

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

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Background—Obesity is characterized by impaired cardiac energetics, which 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 (body mass index, 22 ± 2 kg/m²; n=9–17) and obese (body mass index, 39 ± 7 kg/m²; n=17–46) subjects underwent assessment of diastolic left ventricular function (cine magnetic resonance imaging volume-time curve analysis) and cardiac energetics (phosphocreatine/ATP ratio; ³¹P-magnetic resonance spectroscopy) at rest and during dobutamine stress (heart rate increase, $65 \pm 22\%$ and $69 \pm 14\%$, respectively; $P=0.61$). At rest, obesity was associated with a 22% lower peak filling rate ($P<0.001$) and a 15% lower phosphocreatine/ATP ratio (1.73 ± 0.40 versus 2.03 ± 0.28 ; $P=0.048$). Peak filling rate correlated with fat mass, left ventricular mass, leptin, waist-to-hip ratio, and phosphocreatine/ATP ratio. On multivariable analysis, phosphocreatine/ATP was the only independent predictor of peak filling rate ($\beta=0.50$; $P=0.03$). During stress, a further reduction in phosphocreatine/ATP occurred in obese (from 1.73 ± 0.40 to 1.53 ± 0.50 ; $P=0.03$) but not in normal-weight (from 1.98 ± 0.24 to 2.04 ± 0.34 ; $P=0.50$) subject. For similar levels of inotropic stress, there were smaller increases in peak filling rate in obesity (38% versus 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. (*Circulation*. 2012; 125:1511-1519.)

Key Words: diastole ■ stress ■ obesity ■ magnetic resonance spectroscopy

Asymptomatic diastolic dysfunction is a condition associated with future heart failure.^{1,2} Obesity, both with and without additional comorbidities, has been linked to diastolic dysfunction across a wide range of noninvasive imaging modalities.^{3–5} Despite this and the recent evidence that increased body mass index is associated with worse diastolic function independently of left ventricular (LV) mass, the mechanisms behind diastolic dysfunction in obesity are unknown.⁶

Clinical Perspective on p 1519

It is generally accepted that myocardial relaxation is determined largely by a combination of active (calcium homeostasis, myocardial energetics)⁷ and passive processes related to the physical properties of the LV (intrinsic mechanical stiffness as determined by wall thickness and chamber geometry).⁸ 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 comorbidities (eg, hypertension and diabetes mellitus), which have well-documented independent effects on lusitropy.

Cardiovascular magnetic resonance (MR) imaging, combined with ³¹P-MR spectroscopy (MRS), allows the noninvasive in vivo study of LV geometry and function and of cardiac high-energy phosphate metabolism, enabling interrogation of both active and passive mechanisms of diastolic dysfunction. Cardiovascular MR is not dependent on the generation of an adequate acoustic window or the orientation of the heart within the chest, allowing reproducible imaging regardless of body habitus and degree of chest wall fat, a major advantage in the setting of obesity.^{9–12} 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.

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Table 1. Baseline Anthropometric Characteristics: A Comparison of Normal-Weight and Obese Subjects

	Normal Weight (n=17)	Obese (n=46)
Weight, kg	60±7*	114±23
Body mass index, kg/m ²	21.6±1.6*	38.7±7.1
Visceral fat mass, dm ³	2.4±1.3*	7.3±2.9
Total fat mass, kg	17±3*	51±19
Systolic blood pressure, mm Hg	114±10	118±11
Diastolic blood pressure, mm Hg	72±7*	75±8
Fasting glucose, mmol/L	4.8±0.4*	5.3±0.7
Total cholesterol, mmol/L	5.0±0.8	5.2±0.6
Excess weight, kg	...	42±22
Waist-to-hip ratio	0.82±0.08*	0.93±0.10
Free fatty acid levels, mmol/L	0.34±2.1*	0.54±3.4
Fasting triglycerides, mmol/L	0.7±0.5*	1.4±0.7

* $P < 0.05$, obese versus normal weight.

Furthermore, because many obese subjects with normal LV 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 64 healthy subjects (obese: n=46, 11 male, body mass index >30 kg/m²; normal-weight control subjects: n=18, 5 male, body mass index=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 comorbidities. 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 mellitus (fasting glucose level ≥ 6.7 mmol), fasting total cholesterol level ≥ 6.5 mmol/L, use of any prescription medications, or a history compatible with obstructive sleep apnea. All subjects had a normal 12-lead ECG, normal cardiovascular examination, and normal global and regional resting cardiac function on MR imaging and did not perform >3 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 analyzed as described.⁵ An estimate of insulin resistance was calculated with the homeostatic model assessment–insulin resistant equation: [fasting insulin (μ U/mL)×fasting glucose (mmol/L)]/22.5.

Baseline Diastolic Functional Imaging

All 18 normal-weight subjects (average body mass index, 22±2 kg/m²) and all 46 obese subjects (average body mass index, 39±7 kg/m²) underwent diastolic functional imaging at rest.

All cardiovascular MR scans for the assessment of LV diastolic function at rest were performed on a 1.5-T MR system (Siemens, Germany). Images for ventricular volumes and diastolic function were acquired with a steady-state free precession sequence with an echo time of 1.5 milliseconds, a repetition time of 3.0 milliseconds, in-plane resolution of 1.5×1.5 mm², temporal resolution of 33.74 ms, and a flip angle of 60° as previously described.¹³ All imaging was performed in subjects in the supine position, was prospectively cardiac gated, and was acquired during end-expiratory breath hold.

Diastolic Function Analysis

Analysis of LV volumes was performed with Siemens analytic 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 was normalized to end-diastolic volume, as previously described.⁵

Baseline ³¹P-MRS

Baseline resting ³¹P-MRS was performed in 10 normal-weight and 17 obese subjects. Cardiac high-energy phosphate metabolism was measured with ³¹P-MRS on a 3-T system (Siemens Medical Solutions, Erlangen, Germany) in a prone subject to position the heart as close to the surface coil as possible. All data were acquired with a commercially available 1.5-T ³¹P/¹H surface coil (Siemens Medical Solutions) tuned to 3 T. After piloting along the short axis, horizontal, and vertical long axis of the heart, a ³¹P 3-dimensional acquisition-weighted chemical shift imaging spectral data set was acquired with dimensions of 240×240×200 mm. A matrix size of 12×8×8 (0 filled to 16×16×8) was used. Hence, the spatial resolution was 20×30×25 mm³ (12 mL) interpolated to 15×15×25 mm³ (5.6 mL). ³¹P-spectra were acquired with an echo time of 2.3 ms and a flip angle of 37°, with 10 averages at the center of k space and nuclear Overhauser enhancement (flip angle, 180°), as previously described.¹⁴

³¹P-MRS Analysis

Analysis of the spectra was performed in jMRUI version 2.2 (2005) limited to a single voxel in the basal septum to avoid blood contamination. This voxel was selected by consensus of 2 experienced observers using fast low angle shot images as previously described.¹⁴ Spectra were Fourier transformed, and a 20-Hz line broadening was applied. Spectra were fitted with 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 peak, and the phosphocreatine (PCr)/ATP ratio was determined.¹⁵ Because 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 repetition time and its subsequent effect on the PCr/ATP ratio. The repetition time was fixed at 1.0 seconds, resulting in a total acquisition time of 8 minutes 29 seconds, as previously described.¹⁴

Body Composition Analysis

Bioimpedance Analysis

Bioelectric impedance was used to determine total body fat mass and lean body mass with a Bodystat 1500 analyzer. The use of bioimpedance analysis has become routine in clinical research investigating body composition analysis. Although not the gold standard for the analysis of body composition, it has been shown to have close correlation with dual-energy x-ray absorptiometry assessments in multiple studies.¹⁶

Visceral Fat Mass

A single-breath-hold, contiguous 5-slice, T1-weighted turbo spin-echo sequence centered around the vertebral body of L5 (turbo

factor, 5; echo time, 12 milliseconds; repetition time, 200 milliseconds; slice thickness, 10 mm) was modified so that the sequence served predominantly to suppress the water signal.¹⁷ Transverse slices were then manually contoured to provide a visceral fat volume.

Dobutamine Stress Studies

Dobutamine Infusion Protocol

After the resting 3-dimensional chemical shift imaging ³¹P-spectra (3 T) and resting short-axis stack (1.5 T) were acquired, dobutamine was infused intravenously at incremental rates between 5 and 40 μg/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 dobutamine infusion studies. Heart rate was then maintained at target for the duration of the scans (8 minutes 29 seconds for ³¹P-MRS, 5 minutes for short-axis imaging).

Diastolic Function During Dobutamine Stress

Twelve normal-weight subjects and 21 obese subjects underwent assessment of diastolic function both at rest and during dobutamine stress. During the period of time when the steady-state target heart rate was reached, a short-axis stack (fast imaging with steady-state precession) was also acquired as described above. After the scan acquisition at stress, the dobutamine infusion was then discontinued. The steady-state free precession sequence (temporal resolution, 33.74 milliseconds) allowed acquisition of ≈30 images per cardiac cycle at rest (given a heart rate of 60 bpm) and ≈20 images at stress (given a heart rate of 100 bpm). Analysis of stress diastolic function was performed as described above.

³¹P-MRS During Dobutamine Stress Studies

Nine 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 with SPSS statistical software (version 17.0; SPSS Inc, Chicago, IL). Data were presented as mean±SD. All data were assessed for normal distribution with the Kolmogorov-Smirnov test. Normally distributed data sets were analyzed with the Student *t* test; paired *t* tests were used to compare values during rest and stress studies; and nonnormally distributed data sets were analyzed with Wilcoxon signed-ranks test. Nonsignificance was assumed at *P*<0.05 (2 tailed). Predictors of peak filling rate were determined with forced entry multivariable regression analysis.

Power Calculation

Because the PCr/ATP ratio would not increase during dobutamine infusion, power calculations were performed assuming 1-tailed *t* test analysis. With the use of pilot data, an a priori calculation based on a PCr/ATP ratio (mean PCr/ATP, 1.82; SD=0.24; mean difference, 10% [0.182]; α=0.05) powered the study to detect a 10% drop in the PCr/ATP ratio during cardiac stress in the obese cohort with 17 subjects.

Results

The Effects of Obesity on Cardiac Function and Energetics

The 2 groups were well matched for age (normal-weight group, 43±10 years; obese group, 44±7 years; *P*=0.6), height (normal-weight group, 1.68±0.06 m; obese group, 1.69±0.08 m; *P*=0.6), systolic blood pressure, and fasting total cholesterol (Table 1). Obese subjects were on average 54 kg heavier than the normal-weight subjects. Although fasting glucose was statistically higher in the obese cohort, glucose

Table 2. Left Ventricular Characteristics and Diastolic Filling Parameters: A Comparison of Normal-Weight and Obese Subjects

	Normal Weight (n=17)	Obese (n=46)
Rest heart rate, bpm	62±7	65±7
Normalized peak ventricular filling rate, EDV/s	4.7±0.8*	3.7±0.9
Absolute peak filling rate, mL/s	550±117	530±130
Left ventricular mass, g	90±19*	138±29
Left ventricular EDV, mL	118±22*	146±21
Left ventricular end-systolic volume, mL	38±11*	46±12
Left ventricular ejection fraction, %	68±6	69±5
Left ventricular stroke volume, mL	80±16*	106±14

EDV indicates end-diastolic volume.

**P*<0.05, obese versus normal weight.

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 mm Hg; Table 1).

Diastolic Function

As expected, obesity was associated with a 22% reduction in peak diastolic filling rate compared with lean age- and sex-matched control subjects (*P*<0.001; Table 2).

Myocardial Energetics

Obesity was associated with a 15% reduction in the myocardial PCr/ATP ratio compared with normal-weight subjects (obese, 1.73±0.40; normal weight, 2.03±0.28; *P*<0.05). Furthermore, the PCr/ATP ratio was negatively correlated with the homeostatic model assessment (*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-to-hip ratio, total fat mass (kg), serum leptin (ng/L), LV mass indexed to height^{2.7}, and LV end-diastolic volume (mL) and positively correlated with myocardial PCr/ATP ratio (Table 3 and Figure 1). Variables with values of *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-to-hip ratio, and serum leptin level as independent variables. Multivariable analysis of the peak diastolic filling rate revealed the PCr/ATP ratio (β=0.92; *P*=0.03) as a predictor of peak diastolic filling rate (overall *R*² of the model=0.40; *P*=0.02).

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

	R^2	P
Waist-to-hip ratio	0.10	0.017
Total fat mass	0.24	<0.001
PCr/ATP ratio	0.26	0.008
Fasting leptin	0.21	<0.001
LV mass indexed to height	0.17	0.001
LV end-diastolic volume	0.19	<0.001

PCr indicates phosphocreatine; LV, left ventricular.

Effects of Dobutamine Stress in Obesity

Systolic and Diastolic Function

The effects of dobutamine stress on systolic and diastolic function are summarized in Table 4. Both groups underwent similar levels of inotropic stress with a similar percentage increase in heart rate (obese group, $63 \pm 16\%$ increase;

normal-weight group, $67 \pm 28\%$; $P=0.61$). During peak stress, LV ejection fraction increase was similar between normal-weight and obese subjects (LV ejection fraction increase during stress: obese group, 11%; normal-weight group, 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 (Figure 2 shows the individual absolute and normalized filling rates). In contrast, in obese subjects, a 63% increase in heart rate (from 64 ± 9 to 105 ± 9 bpm) 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 and 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 dependent variable and percentage increase in heart rate as

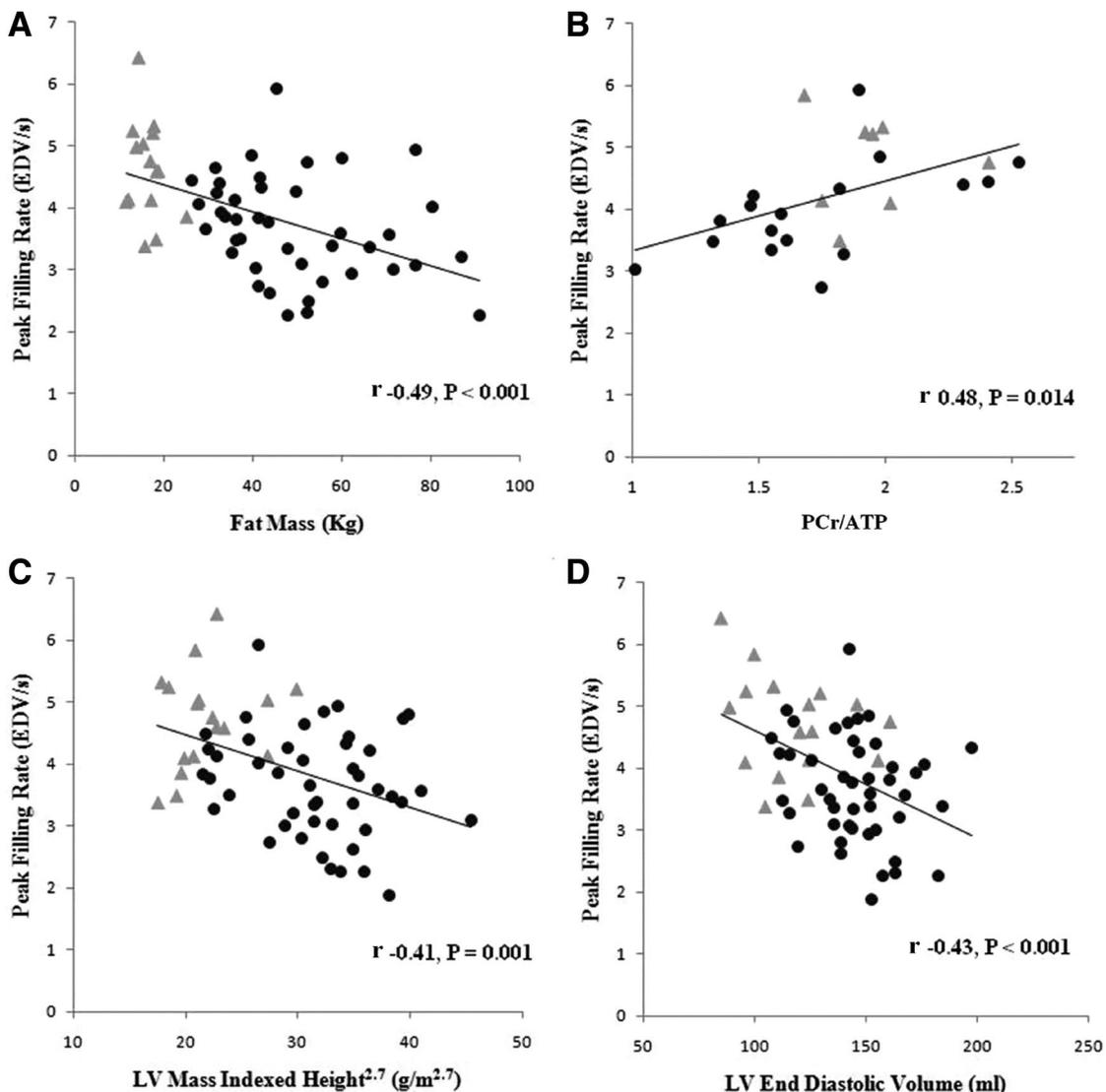


Figure 1. Pearson correlations of peak diastolic filling rate (end-diastolic volume [EDV]/s) and (A) total fat mass (kg), (B) phosphocreatine (PCr)/ATP ratio, (C) left ventricular (LV) mass indexed to height^{2.7} (g/m^{2.7}), and (D) LV EDV (ml). Black circles represent obese subjects; gray triangles, normal-weight subjects.

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

	Normal Weight (n=12)	Obese Subjects (n=21)	P
Rest heart rate, bpm	61±7	64±9	0.27
Stress heart, bpm	102±15	105±9	0.20
Percentage Increase in HR during stress	67±28	63±16	0.61
Normalized rest peak filling rate, EDV/s	4.3±0.9	3.9±0.5	<0.001
Absolute rest peak filling rate, mL/s	561±135	553±139	0.70
Normalized stress peak filling rate, EDV/s	7.6±1.4	5.3±1.1	<0.001
Absolute stress peak filling rate, mL/s	815±229	541±170	<0.001
Increase in diastolic filling rate during stress, %	70±28	38±32	0.01
Left ventricular ejection fraction at rest, %	68±6	68±6	0.95
Left ventricular ejection fraction at peak stress, %	80±5	79±5	0.65
Left ventricular EDV at rest, mL	117±22	125±22	0.58
Left ventricular EDV at peak stress, mL	106±20	101±20	0.002

HR indicates heart rate; EDV, end-diastolic volume.

the independent variable. In the normal-weight group, the percentage increase in heart rate was highly predictive of maximal diastolic filling rate ($r=0.75$, $P<0.001$). In contrast, the obese cohort’s percentage increase in heart rate during catecholamine stress was not predictive of maximal diastolic filling rate ($r=0.25$, $P=0.28$; Figure 3B and 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, $1.98±0.24$ at rest versus $2.03±0.34$ at stress; $P=0.50$). In contrast, during dobutamine infusion, there was a significant, further 12% reduction in

the myocardial PCr/ATP ratio in the obese group ($1.73±0.40$ at rest versus $1.53±0.50$ at stress; $P=0.03$; 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 weight, $0.06±0.27$; obese, $-0.20±0.34$; $P<0.05$). 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 in both the presence and absence of additional cardiovascular risk factors. In this

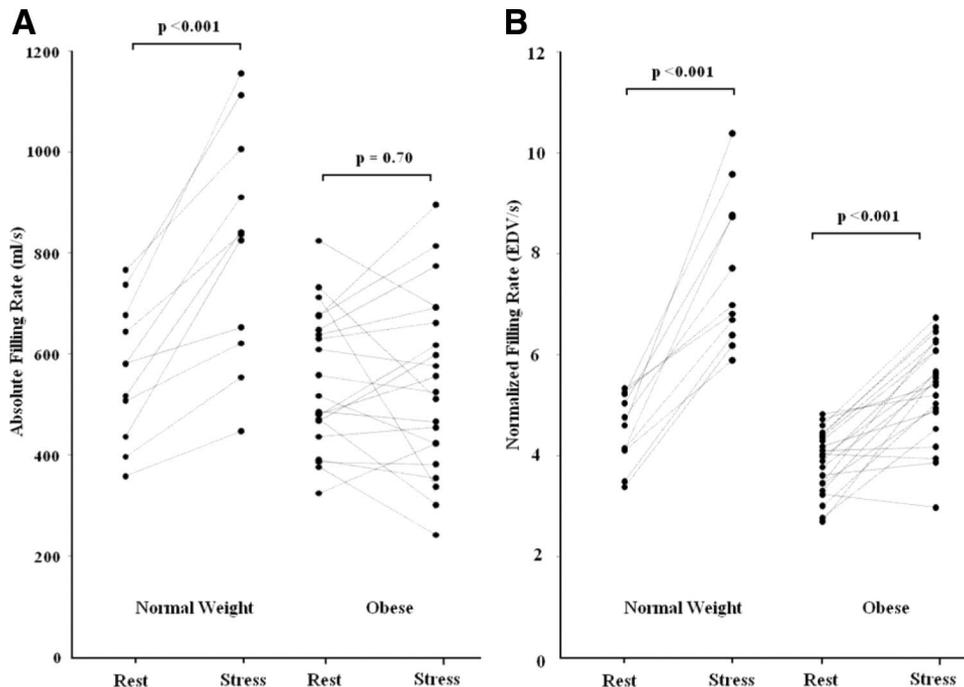


Figure 2. A, Absolute and **(B)** normalized left ventricular filling rates for normal-weight and obese subjects at rest and during catecholamine stress. EDV indicated end-diastolic volume.

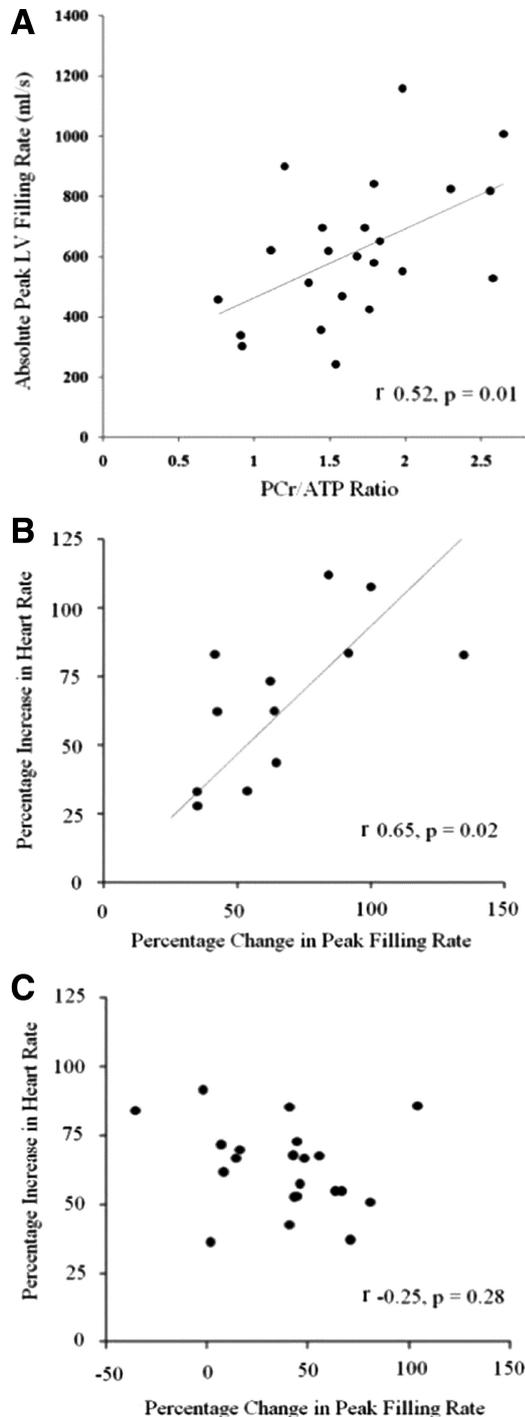


Figure 3. A, The differential effect of catecholamine stress on change in peak filling rate in normal weight and obese subjects. The effect of dobutamine stress on myocardial relaxation rate in (B) normal-weight subjects showing a strong linear relationship between peak filling rate and heart rate and in (C) obese subjects showing no significant relationship. LV indicates left ventricular; PCr, phosphocreatine.

study, we have used cardiovascular MR, 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-to-hip ratio, LV

mass, LV end-diastolic volume, and myocardial energetics and that the myocardial PCr/ATP ratio is also 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

LV hypertrophy, elevated LV 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.⁷ In support of this, we have shown not only that LV 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.¹⁸ The PCr/ATP ratio is decreased in heart failure, correlates with indexes of both systolic¹⁹ and diastolic⁷ LV function and with functional heart failure class,²⁰ and is a better long-term prognostic indicator than LV ejection fraction.²⁰ Patients with dilated cardiomyopathy,²¹ hypertension,⁷ diabetes mellitus,¹⁵ and valvular heart disease²² have 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.

A wealth of data now point to diastole as a highly regulated, highly active process.²³ 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.^{7,24} 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 most energetically demanding of all enzymes involved in contractile function,²⁵ 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 come from animal models,^{12,26} with only 1 prior study showing reduced resting myocardial energetics in human male obesity.²⁷ 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 were 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 expression.²⁸ This would then lead to a

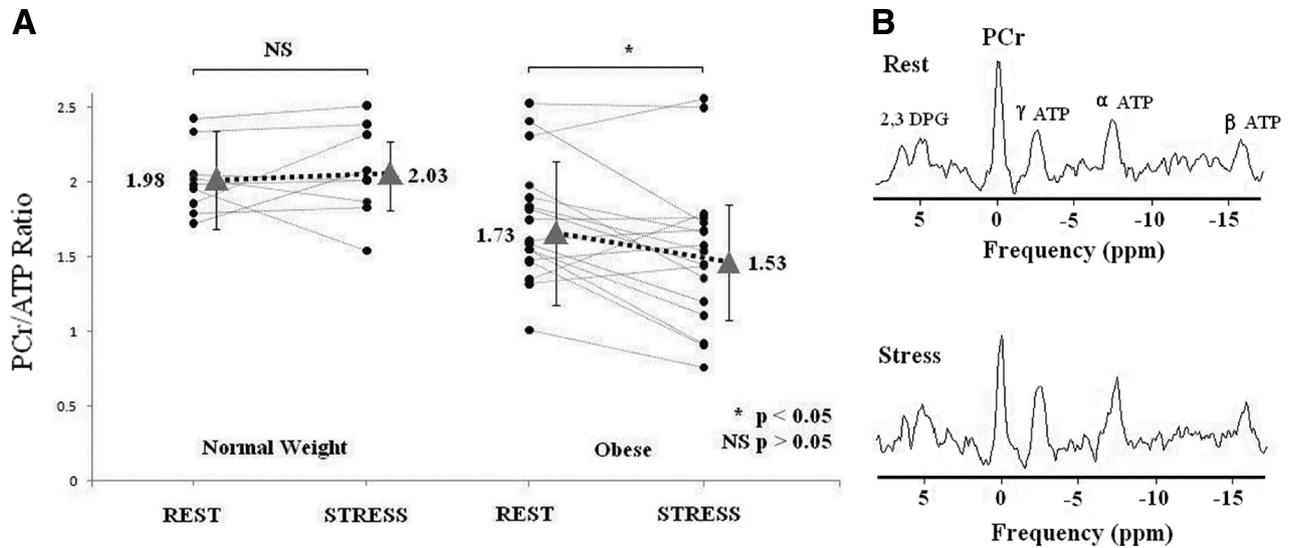


Figure 4. **A**, The effect of catecholamine stress on myocardial energetics in normal-weight and obese subjects (large gray triangles, mean \pm SD values). **B**, Example ^{31}P -magnetic resonance spectra in an obese subject at rest and the same subject during stress showing a significant decrease in phosphocreatine (PCr)/ATP ratio.

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 were 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; larger studies are 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 caused by hypertension.¹⁰

In the normal heart, dobutamine primarily increases heart rate via β -adrenergic stimulation.²⁹ This causes increases in cAMP, which in turn phosphorylate phospholamban, relieving its inhibition on SERCA and increasing the relaxation rate by increasing the rate of Ca^{2+} uptake.³⁰ Thus, it would be predicted that the 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, 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 in obese and normal-weight subjects, 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.^{10,31} 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, the 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 1 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 not surprising 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 further decrease in PCr/ATP ratio is explained by 1 of 2 mechanisms that affect mitochondrial oxidative phosphorylation. First, 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.^{32,35} The second possible explanation is an inadequate blood supply during stress resulting from the combination of LV hypertrophy, known to be present in this cohort, and microvascular dysfunction. Further studies using quantitative myocardial perfusion imaging and oxygenation

imaging are needed to determine whether blood supply limitation is the mechanism upstream of these changes.

Limitations

Despite the increased signal-to-noise ratio that measuring ^{31}P -MRS at 3.0 T affords, measurements taken during dobutamine stress remain noisy with relatively high measurement variability. Thus, 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 apnea was excluded by a questionnaire, formal sleep studies were not performed.

This protocol used pharmacological stress rather than physiological exercise. Although not a direct physiological reproduction of exercise, this technique avoided MR motion artifacts induced by an exercise protocol, thus allowing 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 ischemia was not formally excluded as the cause of decreased energetics, although its presence is most unlikely.

Although assessment of diastolic function with cardiovascular MR in the setting of obesity has significant advantages, allowing reproducible imaging regardless of body habitus and degree of chest wall fat, the temporal resolution (33.74 milliseconds) is significantly slower than that of echocardiographic 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, LV hypertrophy, and diastolic dysfunction. In obese but not normal-weight control subjects, 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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Disclosures

None.

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CLINICAL PERSPECTIVE

Despite the fact that obesity is characterized by diastolic dysfunction, a condition associated with future heart failure, the mechanisms behind it are not known. In this study, we have demonstrated that myocardial energetics are impaired in obesity and that the phosphocreatine/ATP ratio is a predictor of diastolic function. This opens the possibility of a metabolic therapy aimed at improving myocardial energetics in obesity and potentially preventing the progression to heart failure. In addition, we have shown that during moderate inotropic stress, the already lower phosphocreatine/ATP ratio in obesity is further reduced, resulting in additional negative effects on diastolic function. Because the majority of the cardiovascular symptoms in obesity do not occur at rest and occur in subjects with normal left ventricular systolic and respiratory function, these changes in energetics and diastole provide a plausible explanation for exertional breathlessness in obesity. Myocardial energetics appear to be playing a central role in diastolic function in obesity; therefore, metabolic therapies aimed at improving myocardial energetics in obesity may become a means of targeting obesity-related shortness of breath and potentially preventing the development of heart failure.