dot{V}O_{2\text{max}} \) (Table 2), we added HbA1c to the regression model shown in Table 4. Adding HbA1c to the model did not affect the association between SEVR% and \( \dot{V}O_{2\text{max}} \) but did alter the nature of the association between age and \( \dot{V}O_{2\text{max}} \). In this final regression model, age was no longer associated with \( \dot{V}O_{2\text{max}} \), and only sex (standardized B coefficient = –0.37, \( P = 0.009 \)) and SEVR% (standardized B coefficient = 0.35, \( P = 0.009 \)) were associated with \( \dot{V}O_{2\text{max}} \). This model was associated with 49% of the variance in \( \dot{V}O_{2\text{max}} \) (\( R^2 = 0.49, P = 0.0001 \)).

Alx@HR75 was associated with \( \dot{V}O_{2\text{max}} \) (Fig. 1) and age (\( r = 0.35, P = 0.017 \)). We therefore explored the relationship between this measure of wave reflection (as a proxy for arterial stiffness) and \( \dot{V}O_{2\text{max}} \) by repeating the multiple linear regression shown in Table 4, with replacement of SEVR% with Alx@HR75 in this model. In this analysis, there was the expected negative association between the measure of fat and \( \dot{V}O_{2\text{max}} \) (standardized B coefficient = –0.28, \( P = 0.04 \)), and there was a borderline significant association with Alx@HR75 (standardized B coefficient = –0.32, \( P = 0.054 \)) and \( \dot{V}O_{2\text{max}} \). This final model explained 40.5% of the variance in \( \dot{V}O_{2\text{max}} \) (\( R^2 = 0.41, P = 0.001 \)).

### Table 2. Correlations between maximal O2 uptake and measures of diastolic function, wave reflection, insulin sensitivity, microvascular function, body fatness, and physical activity in univariate analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>( r )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>0.18</td>
<td>0.24</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>–0.12</td>
<td>0.43</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>–0.31</td>
<td>0.04</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>–0.35</td>
<td>0.018</td>
</tr>
<tr>
<td>Fat, kg</td>
<td>–0.39</td>
<td>0.008</td>
</tr>
<tr>
<td>DEXA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>–0.37</td>
<td>0.013</td>
</tr>
<tr>
<td>Trunk</td>
<td>–0.07</td>
<td>0.70</td>
</tr>
<tr>
<td>Visceral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td>–0.10</td>
<td>0.54</td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.11</td>
<td>0.45</td>
</tr>
<tr>
<td>CVD risk, %/10 yr</td>
<td>–0.05</td>
<td>0.75</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>–0.12</td>
<td>0.43</td>
</tr>
<tr>
<td>Triglyceride, mmol/l</td>
<td>–0.17</td>
<td>0.28</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td>0.04</td>
<td>0.78</td>
</tr>
<tr>
<td>120 min</td>
<td>–0.21</td>
<td>0.16</td>
</tr>
<tr>
<td>Albumin-to-creatinine ratio</td>
<td>0.18</td>
<td>0.26</td>
</tr>
<tr>
<td>PAEE, METS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/I, mg·kg⁻¹·min⁻¹·mlU⁻¹·l⁻¹</td>
<td>0.26</td>
<td>0.11</td>
</tr>
<tr>
<td>( K_r \times 10^3 ) ml·min⁻¹·100 ml⁻¹·mmHg⁻¹</td>
<td>0.21</td>
<td>0.20</td>
</tr>
<tr>
<td>ED, %</td>
<td>–0.45</td>
<td>0.002</td>
</tr>
<tr>
<td>Alx@HR75</td>
<td>–0.46</td>
<td>0.002</td>
</tr>
<tr>
<td>SEVR, %</td>
<td>0.50</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Blood pressures were measured at the brachial artery.
Multiple regression analyses investigating factors independently associated with diastolic function (SEVR%). Since we showed a strong, independent relationship between a measure of diastolic function (SEVR%) and V\textsubscript{O}\textsubscript{2max} in individuals with central obesity, we explored factors that were associated with SEVR% to determine whether fatness was independently associated with diastolic function. SEVR% was 175 ± 34 in men and 162 ± 23 in women (mean ± SD, P = 0.18). SEVR% was not associated with PAEE (METS; \( r = 0.18, P = 0.26 \)) or age (\( r = 0.05, P = 0.73 \)). However, SEVR% was associated with fatness (\( r = -0.33, P = 0.026 \)) and with IL-6 (\( r = -0.36, P = 0.014 \)). We therefore explored factors that were independently associated with SEVR% in regression modeling with SEVR% as the outcome (with V\textsubscript{O}\textsubscript{2max} excluded from these models). With SEVR% as the outcome and age, sex, IL-6, and truncal (or total or visceral) fat as explanatory factors, IL-6 was inversely associated with SEVR% (Table 5). In these models, no measure of fat quantity was independently associated with diastolic function.

\[ V_{O2\text{max}} \text{ is associated with diastolic function.} \]

\[ V_{O2\text{max}} \text{ is associated with diastolic function.} \]

Table 3. Diastolic function, wave reflection, insulin sensitivity, physical activity, and fatness by tertiles of maximal O\textsubscript{2} uptake

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Unstandardized Coefficient</th>
<th>Standardized Coefficient (( \beta ))</th>
<th>95% CIs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.6</td>
<td>-0.31</td>
<td>-0.50, -0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.27</td>
<td>0.15</td>
<td>-0.40,  -0.11</td>
<td>0.23</td>
</tr>
<tr>
<td>DEXA trunk fat (kg)</td>
<td>-0.30</td>
<td>0.22</td>
<td>-0.17,  -0.74</td>
<td>0.15</td>
</tr>
<tr>
<td>SEVR%</td>
<td>-6.65</td>
<td>0.04</td>
<td>0.37,  0.03</td>
<td>0.007</td>
</tr>
</tbody>
</table>

CIs, confidence intervals. \( R^2 = 0.46, P = 0.0001 \).
During physical activity, an increase in heart rate, myocardial contractility, and ventricular work contributes to increased cardiac output, which markedly increases myocardial O₂ demand. The approximately five- to sixfold increase in O₂ demand of the left ventricle that may occur during physical activity is predominantly met by increasing coronary blood flow (17). During systole, coronary blood flow to the left ventricle is impeded, and therefore the duration of cardiac diastole is an important determinant of myocardial perfusion at a given diastolic perfusion pressure (19, 38). Myocardial O₂ demand mainly depends on heart rate, ejection pressure, and myocardial contractility (41, 46, 47), and the myocardial perfusion relative to the left ventricular workload can be estimated by SEVR (6, 7, 26). As the invasive nature of cardiac catheterization restricts its use in research on healthy volunteers, arterial tonometry has gained popularity in research studies (1). PWA can readily be applied to the study of centrally obese individuals, as the waveform at the radial artery is easily and reproducibly measured at the wrist over the radial artery, which is easily palpable in obese individuals, and this noninvasive technique allows for a valid estimation of diastolic function (SEVR%) and wave reflection as a proxy for arterial stiffness (Alx@HR75) (9, 10). Although SEVR% does not take into account the left ventricular end-diastolic pressure, SEVR% is a good estimate of the subendocardial diastolic index (derived from cardiac catheterization) in individuals without evidence of ischemic heart disease, in whom the left ventricular end-diastolic pressure is normal (9, 10).

**Table 5. Multiple linear regression model with SEVR% as the dependent variable to estimate factors(s) that were independently associated with SEVR%**

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Unstandardized Coefficient</th>
<th>Standardized Coefficient (β)</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.10</td>
<td>-0.03</td>
<td>-1.02, 0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>Sex</td>
<td>-13.8</td>
<td>0.28</td>
<td>-32.5, 4.98</td>
<td>0.15</td>
</tr>
<tr>
<td>DEXA trunk fat (kg)</td>
<td>-1.03</td>
<td>-0.15</td>
<td>-3.19, 1.13</td>
<td>0.34</td>
</tr>
<tr>
<td>IL-6</td>
<td>-10.4</td>
<td>-0.36</td>
<td>-19.4, -1.40</td>
<td>0.025</td>
</tr>
</tbody>
</table>

\[ R^2 = 0.23, \text{ } P = 0.03. \]

Interestingly, there was not a strong relationship between PAEE (METS) and the measure of diastolic function (SEVR%; \( r = 0.18, P = 0.26 \)) or between METS and VO₂max (\( r = 0.18, P = 0.26 \)). Given that neither of these relationships came close to reaching significance, we conclude that the relationship between VO₂max and diastolic function is not confounded by levels of physical activity in this sedentary, obese cohort.

**Relationship between wave reflection and fitness.** We show that the measure of wave reflection (as a proxy for arterial stiffness) was also strongly associated with VO₂max (Fig. 1) in individuals with central obesity. Table 3 shows that wave reflection decreased markedly across increasing tertiles of VO₂max, and Fig. 1 shows the scatter plot for the relationship between VO₂max and wave reflection (Alx@HR%). Recently, the relationship between visceral adiposity and carotid arterial stiffness was examined in a study of 459 patients in whom pericardial fat was assessed by echocardiography as a measure of visceral fat that may impair diastolic function. The authors found a positive correlation between epicardial fat and arterial stiffness parameters and a negative correlation between epicardial fat and diastolic parameters (40), suggesting that visceral fat quantity, or function, may be adversely influencing cardiovascular function. In another very recent study (20), relationships between pericardial fat and measures of cardiac structure and function were assessed by chest and abdominal computed tomography and cardiovascular MR imaging in 997 subjects. The authors concluded that pericardial fat is associated with diastolic function, but the association was not independent of abdominal visceral fat mass. Thus the data suggest that the relationship between pericardial fat and diastolic dysfunction is no stronger than the relationship between abdominal visceral fat and diastolic dysfunction (20).

**Does adipocyte-paracrine signaling influence diastolic function?** Why is there a relationship between pericardial (or visceral) fat mass and diastolic function, and how does this relate to VO₂max? Contact between pericardial fat tissue and the myocardium may directly affect diastolic function because of physical contact between adipose tissue and the myocardium or because adipocyte-derived paracrine signaling impairs diastolic function. Pericardial fat lies on the surface of the myocardium and shares the same coronary blood supply, without fascia separating the two surfaces (31). A study of pericardial fat function has shown higher levels of inflammatory cytokine expression (such as IL-6) in pericardial fat than in matched subcutaneous fat samples (37). We have explored the factors that were associated with diastolic function in our subjects with central obesity to determine whether fatness and, specifically, visceral fat mass were independently associated with diastolic function. Interestingly, although measures of fat quantity were associated with diastolic function in univariate analyses, when the cytokine IL-6 was included in the regression model (Table 5), IL-6, and not any measure of fat quantity, was independently and negatively associated with diastolic function. Whether IL-6 suppresses diastolic function is uncertain, but increased plasma levels of IL-6 and TNF-α have been shown to be negatively associated with left ventricular diastolic function (16), suggesting that there may be a link between low-grade (or high-grade) inflammation and diastolic dysfunction. [We showed no association between diastolic function and TNF-α (data not shown).]
Why is diastolic function related to \( V_{O_2 \text{max}} \) in individuals with central obesity? We cannot be certain of the direction of the relationships we describe in this cross-sectional study of middle-aged, sedentary individuals. However, with that caveat, it is plausible that a low-grade inflammatory response adversely affects diastolic function and, in turn, adversely influences \( V_{O_2 \text{max}} \). The effect of lifestyle modification on left ventricular function in obese patients has recently been investigated in 261 middle-aged patients with no history of cardiac disease and a normal stress echocardiogram. The investigators found that improvements in left ventricular systolic and diastolic function were demonstrated only in patients with a significant reduction of weight and/or insulin resistance (34). In this study, weight reduction and a decrease in HbA1c were independent predictors of improvements in cardiac function. It seems that weight reduction produces comparable changes in cardiac function in individuals with and without congestive heart failure (2). Whether the benefit of decreasing body fat on cardiac function in these studies is mediated by any change in fat function and, specifically, decreased adipocyte-paracrine signaling induced by weight loss is uncertain.

Limitations of the study. The values for central aortic systolic and pulse pressures depend on the validity and applicability of the generalized transfer function used to generate the central aortic waveforms. However, the correspondence between calculated central aortic pressure and directly recorded systolic and pulse pressures has been found to be within 1 mmHg (22, 29, 43). The transfer function used to derive the central aortic pressures is founded on the observation that pressure wave transmission in the upper limb is remarkably consistent under different conditions. This includes the effects of aging, disease, drug therapy, and variation in heart rate, thereby allowing a generalized transfer function to be used to convert the radial to an aortic pressure wave (11). This principle is used by the SphygmoCor device and has been used in a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial in the Conduit Artery Function Evaluation study (54) and was approved by the US Food and Drug Administration in 2001. The data on which approval was given were published in 2004 (22, 42). However, a potential weakness of this technology is that the calibration of central aortic pressures depends on the accuracy of the brachial pressure measurements (13, 15).

In conclusion, we have shown in individuals with central obesity a strong association between fitness (\( V_{O_2 \text{max}} \)) and a measure of diastolic function (SEVR%) that is independent of age, sex, measures of fatness, physical activity levels, skeletal muscle microvascular exchange capacity, and whole body insulin sensitivity.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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