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Impact of Gender on the Myocardial Metabolic Response to Obesity

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OBJECTIVES We sought to determine the gender-specific effects of obesity on myocardial metabolism, work, and efficiency.

BACKGROUND Myocardial metabolism abnormalities may contribute to the development of obesity-related heart failure. Increased myocardial oxygen consumption (MVO_2) and fatty acid (FA) metabolism and decreased efficiency occur with obesity in women. It is unknown whether similar changes occur with obesity in men.

METHODS We quantified cardiac work, efficiency, myocardial blood flow (MBF), MVO_2, glucose, and FA metabolism with echocardiography and positron emission tomography in nonobese and obese men and women ($N = 86$).

RESULTS There were significant differences between the obese ($n = 35$) and nonobese ($n = 51$) subjects in age, body composition, plasma lipids, and insulin resistance in addition to differences between the men ($n = 30$) and women ($n = 56$) in body composition and plasma lipids. Female gender independently predicted increased cardiac work ($p < 0.001$). Female gender also related to lower efficiency ($p < 0.05$). Obesity and female gender independently predicted greater MBF ($p < 0.01$, $p < 0.0005$, respectively) and MVO_2 ($p < 0.0005$, $p < 0.0001$). Myocardial glucose uptake was not different among the 4 subject groups, but obesity and gender interacted in predicting glucose uptake ($p < 0.05$). Lower myocardial glucose utilization was independently predicted by female gender ($p < 0.05$), and it independently predicted lower myocardial glucose utilization/plasma insulin ($p < 0.05$). Obesity and gender significantly interacted in the determination of glucose utilization/plasma insulin ($p = 0.01$). There were no differences in FA uptake among the 4 groups, and although increasing obesity correlated with greater myocardial FA utilization and oxidation; female gender ($p < 0.005$, $p < 0.01$) and plasma triglycerides ($p < 0.05$, $p < 0.005$) were their independent predictors.

CONCLUSIONS Women's and men's myocardial metabolic responses to obesity are not exactly the same. Obesity and gender modulate MBF and MVO_2, are related to myocardial substrate metabolism, and sometimes interact in its prediction. Gender modifies efficiency. Gender-related differences in myocardial metabolism may affect the development of/adaptation to obesity-related cardiac disease. (J Am Coll Cardiol Img 2008;1:424–33) © 2008 by the American College of Cardiology Foundation

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Obesity is an independent risk factor for heart failure and is thought to contribute to 11% of heart failure cases among men and 14% among women, which are alarming percentages given the recent increase in obesity prevalence (1). The etiology of obesity-associated heart failure is not completely understood. There is an increase in plasma volume, neurohormonal activation, and hemodynamic load (2). However, there are also intrinsic changes to the human myocardium that are independent of load (3).

See page 434

One of these changes appears to be an alteration in myocardial metabolism. Because of the inherent link between myocardial substrate metabolism for generation of energy and cardiac function and because increased myocardial fatty acid (FA) metabolism and/or storage detrimentally affects cardiac function in animal models of obesity, we recently investigated obesity's effects on myocardial metabolism in young women (4,5). We showed that myocardial oxygen consumption (MVO_2) directly correlated with increased body mass index (BMI). In addition, we demonstrated that increases in myocardial FA utilization and oxidation were predicted by increasing insulin resistance in these women (5).

There are no data, however, comparing the effects of obesity on myocardial metabolism in men and women. Epidemiologic data have been used by authors to suggest gender-related differences in the heart's response to obesity (1). Also, the results of studies performed only in men with impaired glucose tolerance and control patients do not show the same myocardial FA metabolism changes found in our study of women (6,7). Furthermore, gender affects total body, muscle, hepatic, and myocardial substrate metabolism in nonobese subjects (8–10). Thus, the purpose of this study was to determine whether myocardial metabolic remodeling in response to obesity differs between men and women.

METHODS

Study subjects. In this prospective study, we evaluated young men and premenopausal women. Of the men, 11 were obese (BMI >30 kg/m^2) and 19 were nonobese (BMI <30 kg/m^2); of the women, 24 were obese and 32 were nonobese. None of the data were in our first study of obesity in women. All subjects underwent a screening medical history, physical examination, and phlebotomy for fasting routine chemistries and lipid panels. Obese subjects underwent 2-h glucose tolerance tests. Subjects were excluded if they were >350 pounds, diabetic, hypertensive, smokers, nonsedentary, taking vasoactive or lipid medications, or if they had cardiac disease (per history, physical examination, echocardiograms and, if indicated, rest/stress echocardiograms). The Institutional Review Board at the Washington University School of Medicine approved this study. All subjects signed informed consent.

Experimental procedure. Subjects underwent dual-energy X-ray absorptiometry (QDR-1000/w; Hologic, Bedford, Massachusetts) for body composition measurements. All positron emission tomography (PET) studies were performed on an ECAT 962 HR+ (Siemens Medical Systems, Iselin, New Jersey) at 8:00 AM to avoid circadian variations in patients. Subjects were admitted to the General Clinical Research Center at Washington University; they were given a standardized meal the night before the PET study, and then they fasted for 12 h before PET imaging. Subjects were on telemetry and had their blood pressure measurements taken throughout the study.

Positron emission tomography measurements of myocardial blood flow (MBF) and metabolism. Subjects underwent placement and transmission scans (for attenuation correction). Positron emission tomography imaging was performed after the injection of ^{15}O-water, ^{11}C-acetate, 1-^{11}C-glucose, and 1-^{11}C-palmitate (10–14). Throughout the PET study, we obtained plasma substrates, insulin, and radiolabeled metabolites, which are required for compartmental modeling of the PET data (13,14). Blood and myocardial time-activity curves were used in conjunction with well-established kinetic models to quantify MBF, MVO_2, glucose extraction fraction, and FA extraction fraction (which was further divided into the portions that entered oxidation and slow turnover pools) in patients (15). These extraction fractions were then used in conjunction with MBF and plasma substrate levels to calculate uptake and utilization of glucose and FA and FA oxidation (10,15).

Plasma analyses and whole-body insulin resistance. Plasma insulin and glucose were measured with the utilization of radioimmunoassay (Millipore, Billerica, Massachusetts) and using a Cobas Mira analyzer (Roche Diagnostics, Basel, Switzerland), respectively. Free FAs and lactate in the plasma were measured with an enzymatic colorimetric method (NEFA C kit, WAKO Chemicals, Richmond, Virginia) and photospectrometry (Sigma

ABBREVIATIONS AND ACRONYMS

BMI = body mass index
FA = fatty acid
HOMA = homeostasis model assessment of insulin resistance
LV = left ventricular
MBF = myocardial blood flow
MVO_2 = myocardial oxygen consumption
PET = positron emission tomography

Chemical Co., St. Louis, Missouri). Insulin resistance was calculated with the homeostasis model assessment (HOMA) = (fasting insulin [μU/ml] · fasting glucose [mmol/l]/22.5).

Echocardiography. Immediately after MVO_2 measurement, subjects underwent a 2-dimensional and Doppler echocardiographic examination for quantification of left ventricular (LV) size and function using a Sequoia-C256 (Acuson-Siemens, Mountain View, California) or a Vivid 7 (GE Medical Systems, Horten, Norway). Left ventricular mass was determined with the area-length method. Left ventricular ejection fraction was calculated with utilization of the modified Simpson's method. Cardiac work and efficiency were calculated as previously described (5,10).

Statistical analysis. We used SAS software (SAS Institute, version 9, Cary, North Carolina) for the analyses. Data are listed as mean value ± SD. Skewed variables (plasma triglycerides and myocardial glucose utilization/plasma insulin) were log transformed. Data comparisons between any 2 of the 4 subject sets were made with unadjusted pairwise comparisons. Analyses involving both obesity status and gender were performed with a 2-factor analysis of variance. Outcome variables were MBF, MVO_2, myocardial glucose uptake, utilization, utilization/plasma insulin, myocardial FA uptake, utilization, and oxidation, cardiac work, and efficiency. In our initial analyses, we evaluated interactions between obesity and gender. When the interaction was not significant, we evaluated main effects to assess the significance of the individual factors. In one instance, there was a significant obesity by gender interaction that reflected a greater decrease in myocardial glucose utilization/plasma insulin in men than in women. Because the direction of the effect was the same in both genders, we also report a gender effect in a 2-factor analysis of variance that does not include an interaction term.

To evaluate the independent effect of potential covariates (age, mean arterial pressure, HOMA, and plasma triglycerides) that were associated with outcome measures ($p < 0.10$) and to evaluate the covariate-adjusted significance of gender and obesity, we included these variables in a stepwise analysis of covariance that produced a best set of predictors. In these multivariate models, each independent variable was adjusted for all other independent variables. The relationship between plasma FAs and myocardial FA utilization or oxidation was not analyzed because plasma FAs are used in their calculation. Similarly, HOMA and myocardial glucose utilization/plasma insulin's relationship was not analyzed. A $p < 0.05$ was considered significant.

RESULTS

Clinical characteristics and LV structure/function. The nonobese and obese differed in almost all clinical characteristics (Table 1). The genders differed in body composition, high-density lipoprotein, and triglyceride levels (Table 1). There were racial differences between the men and women ($p < 0.05$) but no racial differences in any of the outcomes (data not shown).

Table 1. Subjects' Clinical Characteristics

	Nonobese		Obese		p Value	
	Men	Women	Men	Women	Obese vs. Nonobese	Men vs. Women
n	19	32	11	24		
Age (yrs)	26 ± 6	27 ± 6	35 ± 5	36 ± 9	<0.0001	NS
Race, % white	79	50	100	71	0.09	<0.05
Weight, kg	79 ± 8	63 ± 8	118 ± 11	113 ± 19	<0.0001	0.14
Body mass index, kg/m^2	24 ± 3	24 ± 3	37 ± 2	42 ± 7	<0.0001	0.17
Fat-free mass, kg	64 ± 6	44 ± 4	78 ± 7	56 ± 8	<0.0001	<0.0001
Fat mass, kg	14 ± 6	19 ± 6	38 ± 6	48 ± 10	<0.0001	<0.05
Fat, %	18 ± 6	30 ± 6	32 ± 4	46 ± 4	<0.0001	<0.0001
Waist circumference, cm	82 ± 5	78 ± 10	120 ± 9	117 ± 16.5	<0.0001	0.17
Total cholesterol, mg/dl	158 ± 27	157 ± 27	190 ± 35	174 ± 40	<0.01	0.45
LDL, mg/dl	91 ± 23	81 ± 23	108 ± 29	97 ± 29	<0.01	0.13
HDL, mg/dl	49 ± 11	62 ± 13	38 ± 7	52 ± 11	<0.0005	<0.0001
Triglycerides, mg/dl	88 ± 33	67 ± 22	247 ± 118	128 ± 71	<0.0001	<0.005
HOMA	0.86 ± 0.38	1.09 ± 0.64	3.83 ± 1.90	2.52 ± 1.09	<0.0001	0.5

HDL = high-density lipoprotein; HOMA = homeostasis model assessment of insulin resistance; LDL = low-density lipoprotein.

Table 2. Hemodynamics and LV Structure and Function

	Nonobese		Obese		p Value	
	Men	Women	Men	Women	Obese vs. Nonobese	Men vs. Women
Hemodynamics						
Systolic blood pressure, mm Hg	114 ± 17	111 ± 12	133 ± 11	127 ± 14	<0.0001	0.44
Diastolic blood pressure, mm Hg	63 ± 9	69 ± 8	73 ± 8	71 ± 6	<0.005	0.16
Mean arterial pressure, mm Hg	81 ± 10	83 ± 6	93 ± 9	89 ± 7	<0.001	0.88
Heart rate, beats/min	56 ± 6	62 ± 10	71 ± 10	70 ± 11	<0.0001	0.12
Rate-pressure product, mm Hg · beats/min	6,507 ± 1,157	6,954 ± 1,289	9,395 ± 1,801	8,798 ± 1,630	<0.0001	0.73
LV structure						
LV mass, g	175 ± 38	121 ± 20	209 ± 29	173 ± 29	<0.0001	<0.0001
LV mass/fat-free mass (g/kg)	2.73 ± 0.42	2.74 ± 0.39	2.71 ± 0.43	3.02 ± 0.68	<0.21	<0.0001
LV systolic function						
Ejection fraction, %	59 ± 5	62 ± 5	59 ± 6	62 ± 5	0.99	0.005
Cardiac work (j/g/min)	0.24 ± 0.07	0.34 ± 0.09	0.29 ± 0.04	0.38 ± 0.11	0.08	<0.0001
LV efficiency (%)	13.8 ± 2.6	13.1 ± 3.6	15.1 ± 3.6	12.3 ± 4.9	0.62	<0.05

LV = left ventricular.

The obese had higher blood pressure, heart rate, rate-pressure product, and LV mass than the nonobese (Table 2). The men had greater LV mass and lower LV mass/fat-free mass, ejection fraction, and cardiac work compared with the women (Table 2). Female gender related to greater work (Table 3 lists all univariate relationships) and was its only independent predictor (Table 3 lists all multivariate model results).

Plasma substrate and insulin levels. Table 4 shows levels during the PET study. Glucose levels were greater in the obese and in men; lactate was greater in men; insulin was greater in the obese.

Myocardial blood flow, MVO_2, and efficiency. Figure 1A depicts MBF (nonobese men, 0.95 ± 0.19 ml · g^{-1} · min^{-1}; obese men 0.99 ± 0.18 ml · g^{-1} · min^{-1}; nonobese women 1.10 ± 0.21 ml · g^{-1} · min^{-1}; and obese women, 1.29 ± 0.30 ml · g^{-1} ·

Table 3. MBF + Myocardial Substrate Uptake and Metabolism: Univariate, Multivariate, and Interaction Analyses

	MBF	MVO_2	Glucose Uptake	Glucose Utilization	Glucose Utilization, Insulin	FA Uptake	FA Utilization	FA Oxidation	Cardiac Work	Efficiency
Univariate analyses results										
Obesity	<0.005	<0.0001	NS	NS	<0.0005	NS	<0.01	<0.001	0.06	NS
Gender	0.0001	<0.0001	NS	<0.05	NS	<.05	<.05	0.05	<0.001	<0.05
Plasma triglyceride	NS	NS	NS	NS	r = −0.43; p = 0.0001	NS	r = 0.31; p = 0.01	r = 0.39; p = 0.001	NS	r = 0.21; p = 0.05
Age	NS	NS	NS	NS	NS	NS	r = 0.24; p = 0.06	r = 0.29; p < 0.05	r = 0.21; p = 0.06	NS
Mean arterial pressure	NS	NS	NS	NS	NS	NS	r = 0.25; p < 0.05	r = 0.31; p = 0.01	NS	NS
Multivariate analyses results										
Obesity	<0.01	<0.0005	NS	NS	NS	NS	NS	NS	NS	NS
Gender	<0.0005	<0.0001	NS	<0.05	<0.05	<0.05	<0.005	<0.01	<0.001	NS
Plasma triglyceride	NS	NS	NS	NS	<0.01	NS	<0.05	<0.005	NS	<0.05
Age	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Mean arterial pressure	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Significance of interactions between obesity and gender on outcomes										
p Values	0.15	0.11	<0.05	0.11	0.01	0.75	0.6	0.78	0.69	0.47

FA = fatty acid; MBF = myocardial blood flow; MVO_2 = myocardial oxygen consumption; NS = not significant.

Table 4. Plasma Substrate and Insulin Levels During the Positron Emission Tomography Study

	Nonobese		Obese		p Value	
	Men	Women	Men	Women	Obese vs. Nonobese	Men vs. Women
Free fatty acids, nmol/ml	516 ± 214	656 ± 325	671 ± 178	705 ± 199	0.09	0.08
Glucose, μmol/ml	4.93 ± 0.29	4.81 ± 0.40	5.35 ± 0.47	5.06 ± 0.49	<0.005	<0.05
Lactate, nmol/ml	745 ± 280	659 ± 170	867 ± 423	576 ± 252	0.67	<0.05
Insulin, μU/ml	3.94 ± 1.66	4.99 ± 2.52	15.96 ± 8.16	11.4 ± 4.6	<0.0001	0.63

min^{-1}). Figure 1B shows MVO_2 (nonobese men, 4.1 ± 0.8 ml · g^{-1} · min^{-1}; obese men, 4.5 ± 1.3 ml · g^{-1} · min^{-1}; nonobese women, 5.8 ± 1.0 ml · g^{-1} · min^{-1}; obese women, 7.1 ± 1.6 ml · g^{-1} · min^{-1}). The effects of gender and obesity on MBF and MVO_2 also are demonstrated in Figures 2, 3, and 4. Female gender and obesity independently predicted MBF and MVO_2, accounting for 22% and 47% of their variability, respectively. Obesity and gender did not interact in determining MBF or MVO_2 (Table 3 lists all interaction results).

Women had lower efficiency than men (Table 2), and female gender independently predicted lower efficiency ($p < 0.05$). However, if plasma triglycerides were added to the multivariate model, gender lost its significance, likely because of the relationship between gender and triglycerides ($p < 0.005$).

In exploratory analyses, we evaluated the effect of cardiac work on MVO_2. Work related in a univariate manner to MVO_2 ($r = 0.36$, $p < 0.001$) but did not independently predict it, likely because of the significant relationship between gender and work. Also, given gender differences in LV mass/fat-free mass, we determined that it significantly interacted with gender in the prediction of MBF, and when added to the model, obesity was no longer an independent predictor. In this model, LV mass/fat-free mass and gender accounted for 32% of the variation in MBF.

Myocardial glucose uptake, utilization, and utilization/plasma insulin. Myocardial glucose uptake was not different among the groups, and although gender and obesity were not significantly related to uptake, they significantly interacted in predicting uptake

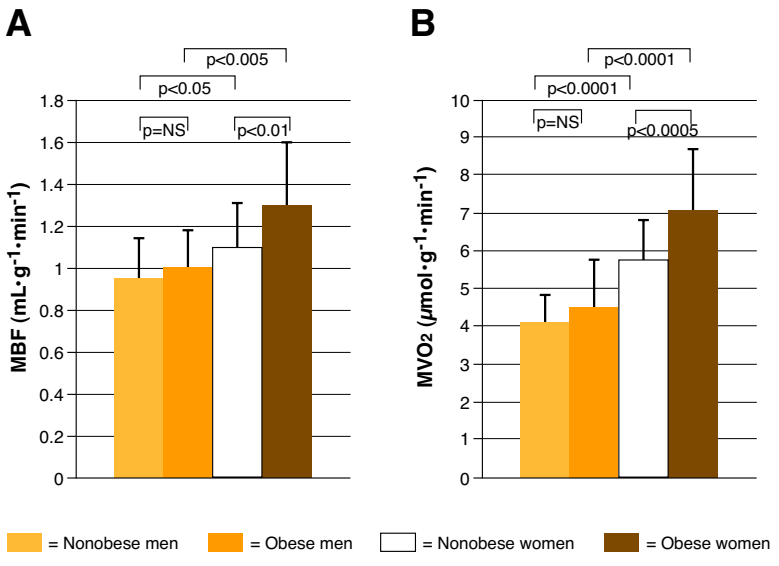

Figure 1. MBF and MVO_2 in obese and nonobese men and women

Panel A shows MBF, which we quantified using positron emission tomography, in the 4 subject groups. The p values for the pairwise comparisons are shown. The obese women had the greatest MBF, which was significantly greater than in the nonobese women or the obese men. The nonobese women also had greater resting MBF than the nonobese men. **Panel B** shows MVO_2 levels in the groups, as determined with the utilization of positron emission tomography. Obese women had the greatest MVO_2, which was significantly greater than the nonobese women and the obese men. Nonobese women also had greater MVO_2 than the nonobese men. MBF = myocardial blood flow; MVO_2 = oxygen consumption.

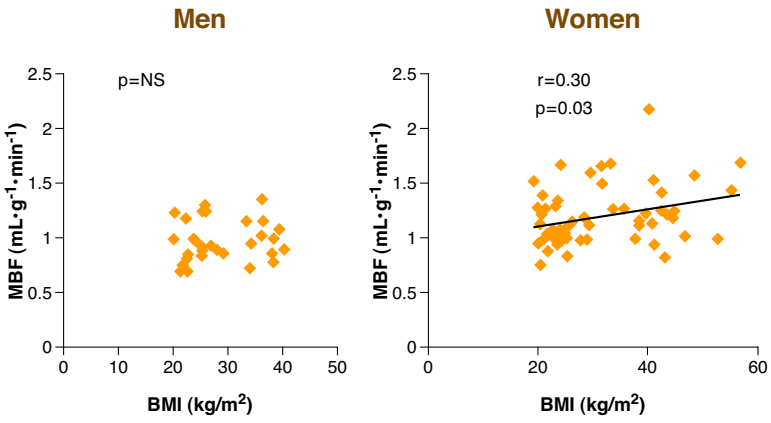

Figure 2. MBF Versus BMI in Men and Women

This figure demonstrates the relationships between MBF, quantified using positron emission tomography, and BMI in men and in women. The correlations between BMI and MBF were only significant in the women. However, r values for the correlations of BMI with MBF in men and women were not statistically different. BMI = body mass index; MBF = myocardial blood flow.

(Fig. 5A, Table 3). Myocardial glucose utilization was not different among the subjects, but female gender predicted lower glucose utilization ($p < 0.05$). Figure 5B shows myocardial glucose utilization/plasma insulin (nonobese men, 90 ± 64 [nmol · g^{-1} · min^{-1}]/[μU · ml^{-1}]; obese men, 17 ± 23 [nmol · g^{-1} · min^{-1}]/[μU · ml^{-1}]; nonobese women, 45 ± 43 [nmol · g^{-1} · min^{-1}]/[μU · ml^{-1}]; and obese women, 25 ± 25 [nmol · g^{-1} · min^{-1}]/[μU · ml^{-1}]. It related inversely to obesity and plasma triglycerides, but not gender. However, in the multivariate analysis, female gender ($p < 0.05$) and plasma triglycerides ($p < 0.01$) predicted lower myocardial glucose utilization/insulin, accounting for 32% of its variability. Obesity and gender interacted in predicting myocardial glucose utilization/insulin (Fig. 5B, Table 3).

Myocardial FA uptake, utilization, and oxidation. There were no differences in myocardial FA uptake among the 4 groups (Figs. 6A to 6C). However, female gender predicted increased FA uptake ($p < 0.05$). Myocardial FA utilization (nonobese men, 111 ± 48 nmol · g^{-1} · min^{-1}; obese men, 149 ± 41

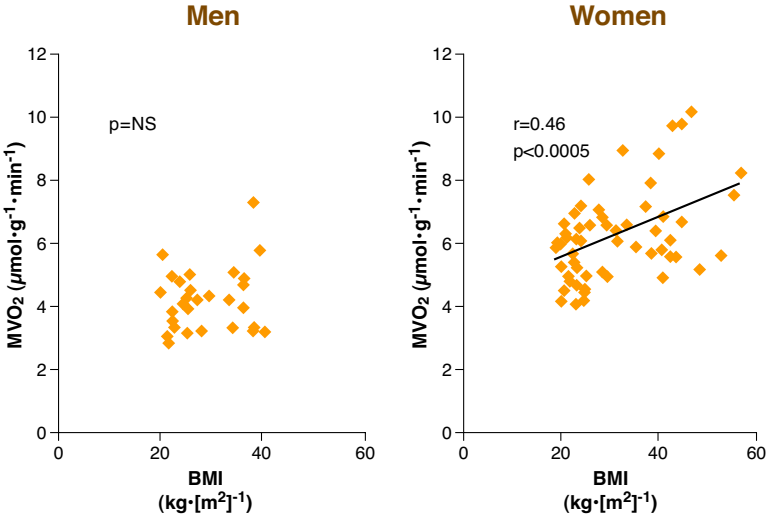

Figure 3. MVO_2 Versus BMI in Men and Women

These graphs show how MVO_2, quantified using positron emission tomography, relates to increasing BMI in men and in women. The correlation between MVO_2 and BMI was only significant in the women. However, r values for the correlations in men and women were not statistically different. BMI = body mass index; MVO_2 = oxygen consumption.

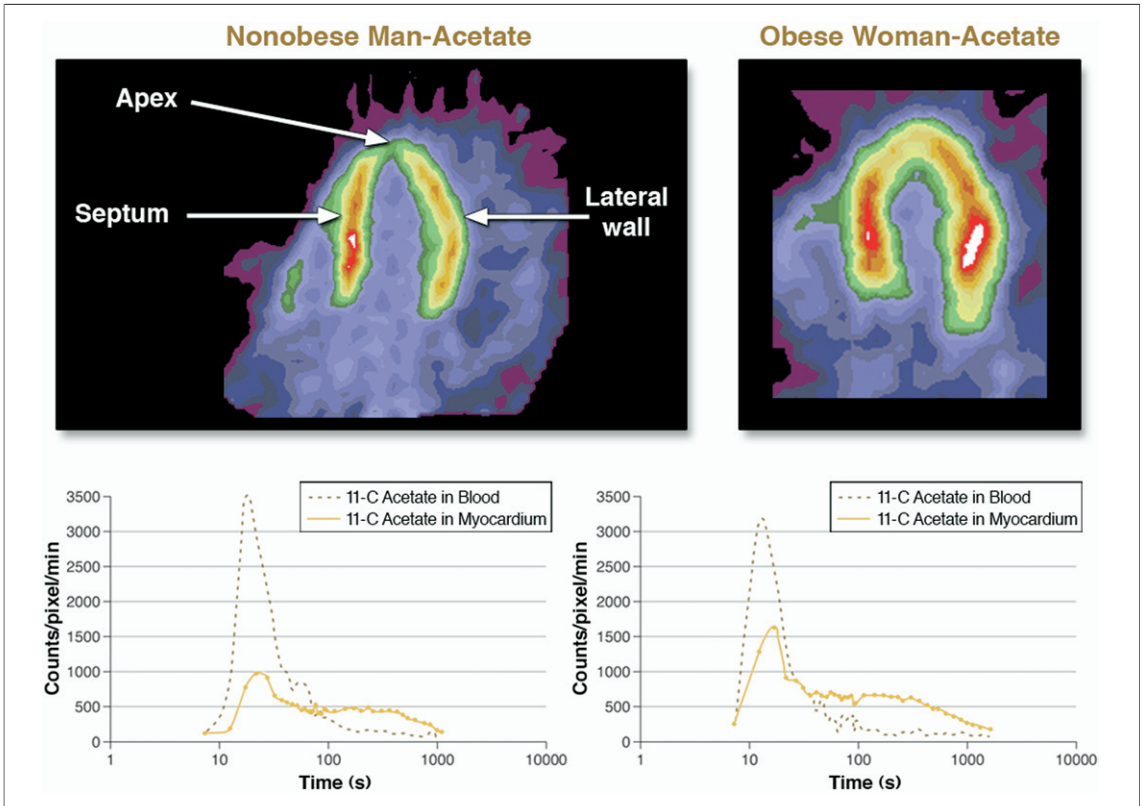

Figure 4. Typical PET Images and Time-Activity Curves

Top left, typical positron emission tomography (PET)-derived, horizontal long-axis image from the myocardium of a nonobese man in our study after injection with 1-^{11}C-acetate. Compared with the nonobese man, the PET-derived image after 1-^{11}C-acetate from an obese women's myocardium shows greater tracer accumulation in the myocardium (more white and red graphically indicate greater counts in the woman's myocardium, corresponding to greater tracer uptake). **Bottom panels,** blood **(dashed lines)** and myocardial time-activity curves **(solid lines)** from the corresponding PET images, which were used in conjunction with compartmental models to quantify MVO_2.

nmol · g^{-1} · min^{-1}; nonobese women, 142 ± 50 nmol · g^{-1} · min^{-1}; and obese women, 169 ± 40 nmol · g^{-1} · min^{-1}), related to obesity, female gender, age, plasma triglyceride levels, and mean arterial pressure (Table 3). However, only female gender and triglyceride levels independently predicted increased FA utilization, accounting for 27% of its variability. Myocardial FA oxidation (nonobese men, 101 ± 44 nmol · g^{-1} · min^{-1}; obese men, 140 ± 41 nmol · g^{-1} · min^{-1}; nonobese women, 122 ± 43 nmol · g^{-1} · min^{-1}; and obese women, 156 ± 40 nmol · g^{-1} · min^{-1}) related to obesity, female gender, age, plasma triglycerides, and mean arterial pressure, but only plasma triglycerides and gender independently predicted it, accounting for 31% of its variability.

DISCUSSION

Our results are the first to demonstrate different myocardial metabolic signatures in men and women in response to obesity. Specifically, both obesity and female gender independently predict greater MBF and MVO_2. Female gender independently predicts greater cardiac work, lower myocardial glucose uptake, utilization, and utilization/plasma insulin. Moreover, obesity and gender interact in determining myocardial glucose uptake and insulin sensitivity, which highlights the complexity of their relationship on influencing myocardial metabolism. Although obesity and myocardial FA metabolism correlate, female gender independently predicts greater FA metabolism, and female gender relates to inefficiency. (Of note, multivariate analyses with utilization of the continuous variable, BMI, instead of obese/nonobese, did not alter any of our results; data not shown.)

Our finding that both obesity and gender affect MBF helps explain the apparently conflicting results of studies regarding obesity and MBF. In our study of women, obesity predicted MBF but, in another study of men, obesity did not (5,16). The interaction between gender and LV mass/fat-free mass also affects MBF. Differences in MBF with

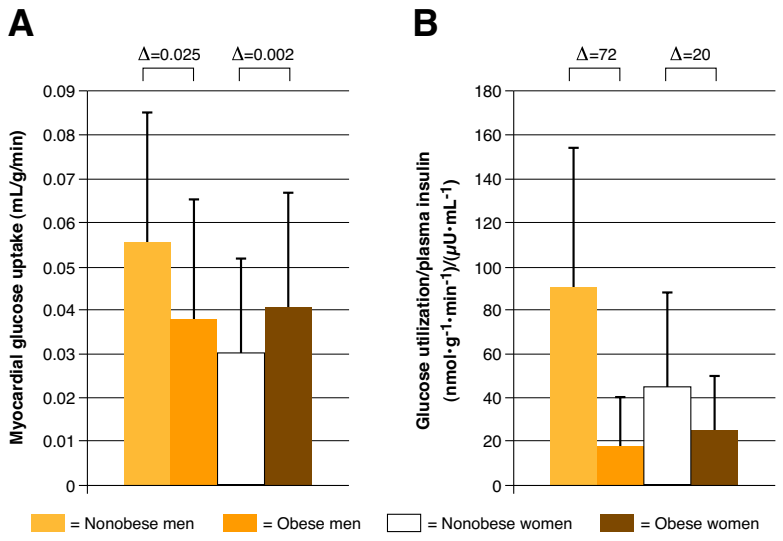

Figure 5. Myocardial Glucose Uptake and Glucose Utilization/Plasma Insulin

Panels A and B show the groups' myocardial glucose uptake and glucose utilization/plasma insulin, respectively. Glucose uptake and utilization were measured with positron emission tomography and insulin with a radioimmunoassay. Obesity's and gender's significant interaction in the prediction of glucose uptake ($p < 0.05$) is shown graphically because both the magnitude and direction of the effect of obesity on myocardial glucose uptake differ in men and women. Obese men have lower uptake than nonobese men; obese women, however, have greater uptake than nonobese women. Obesity and gender also interacted in determining glucose utilization/plasma insulin ($p = 0.01$), as shown by the magnitude of the difference between the obese and nonobese men and that between the obese and nonobese women.

obesity likely involve a complex interaction between vasodilatory and constrictive influences, including sex hormones, genomic differences, hormone receptors, and metabolites, as evidenced by the fact that men and women's vasoactive responses to sex hormones are not the same (17,18).

The increase in MVO_2 with obesity and female gender extends our previous findings that demonstrated increasing MVO_2 with increasing obesity in women (5). Cardiac work influences MVO_2 but was not an independent predictor. (The significant relationship of work with female gender further underscores the complexity of the influences on MVO_2.) The increased MVO_2 observed in women and the obese may be in part the result of increased myocardial FA oxidation related to female gender and obesity because FA oxidation is less oxygen efficient than glucose oxidation. The borderline higher plasma FA levels in the obese and in the women may also increase MVO_2 via up-regulation of uncoupling proteins; greater estrogen levels in women may also increase MVO_2 via up-regulation of uncoupling proteins and their function (19,20). Up-regulation of uncoupling proteins uncouples oxygen consumption from adenosine triphosphate production (for cardiac work), hence, they may also play a role in the lower efficiency observed in women.

Concordant with our previous results in women, obesity at first glance appears to have little effect on glucose metabolism (5). However, with obesity, and increasing whole-body insulin resistance, the myocardium utilizations less glucose/plasma insulin and thus appears insulin resistant. Furthermore, obesity and gender interact significantly in the prediction of glucose uptake and glucose utilization/insulin, and female gender is an independent predictor of lower glucose utilization/plasma insulin. Female gender also predicts less myocardial glucose utilization. Estrogen may be involved in this lower glucose uptake and utilization because it decreases glucose oxidation, gluconeogenesis, and glycogenolysis in other organs and reduces glucose transporter 4 translocation to the cell surface, thereby inhibiting glucose uptake (21–23). Female gender also may decrease glucose metabolism via the Randle cycle as the result of women's greater whole-body FA turnover, delivery to the myocardium, and myocardial FA oxidation (22).

Our results also clarify apparently conflicting results from previous myocardial FA metabolism studies in obese humans: those in women demonstrated increased FA metabolism, whereas those in men did not (5,6,24). Our current study demonstrates that although both obesity and gender are related to myocardial FA metabolism, gender is the

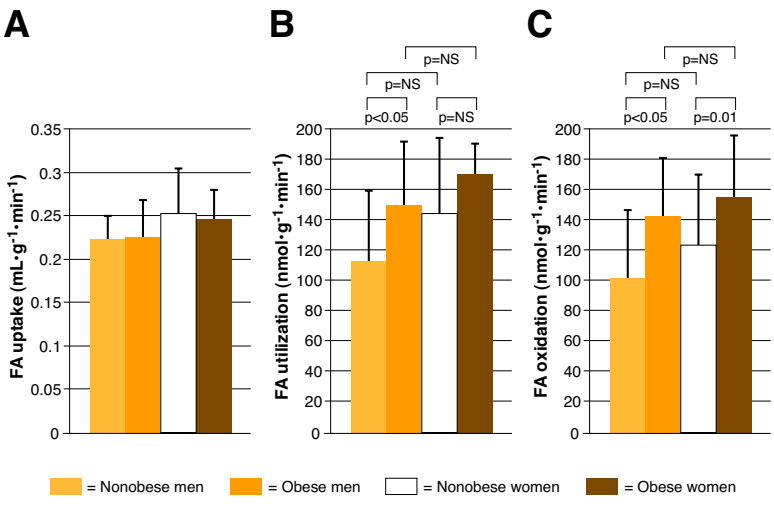

Figure 6. Myocardial FA Uptake and Metabolism

Shown is a depiction of the groups' myocardial fatty acid (FA) uptake (**A**), utilization (**B**), and oxidation (**C**), which were quantified with positron emission tomography. Pairwise comparisons show no difference among the groups in FA uptake, but FA utilization was greater in the obese men compared with nonobese men. Fatty acid oxidation was greater in the obese men compared with nonobese men, and it was greater in the obese women compared with nonobese women.

stronger predictor and therefore must be taken into account when determining obesity's effect. The relationship between plasma triglycerides and obesity may also have caused the relationship between obesity and the measures of FA metabolism to be less significant in multivariate models. The increase in myocardial FA metabolism found in patients with obesity is likely secondary to increased presentation of plasma FA to the myocardium, resulting from obesity's known increase in whole-body FA turnover. Additionally, estrogen increases lipoprotein lipase's and FA oxidation enzymes' activity and so may partly explain the increase in myocardial FA metabolism in women (25,26).

Study limitations. Our findings may not apply to subjects who do not fit our entry criteria. This study was not powered to evaluate the effect of sex hormones and menstrual phase on myocardial metabolism but rather to evaluate the effects of gender and obesity and their interactions. Further studies are needed to determine whether these variables are involved in the mechanism(s) that influence gender-related myocardial metabolic adaptations to obesity. We did not evaluate the metabolism of endogenous substrates or other exogenous substrates (e.g., lactate), although they would be expected to contribute little to myocardial metabolism in the rested state.

Clinical implications. Given the link between metabolism and function, changes in myocardial metabolism due to obesity may contribute to obesity-related contractile dysfunction. Increased MVO_2 in obesity may contribute to decreased function via impaired efficiency of transformation of chemical energy into mechanical function. Increased FA oxidation with obesity may also lead to LV dysfunction, as observed in animal models (27). Further studies are necessary to prove that altered myocardial metabolism (accounting for gender-related differences) contributes to the development of obesity-related cardiac dysfunction.

Myocardial insulin resistance in obesity likely affects the myocardium's ability to adapt to changing conditions. One would speculate that insulin-resistant myocardium would not be able to adapt to ischemia (which requires glucose use) as well as the insulin-sensitive heart. Further investigation in ischemic myocardium is needed.

Our finding of gender-related differences in the myocardial metabolic response to obesity makes it tempting to speculate that the known gender differences in the risk of obesity-related cardiac dysfunction may have a causal relationship. To be certain, differences other than myocardial metabolism likely also influence cardiac dysfunction development in obesity. However, our findings suggest that further study of obesity- and gender-related myocardial metabolic changes may yield novel, gender-specific therapeutic targets for functional improvement.

CONCLUSIONS

The myocardial metabolic response to obesity is complex and affected by gender. Obesity and gender

independently modulate MBF and MVO_2, and although both modulate myocardial substrate metabolism, gender was a stronger predictor and affected efficiency. Finally, it appears that the myocardium can become insulin resistant with obesity, and gender and obesity interact in predicting myocardial glucose uptake and insulin sensitivity.

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Key Words: positron emission tomography ■ gender ■ myocardial blood flow ■ myocardial metabolism ■ myocardial efficiency ■ obesity.