Features of Cardiac Remodeling, Associated With Blood Pressure and Fibrosis Biomarkers, Are Frequent in Subjects With Abdominal Obesity

Romain Eschalier, Patrick Rossignol, Anna Kearney-Schwartz, Chris Adamopoulos, Kyparissi Karatzidou, Renaud Fay, Damien Mandry, Pierre-Y. Marie, Faïez Zannad

Abstract—Incidence and prevalence of abdominal obesity (AO) are growing exponentially. Subjects with AO are at higher risk of developing heart failure. The purpose of the study was to investigate early changes in cardiac and arterial structure and function and extracellular matrix biomarkers in normotensive healthy subjects with AO. Subjects with AO and age- and sex-matched controls underwent echocardiography, MRI (cardiac remodeling index), carotid intima–media thickness, pulse wave velocity, and blood fibrosis biomarkers measurements. We enrolled 87 subjects with AO and 53 controls. Although normotensive, subjects with AO had higher systolic blood pressure (BP; 122±11 versus 116±11 mm Hg; *P*=0.003), left ventricular mass (94±24 versus 84±21 g; *P*=0.034), and cardiac remodeling index (0.67±0.16 versus 0.60±0.10 g/mL; *P*=0.026) but unchanged carotid intima–media thickness and pulse wave velocity. Diastolic dysfunction (E′<10 cm/s) could be detected in 38% of subjects with AO (4% in controls). Left ventricular remodeling, as assessed by cardiac remodeling index, was positively and independently associated with higher BP (systolic BP and mean arterial pressure but not diastolic BP) and AO. Higher BP, AO, and procollagen-III-N-terminal peptide (≥2.4 ng/mL) concentrations (odds ratio, 4.15 [1.42–12.2]; *P*=0.01) were positively associated with diastolic dysfunction. Early cardiac structural remodeling, fibrosis, and diastolic dysfunction were detectable in healthy subjects with AO. Higher BP, procollagen-III-N-terminal peptide, and AO were independently associated with early cardiac structural and functional changes. It is to be investigated whether in subjects with AO, an early BP reduction, even if normotensive, combined with weight loss may avoid adverse cardiac remodeling and protect against progression to heart failure. (Hypertension. 2014;63:740-746.) • Online Data Supplement

Key Words: blood pressure • heart failure, diastolic • obesity, abdominal • procollagen • ventricular remodeling

Obesity has reached worldwide epidemic proportions. The risk of developing chronic heart failure (HF) is higher in patients who are obese and, more specifically so, subjects with abdominal obesity (AO)1 2 independently of other cardiovascular risk factors such as hypertension and diabetes mellitus. In an effort to help healthcare providers with the early identification of patients who are at risk for developing HF, the American College of Cardiology/American Heart Association 2005 classification3 of chronic HF has insisted on the early asymptomatic stages. However, the mechanisms underlying the transition from risk factors (stage A: patients at risk for HF but without structural heart disease or symptoms of HF) to early asymptomatic cardiac and vascular structural (stage B: patients with structural heart disease but without signs or symptoms of HF) and functional changes are still poorly understood.4 At least in hypertension, early cardiac and vascular remodeling is the result of pressure overload and interstitial fibrosis.5 Our group has also reported that early changes in extracellular matrix biomarkers could be detected not only in patients with diabetes mellitus and hypertension6 but also in obese and otherwise healthy subjects.7 Whether subjects with AO develop adverse cardiac and vascular remodeling has not been investigated to date.

The aim of the present study is to assess whether changes in cardiac and arterial remodeling can be detected at an early stage in subjects with AO and otherwise healthy and normotensive and to investigate the contribution of blood pressure (BP) and myocardial fibrosis turnover to such potential changes.

Methods

Subjects’ Selection

White subjects with AO (waist circumference >94 cm for men and >80 cm for women)8 aged 40 to 65 years and age- and sex-matched healthy
volunteers without AO and body mass index <25 kg/m² were consecu-
rently recruited. Subjects with diabetes mellitus (taking antidiabetic
agents or screening visit fasting glucose >7 mmol/L), hypertension
(antihypertensive therapy or BP >140/90 mm Hg at the screening
visit or the enrollment visit), body mass index >40 kg/m², history of
cardiovascular, or endocrine, inflammatory, or malignant diseases
were excluded. The study complied with the Declaration of Helsinki.8
Written informed consent was obtained from all subjects. Local Ethics
Committee approved the study. No clinical trials.gov number was
assigned to this study because it started before July 1, 2005.

Metabolic Phenotyping
Blood was sampled between 8 and 10 am after maintaining a supine
position for 30 minutes and the following were assessed: fasting
glucose, oral glucose tolerance test (to exclude patients with dia-
abetes mellitus), glycohemoglobin, serum creatinine (estimated
glomerular filtration rate by the MDRD [Modification of the Diet
in Renal Disease] formula),9 ultrasensitive C-reactive protein, ala-
nine aminotransferase, lipid profile, leptin, and adiponectin (R&D
Systems, Minneapolis, MN). Body composition was estimated from
the attenuation of radiographs pulsed synchronously between 40 and
100 keV using a LUNARs DPX-IQ system (LUNARs Corporation,
Madison, WI).10

Cardiac Phenotyping
Left ventricular (LV) diastolic function was assessed with transtho-
racic Doppler echocardiography (HD1 5000), with measurements of
peak E wave, peak A wave, E/A ratio, deceleration time of E wave,
together with Doppler tissue imaging of the lateral part of mitral
annulus: peak E’ wave, peak A’ wave, and E/E’ ratio. The European
Society of Echocardiography guidelines were used to grade diastolic
dysfunction,11 diagnosed if E’ was <10 cm/s.
Cardiac MRI was performed on a 1.5-T magnet (Signa Excite;
GE Medical Systems, Milwaukee, WI) equipped with an 8-element
phased-array surface coil. A steady-state free precession pulse se-
quence was used to assess LV function in contiguous short-axis
planes, as previously described in detail elsewhere.12 LV end-diastolic
volume, LV end-systolic volume, LV stroke volume, LV ejection frac-
tion (EF), and LV mass were determined on the contiguous short-axis
slices using dedicated software (MASS, Medis, The Netherlands).
LV mass was determined at end diastole, and papillary muscles and
trabeculations were excluded for LV mass and LV volume measure-
ments.12 Different scales were used to normalize LV mass: height1.7,13
height2.7,14 and fat-free mass.15 Cardiac remodeling index (CRI), in-
dicating concentric LV remodeling, is represented by the ratio of LV
mass/LV end-diastolic volume.16 LV hypertrophy, assessed by MRI,
was defined according to Alfakih et al17 as follows: women ≥60 g/m²
and men ≥77 g/m².

Arterial Phenotyping
During the screening visit as well as at the beginning of the echotrack-
ning/MRI visit (>1 month apart), specialist hypertension nurses mea-
sured BP consecutively 3× (Dinamap oscillometry; cuff sizes, 27–35
and 33–47 cm; systolic BP [SBP], diastolic BP [DBP], and mean arte-
rial pressure [MAP]). The mean of the last 2 readings was recorded
for each series of measurements. Therefore, the 2 last measurements
of the echotracking/MRI visit were taken into account in this analy-
sis. All were performed after an extended rest period of ≥30 min-
utes. Carotid intima–media thickness (IMT) and pulse wave velocity
(PWV) were measured noninvasively as previously described.18

Extracellular Matrix Phenotyping
Radioimmunoassay kits (Orion Diagnostica, Espoo, Finland) were
used for determination of serum collagen peptide concentrations
(biomarkers of collagen synthesis: PINP [aminoterminal propeptide
of type I procollagen] [reference range, 22–87 and 19–83 ng/mL in
men and women, respectively], PICP [C-terminal propeptide of pro-
collagen type I] [reference range, 69–163 ng/mL] was assayed using
ELISA [Quidel Corporation, Santa Clara], aminoterminal propeptide
of type III procollagen [PIIINP; reference range, 2.3–6.4 ng/mL];
biomarker of collagen degradation: ICTP [type 1 collagen telopep-
tide] [reference range, 3.2–3.5 ng/mL]) as previously reported19,20
with interassay variations <9.8%.

Statistical Analysis
All analyses were performed using SAS software 9.2 (SAS Institute,
Cary, NC). The 2-tailed significance level was set at 5%. The sample
size allowed to detect a difference 20.45 SD between groups with
80% power. The study being exploratory by nature, the overall error
rate was not adjusted for multiple testing, and results were appreci-
ated according to their consistency.
Between-group comparisons were performed using the non-
parametric Mann–Whitney test or the χ² test when appropriate.
Multivariate linear regressions were performed on LV mass (g, g/m²,
g/kg, g/height¹.³, and g/height².³), and E/E’. Only significant covariables from Table 1 (besides
AO, which may be forced) were selected using an interactive back-
ward stepwise method. Intercorrelated variables (eg, SBP, DBP, and
MAP) were tested separately in the models. Each biomarker was test-
ed individually in separate models. The conditions of validity of the
models (linearity, normality of residuals, homoscedasticity, absence
of interaction and colinearity, and impact of outliers) were thoroughly
checked for each model. The factors associated with diastolic dys-
function were identified using logistic regression. When the assump-
tion of linearity of the association between diastolic dysfunction and
continuous covariable could not be met, the factor was dichotomized
according to the Youden and closest to (0,1) criteria.21
The results are presented as mean±SD, regression coefficient,
or odds ratio (95% confidence interval). A confirmatory sensitivity
analysis was conducted on a subgroup of 50 patients with AO and 50
controls patients matched on age, sex, and mean BP according to their
propensity score, followed by a second analysis restricted to subjects
with BP <130/85 mm Hg (optimal or normal BP status according to
the 2013 European guidelines of Arterial Hypertension management).

Results
One hundred ninety-two subjects were recruited. Fifty-one
(40 AO) were excluded: 41 (29 AO) because of BP >140/90
mm Hg, 4 took antihypertensive therapy, and 6 were on thyroid
hormone medication (6 AO). One patient could not attend the
second visit. Therefore, our final study population included
140 subjects: 87 subjects in the AO group and 53 controls.

Anthropometric and Metabolic Characteristics
Systolic BP [122±11 versus 116±11 mm Hg; P=0.003]
and MAP (89±8 versus 86±7 mm Hg; P=0.022) were sig-
nificantly higher in subjects with AO (not DBP, 73±8 versus
71±6 mm Hg; P=0.23)—although being still normotensive—
along with a higher heart rate (P<0.0001). Leptin concentra-
tions were significantly higher in AO group than in controls
(24.8±18.6 versus 7.3±4.8 ng/mL; P<0.0001), and a trend
for adiponectin concentrations in AO (3.1±2.3 versus 3.9±2.6;
P=0.095; Table 1).

Cardiac and Arterial Characteristics
Subjects with AO displayed a LV remodeling as assessed by
a significant increase in LV mass (94±24 versus 84±21
g; P=0.034) without reaching LV hypertrophy23 and in CRI
(0.67±0.16 versus 0.60±0.10 g/mL; P=0.026) mainly because
of the increase in LV mass. A significant increase in aminoter-
mal propeptide of type I procollagen (P<0.0001) accompa-
nied by a decrease in type 1 collagen telopeptide (P<0.0001)
concentrations were observed in AO. C-terminal propeptide
of procollagen type I concentrations were higher in controls than in AO group (103±49 versus 87±52 ng/mL; P=0.001). In both groups LVEF was normal (P=0.85). In the AO group, E′ was significantly lower and E/E′ higher than that in controls (P<0.0001 and P=0.004, respectively; Table 2). Thirty-two patients with AO (38%) had diastolic dysfunction (grade I and II) compared with only 4% of controls. AO subjects with diastolic dysfunction compared with AO without diastolic dysfunction displayed a higher BP (DBP and MAP, P=0.002 and P=0.005, respectively, and a trend for SBP, P=0.077), waist circumference (P=0.028), and CRI (P=0.031; Table S1 in the online-only Data Supplement).

The 2 groups (AO versus controls) did not differ significantly in terms of arterial parameters (ie, PWV [P=0.26] and carotid IMT [P=0.33]). Only 4% of the total population presented significant intima–media thickening (defined as carotid IMT >0.90 mm), and no subject had arterial stiffness as defined by a PWV >12 m/s.22 There was no association between PWV or IMT on one hand and LV mass (LVM; scaled or not), CRI, and E′ on the other hand.

### Structural and Functional Determinants of Cardiac and Arterial Remodeling

In multivariate analysis, SBP (regression coefficient±SEM, 0.33±0.13; P=0.013) and MAP (0.43±0.20; P=0.030) were positively and independently associated with LVM (or scaled LVM as expressed in g/kg of fat-free mass or g/m^1.7, data not shown) and MAP (0.34±0.16; P=0.035) with CRI. In multivariate analysis, leptin concentrations were significantly associated with LV mass (−0.37±0.12, P=0.003) but not with CRI or diastolic dysfunction. Adiponectin concentrations were not found associated with LV mass, CRI, or diastolic dysfunction. AO was independently associated with CRI (6.26±2.29; P=0.007) and scaled LVM (g/m^1.7 and g/m^2.7, data not shown) but not with LV mass, which was found mainly associated with female sex and body surface area (Table 3).

In multivariate analysis, diastolic dysfunction was found positively and independently associated with PIINP concentrations above median (≥2.4 ng/mL; odds ratio [OR], 4.15 [1.42–12.2]; P=0.010), AO (OR, 13.3 [2.83–62.4]; P=0.001), and MAP ≥88 mm Hg (OR, 4.29 [1.57–11.7]; P=0.005; Table 4). In bivariate correlation analyses, waist circumference and waist/hip ratio were significantly associated with LV mass (r=0.52 and r=0.59; P<0.0001), CRI (r=0.37 and r=0.49; P<0.0001), and E′ wave (r=−0.46 and −0.31, respectively; P=0.0002).

Finally, considering the higher (although in the normal range) BPs in the AO group, a first sensitivity analysis was performed in a subgroup of 50 patients with AO and 50 control propensity score–matched patients (age, sex, and mean BP). Similar patterns were observed in this subgroup analysis, that is, higher LVM, CRI, and proportion of diastolic dysfunction, with however marginally significant differences (Tables S2 and S3). Multivariate analyses confirmed that (1)
AO was associated with LVM, CRI, and diastolic dysfunction (the latter assessed by E′), and (2) PIIINP was associated with diastolic dysfunction (data not shown). A further sensitivity analysis in subjects with optimal/normal BP status (47 controls and 62 patients with AO with SBP/DBP <130/85 mm Hg) showed that AO (5.18±2.30; \(P=0.027\)) remained associated with CRI whereas BP did not and confirmed the relationship between diastolic dysfunction on one hand and AO (OR, 26.6 [3.04–233]; \(P=0.003\)), PIIINP ≥2.4 ng/mL (OR, 5.96 [1.55–22.9]; \(P=0.01\)), and MAP ≥88 mm Hg (OR, 5.68 [1.62–19.9]; \(P=0.007\)) on the other hand.

**Discussion**

**Cardiac and Arterial Remodeling: Changes in Structure and Function**

The main and novel finding of our study is that in asymptomatic and normotensive healthy subjects with AO, cardiac remodeling (consisting of an increased LV mass) as well as features of cardiac concentric remodeling, which were associated with the AO, and diastolic dysfunction are detectable (the latter associated with increased collagen type III turnover). Importantly, we also examined the possible determinants of such early changes and found that, although in the normal range, BP was strongly associated with indices of cardiac remodeling and diastolic dysfunction in subjects with AO, suggesting a synergistic effect of AO amplifying the deleterious effects of BP.

To analyze the specific effect of AO, we have carefully selected healthy asymptomatic young adult subjects with no hypertension and no known cardiovascular disease. We have also excluded patients with morbid obesity.

Although in elderly patients and patients with hypertension LV hypertrophy,\(^5\) BP,\(^23\) and arterial stiffness\(^24\) are major factors leading to diastolic dysfunction and subsequently to HF with preserved EF, in our AO asymptomatic subjects, we could show that increased LV mass and diastolic dysfunction could be detected early, before LV hypertrophy, hypertension, and arterial stiffening can be diagnosed.
Furthermore, increased collagen type III turnover was observed in the study participants with diastolic dysfunction. We also investigated the relationship between LV geometric remodeling, LV function, and markers of myocardial collagen fibrosis indicating cardiac extracellular matrix remodeling. Irrespective of the study group, we were able to identify that collagen type III turnover was positively associated with diastolic dysfunction.

Our finding is novel but consistent with our previous report of increased PIIINP in asymptomatic obese subjects. In such subjects, we had previously reported that PIIINP was independently associated with insulin resistance, which is a common state in AO, and could contribute specifically to increase myocardial fibrosis. Our results further suggest that enhanced collagen type III turnover is associated with early diastolic dysfunction independently from the adipokine pathways (the latter associated with LVM but not with diastolic dysfunction). In our previous report, in obese healthy subjects, PIIINP and E/A ratio were significantly positively correlated. The transformation of the extracellular matrix into a more substantial collagen component potentiated by the increase in LV mass may alter ventricular filling, possibly contributing to the development of LV diastolic dysfunction in subjects with AO. Consistently in patients with hypertension, Martos et al showed that type I collagen telopeptide, C-terminal propeptide of procollagen type I, and PIIINP concentrations were showed that type 1 collagen telopeptide, C-terminal propeptide of procollagen type I, and PIIINP concentrations were significantly positively correlated. Irrespective of the study group, we were able to identify that collagen type III turnover was positively associated with diastolic dysfunction.

BP and AO as Therapeutic Targets to Prevent Adverse Cardiac Remodeling?

Subjects with AO had higher SBP and MAP than controls whereas remaining within the normal range and as such not currently eligible for an antihypertensive treatment. Systolic BP and MAP were positively associated with changes in cardiac structure (LV mass, scaled LV mass, and CRI). Furthermore, patients with MAP ≥88 mm Hg had a 4-fold increase in the rate of diastolic dysfunction. Interestingly, BP may be a predominant determinant of structural (LVM and CRI) and functional (diastolic dysfunction) cardiac changes only in high-normal and hypertensive (SBP/DBP ≥ 130/85 mm Hg) subjects with AO but not strictly in normotensive ones.

Although it has already been repeatedly demonstrated that hypertension, via LV hypertrophy and arterial stiffness, leads to diastolic dysfunction, this is the first instance, to our knowledge, demonstrating that BP within the normal range is shown as a determinant of diastolic dysfunction. Some studies highlighted that diastolic dysfunction could be associated with BP in normal range in general population but some were treated for hypertension. Law et al emphasized the key role of BP reduction in everyone to prevent cardiovascular diseases in the setting of the largest meta-analysis of randomized trials on hypertension management. Lowering SBP (by 10 mm Hg) or DBP (by 5 mm Hg) using any of the main classes of BP-lowering drugs reduced cardiovascular events (25% for HF) regardless of BP level before treatment. Furthermore, Julia et al (TROPHY [Trial of Preventing Hypertension] Study) described that subjects at high risk to develop hypertension may benefit from an early intervention to reduce BP by RAAS (renin–angiotensin–aldosterone system) blockers to decrease the risk of incident hypertension and its consequences. In TROPHY Study, subjects were similar to our present study: they were young (48.6±7.9 years old), overweight (body mass index, 29.9±5.1 kg/m²), and most displayed a BP in the high-normal category (SBP, 133.9±4.3 mm Hg; and DBP, 85.1±5.4 mm Hg).

Table 3. Factors Associated With Left Ventricular Mass and Cardiac Remodeling Index in Multivariate Analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>Regression Coefficient±SEM</th>
<th>P Value</th>
<th>Variance Explained, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVM, g</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AO (yes vs no)</td>
<td>−4.77±4.44</td>
<td>0.28</td>
<td>0.4</td>
</tr>
<tr>
<td>FS (yes vs no)</td>
<td>−12.15±4.62</td>
<td>0.010</td>
<td>2.3</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>56.4±12.2</td>
<td>&lt;0.0001</td>
<td>7.2</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>0.33±0.13</td>
<td>0.013</td>
<td>2.1</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>−0.37±0.12</td>
<td>0.003</td>
<td>3.2</td>
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<tr>
<td>CRI, 10⁻⁵ g/mL</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AO (yes vs no)</td>
<td>6.26±2.29</td>
<td>0.007</td>
<td>4.5</td>
</tr>
<tr>
<td>FG (yes vs no)</td>
<td>−11.26±2.45</td>
<td>&lt;0.0001</td>
<td>12.6</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>0.34±0.16</td>
<td>0.035</td>
<td>2.7</td>
</tr>
</tbody>
</table>

P values are from linear regression. AO indicates abdominal obesity; BSA, body surface area; CRI, cardiac remodeling index; FS, female sex; LVM, left ventricular mass; MAP, mean arterial pressure; and SBP, systolic blood pressure.

*Independence of other factors.

BP and AO as Therapeutic Targets to Prevent Adverse Cardiac Remodeling?

Subjects with AO had higher SBP and MAP than controls whereas remaining within the normal range and as such not currently eligible for an antihypertensive treatment. Systolic BP and MAP were positively associated with changes in cardiac structure (LV mass, scaled LV mass, and CRI). Furthermore, patients with MAP ≥88 mm Hg had a 4-fold increase in the rate of diastolic dysfunction. Interestingly, BP may be a predominant determinant of structural (LVM and CRI) and functional (diastolic dysfunction) cardiac changes only in high-normal and hypertensive (SBP/DBP ≥ 130/85 mm Hg) subjects with AO but not strictly in normotensive ones.

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Table 4. Factors Associated With Diastolic Dysfunction in Multivariate Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AO (yes vs no)</td>
<td>13.3 (2.83–66.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>PIIINP ≥2.4 ng/mL</td>
<td>4.15 (1.42–12.2)</td>
<td>0.010</td>
</tr>
<tr>
<td>MAP ≥88 mm Hg</td>
<td>4.29 (1.57–11.7)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

P values are from logistic regression. AO indicates abdominal obesity; CI, confidence interval; DD, diastolic dysfunction (E′ <10 cm/s); MAP, mean arterial pressure; OR, odds ratio; and PIIINP, aminoterminal propeptide of type III procollagen.
and angiotensin receptor blocker may decrease the incidence of HF prevention in subjects with AO. Accordingly, in a general population, a waist circumference reduction was found associated with a lower risk to develop hypertension.38

Study Limitations
Our study presents certain limitations. This study is a cross-sectional study, which prohibits from inferring a causative link. Our results may not apply to patients with morbidity, which were not included herein. There is no consensus for normalization of LV mass by different types of scaling (height, fat-free mass, body surface area, etc), and parameters used are different according to echocardiography or MRI methods. However, our findings on LV remodeling were consistent throughout the different definitions used for LV mass scaling. BP status of our patients was only analyzed by office BPs although several standardized measurements were performed at each given visit. Furthermore, we previously described thanks to an MRI substudy that there was no difference in aortic PWV between controls and patients with AO.36 We may hypothesize that arterial changes may not have occurred yet in the subjects we have investigated, who were young and normotensives. Circulating collagen peptides are not specific to cardiac tissue, but previous histological studies observed a significant correlation between collagen peptides serum concentrations and cardiac fibrosis. Circulating collagen peptides are therefore an acceptable surrogate to evaluate myocardial turnover as well as of enhanced collagen type III turnover associated with diastolic dysfunction without arterial changes. These alterations may help identifying subjects with AO at higher risk for developing HF with preserved EF and who could potentially benefit from early preventive interventions such as BP lowering, even in normotensive subjects, and weight loss.

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Disclosures
None.

References
Normal blood pressure and myocardial fibrosis in healthy, asymptomatic, nonhypertensive subjects with abdominal obesity were associated with cardiac remodeling. Subjects with abdominal obesity could potentially benefit from early preventive interventions, such as BP lowering, even in normotensive subjects, and weight loss.
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FEATURES OF CARDIAC REMODELING, ASSOCIATED WITH BLOOD PRESSURE AND FIBROSIS BIOMARKERS, ARE FREQUENT IN SUBJECTS WITH ABDOMINAL OBESITY

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**Supplemental Table S1.** Characteristics of AO subjects according to diastolic dysfunction

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tr>
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<td>n</td>
<td>m ± SD</td>
<td>n</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>32</td>
<td>19/13</td>
<td>52</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32</td>
<td>56 ± 5</td>
<td>52</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32</td>
<td>31.9 ± 3.0</td>
<td>52</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>32</td>
<td>2.10 ± 0.16</td>
<td>52</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>32</td>
<td>105 ± 7</td>
<td>52</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>32</td>
<td>0.97 ± 0.08</td>
<td>52</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>32</td>
<td>124 ± 10</td>
<td>52</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>32</td>
<td>75 ± 8</td>
<td>52</td>
</tr>
<tr>
<td>Mean AP (mmHg)</td>
<td>32</td>
<td>92 ± 7</td>
<td>52</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>32</td>
<td>69 ± 10</td>
<td>52</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>32</td>
<td>2.24 ± 1.86</td>
<td>52</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>32</td>
<td>5.92 ± 1.07</td>
<td>52</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>32</td>
<td>1.34 ± 0.38</td>
<td>52</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>32</td>
<td>3.58 ± 0.96</td>
<td>52</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>32</td>
<td>20.0 ± 15.6</td>
<td>52</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>32</td>
<td>2.7 ± 2.0</td>
<td>52</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>30</td>
<td>5.20 ± 0.67</td>
<td>50</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)</td>
<td>31</td>
<td>5.8 ± 0.4</td>
<td>50</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>32</td>
<td>5.4 ± 8.3</td>
<td>52</td>
</tr>
<tr>
<td>Protidemia (g/l)</td>
<td>32</td>
<td>73 ± 5</td>
<td>51</td>
</tr>
<tr>
<td>Parameter</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>e-GFR (ml/min/1.73m²)</td>
<td>32 77 ± 10</td>
<td>52 75 ± 11</td>
<td>0.18</td>
</tr>
<tr>
<td>PINP (ng/ml)</td>
<td>32 37 ± 13</td>
<td>52 32 ± 16</td>
<td>0.059</td>
</tr>
<tr>
<td>PICP (ng/ml)</td>
<td>32 87 ± 52</td>
<td>52 85 ± 53</td>
<td>0.68</td>
</tr>
<tr>
<td>PIINP (ng/ml)</td>
<td>28 2.7 ± 1.1</td>
<td>50 2.4 ± 1.5</td>
<td>0.19</td>
</tr>
<tr>
<td>ICTP (ng/ml)</td>
<td>31 3.7 ± 1.2</td>
<td>52 3.8 ± 0.8</td>
<td>0.16</td>
</tr>
<tr>
<td>LVM (g) †</td>
<td>26 101 ± 28</td>
<td>44 89 ± 20</td>
<td>0.085</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>26 47 ± 11</td>
<td>44 44 ± 8</td>
<td>0.20</td>
</tr>
<tr>
<td>LVM/FFM (Palmieri, g/kg)</td>
<td>26 1.73 ± 0.29</td>
<td>44 1.78 ± 0.25</td>
<td>0.77</td>
</tr>
<tr>
<td>LVM (Chirinos, g/m³)</td>
<td>26 40.8 ± 9.0</td>
<td>44 37.8 ± 6.6</td>
<td>0.17</td>
</tr>
<tr>
<td>LVM (De Simone, g/m²³)</td>
<td>26 24.1 ± 4.6</td>
<td>44 22.9 ± 3.7</td>
<td>0.28</td>
</tr>
<tr>
<td>LVEF (%)†</td>
<td>26 58 ± 6</td>
<td>44 61 ± 7</td>
<td>0.018</td>
</tr>
<tr>
<td>LVEDV (ml) †</td>
<td>26 138 ± 30</td>
<td>44 142 ± 29</td>
<td>0.82</td>
</tr>
<tr>
<td>LVESV (ml) †</td>
<td>26 59 ± 17</td>
<td>44 57 ± 22</td>
<td>0.24</td>
</tr>
<tr>
<td>LVEV (ml) †</td>
<td>26 79 ± 16</td>
<td>44 85 ± 12</td>
<td>0.097</td>
</tr>
<tr>
<td>CO (LVEV x HR, l/min)</td>
<td>26 5.70 ± 1.24</td>
<td>44 5.96 ± 1.15</td>
<td>0.32</td>
</tr>
<tr>
<td>CRI (LVM/LVEDV, g/ml)</td>
<td>26 0.74 ± 0.19</td>
<td>44 0.64 ± 0.12</td>
<td>0.031</td>
</tr>
<tr>
<td>E (cm/s) ‡</td>
<td>32 58 ± 12</td>
<td>52 74 ± 17</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>A (cm/s) ‡</td>
<td>32 59 ± 10</td>
<td>52 61 ± 15</td>
<td>0.91</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>32 1.02 ± 0.26</td>
<td>52 1.26 ± 0.30</td>
<td>0.0009</td>
</tr>
<tr>
<td>E' (cm/s) ‡</td>
<td>32 8.6 ± 0.9</td>
<td>52 12.4 ± 1.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>A' (cm/s) ‡</td>
<td>32 11.3 ± 3.0</td>
<td>52 10.7 ± 2.5</td>
<td>0.35</td>
</tr>
<tr>
<td>E/E' ratio</td>
<td>32 6.9 ± 1.6</td>
<td>52 6.1 ± 1.5</td>
<td>0.027</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>24 8.0 ± 1.6</td>
<td>43 7.4 ± 1.0</td>
<td>0.25</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>26 0.66 ± 0.14</td>
<td>44 0.62 ± 0.14</td>
<td>0.16</td>
</tr>
</tbody>
</table>
AP: arterial pressure, BMI: body mass index, BP: blood pressure, CO: cardiac output, CRI: cardiac remodeling index, eGFR: estimated glomerular filtration rate (Modification in Diet Renal Disease 4-variable formula), F: female, FFM: fat-free mass (assessed using DEXA), HDL: high density lipoprotein, ICTP: type I collagen telopeptide, IMT: intima-media thickness, LDL: low density lipoprotein, LVEDV: LV end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: LV end-systolic volume, LVEF: LV ejection volume, LVM: left ventricular mass, M: male, LVM FFM: LVM indexed by fat free mass, LVMi: LVM indexed by BSA (Boyd), LVMheight\(^{1.7}\): LVM indexed by height\(^{1.7}\), LVMheight\(^{2.7}\): LVM indexed by height\(^{2.7}\), MBP: mean blood pressure, M: male, MDRD: Modification in Diet Renal Disease, PICP: carboxyterminal propeptide of type I procollagen, PINP: aminoterminal propeptide of type I procollagen, PIIINP: aminoterminal propeptide of type III procollagen, PWV: pulse wave velocity, SBP: systolic blood pressure.

* p-values from the Mann-Whitney or Chi-Squared test as appropriate.
† Assessed by cardiac magnetic resonance imaging
‡ Assessed by transthoracic echocardiography
Supplemental Table S2. Anthropometric and metabolic characteristics of the study population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Abdominal obesity</th>
<th>Matched controls</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50 53.7 ± 6.2</td>
<td>50 53.9 ± 5.9</td>
<td>0.98</td>
</tr>
<tr>
<td>Female gender</td>
<td>50 29 (58%)</td>
<td>50 28 (56%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>50 53.0 ± 10.6</td>
<td>50 47.4 ± 8.8</td>
<td>0.005</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>50 118 ± 10</td>
<td>50 116 ± 11</td>
<td>0.61</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>50 71 ± 7</td>
<td>50 72 ± 6</td>
<td>0.65</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>50 87 ± 7</td>
<td>50 87 ± 7</td>
<td>0.88</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>50 26.55 ± 18.43</td>
<td>50 7.22 ± 4.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>50 3.44 ± 2.32</td>
<td>50 3.73 ± 2.49</td>
<td>0.64</td>
</tr>
</tbody>
</table>

BMI: body mass index, CRP: C reactive protein, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, F: female, HDL: High-density lipoprotein, HR: heart rate, bpm: beats per minute, LDL: Low density lipoprotein, M: male, MBP: mean blood pressure, MDRD: Modification in Diet Renal Disease, SBP: systolic blood pressure.

* p-values from the Mann-Whitney or Chi-Squared test as appropriated.
### Cardiac and arterial characteristics of the study population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Abdominal obesity (AO)</th>
<th>Control group</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>PINP (ng/ml) 50</td>
<td>35.0 ± 16.7</td>
<td>22.1 ± 14.5</td>
<td>0.0003</td>
</tr>
<tr>
<td>PICP (ng/ml) 50</td>
<td>91 ± 63</td>
<td>103 ± 49</td>
<td>0.007</td>
</tr>
<tr>
<td>PIIINP (ng/ml) 45</td>
<td>2.43 ± 1.48</td>
<td>3.33 ± 6.84</td>
<td>0.27</td>
</tr>
<tr>
<td>ICTP (ng/ml) 50</td>
<td>3.80 ± 0.97</td>
<td>4.53 ± 0.86</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVM (g) † 42</td>
<td>92 ± 23</td>
<td>84 ± 22</td>
<td>0.096</td>
</tr>
<tr>
<td>LVM (g/height(^\text{2.7})) 42</td>
<td>23.3 ± 3.7</td>
<td>20.7 ± 4.2</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEDV (ml) † 42</td>
<td>141 ± 31</td>
<td>140 ± 26</td>
<td>0.81</td>
</tr>
<tr>
<td>CRI = LVM/LVEDV (g/ml) 42</td>
<td>0.66 ± 0.15</td>
<td>0.60 ± 0.11</td>
<td>0.14</td>
</tr>
<tr>
<td>Diastolic dysfunction (E’ &lt; 10 m/s)</td>
<td>50 (34%)</td>
<td>49 (4%)</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

CO: cardiac output, CRI: cardiac remodeling index, ICTP: type 1 collagen telopeptide, IMT: intima-media thickness, LVEDV: LV end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: LV end-systolic volume, LVEV: LV ejection volume, LVM: left ventricular mass, M: male, LVM FFM: LVM indexed by fat free mass, LVMi: LVM indexed by BSA (Boyd), LVM\(_\text{height}^{2.7}\): LVM indexed by height\(^2.7\), LVM\(_\text{height}^{2.7}\): LVM indexed by height\(^{2.7}\), MBP: mean blood pressure, MDRD: Modification in Diet Renal Disease, PICP: carboxyterminal propeptide of type I procollagen, PINP: aminoterminal propeptide of type I procollagen, PIIINP: aminoterminal propeptide of type III procollagen, PWV: pulse wave velocity, SBP: systolic blood pressure, * p-values from the Mann-Whitney test. † Assessed by cardiac magnetic resonance imaging ‡ Assessed by transthoracic echocardiography.