Abnormal Left Ventricular Energy Metabolism in Obese Men With Preserved Systolic and Diastolic Functions Is Associated With Insulin Resistance

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OBJECTIVE — Perturbations in cardiac energy metabolism might represent early alterations in diabetes preceding functional and pathological changes. We evaluated left ventricular (LV) structure/geometry and function in relation to energy metabolism and cardiovascular risk factors in overweight/obese men using magnetic resonance techniques.

RESEARCH DESIGN AND METHODS — We studied 81 healthy men (aged 22–55 years, with BMI between 19 and 35 kg/m^2) by means of cardiac magnetic resonance imaging and ^{31}P-magnetic resonance spectroscopy in the resting and fasted conditions and stratified them in quartiles of BMI (cut offs: 23.2, 25.5 and 29.0 kg/m^2).

RESULTS — LV mass increased across quartiles of BMI; meanwhile, the volumes did not differ. Parameters of LV systolic and diastolic function were not different among quartiles. The phosphocreatine-to-ATP ratio was reduced across increasing quartiles of mean ± SD BMI (2.25 ± 0.52, 1.89 ± 0.26, 1.99 ± 0.38, and 1.79 ± 0.29; $P < 0.006$) in association with insulin sensitivity (computer homeostasis model assessment 2 model); this relation was independent of age, BMI, blood pressure, wall mass, HDL cholesterol, triglycerides, smoking habits, and metabolic syndrome.

CONCLUSIONS — Abnormal LV energy metabolism was detectable in obese men in the presence of normal function, supporting the hypothesis that metabolic remodeling in insulin resistant states precedes functional and structural/geometrical remodeling of the heart regardless of the onset of overt hyperglycemia.

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Abbreviations: FFA, free fatty acid; HOMA, homeostasis model assessment; HOMA-S%, HOMA of insulin sensitivity; LV, left ventricular; MRI, magnetic resonance imaging; MRS, ^{31}P-magnetic resonance spectroscopy; PCr, phosphocreatine; TSH, thyroid-stimulating hormone.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Cardiovascular disease is the leading cause of death in patients with type 2 diabetes (1,2). The existence of a diabetic cardiomyopathy distinct from ischemic injury was confirmed, but the challenge of recognizing its specific features remained unresolved because diabetes could also provoke cardiac damage via coronary macrovascular disease, autonomic dysfunction, and coronary microvascular disease (3). It was proposed that altered metabolism and impaired insulin action in the heart might be cause and consequence of altered cardiac function (4) and that metabolic remodeling in diabetes might precede, cause, and sustain the functional and structural/geometrical remodeling of the heart (5). In keeping with this hypothesis, cardiac energy metabolism was found to be abnormal in patients with type 2 diabetes despite the lack of major cardiac dysfunctions (6) or the presence of diastolic dysfunction (7). Those studies were performed in middle-age individuals (52–57 years old) in whom diabetes was diagnosed 1 (7) to 3 (6) years earlier. Therefore, the question whether the alterations of cardiac energy metabolism were due to the hyperglycemic state itself or whether they were secondary to the metabolic features characterizing the prediabetic state remained unanswered.

This study was undertaken to assess whether obesity was associated with impaired cardiac structure/geometry, function, and energy metabolism and to establish whether these potential alterations were associated with the cardiovascular and metabolic risk factors accompanying insulin resistance conditions.

RESEARCH DESIGN AND METHODS

We selected 81 apparently healthy men with no previous history of diabetes, hypertension, dyslipidemias, coronary, cerebral, or peripheral vascular events, no history of dilated cardiomyopathy, no previous knowledge of a pathological ejection fraction or of resting elec-

trocardiogram markers of cardiac ischemia, and no features compatible with the NYHA (New York Heart Association) classes for heart failure. They were not taking any medications, were 18–55 years old, and had 18–35 kg/m^2 range of BMI; body weight was stable for at least 6 months. We assessed the habitual physical activity using a questionnaire based on three components: physical activity at work, sport during leisure time, and physical activity during leisure time excluding sports (8) as previously reported (9,10). We assessed the metabolic syndrome using the Adult Treatment Panel III definition with the exception of the waist criteria; instead, a BMI >30 kg/m^2 was used. All subjects gave informed consent after explanation of purposes, nature, and potential risks of the study. The protocol was approved by the Ethical Committee of the Istituto Scientifico San Raffaele.

Experimental procedures

Subjects were instructed to consume an isocaloric diet and to abstain from exercise activity for 3 days before the magnetic resonance imaging (MRI) and ^{31}P-magnetic resonance spectroscopy (MRS) studies. Volunteers underwent the protocol at 7:30–9:30 A.M. in the resting state after a 10-h overnight fasting period and after the collection of venous blood for the assessment of plasma glucose, total cholesterol, HDL cholesterol, triglycerides, free fatty acids (FFAs), insulin, leptin, adiponectin, resistin, thyroid-stimulating hormone (TSH), and creatinine.

Cardiac MRS

We performed cardiac MRS using a whole-body scanner (Gyroscan Intera Master 1.5 MR System; Philips Medical Systems, Best, Netherlands). ^{31}P spectra were obtained by means of a 10-cm diameter surface coil used for transmission and detection of radio frequency signals at the resonance frequency of ^{31}P (at 1.5 T, 25.85 MHz) as previously described (11). In this setting, the volume of interest was 5 (caudocranial) × 6 × 6 cm.

Cardiac MRI We performed MRI with the above-described scanner using an enhanced gradient system with a maximum gradient strength of 30 mT/m and a maximum gradient slew rate of 150 mT · m^{-1} · s^{-1} and using the Cardiac Research software patch (operating system 9). The examination was performed using a 5-element cardiac phased array coil (SENSE-cardiac) and retrospective electrocardiogram triggering obtained with Vectorcardiogram system (12) and standard MRI methodology as previously described (11).

Anaytical determinations

We measured glucose concentration with the glucose oxidase method (Beckman Coulter, Fullerton, CA). FFAs, triglycerides, total cholesterol, and HDL cholesterol were measured as previously described (9,10). Plasma insulin (intra- and interassay coefficient of variation <3 and 6%, respectively; cross-reactivity with C-peptide and proinsulin <1%) and leptin was measured with radioimmunoassay (Linco Research, St. Charles, MO). Serum resistin (BioVendor Laboratory Medicine, Brno, Czech Republic) and adiponectin (B-Bridge International, Sunnyvale, CA) were measured by ezyme-linked immunosorbent assay kits kits. Serum creatinine was measured using an enzymatic method on a Hitachi 747 (11). TSH was measured by immunofluorimetric method. We measured blood pressure twice with volunteers in the lying position.

Calculations

MRS analysis. ^{31}P-MR spectra, transferred to a remote SUN-SPARC workstation, were quantified automatically in the time domain, using Fitmasters. We corrected ATP for the contribution originated from blood in the cardiac chambers based on a previous study (13). We corrected PCr/ATP ratios for partial saturation effects using T1 values obtained from inversion recovery experiments. Based on the repetition time of 3.6 s, we applied a saturation correction factor of 1.35 (14,15). An estimate of the signal-to-noise ratio of each spectra was obtained from the relative Cramer-Rao standard deviation calculated for the PCr-to-ATP ratio (15).

MRI analysis. Image analysis was performed using an image-processing workstation (EasyVision; Philips Medical Systems) by using the cardiac analysis software package as previously described (11).

Insulin sensitivity. We estimated insulin sensitivity and secretion by the updated computer model homeostasis model assessment (HOMA)2 (16) available from www.ocdem.ox.ac.uk.

Statistical analysis

Data in text, tables, and figures are means ± SD. Analysis was performed using SPSS software (version 10.0; SPSS, Chicago, IL). When parameters showed a skewed distribution (Kolmogorov-Smirnov test of normality), they were log transformed before the analysis (systolic and diastolic blood pressure, triglycerides, leptin, and TSH), and one-way ANOVA with Bonferroni post hoc analysis or Kruskal-Wallis nonparametric test was used to compare variables between quartiles of BMI when appropriate. Two-tailed Person's correlation was performed to establish partial correlation coefficients between variables. Nonparametric correlation coefficient was obtained using Spearman's rho when appropriate. We defined statistical significance as a P value <0.05. A prior power calculation analysis indicated that 17 subjects per group were required to provide a power of 90% to detect a 20% difference in PCr-to-ATP ratio between groups.

RESULTS

Anthropometric and biochemical characteristics of study subjects

The anthropometric features of study subjects are summarized in Table 1. Age was not different among quartiles. Systolic blood pressure was higher in quartile IV than in quartiles I and II. HDL cholesterol was lower in quartile IV when compared with quartiles I and II, and serum triglycerides concentration was higher in quartile IV compared with quartile I. Fasting FFA was not different among quartiles. Adiponectin and resistin were not different among quartiles, while plasma leptin concentration was higher proportionally to BMI. The habitual physical activity was lower in quartile IV than in quartile I, due to the sport activity index (3.39 ± 1.04, 2.55 ± 0.91, 2.29 ± 0.71, and 2.17 ± 0.38 for quartiles I–IV, respectively; $P < 0.001$), which was higher in quartile I than in all the other quartiles ($P < 0.03$).

Insulin sensitivity

Fasting plasma glucose was not different among quartiles ($P = 0.14$). In contrast, plasma insulin was higher in quartiles III and IV than quartiles I and II ($P < 0.05$). Markers of insulin sensitivity (HOMA of insulin sensitivity [HOMA-S%] and HOMA2) were lower in quartiles III and

Table 1—*Anthropometric, metabolic, and laboratory features and lifestyle habits of study subjects stratified for quartiles of BMI (kg/m²)*

	Quartile I	Quartile II	Quartile III	Quartile IV
	21.7 ± 1.3 (18.5–23.2)	24.6 ± 0.7 (23.3–25.5)	26.9 ± 0.9 (25.5–29.0)	32.0 ± 1.7 (30.0–35.3)
Age (years)	31 ± 7	35 ± 6	37 ± 9	37 ± 9
Height (cm)	177 ± 6	177 ± 6	177 ± 7	175 ± 8
Weight (kg)*	68 ± 4	77 ± 5	84 ± 7	98 ± 9
Systolic BP (mmHg)	121 ± 11	119 ± 6	125 ± 9	129 ± 9†
Diastolic BP (mmHg)	79 ± 10	78 ± 6	83 ± 8	83 ± 7
Creatinine (μmol/l)	78 ± 17	80 ± 12	79 ± 10	80 ± 13
Glucose (mmol/l)	4.8 ± 0.3	4.9 ± 0.5	5.0 ± 0.6	5.2 ± 0.5
Insulin (pmol/l)	66 ± 31	70 ± 28	101 ± 35†	105 ± 38†
Cholesterol (mmol/l)				
Total	4.22 ± 0.68	4.81 ± 0.61	5.08 ± 1.30	4.84 ± 1.29
HDL	1.49 ± 0.34	1.47 ± 0.37	1.32 ± 0.29	1.12 ± 0.29†
Triglycerides	0.87 ± 0.51	1.02 ± 0.82	1.09 ± 0.45	1.91 ± 0.99‡
FFAs (mmol/l)	0.59 ± 0.19	0.58 ± 0.25	0.62 ± 0.22	0.60 ± 0.16
Leptin (ng/ml)	2.9 ± 1.2	6.5 ± 5.2	7.0 ± 3.3‡	13.5 ± 6.0*
Adiponectin (μg/ml)	6.9 ± 3.7	6.9 ± 3.7	6.2 ± 2.8	5.2 ± 1.2
Resistin (ng/ml)	3.5 ± 1.0	3.4 ± 1.4	3.4 ± 0.8	3.4 ± 0.4
TSH (mU/l)	1.2 ± 0.9	1.2 ± 1.2	1.1 ± 1.0	1.5 ± 0.6
Smoking habits	3/20	6/21	8/20	5/20
PAI	9.1 ± 1.6	8.1 ± 1.2	8.0 ± 1.3	7.7 ± 0.9‡
HOMA2-S%	88 ± 38	78 ± 34	52 ± 19†	49 ± 20†
HOMA2-B%	128 ± 40	126 ± 28	160 ± 42†	156 ± 41
HOMA2	1.39 ± 0.65	1.52 ± 0.58	2.15 ± 0.76†	2.4 ± 0.97†

Data are means ± SD (BMI range). *$P < 0.001$ vs. all other quartiles; †$P < 0.05$ vs. quartiles I and II; ‡$P < 0.03$ vs. quartile I; one-way ANOVA and Bonferroni post hoc analysis. BP, blood pressure; HOMA-B%, HOMA of β-cell function; PAI, physical activity index.

IV than in quartiles I and II ($P < 0.05$). HOMA2 of β-cell function, as a marker of insulin secretion, was higher in quartile III in comparison with quartiles I and II.

LV anatomical and functional features

Morphological parameters of the LV are summarized in Table 2. The end diastolic wall mass was higher in quartile IV in comparison with quartiles I and II. End LV diastolic and systolic volumes were not different among quartiles. The end di-

Table 2—*Morphologic parameters and functional features of study subjects stratified for quartiles of BMI (kg/m²)*

	Quartile I	Quartile II	Quartile III	Quartile IV
	21.7 ± 1.3 (18.5–23.2)	24.6 ± 0.7 (23.3–25.5)	26.9 ± 0.9 (25.5–29.0)	32.0 ± 1.7 (30.0–35.3)
Heart rate (beats/min)	63 ± 13	63 ± 9	63 ± 10	65 ± 9
Morphologic features				
End diastolic volume (ml)	143 ± 22	141 ± 21	148 ± 33	144 ± 28
End systolic volume (ml)	56 ± 14	55 ± 13	56 ± 16	51 ± 14
End diastolic wall mass (g)	138 ± 24	133 ± 21	145 ± 17	157 ± 19*
End diastolic wall mass/volume ratio (g/ml)	0.97 ± 0.16	0.94 ± 0.10	1.02 ± 0.18	1.12 ± 0.19*
Systolic function				
Stroke volume (ml)	87 ± 13	86 ± 11	92 ± 19	93 ± 16
Cardiac output (l/min)	5.4 ± 1.4	5.4 ± 0.9	5.6 ± 1.0	6.0 ± 1.2
Ejection fraction (%)	61 ± 5	62 ± 5	62 ± 4	65 ± 4
Diastolic function				
Early PFR (ml/s)	464 ± 78	475 ± 74	432 ± 92	469 ± 96
Atrial PFR (ml/s)	213 ± 54	219 ± 42	238 ± 84	261 ± 64
E/A peak flow	2.31 ± 0.69	2.24 ± 0.49	1.99 ± 0.70	1.88 ± 0.49
Deceleration time (ms)	176 ± 26	183 ± 34	197 ± 39	183 ± 35

Data are means ± SD (BMI range) from two-tailed, independent-Samples *t* test. †$P < 0.05$ vs. quartiles I and II in one-way ANOVA and Bonferroni post hoc analysis. PFR: peak filling rate

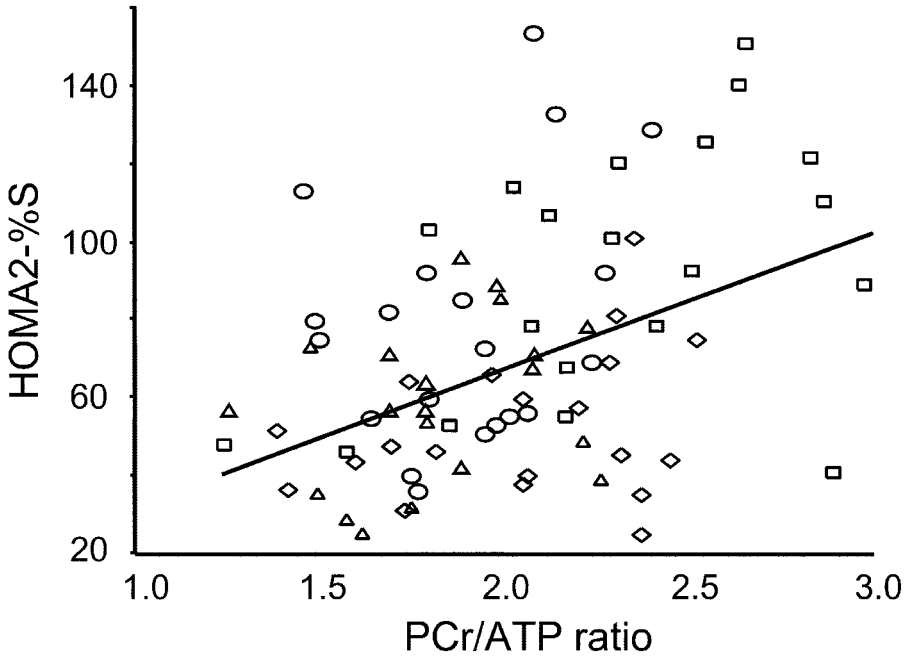

Figure 1—*Association between the PCr-to-ATP ratio and HOMA2-S in quartile I (□), quartile II (○), quartile III (◇), and quartile IV (△)* (r = *0.43;* P < *0.001).*

astolic wall mass-to-volume ratio was consequently higher in quartile IV in comparison with quartiles I and II ($P = 0.02$). Parameters of systolic (stroke volume, cardiac output and ejection fraction) and diastolic (early and atrial peak filling rates and deceleration time) function were not different among quartiles.

LV PCr-to-ATP ratio

The PCr-to-ATP ratio was higher in quartile I (2.25 ± 0.52) in comparison with quartiles IV (1.79 ± 0.29; $P < 0.009$), III (1.89 ± 0.26; $P < 0.02$) and II (1.99 ± 0.38; $P < 0.05$). The accuracy was excellent (rCRSD 15 ± 5%, 16 ± 3%, 17 ± 4% and 18 ± 3% in quartiles I, II, III and IV, respectively; $P = 0.11$). The volume of interest size was not different among quartiles (178 ± 53, 157 ± 61, 160 ± 44, and 178 ± 49 cm^3, respectively; $P = 0.62$). Intra-assay variability was 7 ± 4%. Interassay variability was 12 ± 5%. The distance between the center of the coil and the anterior margin of the LV wall was small but different, because of the thorax morphology, across quartiles (4.0 ± 0.8, 4.2 ± 0.5, 4.5 ± 0.7, and 5.3 ± 0.7 cm; $P < 0.001$). We assessed the effect of this difference on the PCr-to-ATP ratio in a subgroup of seven volunteers (aged 31 ± 3 years, BMI 23.3 ± 1.2 kg/m^2) in which two spectroscopic acquisitions were obtained. The first acquisition was acquired under conditions where the chest and heart were displaced using a 1.5-cm spacer so that the distance between the coil and the heart was similar to the mean distance measured in quartile IV, while the second acquisition was acquired without the spacer. PCr-to-ATP ratios obtained with the spacer (2.13 ± 0.31) or without it (1.85 ± 0.27) were not different ($P = 0.22$).

Effects of hemodynamic and metabolic variables on the correlation between BMI and PCr/ATP ratio

Pearson correlation analysis showed that the PCr/ATP ratio was associated with the BMI ($r = -0.26$; $P = 0.022$), fasting plasma glucose ($r = -0.32$; $P = 0.01$), insulin ($r = -0.32$; $P = 0.012$), leptin ($r = -0.28$; $P = 0.039$), Adult Treatment Panel III–defined criteria of metabolic syndrome ($r = -0.29$; $P = 0.012$), HOMA2-S% ($r = 0.44$; $P = 0.001$; Fig. 1), HOMA2 ($r = 0.34$; $P = 0.007$), and physical activity index ($r = 0.27$; $P = 0.035$). When we performed multivariate regression analysis adjusting for the parameters described above, HOMA2-S% was the only variable always associated with the PCr/ATP (Table 3).

CONCLUSIONS — The cardiac metabolic adaptation or maladaptation in response to diabetes could be considered at the basis of the functional and structural/geometrical abnormalities affecting the diabetic heart (4,5); two studies demonstrated an alteration of LV energy metabolism in type 2 diabetic patients without concomitant cardiac disease (6,7). These studies were performed in humans with established diabetes with high prevalence of comorbid conditions and use of multiple drugs; therefore, the understanding of this alteration was extremely complex. It remained uncertain whether the abnormal cardiac energy metabolism was subsequent to the development of overt hyperglycemia or whether it was already present in the pre-diabetic state. The novel contribution of the present study was that the alteration of the LV energy metabolism affecting type 2 diabetic patients was manifested in young overweight/obese individuals in the absence of established comorbid conditions, drug administration, or overt hyperglycemia. The abnormal cardiac energy homeostasis was not simply dependent on glucose toxicity, and other additional factors might begin to influence cardiac metabolism before the development of overt hyperglycemia.

Taking into account that the overweight/obese individuals belonging to quartiles II, III, and IV had lower PCr-to-ATP ratios in the absence of major LV dysfunctions, the impact of functional abnormalities had to be excluded. Plausible explanations for the finding were as follows: *1*) increased LV mass, *2*) simultaneous expression of metabolic and cardiovascular risk factors (metabolic syndrome), *3*) insulin resistance, *4*) intrinsic or acquired cardiac metabolic abnormalities. In support of the first potential explanation, the individuals belonging to quartile IV were characterized by slightly higher systolic blood pressure in comparison with the individuals of quartiles I and II (Table 1) and showed higher end diastolic wall mass (Table 2). In patients with hypertension and LV hypertrophy, PCr-to-ATP ratio was reduced (17), and this reduction was associated with the progression of heart failure in patients with dilated and hypertrophic cardiomyopathy (18). The second plausible explanation was supported by the fact that the individuals of quartile IV were characterized by reduced serum HDL cholesterol, increased serum triglycerides, and a trend for higher plasma glucose. These parameters are included in the definition of the metabolic syndrome,

Table 3—*Two-tailed Pearson's correlation and adjusted partial correlation coefficients with PCr/ATP ratio*

Variables	Univariate	Multivariate Model 1	Multivariate Model 2	Multivariate Model 3	Multivariate Model 4
Age		—	—	—	—
R	0.19	—	—	—	—
P	0.11	—	—	—	—
BMI		—	—	—	—
r	−0.26	—	—	—	—
P	0.022	—	—	—	—
SBP		—	—	—	—
r	−0.11	−0.00	—	—	—
P	0.33	0.98	—	—	—
EDWM		—	—	—	—
r	0.0	0.13	—	—	—
P	0.98	0.29	—	—	—
HDL		—	—	—	—
r	0.15	0.06	−0.07	—	—
P	0.23	0.62	0.61	—	—
Triglycerides		—	—	—	—
r	−0.16	−0.06	−0.04	—	—
P	0.20	0.66	0.74	—	—
PAI		—	—	—	—
r	0.273	0.23	0.21	0.21	—
P	< 0.035	0.08	0.12	0.13	—
ATP III–defined MS		—	—	—	—
r	−0.29	−0.13	−0.15	−0.14	−0.12
P	< 0.012	0.25	0.23	0.29	0.41
HOMA2-S%		—	—	—	—
r	0.43	0.37	0.38	0.40	0.34
P	< 0.001	0.007	0.005	0.003	0.017

Model 1 adjusted for age and BMI; Model 2 adjusted for age, BMI, PAS, and EDWM; Model 3 adjusted for age, BMI, SBP, EDWM, HDL cholesterol, and triglycerides; Model 4 adjusted for age, BMI, SBP, EDWM, HDL cholesterol, triglycerides, and physical activity index (PAI). EDWM, end diastolic wall mass; SBP, systolic blood pressure.

which is considered a major risk factor for cardiovascular disease. In the univariate analysis, the metabolic syndrome was inversely associated with the PCr-to-ATP ratio (Table 3). It is not clear whether the metabolic syndrome has a single cause, but insulin resistance is considered its most important underlying risk factor (19). In this respect, HOMA2-S% was impaired across quartiles of BMI and was associated with the PCr-to-ATP ratio in univariate analysis (Fig. 1); multivariate analyses showed that the HOMA2-S% was the most relevant predictive factor of the PCr-to-ATP ratio, and only the degree of habitual physical activity attenuated, but did not abolish, the association (Table 3). Abnormal tissue energy metabolism, in association with whole-body insulin resistance, was described also in the skeletal muscle of type 2 diabetic patients (6) and of their nondiabetic, first-degree relatives (20).

How insulin resistance may influence cardiac metabolism is a matter of intense investigations. Excessive intramyocardiocellular fat content was described in patients with essential hypertension (21), in association with higher BMI (22), in obese, diabetic patients with nonischemic heart failure (23) and in moderately obese subjects (24). We did not assess the intracardiac fat content, and we did not find any correlation between PCr-to-ATP ratio and plasma FFA concentration as a marker of lipotoxicity. This lack of association was in contrast with the finding reported in patients with overt type 2 diabetes (6). This dichotomy may be due to the different features of the study groups. It is recognized as a dominance of fatty acid metabolism by the heart in the fasted state; when the heart is acutely stressed, it switches from fat to carbohydrates as fuel (25) because of a more convenient balance of oxygen consumption. In fact, artificial elevation of FFA in diabetic hearts reduces cardiac efficiency via an oxygen waste for noncontractile purposes (26). This scenario was supported by our finding in patients with heart failure in whom treatment with Trimetazidine, a partial fatty acids oxidation inhibitor, induced improvement of the LV function and PCr/ATP ratio (27), likely switching the energy substrate preference (28). Hence, we may speculate that in patients with overt type 2 diabetes, the increased FFAs availability, pushing their own oxidative disposal, induces a detrimental and proportional effect on the PCr-to-ATP ratio (6). Peterson et al. (29), using positron emission tomography in combination with echocardiography, showed that in young obese women cardiac efficiency was impaired in association with insulin resistance and myocardial fatty acids uptake, utilization, and oxidation regardless of FFA levels.

The present work had some limitations. We estimated insulin sensitivity and secretion using surrogate indexes. Even if they have the potential to provide meaningful insights into glucose metabolism (30), they are less sensitive and specific than the insulin clamp. We could not exclude that the association between insulin sensitivity and the PCr-to-ATP ratio could be stronger if more specific measures were employed. We must also state that a minimal concentric rearrangement

of the LV geometry was detected in the individuals within quartile IV (Table 2); the ejection fraction may therefore be a crude estimate of the LV pump performance. The use of a more direct measure of load-independent wall mechanics (obtained by means of tagging MRI or tissue Doppler echocardiography) (31), which was not adopted in the present study, could reveal the presence of a minimal dysfunction in this subgroup. This limitation did not detract from the importance of the alteration of energy metabolism, which was also observed in the individuals within quartiles II and III.

In conclusion, abnormal LV energy metabolism was detectable in obese but otherwise healthy men, supporting the hypothesis that metabolic remodeling in insulin resistant states preceded the onset of frank hyperglycemia and the development of major functional and structural/geometrical remodeling of the heart. Based on this cross-sectional study, insulin resistance may be a relevant factor to the reduced LV PCr-to-ATP ratio; longitudinal studies addressing the association between these metabolic alterations and the future development of cardiac dysfunctions are warranted.

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