Effects of Catecholamine Stress on Diastolic Function and Myocardial Energetics in Obesity

Running title: Rider et al.; Myocardial energetics and diastolic function in obesity

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Abstract:

**Background** - Obesity is characterized by impaired cardiac energetics that may play a role in the development of diastolic dysfunction and inappropriate shortness of breath. We assessed whether, in obesity, derangement of energetics and diastolic function is further altered during acute cardiac stress.

**Methods and Results** - Normal weight (BMI 22 ± 2; n = 9-17) and obese subjects (BMI 39 ± 7; n=17-46) underwent assessment of diastolic LV function (cine-MRI volume-time curve analysis) and cardiac energetics (PCr/ATP ratio; 31P-MR spectroscopy) at rest and during dobutamine stress (heart rate increase 65 ± 22 and 69 ± 14%, respectively, p = 0.61). At rest, obesity was associated with a 22% lower peak filling rate (PFR) (p<0.001) and a 15% lower PCr/ATP ratio (1.73 ± 0.40 vs 2.03 ± 0.28, p=0.048). PFR correlated with fat mass, LV mass, leptin, waist-hip ratio and with PCr/ATP ratio. On multivariable analysis, PCr/ATP was the only independent predictor of PFR (β=0.50, p=0.03). During stress, a further reduction in PCr/ATP occurred in obesity (from 1.73 ± 0.40 to 1.53 ± 0.50, p=0.03) but not in normals (from 1.98 ± 0.24 to 2.04 ± 0.34, p = 0.50). For similar levels of inotropic stress, there were smaller increases in PFR in obesity (38% vs 70%, p=0.01).

**Conclusions** - In obesity, cardiac energetics are further deranged during inotropic stress, in association with continued diastolic dysfunction. Myocardial energetics may play a key role in the impairment of diastolic function in obesity.

**Key words:** Diastolic Dysfunction, Dobutamine Stress MRI, Magnetic Resonance Spectroscopy Diagnosis, Obesity
**Introduction**

Asymptomatic diastolic dysfunction is a condition associated with future heart failure. Obesity, both with and without additional co-morbidities, has been linked to diastolic dysfunction across a wide range of non-invasive imaging modalities. Despite this, and the recent evidence that increased body-mass index is associated with worse diastolic function independent of left ventricular (LV) mass, the mechanisms behind diastolic dysfunction in obesity are unknown.

It is generally accepted that myocardial relaxation is largely determined by a combination of both active (calcium homeostasis, myocardial energetics) and passive processes related to the physical properties of the left ventricle (intrinsic mechanical stiffness as determined by wall thickness and chamber geometry). No studies to date have been able to investigate both active and passive elements of relaxation in obesity.

Through the study of diastolic function in obese subjects free of cardiovascular risk factors, the effects of obesity per se on diastolic function can be separated from the confounding effects of obesity-related co-morbidities (e.g. hypertension and diabetes), which have well-documented independent effects on lusitropy.

Cardiovascular magnetic resonance (CMR) imaging, in combination with $^{31}$P-MR spectroscopy, allows the non-invasive *in vivo* study of left ventricular geometry and function as well as of cardiac high-energy phosphate metabolism, enabling interrogation of both active and passive mechanisms of diastolic dysfunction. CMR is not dependant on the generation of an adequate acoustic window nor the orientation of the heart within the chest, allowing reproducible imaging irrespective of body habitus and degree of chest wall fat, a major advantage in the setting of obesity. With the addition of serum markers of obesity, which have been linked to diastolic function (leptin, free fatty acid levels), and quantification of abdominal visceral fat and...
total body adiposity, this study aimed to investigate the determinants of resting diastolic
dysfunction in obesity.

Furthermore, as many obese subjects with normal left ventricular systolic and respiratory
function experience activity-limiting breathlessness during exercise, the study of diastole in the
resting state is not in itself adequate to fully characterize the effects of obesity on diastole. If
altered high energy phosphate metabolism is playing a role in the pathogenesis of diastolic
dysfunction, we hypothesized that any energetic deficit observed in this population at rest would
be exacerbated during stress, limiting myocardial energetic reserve and further limiting lusitropic
reserve. This would provide a plausible explanation for the seemingly disproportionate
breathlessness observed in obesity during exercise.

To investigate this, we recorded both myocardial high-energy phosphate metabolism and
diastolic function during simulated exercise in the form of dobutamine stress in obese and
normal weight subjects.

Methods

Ethics and Study Cohort

A total of sixty-four healthy subjects (46 obese, male 11, BMI > 30kg/m² and 18 normal weight
controls, 5 male; BMI 18.5-24.9 kg/m²) were included (Table 1). The study was approved by the
local ethics committee, and informed written consent was obtained from each patient.

All subjects were screened for identifiable cardiac risk factors and obesity-related co-
morbidities. Subjects were excluded if they had a history of; any cardiovascular disease, chest
pain, tobacco smoking, hypertension, peripheral vascular disease, contraindications to MR
imaging, diabetes (fasting glucose level ≥ 6.7 mmol), a fasting total cholesterol level ≥ 6.5
mmol/l, use of any prescription medications or a history compatible with obstructive sleep apnoea. All subjects had a normal 12 lead electrocardiogram, normal cardiovascular examination, normal global and regional resting cardiac function on MR imaging, and did not perform more than three sessions (defined as 30 minutes) of sweat-producing exercise per week.

**Blood tests**

Fasting blood tests for glucose, triglycerides, cholesterol, leptin, insulin and free fatty acids were taken on the day of the scanning and analysed as described\(^5\). An estimate of insulin resistance was calculated using the HOMA-IR equation (fasting insulin (\(\mu U/ml\)) x fasting glucose (mmol/l))/22.5).

**Baseline Diastolic Functional Imaging**

All 18 normal weight (average BMI 22 ± 2) and all 46 obese subjects (average BMI 39 ± 7) underwent diastolic functional imaging at rest.

All CMR scans for the assessment of LV diastolic function at rest were performed on a 1.5 Tesla MR system (Siemens, Germany). Images for ventricular volumes and diastolic function were acquired using a steady state free precession (SSFP) sequence with an echo time (TE) of 1.5ms, a repetition time (TR) of 3.0ms, in plane resolution 1.5 x 1.5 mm\(^2\), temporal resolution 33.74 ms and a flip angle of 60° as previously described\(^{13}\). All imaging was performed supine, was prospectively cardiac gated and acquired during end-expiratory breathhold.

**Diastolic Function Analysis**

Analysis for left ventricular volumes was performed using Siemens analytical software (ARGUS©). From manually contoured short axis slices from base to apex, and across the cardiac cycle, volume-time curves were generated. Diastolic peak filling rate (PFR) was normalized to end-diastolic volume (EDV), as previously described.\(^5\)
Baseline $^{31}$P Magnetic Resonance Spectroscopy

Baseline resting $^{31}$P MRS was performed in 10 normal weight and 17 obese subjects. Cardiac high-energy phosphate metabolism was measured using $^{31}$P MRS on a 3-Tesla system, (Siemens Medical Solutions, Erlangen, Germany), with the subject in the prone position, to position the heart as close to the surface coil as possible. All data was acquired with a commercially available 1.5T $^{31}$P/$^1$H surface coil, (Siemens Medical Solutions, Erlangen, Germany) tuned to 3T. After piloting along the short axis, horizontal and vertical long axis of the heart, a $^{31}$P-3D acquisition weighted chemical shift imaging (CSI) spectral data set was acquired with dimensions of 240 x 240 x 200 mm. A matrix size of 12 x 8 x 8 (zero filled to 16 x 16 x 8) was used. Hence, the spatial resolution was 20 x 30 x 25 mm$^3$ (12ml) interpolated to 15 x 15 x 25 mm$^3$ (5.6ml). $^{31}$P spectra were acquired with a TE 2.3 ms, flip angle 37°, with 10 averages at the centre of k-space and Nuclear Overhauser Enhancement (NOE flip angle 180°) as previously described 14.

$^{31}$P Magnetic Resonance Spectroscopy Analysis

Analysis of the spectra was performed in jMRUI v2.2 (2005) limited to a single voxel in the basal septum to avoid blood contamination. This voxel was selected by consensus of two experienced observers using FLASH images as previously described14. Spectra were Fourier-transformed, and a 20-Hz line broadening was applied. Spectra were fitted using an in house fitting program within jMRUI. After fitting, the spectra were corrected for saturation and for blood contamination according to the 2,3-diphosphoglycerate (2,3-DPG) peak, and the PCr/ATP ratio was determined.15 As dobutamine stress produces an inherent increase in heart rate during the period of spectral acquisition, non-ECG gated spectra were acquired to remove the influence of variable TR and its subsequent effect on the PCr/ATP ratio. The repetition time was fixed at 1.0s, resulting in a total acquisition time of 8 minutes 29 seconds, as previously described14.
Body Composition analysis

Bio-Impedance analysis

Bio-electrical impedance was used to determine total body fat mass, and lean body mass using Bodystat ©1500 analyser. The use of bioimpedance analysis has become routine in clinical research investigating body composition analysis. Although not the gold standard for analysis of body composition, it has been shown to have close correlation with DEXA assessments in multiple studies.

Visceral fat mass

A single breathold, contiguous 5 slice, T1 weighted Turbo Spin Echo sequence centred around the vertebral body of L5 (turbo factor 5, echo time TE 12ms, TR 200ms, slice thickness 10mm) was modified so that the sequence served to predominantly suppress the water signal. Transverse slices were then manually contoured to provide a visceral fat volume.

Dobutamine Stress Studies

Dobutamine Infusion Protocol

After the resting 3D-CSI $^{31}$P spectra (3T) and resting short axis stack (1.5T) were acquired, dobutamine was infused intravenously at incremental rates between 5ug/kg and 40 ug/kg with a target of 65% of age maximal heart rate. During this time, blood pressure was measured every minute. Heart rate, blood pressure, pulse oximetry and cardiac electrograph complex morphology were also monitored continuously during both of the dobutamine infusion studies. Heart rate was then maintained at target for the duration of the scans (8 minutes 29 seconds for $^{31}$P MRS, 5 minutes for short axis imaging).

Diastolic Function during Dobutamine Stress

12 normal weight subjects and 21 obese subjects underwent assessment of both diastolic function
at rest and during dobutamine stress. During the period of time where “steady state” target heart rate was reached, a short axis stack (FISP) was also acquired as described above. After the scan acquisition at stress, the dobutamine infusion was then discontinued. The SSFP sequence (temporal resolution 33.74 ms) allowed acquisition of around 30 images per cardiac cycle at rest (given a heart rate of 60 beats per minute) and around 20 images at stress (given a heart rate of 100 beats per minutes). Analysis of stress diastolic function was performed as described above.

31P Magnetic Resonance Spectroscopy during Dobutamine Stress Studies

9 of the normal weight subjects and 17 of the obese subjects underwent assessment of myocardial energetics during dobutamine stress.

Statistical Analysis

All statistical analyses were performed using SPSS statistical software (version 17.0; SPSS Inc., Chicago, Ill., USA). Data were presented as mean ± standard deviation. All data was assessed for normal distribution using the Kolmogorov-Smirnov test. Normally distributed datasets were analysed using the Student’s t test, paired t-test were used to compare values during rest versus stress studies, non-normally distributed data sets were analysed using Wilcoxon signed ranks test. Non- Significance was assumed at a probability value of P < 0.05 (two tailed). Predictors of peak filling rate were determined with forced entry multivariable regression analysis.

Power Calculation

As PCr/ATP ratio would not increase during dobutamine infusion power calculations were performed assuming one tailed t-test analysis. Using pilot data, a priori calculation based on a PCr/ATP ratio (mean PCr/ATP 1.82, SD = 0.24, mean different 10% (0.182) alpha = 0.05) powered the study to detect a 10% drop in PCr/ATP ratio during cardiac stress in the obese cohort with 17 subjects.
Results

The Effects of Obesity on Cardiac Function and Energetics

The two groups were well matched for age (normal weight 43 ± 10 vs obese 44 ± 7yrs, p=0.6), height (normal weight 1.68 ± 0.06 vs obese 1.69 ± 0.08 m, p=0.6), systolic blood pressure and fasting total cholesterol (Table 1). Obese subjects were on average 44kg heavier than the normal weight subjects. Although fasting glucose was statistically higher in the obese cohort, glucose measurements were well within the normal adult range (5.2 ± 0.6 mmol/l). Fasting free fatty acid levels were also higher in the obese cohort. Diastolic blood pressure was statistically higher in the obese cohort although within the normal range (75 ± 8 mmHg, Table 1).

Diastolic Function

As expected, obesity was associated with a 22% reduction in peak diastolic filling rate when compared to lean age and sex matched controls (p<0.001, Table 2).

Myocardial Energetics

Obesity was associated with a 15% reduction in the myocardial PCr/ATP ratio when compared to normal weight subjects (Obese 1.73 ± 0.40 vs Normal 2.03 ± 0.28, p<0.05). Furthermore, the PCr/ATP ratio was negatively correlated with HOMA (r = 0.23, p =0.02) and LV mass indexed to height^2.7 on linear regression analysis (r = 0.44, p = 0.03).

Determinants of Peak Diastolic Filling Rate in Obesity at Rest

Because of the number of independent variables involved, we adopted a model-building strategy to assess the potential association between the above variables and LV peak diastolic filling rate. Hence, we first performed a simple regression analysis to examine associations between the baseline variables. On simple linear regression, diastolic peak filling rate was negatively correlated with waist: hip ratio, total fat mass (kg), serum leptin (ng/l), LV mass indexed to
height\(^2\), LV end-diastolic volume (ml) and positively correlated with myocardial PCr/ATP ratio (Table 3, Figure 1). Variables with P<0.05 and the strongest relationship with peak filling rate were then included in the multiple linear regression by a stepwise selection method to assess the "best" subset in predicting diastolic filling. The strongest stepwise multivariable model consisted of maximal diastolic filling rate as the dependent variable and total fat mass, PCr/ATP ratio, waist: hip ratio and serum leptin level as independent variables. Multivariable analysis of the peak diastolic filling rate revealed the PCr/ATP ratio (\(\beta= 0.92, p = 0.03\)) as a predictor of peak diastolic filling rate (overall R\(^2\) of the model = 0.40, p=0.02).

**Effects of Dobutamine Stress in Obesity**

**Systolic and Diastolic Function**

The effect of dobutamine stress on systolic and diastolic function is summarized in Table 4. Both groups underwent similar levels of inotropic stress with a similar percentage increase in heart rate (Obese, + 63 ± 16% increase vs. Normal Weight, + 67 ± 28 %; \(p= 0.61\)). During peak stress, left ventricular ejection fraction increase was similar between normal weight and obese subjects (LVEF increase during stress obese + 11%, normal weight +11% \(p= 0.92\)).

As would be expected from the action of dobutamine, in normal weight subjects, with an increase in heart rate of 65% during stress (from 61 ± 7 to 102 ± 15 bpm), there was a 70% increase in maximal peak diastolic filling rate (individual absolute and normalized filling rates are shown in Figure 2). In contrast, in obese subjects, a 63% increase in heart rate (from 64 ± 9 to 105 ± 9) resulted in a significantly lower 38% increase in normalized peak filling rate (\(p=0.01\), Table 4). In addition absolute peak filling rate was similar at rest and during stress (Figure 2, Table 4).

To examine the relationship between heart rate increase and maximal diastolic filling
rate, linear regression analysis was undertaken, with percentage increase in diastolic filling rate as the dependant variable and percentage increase in heart rate as the independent variable. In the normal weight group, percentage increase in heart rate was highly predictive of maximal diastolic filling rate ($r = 0.75$, $p<0.001$). In contrast to this, the obese cohort during catecholamine stress percentage increase in heart rate was not predictive of maximal diastolic filling rate ($r = 0.25$, $p = 0.28$, Figure 3B & 3C).

**Myocardial Energetics**

In agreement with previous studies, during moderate catecholamine stress, there was no significant change in the PCr/ATP ratio in normal weight subjects (PCr/ATP rest $1.98 \pm 0.24$ vs $2.03 \pm 0.34$ at stress, $p=0.50$). In contrast, during dobutamine infusion there was a significant, further 12% reduction in myocardial PCr/ATP ratio in the obese group (rest $1.73 \pm 0.40$ vs stress $1.53 \pm 0.50$, $p=0.03$, Figure 4A), which was already reduced at rest. In addition, the change in PCr/ATP ratio occurring between rest and stress was also significantly different for obese and normal weight individuals (normal, $+0.06 \pm 0.27$ vs obese $-0.20 \pm 0.34$, $p < 0.05$). Examples of $^{31}$P MR spectra at rest and during stress in an obese subject are shown in Figure 4B.

**Discussion**

Diastolic dysfunction is linked to increased mortality and is a well recognized consequence of obesity, both in the presence and absence of additional cardiovascular risk factors. In this study, we have utilised CMR, with both functional imaging and $^{31}$P spectroscopy, to study obese subjects free of comorbidities. Thus, we investigated the effects of obesity per se on both active and passive mechanisms of diastolic function. We have shown that, in obesity, diastolic function is correlated to fat mass, serum leptin, waist: hip ratio, left ventricular mass, left ventricular end-
diastolic volume and with myocardial energetics, and that the myocardial PCr/ATP ratio is, in
addition, a predictor of diastolic function. In addition, we provide evidence that during
catecholamine stress, the myocardial energy deficit seen at rest in obesity is worsened,
unmasking further diastolic dysfunction.

**Altered Energetics and Diastolic Function in Obesity**

Left ventricular hypertrophy, elevated left ventricular mass and elevated end-diastolic volume
represent an adaptation to the expanded intravascular volume present in obesity.

Hypertrophy is thought to cause diastolic dysfunction not only via a mechanical change in the
stiffness of the ventricle but also via reduced myocardial energetics. In support of this, we have
not only shown that left ventricular mass is predictive of diastolic function on linear regression,
but also that the PCr/ATP ratio is a predictor of diastolic function, and is correlated with insulin
resistance and LV mass. Although no direct proof of cause-and-effect, these findings suggest that
impaired energy metabolism contributes to diastolic dysfunction in obesity and may be related to
insulin resistance.

The myocardial PCr/ATP ratio itself is a sensitive index of the energetic state of the heart
The PCr/ATP ratio is decreased in heart failure, correlates with indices of both systolic and
diastolic left ventricular function and with functional heart failure class, and is a better long
term prognostic indicator than left ventricular ejection fraction. Patients with dilated
cardiomyopathy, hypertension, diabetes and valvular heart disease have all been shown
to have significantly lower myocardial PCr/ATP ratios, suggesting that abnormal cardiac energy
metabolism is a uniform phenomenon in the hypertrophied and/or failing heart.

There is now a wealth of data that points to diastole being a highly regulated, highly
active process. In view of this, abnormalities of myocardial high-energy phosphate metabolism
may also account for changes in diastolic stiffness. The association between reduced myocardial energetics and diastolic dysfunction has been shown in multiple studies \(^7\),\(^26\). This is in line with the concept that an impairment in high-energy phosphate metabolism initially affects the ability of the sarcoplasmic reticular Ca\(^{2+}\) ATPase (SERCA), the energetically most demanding of all enzymes involved in contractile function \(^27\), to lower cytosolic Ca\(^{2+}\) and thus impairs diastolic function.

So far, the vast majority of data supporting an impairment in myocardial energetics in obesity comes from animal models \(^12\),\(^28\) with only one prior study showing reduced resting myocardial energetics in human male obesity \(^29\). Here, we confirm that the myocardial PCr/ATP ratio is reduced in obesity but also show that it is correlated to insulin resistance and is a predictor of peak filling rate.

The most likely mechanism for impaired energetics at rest in obesity is a loss of the total creatine pool, in proportion to the loss of PCr, as occurs in many other forms of hypertrophy \(^18\). Elevated free fatty acids, which are reported in obesity and also observed in this study, might be an additional mechanism. Elevations in free fatty acid levels are thought to increase mitochondrial uncoupling via increased myocardial uncoupling protein 3 (UCP3) expression \(^30\). This would then lead to a mechanism by which reduced high energy phosphate levels, caused by increased mitochondrial uncoupling as a result of elevated free fatty acid levels, may manifest as diastolic dysfunction. In this obese cohort, myocardial energetics were reduced, free fatty acid levels elevated, and diastolic dysfunction was evident. However, there was no statistically significant relationship between PCr/ATP ratio and serum free fatty acid levels in our obese cohort, either and larger studies would be needed to explore these associations in greater detail.

**Catecholamine Stress Exacerbates Energetic and Functional Derangement in Obesity**
Cardiac $^{31}$P MRS stress testing has previously shown that an energetic deficit of the heart can be exacerbated or unmasked during inotropic stimulation in patients with LV hypertrophy due to hypertension $^{10}$.

In the normal heart, dobutamine primarily increases heart rate via β-adrenergic stimulation. $^{31}$ This causes increases in cAMP which in turn phosphorylate phospholamban relieving its inhibition on SERCA, increasing relaxation rate via increasing the rate of Ca$^{2+}$ uptake. $^{32}$ Thus, it would be predicted that diastolic filling rate is linearly related to heart rate. Indeed, in the normal weight group heart rate increase was closely correlated with diastolic filling rate increase (Figure 3B). In contrast to this, in the obese cohort, there was no correlation between the increase in heart rate and the increase in diastolic filling rate ($R = -0.25$, $p = 0.28$). This loss of the correlation between heart rate and diastolic function in obesity has not been described before.

Although the heart rate recorded at stress was similar to in obese and normals, the peak relaxation rate and percentage increase in relaxation rate during stress were significantly lower in obesity, suggesting that impairment of diastolic function at rest is not resolved during stress. The reasons for this remain to be fully investigated, but our study suggests that altered myocardial energetics are at least a contributing mechanism.

The normal human myocardium is well adapted to inotropic stimulation and the energetic requirements of the heart are adequately provided for by oxidative phosphorylation at all but the highest levels of physiological stress. $^{10,33}$ Our study confirms that moderate catecholamine stress has no significant effect on myocardial PCr/ATP ratios in normal weight individuals. However, we demonstrate, for the first time, that catecholamine stress further exacerbates the energetic deficit in obesity.
In our study, the worsening of cardiac energetics during stress in obesity was accompanied by a lesser augmentation of lusitropic function. Furthermore, across the whole group PCr/ATP ratio recorded at stress was strongly correlated with both absolute and normalized LV peak filling rate. Therefore, it is likely that myocardial energetics are at least one pathophysiological mechanism behind this further derangement of myocardial relaxation.

With a reduction in PCr/ATP during stress, the energy requirements of SERCA-driven Ca\(^{2+}\) movement into the sarcoplasmic reticulum would be further impaired, resulting in reduced removal of cytosolic Ca\(^{2+}\) and a reduced ventricular relaxation rate. Given the greater susceptibility of diastole to energetic depletion, it is unsurprising that systolic function remained unaltered.

In contrast to the changes at rest, the further drop in PCr/ATP with stress is not related to a change in the total creatine pool, which cannot decrease rapidly during stress. Instead, it is likely that the acute decrease in PCr/ATP ratio is explained by one of two mechanisms that affect mitochondrial oxidative phosphorylation. Firstly, there is evidence for an intrinsic metabolic defect in mitochondrial function in obesity, with animal models showing reduced skeletal muscle oxidative capacity, and a reduction of electron transport chain activity in obesity.\(^{34,35}\) The second possible explanation is an inadequate blood supply during stress, as a result of the combination of both left ventricular hypertrophy, known to be present in this cohort, and microvascular dysfunction. Further studies employing quantitative myocardial perfusion imaging and oxygenation imaging (BOLD) are needed to determine whether blood supply limitation is the mechanism upstream of these changes.

**Limitations**

Despite the increased signal to noise that measuring \(^{31}\)P magnetic resonance spectroscopy at 3.0T
affords, measurements taken during dobutamine stress remain noisy with relatively high
measurement variability. As such, this method, although providing a means to test for group
differences in a research study, remains unsuitable for the reliable assessment of stress energetics
on an individual subject basis.

Although obstructive sleep apnoea was excluded via questionnaire, formal sleep studies
were not performed.

This protocol utilized pharmacological stress rather than physiological exercise. Although
not a direct physiological reproduction of exercise, this technique avoided MR motion artefacts
induced by an exercise protocol, thus allowing for accurate measurement of cardiac function in
obese patients under stress.

A comprehensive evaluation of the coronary arteries in the form of angiography was not
undertaken for ethical reasons. In view of this, although no symptoms or regional wall motion
abnormalities occurred during the dobutamine stress examination, and there was no history of
coronary artery disease or chest pain, coronary artery ischaemia was not formally excluded as the
cause of decreased energetic, although its presence is most unlikely.

Although assessment of diastolic function with CMR in the setting of obesity has
significant advantages, allowing reproducible imaging irrespective of body habitus and degree of
chest wall fat, the temporal resolution (33.74ms) is significantly slower than echo Doppler
techniques which would allow further characterization of diastolic function.

Conclusions

Obesity, in the absence of cardiovascular risk factors, is characterized by altered high energy
phosphate metabolism, left ventricular hypertrophy and by diastolic dysfunction. In obese, but
not in normal weight controls, inotropic stimulation results in a further derangement in both myocardial energetics and myocardial relaxation. These findings suggest a mechanism for obesity-related shortness of breath. In view of this, metabolic therapies aimed at improving myocardial energetics in obesity may become a means of targeting obesity related shortness of breath.

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**Conflict of Interest Disclosures:** None

**References:**


**Table 1.** Baseline anthropometric characteristics, a comparison of normal and obese subjects.

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<tr>
<th></th>
<th>Normal Weight (N=17)</th>
<th>Obese (N=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>60 ± 7 *</td>
<td>114 ± 23</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>21.6 ± 1.6 *</td>
<td>38.7 ± 7.1</td>
</tr>
<tr>
<td><strong>Visceral Fat Mass (dm³)</strong></td>
<td>2.4 ± 1.3 *</td>
<td>7.3 ± 2.9</td>
</tr>
<tr>
<td><strong>Total Fat Mass (kg)</strong></td>
<td>17 ± 3 *</td>
<td>51 ± 19</td>
</tr>
<tr>
<td><strong>Systolic Blood Pressure (mmHg)</strong></td>
<td>114 ± 10</td>
<td>118 ± 11</td>
</tr>
<tr>
<td><strong>Diastolic Blood Pressure (mmHg)</strong></td>
<td>72 ± 7 *</td>
<td>75 ± 8</td>
</tr>
<tr>
<td><strong>Fasting Glucose (mmol/l)</strong></td>
<td>4.8 ± 0.4 *</td>
<td>5.3 ± 0.7</td>
</tr>
<tr>
<td><strong>Total Cholesterol (mmol/l)</strong></td>
<td>5.0 ± 0.8</td>
<td>5.2 ± 0.6</td>
</tr>
<tr>
<td><strong>Excess Weight (kg)</strong></td>
<td>—</td>
<td>42 ± 22</td>
</tr>
<tr>
<td><strong>Waist: Hip Ratio</strong></td>
<td>0.82 ± 0.08 *</td>
<td>0.93 ± 0.10</td>
</tr>
<tr>
<td><strong>Free Fatty Acid Levels (mmol/l)</strong></td>
<td>0.34 ± 21 *</td>
<td>0.54 ± 34</td>
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<tr>
<td><strong>Fasting Triglyceride (mmol/l)</strong></td>
<td>0.7 ± 0.5 *</td>
<td>1.4 ± 0.7</td>
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* = p<0.05 Obese vs Normal
Table 2. Left Ventricular Characteristics and Diastolic Filling Parameters, A Comparison of Normal and Obese Subjects

<table>
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<tr>
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<th>Normal Weight (N=17)</th>
<th>Obese (N=46)</th>
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<tbody>
<tr>
<td>Rest Heat Rate (Beats Per Minute)</td>
<td>62 ± 7</td>
<td>65 ± 7</td>
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<tr>
<td>Normalized Peak Ventricular Filling Rate (EDV/s)</td>
<td>4.7 ± 0.8 *</td>
<td>3.7 ± 0.9</td>
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<tr>
<td>Absolute Peak Filling Rate (ml/s)</td>
<td>550 ± 117</td>
<td>530 ± 130</td>
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<tr>
<td>Left Ventricular Mass (g)</td>
<td>90 ± 19 *</td>
<td>138 ± 29</td>
</tr>
<tr>
<td>Left Ventricular end-diastolic volume (ml)</td>
<td>118 ± 22 *</td>
<td>146 ± 21</td>
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<tr>
<td>Left Ventricular end-systolic volume (ml)</td>
<td>38 ± 11 *</td>
<td>46 ± 12</td>
</tr>
<tr>
<td>Left Ventricular Ejection Fraction (%)</td>
<td>68 ± 6</td>
<td>69 ± 5</td>
</tr>
<tr>
<td>Left Ventricular Stroke Volume (ml)</td>
<td>80 ± 16 *</td>
<td>106 ± 14</td>
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* = p < 0.05 Obese vs Normal

Table 3. Linear Regression Analysis for Left Ventricular Peak Filling Rate

<table>
<thead>
<tr>
<th></th>
<th>$R^2$</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Waist Hip Ratio</td>
<td>0.10</td>
<td>0.017</td>
</tr>
<tr>
<td>Total Fat Mass (kg)</td>
<td>0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCr/ATP Ratio</td>
<td>0.26</td>
<td>0.008</td>
</tr>
<tr>
<td>Fasting Leptin (ng/l)</td>
<td>0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV Mass Indexed to Height (g/m^2.7)</td>
<td>0.17</td>
<td>0.001</td>
</tr>
<tr>
<td>Left Ventricular End-diastolic Volume (ml)</td>
<td>0.19</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4. The Effect of Catecholamine Stress on Myocardial Relaxation Rates in Obese and Normal Weight Subjects

<table>
<thead>
<tr>
<th></th>
<th>Normal Weight (N=12)</th>
<th>Obese Subjects (N=21)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest Heat Rate (Beats Per Minute)</td>
<td>61 ± 7</td>
<td>64 ± 9</td>
<td>0.27</td>
</tr>
<tr>
<td>Stress Heart Rate (Beats Per Minute)</td>
<td>102 ± 15</td>
<td>105 ± 9</td>
<td>0.20</td>
</tr>
<tr>
<td>Percentage Increase in HR during Stress</td>
<td>67 ± 28</td>
<td>63 ± 16</td>
<td>0.61</td>
</tr>
<tr>
<td>Normalized Rest Peak Filling Rate (EDV/s)</td>
<td>4.3 ± 0.9</td>
<td>3.9 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Absolute Rest Peak Filling Rate (ml/s)</td>
<td>561 ± 135</td>
<td>553 ± 139</td>
<td>0.70</td>
</tr>
<tr>
<td>Normalized Stress Peak Filling Rate (EDV/s)</td>
<td>7.6 ± 1.4</td>
<td>5.3 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Absolute Stress Peak Filling Rate (ml/s)</td>
<td>815 ± 229</td>
<td>541 ± 170</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage Increase in Diastolic Filling Rate During Stress</td>
<td>70 ± 28</td>
<td>38 ± 32</td>
<td>0.01</td>
</tr>
<tr>
<td>Left Ventricular Ejection Fraction (%) at rest</td>
<td>68 ± 6</td>
<td>68 ± 6</td>
<td>0.95</td>
</tr>
<tr>
<td>Left Ventricular Ejection Fraction (%) at peak stress</td>
<td>80 ± 5</td>
<td>79 ± 5</td>
<td>0.65</td>
</tr>
<tr>
<td>Left Ventricular end-diastolic volume (ml) at rest</td>
<td>117 ± 22 *</td>
<td>125 ± 22</td>
<td>0.58</td>
</tr>
<tr>
<td>Left Ventricular end-diastolic volume (ml) at peak stress</td>
<td>106 ± 20</td>
<td>101 ± 20</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Figure Legends:

**Figure 1.** Pearson correlations of Peak Diastolic Filling Rate (EDV/s) and (A) Total Fat Mass (kg), (B) PCr/ATP Ratio, (C) Left Ventricular Mass Indexed to Height$^{2.7}$ (g/m$^2$) and (D) Left Ventricular End-Diastolic Volume (ml). Black circles represent obese subjects, grey triangles represent normal weight subjects.

**Figure 2.** (A) Absolute and (B) normalized LV filling rates for normal weight and obese subjects at rest and during catecholamine stress.

**Figure 3.** (A) The Differential Effect Of Catecholamine Stress On Change In Peak Filling Rate In Normal Weight And Obese Subjects. The Effect Of Dobutamine Stress On Myocardial Relaxation Rate In Normal Weight Subjects (B) Showing a Strong Linear Relationship Between Peak Filling Rate and Heart Rate, and (C) Obese Subjects With No Significant Relationship.

**Figure 4.** (A) The Effect of Catecholamine Stress on Myocardial Energetics In Normal Weight and Obese Subjects (mean values ± SD are represented by larger grey triangles) (B) Example $^{31}$P MR Spectra in an obese subject at rest and the same subject during stress showing a significant decrease in PCr/ATP ratio.
Effects of Catecholamine Stress on Diastolic Function and Myocardial Energetics in Obesity
Oliver J. Rider, Jane M. Francis, Mohammed K. Ali, Cameron Holloway, Tammy Pegg, Matthew D. Robson, Damian Tyler, James Byrne, Kieran Clarke and Stefan Neubauer

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