Left Ventricular Function Impairment in Patients With Normal-Weight Obesity

Contribution of Abdominal Fat Deposition, Profibrotic State, Reduced Insulin Sensitivity, and Proinflammatory Activation

Wojciech Kosmala, MD, PhD; Diana Jedrzejuk, MD, PhD; Roksolina Derzhko, MD, PhD; Monika Przewlocka-Kosmala, MD, PhD; Andrzej Mysiak, MD, PhD; Grazyna Bednarek-Tupikowska, MD, PhD

**Background**—Obesity predisposes to left ventricular (LV) dysfunction and heart failure; however, the risk of these complications has not been assessed in patients with a normal body mass index (BMI) but increased body fat content (normal-weight obesity, NWO). We hypothesized that LV performance in NWO may be impaired and sought to investigate potential contributors to cardiac functional abnormalities.

**Methods and Results**—One hundred sixty-eight subjects (age, 38±7 years) with BMI <25 kg/m² and no history of any disease affecting the myocardium were classified on the basis of body fat content into 2 groups: with NWO and without NWO. Echocardiographic indices of LV systolic and diastolic function, including myocardial velocities and deformation, serological fibrosis markers, indicators of proinflammatory activation, and metabolic control, were evaluated. Subjects with NWO demonstrated impaired LV systolic and diastolic function, increased fibrosis intensity (assessed by procollagen type I carboxy-terminal propeptide [PICP]), impaired insulin sensitivity, and increased proinflammatory activation as compared with individuals with normal body fat. The independent correlates of LV systolic and diastolic function variables were as follows: for strain, IL-18 (β=−0.17, P<0.006), C-reactive protein (β=−0.20, P<0.002) and abdominal fat deposit (β=−0.20, P<0.003); for tissue S velocity, PICP (β=−0.21, P<0.002) and abdominal fat deposit (β=−0.43, P<0.001); for tissue E velocity, abdominal fat deposit (β=−0.30, P<0.0001), PICP (β=−0.31, P<0.0001) and homeostasis model assessment of insulin resistance index (HOMA IR; β=−0.20, P<0.002); and for E/e'-PICP, IL-18 (both β=0.18, P<0.01) and HOMA IR (β=0.16, P<0.04).

**Conclusions**—In patients with NWO, subclinical disturbances of LV function are independently associated with the extent of abdominal fat deposit, profibrotic state (as reflected by circulating PICP), reduced insulin sensitivity, and proinflammatory activation. 


**Key Words:** normal-weight obesity ■ left ventricular function ■ echocardiography

The prevalence of obesity has attained epidemic proportions worldwide, becoming a major health concern.1-3 One of the most important ramifications posed by obesity is the development of left ventricular (LV) dysfunction and heart failure, independent of the associated disorders such as ischemic heart disease, hypertension, and diabetes, which contribute to the increasing cardiovascular morbidity and mortality.4-7 Despite the fact that according to the standard World Health Organization definition obesity should be considered as an excessive accumulation of fat, body mass index (BMI) estimation has become a dominant approach in the identification of obese subjects.8 However, a considerable disadvantage of BMI is its inability to distinguish increased body fat content from augmented lean body mass, which may be a reason of misclassification of some individuals with an excess of adipose tissue as being nonobese.8-12

**Editorial see p 286**

**Clinical Perspective on p 356**

Because the adverse effects of adiposity on the circulatory system are strictly associated with the biological milieu provided by fat tissue, increased fat deposition might predispose to cardiac complications even at a low BMI. In support of this, previous studies have demonstrated that patients with a normal BMI but elevated body fat content (normal-weight obesity, NWO) represent a population with a high prevalence...
of cardiometabolic dysregulation and increased cardiovascular risk.\textsuperscript{13–17}

Taking into account a negative impact of adipose tissue, especially its visceral compartment, on the heart associated with the release of cardioinhibitory cytokines and fibrosis mediators and the promotion of insulin resistance,\textsuperscript{18–20} we hypothesize that cardiac function characteristics in patients with NWO may be impaired. Therefore, we sought to evaluate LV performance and to investigate the factors representing metabolic, profibrotic and proinflammatory aspects of the activity of fat tissue, which might contribute to myocardial dysfunction in this population.

Methods

Patient Selection

We analyzed 168 subjects age \( \geq \) 20 years with BMI within the normal range (18.5–24.9 kg/m\(^2\)) who were prospectively recruited from the community. Our sample was drawn from the registers of persons who participated in health screening programs in Wroclaw municipality. All subjects underwent a medical evaluation including clinical history, physical examination, routine blood analysis, lipid profile, a 75-g oral glucose tolerance test (OGTT), ECG, and echocardiography.

The initial assessment of eligibility for the study was carried out in 580 individuals, 345 of whom were excluded due to abnormal BMI. Other exclusion criteria encompassed any heart disease (found in 8 of the remainder subjects), hypertension (in 19), diabetes mellitus and other endocrine or systemic diseases (in 6), renal disorders (in 5), pulmonary disease (in 10), hepatic disease (in 4), rheumatic disease (in 8), neoplastic disease (in 6), skeletal disease (in 1), pregnancy (in 1), or current use of any medications (in 55).

Coronary artery disease was excluded on the basis of a negative history and normal stress ECG or echocardiogram.

Subjects were informed regarding the purpose of the study and provided written informed consent. Investigations were in accordance with the Declaration of Helsinki and were approved by the local ethics committee.

Clinical Evaluation

Anthropometric assessment including height, body weight, and hip and waist circumference was performed after an overnight fast. Blood pressure was measured using a manual sphygmomanometer device with the subject remaining in the sitting position for at least 5 minutes. Three readings were taken at 2-minute intervals and then averaged.

Body Composition Evaluation

Body composition was assessed by dual energy x-ray absorptiometry (Lunar DPX-plus, Lunar Corporation, Madison, WI). Scans were performed according to the manufacturer’s instructions with individuals in the supine position. Abdominal fat content (android fat deposit) was determined in the region of interest extending from the upper edge of the second lumbar vertebra to the lower edge of the fourth lumbar vertebra.\textsuperscript{21} Gynoid fat deposit was estimated in the region of interest bounded superiorly by the upper part of trochanter major of the femur and inferiorly by the bottom of the knees.

Normal-Weight Obesity

NWO was defined as the combination of a normal BMI (18.5–24.9 kg/m\(^2\)) and increased body fat content according to the sex- and age-adjusted cutoff values: 20 to 39 years, \( > 19\% \) and \( > 32\% \); 40 to 59 years, \( > 21\% \) and \( > 33\% \); and 60 to 79 years, \( > 24\% \) and \( > 35\% \) for men and women, respectively.\textsuperscript{22}

Blood Assays

Peripheral blood samples were obtained between 8 and 9 AM after a 30-minute rest in the supine position. Serum glucose was evaluated by enzymatic assay (Dade Behring, Inc, Newark, DE). Serum insulin was determined using a chemiluminescent enzyme immunoassay (Immulate 2000, Diagnostic Products Corp., Los Angeles, CA). The homeostasis model assessment (HOMA IR), an index of insulin resistance, was calculated as the product of fasting insulin multiplied by fasting glucose divided by 22.5.

Serum C-reactive protein (CRP) measurements were performed using a particle-enhanced immunephelometric assay (CardioPhase, Dade Behring Inc, Marburg, Germany); intra-assay and interassay coefficients of variation (CV) were 3.9\% and 4.8\%. The ELISA method was used for the quantification of serum IL-6 (BioSource, Nivelles, Belgium), serum IL-18 (MBL Medical & Biological Laboratories Co, Ltd, Nagoya, Japan), and plasma NT-proBNP (Biomedica Slovakia s.r.o., Bratislava, Slovakia); intra-assay and interassay CV were, for IL-6, 5.8\% and 7.3\%; for IL-18, 5.9\% and 6.7\%; and for NT-proBNP, 6.9\% and 8.2\%.

Serological Markers of Fibrosis

Procollagen type I carboxy-terminal propeptide (PICP) and procollagen type III amino-terminal propeptide (PIIINP) are released during collagen biosynthesis and may reflect the intensity of myocardial fibrosis. Serum PICP was assessed with ELISA (Takara Bio, Shiga, Japan); intra-assay and interassay CV were 4.9\% and 5.5\%. Serum PIIINP was quantified by radioimmunoassay (Orion Diagnostica, Espoo, Finland); intra-assay and interassay CV were 3.9\% and 5.3\%.

Echocardiography

Echocardiographic examinations were carried out using Vivid 7 and System Five machines (GE, Vingmed Ultrasound, Horten, Norway) equipped with phased-array 2.5-MHz multifrequency transducers.

Conventional Echocardiography

Cardiac dimensions and wall thicknesses were measured according to standard recommendations.\textsuperscript{23} LV mass was estimated by the Devereux-modified American Society of Echocardiography cube formula and indexed for height to the power of 2.7 to achieve the LV mass index.\textsuperscript{24} LV ejection fraction was computed from a modified Simpson biplane method.

Pulsed-wave Doppler recordings of the LV inflow were obtained from the apical 4-chamber view with the sample volume placed between the tips of the mitral leaflets. Peak early and late diastolic flow velocity, the ratio of peak early and late diastolic flow velocities, and deceleration time of early diastolic flow wave were assessed.

Tissue Doppler Imaging

Real-time color Doppler myocardial imaging data were acquired in the 3 apical views to assess LV longitudinal function. The image sector angle and the optimal depth of imaging were adjusted to maximize frame rate. Pulse repetition frequency was set at the lowest value without aliasing. The ultrasonic beam was aligned with the myocardial segment of interest to give an insonation angle \( < 20^\circ \). Digital data were saved in a cine-loop format and transferred to a dedicated workstation (GE, Echopac, Horten, Norway) for subsequent off-line analysis.

Myocardial Velocities

Regional myocardial velocity curves were obtained from color Doppler acquisitions in the basal segment of the interventricular septum to evaluate peak systolic velocity and peak early diastolic velocity. Pulsed-wave tissue Doppler profiles acquired in the septal and lateral aspects of the annulus were used for the assessment of peak early diastolic mitral annular velocity (e’). The ratio of mitral inflow early diastolic velocity to the average e’ velocity obtained from the septal and lateral sides of the mitral annulus (E/e’) was calculated to approximate LV filling pressure.

Myocardial Deformation

LV myocardial deformation curves were derived from the apical, mid, and basal segments of each LV wall. Strain rate was assessed from the spatial velocity gradient over a computation distance of
12 mm. Strain rate profiles were then integrated over time to obtain the natural strain curves using end-diastole, defined by the R-peak of ECG. Variables evaluated from myocardial deformation curves included peak strain (defined as the greatest negative value on the strain curve), peak systolic strain rate (SRs), and peak early diastolic strain rate (SRe).

Calibrated Integrated Backscatter
Integrated backscatter curves were acquired in the parasternal long-axis view by positioning a 9×9-pixel sample volume in the basal septum, posterior wall, and pericardium in end-diastole. Calibrated integrated backscatter was computed by subtracting average pericardial integrated backscatter intensity from average myocardial integrated backscatter intensity of the septum and posterior wall.

All strain, strain rate, myocardial velocity, and integrated backscatter profiles were averaged over 3 consecutive heart cycles. The results for strain and strain rate were presented as the average values from all segments analyzed.

Reproducibility
To assess the reproducibility of tissue Doppler measurements, 15 randomly selected examinations were analyzed twice by 2 observers (W.K. and R.D.) blinded to the patients’ obesity data on 2 separate days with the time interval of 4 weeks, and the intraobserver and interobserver variability, estimated as the mean difference and standard deviation of the differences between different analyses from the same observer and between the observers, respectively, was 1.6±1.2% and 1.8±1.2% for strain, 0.1±0.1 and 0.1±0.1 s−1 for strain rate, 0.2±0.8 and 0.3±0.7 cm/s for myocardial velocities, and −2.9±2.5 and −3.0±2.6 dB for calibrated integrated backscatter.

Statistical Analysis
Data are presented as mean±SD. Intergroup comparisons were carried out by a 2-sided Student

t test for continuous variables and by χ² test for categorical variables. Homogeneity of variances was evaluated by the Levene test. The outcome variables were strain, SRs, SRe, peak systolic myocardial velocity (Sm), peak early diastolic myocardial velocity (Em), and E/e’ ratio. The associations between variables were studied with the use of Pearson correlation coefficient and forward stepwise multiple regression analysis. Variables with a P level <0.20 were considered in the multivariable models. To avoid a significant collinearity of independent factors, the variables with the tolerance (calculated as 1−R² of a variable with all other independent variables) <0.1 and the variance inflation factor (calculated as 1/(1−R²)) >10 were excluded from the models as being a possible cause of overadjustment. Skewered variables were analyzed as log-transformed values. All calculations were performed with standard statistical software (Statistica for Windows 10, StatSoft Inc, Tulsa, OK). The level of statistical significance was set at probability value <0.05.

Results
Clinical and Laboratory Characteristics
The criteria of NWO were satisfied in 73 subjects (43%), including 38 women and 35 men (40% and 48% of the female and male subpopulation, respectively; P=0.24).

By definition, total fat mass and total fat percentage, as well as other variables related to the excess of adipose tissue (waist circumference, waist-to-hip ratio, abdominal and gynoid fat deposits, the ratio of abdominal to gynoid fat, and, despite its values being within the normal range, BMI), were significantly higher in subjects with NWO than in their slim peers.

The NWO group demonstrated a less favorable lipid profile (higher LDL and triglycerides, and lower HDL), diminished insulin sensitivity (indicated by higher insulin level and HOMA IR), higher OGTT 2-hour glucose concentration, inflammatory

Table 1. Clinical and Laboratory Characteristics of Studied Sample

<table>
<thead>
<tr>
<th>Age, y</th>
<th>NWO (n=73)</th>
<th>NWO (n=95)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>39.2±9.6</td>
<td>36.8±6.1</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>23.5±0.8</td>
<td>21.1±1.8</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>86±9</td>
<td>75±7</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>0.84±0.08</td>
<td>0.78±0.07</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>113±11</td>
<td>111±12</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>71±8</td>
<td>71±8</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>85±12</td>
<td>83±9</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>111±20</td>
<td>102±18</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>6.0±2.1</td>
<td>4.6±2.0</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>1.25±0.46</td>
<td>0.94±0.42</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>196±25</td>
<td>194±28</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>121±23</td>
<td>110±20</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>58±14</td>
<td>71±17</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>80±33</td>
<td>60±31</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>35.8±21.4</td>
<td>36.3±27.3</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>150±35</td>
<td>125±47</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>5.1±2.4</td>
<td>4.7±1.5</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>292±132</td>
<td>258±96</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>18.4±6.8</td>
<td>17.2±4.1</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>4.0±4.2</td>
<td>1.0±0.5</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>21.2±3.2</td>
<td>13.3±4.2</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>30.0±5.6</td>
<td>22.7±7.0</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>47.8±5.2</td>
<td>47.9±7.1</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>2.0±0.4</td>
<td>1.1±0.4</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>5.9±1.6</td>
<td>4.3±1.7</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>0.35±0.13</td>
<td>0.26±0.10</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

NWO indicates normal-weight obesity; BMI, body mass index; OGTT, oral glucose tolerance test; HOMA IR, homeostasis model assessment of insulin resistance index; PICP, procollagen type I carboxy-terminal propeptide; PIINP, procollagen type II amino-terminal propeptide; and IL, interleukin.

activation (evidenced by higher CRP), and more intensive collagen anabolism (reflected by higher PICP, Table 1).

LV Structure and Function
No significant differences were found between the groups with and without NWO regarding LV end-diastolic dimension, interventricular septum thickness, LV posterior wall thickness, and LV mass index. Left atrial dimension was larger in subjects with NWO than in those with a normal body fat content.

Altered myocardial acoustic properties indicating increased tissue density in subjects with NWO were expressed by significantly higher calibrated integrated backscatter in the basal septum and posterior wall (Table 2 and Figure 1).

LV diastolic function impairment in the NWO group was reflected by lower SRe and Em and higher E/e’ ratio. Reduced values of strain, SRs, and Sm in subjects with NWO were indicative of LV systolic function disturbances (Table 2 and Figures 1 and 2). Conventional echocardiographic variables of LV performance (LV ejection fraction, E/A ratio, and DT) did not differ between participants with and without excess fat (Table 2).

All the aforementioned significant differences between subjects with and without NWO were shown for both sexes,
Table 2. Echocardiographic Characteristics of Studied Sample

<table>
<thead>
<tr>
<th></th>
<th>NWO (+)</th>
<th>NWO (-)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=73</td>
<td>n=95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>48.2±3.6</td>
<td>47.3±4.2</td>
<td>0.14</td>
</tr>
<tr>
<td>IVS, mm</td>
<td>9.3±1.4</td>
<td>9.0±1.3</td>
<td>0.15</td>
</tr>
<tr>
<td>PW, mm</td>
<td>7.5±1.2</td>
<td>7.2±1.1</td>
<td>0.09</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>32.6±7.8</td>
<td>31.2±6.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Left atrial dimension, mm</td>
<td>36.1±3.5</td>
<td>33.6±3.7</td>
<td>0.001</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>69.7±3.0</td>
<td>69.9±4.0</td>
<td>0.72</td>
</tr>
<tr>
<td>E/A</td>
<td>1.43±0.30</td>
<td>1.41±0.25</td>
<td>0.60</td>
</tr>
<tr>
<td>DT, ms</td>
<td>201±25</td>
<td>199±18</td>
<td>0.65</td>
</tr>
<tr>
<td>IB post, dB</td>
<td>-22.6±4.3</td>
<td>-24.6±4.8</td>
<td>0.01</td>
</tr>
<tr>
<td>IB AS, dB</td>
<td>-17.6±4.4</td>
<td>-23.0±5.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Strain, %</td>
<td>19.5±2.1</td>
<td>21.8±1.7</td>
<td>0.001</td>
</tr>
<tr>
<td>SRs, s⁻¹</td>
<td>1.51±0.20</td>
<td>1.64±0.20</td>
<td>0.001</td>
</tr>
<tr>
<td>SRs, s⁻¹</td>
<td>2.03±0.29</td>
<td>2.36±0.26</td>
<td>0.001</td>
</tr>
<tr>
<td>Sm, cm/s</td>
<td>6.3±1.3</td>
<td>7.3±1.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Em, cm/s</td>
<td>8.3±2.0</td>
<td>10.2±1.8</td>
<td>0.001</td>
</tr>
<tr>
<td>E'/e'</td>
<td>8.8±1.6</td>
<td>7.2±1.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

NWO indicates normal-weight obesity; LV, left ventricular; IVS, interventricular septal thickness at end-diastole; PW, LV posterior wall thickness at end-diastole; E, peak early diastolic mitral flow velocity; A, peak late diastolic mitral flow velocity; DT, deceleration time of early mitral diastolic flow; IB post, calibrated integrated backscatter in the basal posterior wall; IB AS, calibrated integrated backscatter in the basal anteroseptum; SRs, peak systolic strain rate; Sm, peak systolic myocardial velocity; Em, peak early diastolic myocardial velocity; and e’, peak early diastolic mitral annular velocity.

Normal values in healthy populations: strain: 22.1±2.5 [25], 17.4±5.0% [26]; SRs: 1.8±0.4 s⁻¹ [5], 1.31±0.25 s⁻¹ [25], 1.4±0.4 s⁻¹ [26]; Sm: 5.9±1.2 cm/s [5], 5.7±1.6 cm/s [26]; Em: 8.8±2.2 cm/s [5], 8.8±2.5 cm/s [26]; IB post: 29.0±6.2 dB; and IB AS: 22.6±6.6 dB [28].

except for HDL lacking significance in females and calibrated integrated backscatter in posterior wall in men (online-only Data Supplement Tables I and II).

Interrelations

Significant correlations of cardiac functional variables are presented in Table 3. Selected scatterplots are shown in Figure 3.

A series of stepwise multiple regression models were developed to identify the independent associations of LV systolic and diastolic function. The set of variables tested in these models included all factors significantly associated with a dependent variable, and, in addition, sex. The variables were put into the stepwise models in order of descending significance in the univariate analyses. The independent determinants were abdominal fat mass, PICP, calibrated integrated backscatter in the basal septum, HOMA IR, IL-18, CRP, and patient age (Table 4).

Discussion

The main clinical findings of the present study are that (1) patients with NWO demonstrate subclinical LV systolic and diastolic function impairment, and (2) these functional changes are independently determined by the extent of abdominal fat deposit, profibrotic state (as reflected by circulating PICP), reduced insulin sensitivity, and proinflammatory activation.

Cardiovascular disease is the most serious complication of obesity. Although the coronary aspect of myocardial involvement is often the focus of concern in obese patients, the risk of heart failure may be even more important and therefore deserves special attention. Cardiac derangements in obesity have been suggested to be accounted for by a number of plausible mechanisms, which include inflammatory activation with cytokine-induced cardiodepressant effects; exaggerated myocardial fibrosis (mediated largely by angiotensin II, aldosterone, and transforming growth factor (β1); intracellular lipid accumulation and lipotoxicity with subsequent cardiomyocyte apoptosis; neurohormonal upregulation, especially the
Table 3. Significant Correlations of LV Function Variables

<table>
<thead>
<tr>
<th></th>
<th>Systolic Variables</th>
<th>Diastolic Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strain</td>
<td>SRs</td>
</tr>
<tr>
<td>r</td>
<td>Value</td>
<td>r</td>
</tr>
<tr>
<td>p</td>
<td>P</td>
<td>p</td>
</tr>
<tr>
<td>Age</td>
<td>-0.36</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.37</td>
<td>0.001</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>-0.39</td>
<td>0.001</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>-0.37</td>
<td>0.001</td>
</tr>
<tr>
<td>Body fat mass</td>
<td>-0.42</td>
<td>0.001</td>
</tr>
<tr>
<td>Abdominal fat mass</td>
<td>-0.46</td>
<td>0.001</td>
</tr>
<tr>
<td>Abdominal/gynoid fat mass</td>
<td>-0.20</td>
<td>0.01</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>-0.09</td>
<td>0.24</td>
</tr>
<tr>
<td>HOMA IR</td>
<td>-0.18</td>
<td>0.02</td>
</tr>
<tr>
<td>PICP</td>
<td>-0.10</td>
<td>0.21</td>
</tr>
<tr>
<td>PIIINP</td>
<td>-0.08</td>
<td>0.30</td>
</tr>
<tr>
<td>IL-18</td>
<td>-0.16</td>
<td>0.04</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>-0.35</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-0.06</td>
<td>0.46</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>-0.05</td>
<td>0.51</td>
</tr>
<tr>
<td>LV mass index</td>
<td>-0.31</td>
<td>0.001</td>
</tr>
<tr>
<td>IB AS</td>
<td>-0.07</td>
<td>0.25</td>
</tr>
<tr>
<td>IB post</td>
<td>-0.09</td>
<td>0.25</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; SRs, peak systolic strain rate; SRs, peak early diastolic strain rate; Sm, peak systolic myocardial velocity; Em, peak early diastolic myocardial velocity; E/e’, ratio of mitral inflow early diastolic velocity to the average e’ velocity obtained from the septal and lateral sides of the mitral annulus; BMI, body mass index; HOMA IR, homeostasis model assessment of insulin resistance index; PICP, procollagen type I carboxy-terminal propeptide; PIIINP, procollagen type III amino-terminal propeptide; IL, interleukin; IB post, calibrated integrated backscatter in the basal posterior wall; and IB AS, calibrated integrated backscatter in the basal anteroseptum.

As most of the aforementioned mechanisms are attributable to the excessive accumulation of adipose tissue rather than to an increased total body weight per se, it is tempting to suppose that the risk of cardiac complications in patients with excess body fat and a normal BMI might parallel that evidenced in obesity diagnosed on the basis of the BMI criteria. In the currently investigated population with NWO, as well as in other studies exploring obesity profiles, increased body fat content was associated with larger amounts of adipose tissue in abdominal and gynoid depots; however, the proportion of these two components was altered with the predominance of the abdominal distribution. This might be of paramount relevance for the development of cardiac impairment in view of different biological roles of abdominal and gynoid fat, with the former secreting various compounds affecting the myocardium and contributing to metabolic alterations and the latter protecting against cardiovascular diseases (through the mechanisms linked to the larger lipoprotein lipase activity and more efficacious storage of free fatty acids, as well as enhanced release of adiponectin exerting favorable cardiometabolic effects). Consistent with these considerations, we showed higher CRP (a marker of inflammation), PICP (a marker of collagen I synthesis), insulin, and HOMA IR in individuals with NWO that might attest to the inflammatory and fibrotic upregulation, and metabolic disturbances associated with excess body fat.

Figure 2. Percentage differences in left ventricular function variables between patients with and without normal-weight obesity in relation to the average values in the studied sample. SRs indicates peak systolic strain rate; SRs, peak early diastolic strain rate; Sm, peak systolic myocardial velocity; Em, peak early diastolic myocardial velocity; and E/e’, ratio of mitral inflow early diastolic velocity to the average e’ velocity obtained from the septal and lateral sides of the mitral annulus.

As most of the aforementioned mechanisms are attributable to the excessive accumulation of adipose tissue rather than to an increased total body weight per se, it is tempting to suppose that the risk of cardiac complications in patients with excess body fat and a normal BMI might parallel that evidenced in obesity diagnosed on the basis of the BMI criteria. In the currently investigated population with NWO, as well as in other studies exploring obesity profiles, increased body fat content was associated with larger amounts of adipose tissue in abdominal and gynoid depots; however, the proportion of these two components was altered with the predominance of the abdominal distribution. This might be of paramount relevance for the development of cardiac impairment in view of different biological roles of abdominal and gynoid fat, with the former secreting various compounds affecting the myocardium and contributing to metabolic alterations and the latter protecting against cardiovascular diseases (through the mechanisms linked to the larger lipoprotein lipase activity and more efficacious storage of free fatty acids, as well as enhanced release of adiponectin exerting favorable cardiometabolic effects). Consistent with these considerations, we showed higher CRP (a marker of inflammation), PICP (a marker of collagen I synthesis), insulin, and HOMA IR in individuals with NWO that might attest to the inflammatory and fibrotic upregulation, and metabolic disturbances associated with excess body fat.

The key observation in the present study was that subjects with NWO exhibited asymptomatic LV systolic and diastolic function impairment, as compared with their counterparts with a normal fat deposition. Cardiac morphological changes...
in the group with NWO included larger left atrial dimension, likely being a consequence of LV diastolic dysfunction and/or an expanded intravascular volume, and higher myocardial reflectivity (assessed by calibrated integrated backscatter minus variable directly related to the myocardial collagen content), implying increased heart muscle fibrosis. The absence of increased LV mass in patients with NWO might be attributable to the fact that in early-stage disease represented by NWO, the effects of excess body fat promoting myocardial hypertrophy are not evident yet.

The spectrum of independent contributors to impaired cardiac performance included patient age, abdominal fat mass, PICP, calibrated integrated backscatter, HOMA IR, IL-18, and CRP, which indicates a multifactorial origin of LV dysfunction accompanying NWO, with the adipose tissue-related factors playing a pivotal role. The presence of abdominal fat among the above independent correlates suggests that its contribution to the demonstrated derangements extends beyond what is associated with increased fibrosis, inflammation, or decreased insulin sensitivity. The emergence of IL-18 as a determinant of cardiac disturbances is particularly worth noting, as this pleiotropic cytokine is thought to be an important mediator, integrating subclinical inflammation associated with excessive fat deposition and insulin resistance, which corroborates its potential utility as a cardiovascular risk marker in obesity.

We have not found sex to be an independent contributor to the observed cardiac disturbances. However, given the results of some previous studies implying that females are more prone to the adverse effects of abdominal obesity, this issue needs further exploration.

In contrast to echocardiography, NT-proBNP, a gold laboratory standard in heart failure, proved to be unhelpful in detecting LV functional impairment in the studied population, which might be linked to the postulated inverse relationship between obesity and natriuretic peptide levels or a limited sensitivity of this marker in subclinical disease.

Limitations
The cross-sectional observational character of the present study precludes conclusions about the causal nature of demonstrated relations. We cannot clearly ascertain the absence of coronary artery disease on the basis of the noninvasive strategy used in the study protocol in all the study participants; however, this seems unavoidable, because an angiographic verification would not be justified in asymptomatic
Table 4. Predictors of Left Ventricular Systolic and Diastolic Function Indices

<table>
<thead>
<tr>
<th></th>
<th>Systolic Variables</th>
<th>Diastolic Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strain $R^2=0.42$; $P&lt;0.0001$</td>
<td>Sm $R^2=0.33$; $P&lt;0.0001$</td>
</tr>
<tr>
<td>Age</td>
<td>Coeff 0.26 0.06 0.001 $P&lt;0.0001$</td>
<td>Coeff 0.46 0.05 0.0001 $P&lt;0.0001$</td>
</tr>
<tr>
<td>Abdominal fat mass</td>
<td>Coeff 0.20 0.06 0.003 $P&lt;0.0001$</td>
<td>Coeff 0.22 0.06 0.001 $P&lt;0.0001$</td>
</tr>
<tr>
<td>IPCP</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>IB AS</td>
<td>$-0.36 0.06 0.0001$ $-0.34 0.06 0.0001$</td>
<td>$-0.32 0.05 0.0001$ $-0.31 0.05 0.0001$</td>
</tr>
<tr>
<td>HOMA IR</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>IL-18</td>
<td>$-0.17 0.06 0.006$ ...</td>
<td>...</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>$-0.20 0.06 0.002$ ...</td>
<td>...</td>
</tr>
</tbody>
</table>

SRs indicates peak systolic strain rate; SRe, peak early diastolic strain rate; Sm, peak systolic myocardial velocity; Em, peak early diastolic myocardial velocity; E/e', ratio of mitral inflow early diastolic velocity to the average e' velocity obtained from the septal and lateral sides of the mitral annulus; PICP, procollagen type I carboxy-terminal propeptide; IB AS, calibrated integrated backscatter in the basal anteroseptum; HOMA IR, homeostasis model assessment of insulin resistance index; and IL, interleukin.

Coef indicates sample estimate of the regression parameter; SE, standard error of the estimated regression coefficient.

individuals for ethical reasons. The abdominal fat assessment by dual energy x-ray absorptiometry does not permit differentiation between visceral and subcutaneous depots, which might have influenced the results, especially by distorting some associations. As all the study subjects were white, the extrapolation of the present findings to other ethnic groups is uncertain. The sample size might have been insufficient to evidence the significance of some differences, for example, concerning IL-18. As numerous comparisons were performed with no adjustment for multiple testing, the increased risk of type 1 error should be acknowledged.

Conclusions and Clinical Implications

The results of this study indicate that LV systolic and diastolic function is impaired in subjects with NWO and among the contributors are increased abdominal fat deposition and the factors associated with adiposity, that is, profibrotic state, decreased insulin sensitivity, and inflammatory upregulation. Due to a persistent synergistic influence of these pathologies, initially preclinical myocardial dysfunction may progress in time to the overt cardiomyopathy, with some alterations becoming irreversible. The additional disadvantage for subjects with NWO is attenuated self-awareness of being at increased cardiovascular risk, resulting from their normal BMI. Timely preventive and therapeutic measures including lifestyle modifications aimed at reducing body fat content, and, in some cases, specific pharmacological treatments targeting, for example, a limitation of excessive fibrosis, might be beneficial in patients with NWO, however this needs further evaluation.

Sources of Funding

This work was supported by an internal grant from Wroclaw Medical University.

Disclosures

None.

References


Obesity is a major health concern worldwide. Left ventricular (LV) dysfunction and heart failure are the most serious complications, contributing to obesity’s increasing morbidity and mortality. Despite the World Health Organization’s definition of obesity as an excessive fat accumulation, body mass index (BMI) estimation has become a dominant approach in the promotion of insulin resistance, increased fat deposition, and cardiometabolic dysregulation. Raising levels of interleukin-18 independent of body fat and fat-free mass: results from the MONICA/KORA study. Diabetes Care. 2006;29:174–175.


CLINICAL PERSPECTIVE

Obesity is a major health concern worldwide. Left ventricular (LV) dysfunction and heart failure are the most serious complications, contributing to obesity’s increasing morbidity and mortality. Despite the World Health Organization’s definition of obesity as an excessive fat accumulation, body mass index (BMI) estimation has become a dominant approach in the identification of obese subjects. However, because the adverse effects of adiposity on the circulatory system are strictly associated with the biological milieu provided by fat tissue including the release of cardioinhibitory cytokines and fibrosis mediators and the promotion of insulin resistance, increased fat deposition might predispose to cardiac derangements even at a low BMI. In view of this, we hypothesized that cardiac function in patients with a normal BMI but elevated body fat content (normal-weight obesity, NWO) may be impaired and sought to investigate the factors representing different aspects of the activity of fat tissue that might contribute to myocardial dysfunction in this population. We found that subjects with NWO demonstrated impaired LV systolic and diastolic function, increased fibrosis, decreased insulin sensitivity, and increased proinflammatory activation as compared with individuals with normal body fat. LV function disturbances were independently associated with the extent of abdominal fat deposition as well as with proinflammatory, metabolic, and proinflammatory alterations. It is possible that the demonstrated preclinical cardiac impairment may progress in time to overt cardiomyopathy and that timely preventive and therapeutic measures including lifestyle modifications aimed at reducing body fat, and, in some cases, specific pharmacological treatments, might be beneficial in NWO. However, this needs further evaluation.
Left Ventricular Function Impairment in Patients With Normal-Weight Obesity: Contribution of Abdominal Fat Deposition, Profibrotic State, Reduced Insulin Sensitivity, and Proinflammatory Activation

Wojciech Kosmala, Diana Jedrzejuk, Roksolana Derzhko, Monika Przewlocka-Kosmala, Andrzej Mysiak and Grazyna Bednarek-Tupikowska

Circ Cardiovasc Imaging. 2012;5:349-356; originally published online March 9, 2012; doi: 10.1161/CIRCIMAGING.111.969956

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/5/3/349

Data Supplement (unedited) at:
http://circimaging.ahajournals.org/content/suppl/2012/03/09/CIRCIMAGING.111.969956.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/
Supplementary Table 1. Clinical and laboratory characteristics of studied sample stratified by sex.

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=96</td>
<td>n=38</td>
<td>n=72</td>
<td>n=35</td>
<td>n=37</td>
</tr>
<tr>
<td>NWO(+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>38.3±9.4</td>
<td>38.7±6.4</td>
<td>40.1±12.3</td>
<td>36.9±5.8</td>
<td>0.15</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.4±0.9</td>
<td>21.4±1.7</td>
<td>23.6±1.0</td>
<td>20.6±2.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>79±5</td>
<td>72±6</td>
<td>94±4</td>
<td>80±7</td>
<td>0.001</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.79±0.07</td>
<td>0.74±0.05</td>
<td>0.90±0.05</td>
<td>0.84±0.06</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>113±14</td>
<td>110±12</td>
<td>113±11</td>
<td>114±12</td>
<td>0.69</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>70±8</td>
<td>70±7</td>
<td>71±7</td>
<td>72±8</td>
<td>0.66</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>83±9</td>
<td>81±8</td>
<td>87±15</td>
<td>85±9</td>
<td>0.43</td>
</tr>
<tr>
<td>OGTT 2-h glucose, mg/dL</td>
<td>109±21</td>
<td>101±18</td>
<td>113±19</td>
<td>103±17</td>
<td>0.02</td>
</tr>
<tr>
<td>Fasting insulin, mIU/L</td>
<td>5.5±2.1</td>
<td>4.9±2.2</td>
<td>6.6±1.5</td>
<td>4.3±1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>HOMA IR</td>
<td>1.13±0.45</td>
<td>0.98±0.43</td>
<td>1.39±0.37</td>
<td>0.90±0.39</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>199±28</td>
<td>192±29</td>
<td>194±20</td>
<td>198±25</td>
<td>0.51</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dL</td>
<td>114±24</td>
<td>106±20</td>
<td>128±17</td>
<td>116±20</td>
<td>0.04</td>
</tr>
<tr>
<td>Measure</td>
<td>Value 1</td>
<td>Value 2</td>
<td>p-value</td>
<td>Value 3</td>
<td>Value 4</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td>66±13</td>
<td>72±21</td>
<td>0.07</td>
<td>49±6</td>
<td>69±6</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>83±35</td>
<td>62±35</td>
<td>0.01</td>
<td>75±32</td>
<td>58±19</td>
</tr>
<tr>
<td>NT-proBNP, pg/ml</td>
<td>36.2±21.8</td>
<td>38.8±28.2</td>
<td>0.67</td>
<td>35.4±19.7</td>
<td>32.2±22.6</td>
</tr>
<tr>
<td>PICP, μg/L</td>
<td>159±33</td>
<td>138±40</td>
<td>0.01</td>
<td>139±32</td>
<td>109±42</td>
</tr>
<tr>
<td>PIIINP, μg/L</td>
<td>5.6±2.5</td>
<td>5.0±1.8</td>
<td>0.17</td>
<td>4.5±1.7</td>
<td>4.2±1.4</td>
</tr>
<tr>
<td>IL-18, pg/mL</td>
<td>280±138</td>
<td>251±98</td>
<td>0.21</td>
<td>305±129</td>
<td>270±106</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>18.7±7.4</td>
<td>17.2±4.7</td>
<td>0.22</td>
<td>18.0±3.7</td>
<td>17.1±4.4</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>3.6±4.0</td>
<td>1.0±0.6</td>
<td>0.001</td>
<td>4.5±3.2</td>
<td>0.9±0.3</td>
</tr>
<tr>
<td>Body fat mass, kg</td>
<td>22.5±3.2</td>
<td>15.2±2.4</td>
<td>0.001</td>
<td>19.8±2.3</td>
<td>10.4±3.4</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>35.3±2.2</td>
<td>27.3±2.9</td>
<td>0.001</td>
<td>24.6±1.8</td>
<td>15.8±2.5</td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td>40.2±3.6</td>
<td>41.6±3.7</td>
<td>0.08</td>
<td>56.1±2.8</td>
<td>57.4±5.1</td>
</tr>
<tr>
<td>Abdominal fat mass, kg</td>
<td>1.8±0.4</td>
<td>1.0±0.3</td>
<td>0.001</td>
<td>2.4±0.2</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>Gynoid fat mass, kg</td>
<td>6.8±1.5</td>
<td>5.1±0.9</td>
<td>0.001</td>
<td>5.0±0.7</td>
<td>3.0±1.1</td>
</tr>
<tr>
<td>Abdominal/gynoid fat mass</td>
<td>0.26±0.07</td>
<td>0.21±0.06</td>
<td>0.001</td>
<td>0.47±0.08</td>
<td>0.39±0.07</td>
</tr>
</tbody>
</table>
Supplementary Table 2. Echocardiographic characteristics of studied sample stratified by sex.

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NWO(+) n=38</td>
<td>NWO(-) n=58</td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>46.9±3.5</td>
<td>46.0±3.5</td>
</tr>
<tr>
<td>IVS, mm</td>
<td>9.0±1.7</td>
<td>8.8±1.2</td>
</tr>
<tr>
<td>PW, mm</td>
<td>6.9±1.2</td>
<td>6.7±1.0</td>
</tr>
<tr>
<td>LV mass index, g/m²ⁿ⁷</td>
<td>32.0±8.3</td>
<td>31.1±5.3</td>
</tr>
<tr>
<td>Left atrial dimension, mm</td>
<td>35.0±3.1</td>
<td>33.2±2.8</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>69.5±3.6</td>
<td>69.3±3.6</td>
</tr>
<tr>
<td>E/A</td>
<td>1.52±0.25</td>
<td>1.47±0.25</td>
</tr>
<tr>
<td>DT, ms</td>
<td>193±24</td>
<td>198±20</td>
</tr>
<tr>
<td>IB post, dB</td>
<td>-21.6±4.7</td>
<td>-24.1±5.4</td>
</tr>
<tr>
<td>IB AS, dB</td>
<td>-18.6±3.7</td>
<td>-22.5±5.3</td>
</tr>
<tr>
<td>Strain, %</td>
<td>20.2±2.3</td>
<td>21.7±1.7</td>
</tr>
<tr>
<td>SRs, s⁻¹</td>
<td>1.54±0.21</td>
<td>1.63±0.18</td>
</tr>
<tr>
<td>SRe, s⁻¹</td>
<td>2.07±0.30</td>
<td>2.28±0.25</td>
</tr>
<tr>
<td></td>
<td>Sm, cm/s</td>
<td>Em, cm/s</td>
</tr>
<tr>
<td>----</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>1</td>
<td>6.0±1.3</td>
<td>8.7±2.1</td>
</tr>
<tr>
<td>2</td>
<td>6.9±1.2</td>
<td>10.1±1.9</td>
</tr>
<tr>
<td>3</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>4</td>
<td>6.6±1.4</td>
<td>7.7±1.8</td>
</tr>
<tr>
<td>5</td>
<td>7.9±1.3</td>
<td>10.4±1.9</td>
</tr>
<tr>
<td>6</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Normal values in healthy populations: strain - 22.1±4.0 % [1], 22.9±3.6 % [2], 17.4±5.0 % [3]; SRs - 1.8±0.4 s⁻¹ [1], 1.31±0.25 s⁻¹ [2], 1.4±0.4 s⁻¹ [3]; SRe - 2.5±0.5 s⁻¹ [4], 1.8±0.6 s⁻¹ [3]; Sm – 5.9±1.2 cm/s [1], 5.7±1.6 cm/s [3]; Em – 8.8±2.2 cm/s [1], 8.8±2.5 cm/s [3]; IB post 29.0±6.2 dB and IB AS 22.6±6.6 dB [5].

A - peak late diastolic mitral flow velocity; DT - deceleration time of early mitral diastolic flow; E - peak early diastolic mitral flow velocity; e’ – peak early diastolic mitral annular velocity; Em - peak early diastolic myocardial velocity; IB AS - calibrated integrated backscatter in the basal antero-septum; IB post – calibrated integrated backscatter in the basal posterior wall; IVS – interventricular septal thickness at end diastole; PW – LV posterior thickness at end diastole; Sm - peak systolic myocardial velocity; SRe - peak early diastolic strain rate; SRs - peak systolic strain rate.