Effect of Obesity and Insulin Resistance on Myocardial Substrate Metabolism and Efficiency in Young Women

Linda R. Peterson, MD; Pilar Herrero, MS; Kenneth B. Schechtman, PhD; Susan B. Racette, PhD; Alan D. Waggoner, MHS, RDMS; Zulia Kisrieva-Ware, MD, PhD; Carmen Dence, MS; Samuel Klein, MD; JoAnn Marsala, RN; Timothy Meyer, MS; Robert J. Gropler, MD

Background—Obesity is a risk factor for impaired cardiac performance, particularly in women. Animal studies suggest that alterations in myocardial fatty acid metabolism and efficiency in obesity can cause decreased cardiac performance. In the present study, we tested the hypothesis that myocardial fatty acid metabolism and efficiency are abnormal in obese women.

Methods and Results—We studied 31 young women (body mass index [BMI] 19 to 52 kg/m²); 19 were obese (BMI >30 kg/m²). Myocardial oxygen consumption (MVₐO₂) and fatty acid uptake (MFAUp), utilization (MFAU), and oxidation (MFAO) were quantified by positron emission tomography. Cardiac work was measured by echocardiography, and efficiency was calculated as work/MVₐO₂. BMI correlated with MVₐO₂ (r=0.58, P=0.0006), MFAUp (r=0.42, P<0.05), and efficiency (r=-0.40, P<0.05). Insulin resistance, quantified by the glucose area under the curve (AUC) during an oral glucose tolerance test, correlated with MFAUp (r=0.55, P<0.005), MFAU (r=0.62, P<0.001), and MFAO (r=0.58, P<0.005). A multivariate, stepwise regression analysis showed that BMI was the only independent predictor of MVₐO₂ and efficiency (P=0.0005 and P<0.05, respectively). Glucose AUC was the only independent predictor of MFAUp, MFAU, and MFAO (P<0.05, <0.005, and <0.005, respectively).

Conclusions—In young women, obesity is a significant predictor of increased MVₐO₂ and decreased efficiency, and insulin resistance is a robust predictor of MFAUp, MFAU, and MFAO. This increase in fatty acid metabolism and decrease in efficiency is concordant with observations made in experimental models of obesity. These metabolic changes may play a role in the pathogenesis of decreased cardiac performance in obese women. (Circulation. 2004;109:2191-2196.)

Key Words: obesity ■ metabolism ■ insulin

Obesity is an independent risk factor for clinical heart failure. Obese persons have altered left ventricular (LV) remodeling, increased hemodynamic load, and enhanced neurohumoral activation, which are likely involved in the pathogenesis of obesity-related heart failure. In addition, data from studies conducted in animal models suggest that obesity and insulin resistance cause alterations in myocardial fatty acid metabolism and efficiency (cardiac work/myocardial oxygen consumption) that occur early in the cascade of events that lead to impaired LV contractility. In animal models, obesity and insulin resistance increase plasma fatty acid availability and myocardial fatty acid uptake (MFAUp), which causes a shift in substrate metabolism toward a preference for fatty acid utilization (MFAU). In these models, there is an initial increase in myocardial fatty acid oxidation (MFAO) and myocardial oxygen consumption (MVₐO₂), which can decrease cardiac efficiency. Over time, a mismatch between MFAUp and MFAO develops and leads to an accumulation of fatty acid intermediates and increased ceramide production, which cause cardiomyocyte apoptosis and impairment of cardiac function. Other data from studies conducted in animals demonstrate that increased fatty acid availability and myocardial lipid content predispose the myocardium to increased oxidative stress and myocardial injury.

It is not known whether the changes in myocardial fatty acid metabolism and efficiency observed in animal models of obesity and insulin resistance also occur in humans. Therefore, the purpose of the present study was to determine the effect of obesity and insulin resistance in women on myocardial fatty acid metabolism, oxygen consumption, and efficiency. We limited our study population to women because obesity is more common in women than in men, and the relative risk of heart failure is greater in obese women than in obese men. We hypothesized that obesity and insulin resistance would increase myocardial fatty acid metabolism...
and oxygen consumption, thereby decreasing myocardial efficiency in young women.

Methods

Study Subjects
Thirty-one premenopausal women, 19 to 37 years old, participated in this study. Twelve were not obese (body mass index [BMI] 23±3 kg/m², 26±4 years old) and 19 were obese (BMI 38±7 kg/m², 30±4 years old). All of the obese women had excess abdominal fat distribution (waist circumference 108±15 cm) and had been obese for an average of 12±5 years. All subjects completed a comprehensive medical evaluation that included a history, physical examination, ECG, routine blood tests, lipid profile, and, with the exception of 2 subjects, a 2-hour glucose tolerance test. Body fat mass and fat-free mass (FFM) were determined by dual-energy x-ray absorptiometry (DXA, Hologic, QDR-1000/w). Subjects who had diabetes, hypertension (defined as a systolic or diastolic blood pressure >140 or 90 mm Hg, respectively), a history of coronary artery or other cardiac disease, or a history of smoking cigarettes within the last 12 months or who were pregnant, lactating, or taking vasoactive medications were excluded from the study. Written informed consent was obtained before participation in this study, which was approved by the Institutional Review Board and the General Clinical Research Center of Washington University School of Medicine.

Experimental Procedure
Subjects were admitted to the General Clinical Research Center at Washington University School of Medicine the evening before the positron emission tomography (PET) study. At 6 PM, subjects ingested a standard meal containing 12 kcal/kg body weight for nonobese subjects and 12 kcal/kg adjusted body weight for obese subjects (adjusted body weight = ideal body weight + [actual body weight – ideal body weight] × (0.25)). The following morning, after subjects fasted overnight (12 hours), an 18- or 20-gauge catheter was inserted into an antecubital vein for radiopharmaceutical injection. Subjects fasted overnight (12 hours), and a 2-hour glucose tolerance test. Body fat mass and, with the exception of 2 subjects, a 2-hour glucose tolerance test. Body fat mass and fat-free mass (FFM) were determined by dual-energy x-ray absorptiometry (DXA, Hologic, QDR-1000/w). Subjects who had diabetes, hypertension (defined as a systolic or diastolic blood pressure >140 or 90 mm Hg, respectively), a history of coronary artery or other cardiac disease, or a history of smoking cigarettes within the last 12 months or who were pregnant, lactating, or taking vasoactive medications were excluded from the study. Written informed consent was obtained before participation in this study, which was approved by the Institutional Review Board and the General Clinical Research Center of Washington University School of Medicine.

Cardiac PET Imaging
All studies were performed during resting conditions starting at 8 AM and ending at 1:30 PM to avoid circadian variations in myocardial metabolism. Measurements of myocardial blood flow (MBF), MVO2, glucose uptake (MGU) and utilization (MGU), and MFAUp, MFAU, and MFAO were obtained with PET with [6,6-2H2]O-water, [1-13C]acetate, [1-13C]glucose, and [1-13C]palmitate, respectively, using validated techniques as reported previously. The interval between each radiopharmaceutical injection allowed for 5 half-lives of decay time of the preceding radiopharmaceutical. Subject motion was monitored and kept to a minimum during the image acquisition times. Two subjects did not have myocardial fatty acid metabolism data collected, and 3 did not have myocardial glucose metabolism data collected owing to technical difficulties. The procedure was well tolerated by the subjects.

Echocardiography
All subjects had a complete 2D and Doppler echocardiographic examination with a Sequoia-C526 (Acuson-Siemens) immediately after the scan for MVO2 determination was performed. Subjects remained at rest and supine for the echo-derived measurements. LV end-diastolic volume, end-systolic volume, mass, and mass index were determined according to the recommendations of the American Society of Echocardiography. LV mass was also expressed relative to FFM in the obese subjects; over 4.1 g/kg FFM was considered to be LV hypertrophy. Relative wall thickness (RWT) was calculated as (2×posterior wall thickness at end diastole)/LV diastolic dimension. LV ejection fraction (EF) was calculated by the modified Simpson method. Cardiac output was defined as the time-velocity integral of the LV outflow×LV outflow tract area. Cardiac index was calculated as cardiac output/body surface area, and cardiac work as mean arterial pressure×cardiac output×1.36. Cardiac work was then converted to joules. After cardiac work and MVO2 were converted to their energy equivalents (J · g⁻¹ · min⁻¹), LV efficiency was calculated as the ratio of the 2 measurements×100%. Analyses

Plasma glucose concentration was determined by automated glucose analyzers (YSI 2300 State Plus, YSI Life Sciences, and a Cobas Mira analyzer, Roche Diagnostics). Plasma insulin was measured by radioimmunoassay (Linco Research Co). Plasma free fatty acid and lactate concentrations were measured by an enzymatic colorimetric method (NEFA C kit, WAKO Chemicals USA, Inc) and a spectrophotometry kit (Sigma Chemicals), respectively. Insulin resistance was quantified by the glucose area under the curve (AUC) obtained during the oral glucose tolerance test as described previously.

Statistical Analyses

SAS software (SAS Institute) was used for the statistical analyses. All comparisons were made with a Student’s t test for unpaired samples. Linear regression was used to describe the relationship between the PET or echocardiographic measurements and BMI and between PET or echocardiographic measurements and glucose AUC. Multivariate, stepwise regression analyses were used to determine the independent predictors of MVO2, MFAUp, MFAU, and efficiency. For each multivariate analysis, BMI was the first variable inserted into the analysis, followed by the other continuous variables in order of their significance as determined by the univariate correlations. We required the continuous variables to have a univariate correlation with a P ≤ 0.10 to be put in the multivariate model. The predetermined independent variables that were tested for this level of correlation with the dependent variables were BMI, age, glucose AUC, RWT, and the total cholesterol/HDL ratio. All data are expressed as mean±SD. A probability value of <0.05 was considered significant.

Results

Metabolic characteristics of the study subjects are shown in Table 1. The obese women were older (P < 0.05), had a higher glucose AUC, serum LDL cholesterol concentration, and total cholesterol/HDL ratio, and they had a lower HDL cholesterol concentration. BMI and glucose AUC were positively correlated (r = 0.44, P < 0.05).

Average basal plasma glucose, fatty acid, and lactate concentrations during the PET study were similar in both groups (Table 1). However, plasma insulin concentration was higher in obese than in nonobese subjects (P < 0.005).

Hemodynamic and cardiac structure and function parameters are shown in Table 2. The rate-pressure product trended

| TABLE 1. Metabolic Characteristics of the Study Subjects |
|-----------------|-----------------|-----------------|
|                  | Nonobese        | Obese           |
|                  | (n=12)           | (n=19)           |
| Glucose AUC, mg/dL×120 min | 12 547±1998 | 14 395±2233*    |
| Total cholesterol, mg/dL | 173±23      | 181±29          |
| LDL cholesterol, mg/dL | 90±29       | 113±29          |
| HDL cholesterol, mg/dL | 66±24       | 45±8†           |
| Total cholesterol/HDL cholesterol | 2.9±1.0 | 4.2±0.7‡         |
| Triglycerides, mg/dL | 86±42       | 98±57           |
| Glucose, μmol/mL | 4.8±0.4     | 4.5±0.4         |
| Fatty acids, nmol/mL | 616±208    | 589±124         |
| Lactate, nmol/mL | 583±134     | 561±293         |
| Insulin, μU/mL   | 4.4±2.4     | 8.3±3.8†        |

Values represent mean±SD. Obese vs nonobese: *P < 0.05; †P < 0.005; ‡P < 0.0005.
higher in the obese than in the nonobese subjects (P<0.11), primarily because of a trend toward a higher systemic blood pressure in the obese women. Cardiac output (P<0.05) but not cardiac index was also higher in obese than in nonobese women. LV mass was higher in obese women, but the LV mass relative to body surface area was not significantly different between groups. Only 1 obese woman had LV hypertrophy on the basis of her LV mass/FFM index.22

MBF and M\(\text{V}_2\)

MBF was not significantly different between the nonobese and obese groups (1.00±0.24 versus 1.15±0.36 mL·g\(^{-1}\)·min\(^{-1}\), respectively), but there was a significant and positive relationship between MBF and BMI (\(r=0.40\), \(P<0.05\)). The only other univariate predictor of MBF was RWT (\(r=0.40\), \(P<0.05\)). In contrast, M\(\text{V}_2\) was higher in obese subjects (2.72±.65 versus 2.24±.49 J·g\(^{-1}\)·min\(^{-1}\); \(P<0.05\)). Moreover, M\(\text{V}_2\) directly correlated with BMI (\(r=0.58\), \(P=0.0006\); Figure 1A) and RWT (\(r=0.51\), \(P<0.005\)). A stepwise multivariate analysis showed that BMI was the only independent predictor of M\(\text{V}_2\) (\(P=0.0005\)).

Myocardial Efficiency

Cardiac work was not different between the groups (Table 2), but obese women were less efficient than nonobese subjects because of greater M\(\text{V}_2\) in the obese group. LV efficiency had a significant inverse correlation with BMI (\(r=-0.40\), \(P<0.05\); Figure 1B). LV efficiency also correlated inversely with RWT (\(r=-0.43\), \(P<0.05\)), but BMI was the only independent predictor of efficiency (\(P<0.05\)).

Myocardial Fatty Acid and Glucose Metabolism

MFAUp tended to be higher in obese women (0.36±0.06 versus 0.32±0.06 mL·g\(^{-1}\)·min\(^{-1}\), \(P<0.06\)). MFAU and MFAO were not significantly different between obese and nonobese groups (215±62 versus 192±62 nmol·g\(^{-1}\)·min\(^{-1}\) and 198±60 versus 181±61 nmol·g\(^{-1}\)·min\(^{-1}\), respectively). Consistent with these findings, MFAUp but not MFAU or MFAO was significantly related to BMI (\(r=0.42\), \(P<0.05\)).

Insulin resistance, defined as the plasma glucose AUC during the oral glucose tolerance test, was positively related to MFAUp, MFAU, and MFAO (Figure 2). Changes in BMI did not account for changes in MFAUp when plasma glucose AUC was added to the stepwise multivariate analysis model. Moreover, plasma glucose AUC became the only statistically significant independent predictor of MFAUp, MFAU, and MFAO.

Neither MGUp nor MGU was significantly different between the obese and nonobese women (0.028±0.017 versus...
Discussion

This is the first study to demonstrate that obesity is associated with specific alterations in myocardial substrate metabolism, efficiency, and structure. We found that an increase in BMI is associated with an increase in MVo₂ and a shift in myocardial substrate metabolism toward greater fatty acid use. The dependence on myocardial fatty acid metabolism increases with increasing insulin resistance and cannot be completely explained by an increase in serum fatty acid levels. In addition, obesity is associated with a decrease in the efficiency of myocardial energy transduction to contractile work and with concentric LV remodeling. These alterations are similar to observations made in experimental animal models of obesity and may be responsible for the impaired cardiac contractility often seen in obese persons.

The increase in MVo₂ associated with an increase in BMI observed in subjects in the present study is likely related to the effect of obesity on cardiac remodeling and the fact that obesity increases sympathetic tone, preload, and fatty acid metabolism. RWT, which reflects concentric LV remodeling, was significantly related to MVo₂ in obese women in the present study and thus likely contributed to their increased MVo₂. Increased fatty acid uptake and oxidation by the heart can also increase MVo₂, because more oxygen is required to generate ATP from fatty acid than by glucose metabolism, and increased oxygen may be consumed by fatty acid esterification and reactive oxygen species production.

Our finding that increasing BMI was an independent predictor of decreased efficiency extends the findings of previous ex vivo studies to obese humans. These previous studies demonstrated that increased MVo₂, MFAUp, and MFAO were associated with decreased efficiency. The results of the present study show that obese humans, who have alterations in MVo₂ and myocardial fatty acid metabolism, also have changes in the translation of energy to contractile function.

The present data demonstrate that increasing insulin resistance is directly associated with a progressive increase in myocardial metabolism of fatty acids in obese women. Moreover, the alteration in substrate metabolism occurred before there was 2D echocardiographic evidence of impaired LV contractility, which suggests that increased MFAUp and metabolism precedes and ultimately leads to impaired contractility and heart failure. These results are consistent with data from studies conducted in animal models that demonstrate myocardial fatty acid metabolism increases before ventricular contractile function is impaired early in the course of developing obesity and insulin resistance.

The present data support the notion that progressive insulin resistance and alterations in myocardial substrate metabolism lead to myocardial contractile dysfunction associated with obesity. The young, obese women in the present study displayed evidence of insulin resistance, on the basis of plasma glucose AUC during an oral glucose tolerance test, that was presumably responsible for increased MFAUp, MFAU, and MFAO, although increased levels of adipokines, such as leptin, may also be partly responsible for the increased myocardial fatty acid metabolism in obesity.

The values for myocardial metabolism for 1 subject appeared to be an outlier from the other subjects. All correlations between BMI and MVo₂, BMI and myocardial efficiency, and glucose AUC and myocardial fatty acid metabolism remained statistically significant after this subject was excluded from the analyses.

Figure 2. A, Univariate relationship between MFAUp and insulin resistance, as measured with glucose AUC during oral glucose tolerance test. B, Univariate relationship between MFAU and insulin resistance. C, Univariate relationship between MFAO and insulin resistance.

0.028±0.024 mL·g⁻¹·min⁻¹ and 133±78 versus 128±112 nmol·g⁻¹·min⁻¹, respectively). In addition, neither BMI nor plasma glucose AUC was significantly correlated with any of the measures of myocardial glucose metabolism.

The values for myocardial metabolism for 1 subject appeared to be an outlier from the other subjects. All correlations between BMI and MVo₂, BMI and myocardial efficiency, and glucose AUC and myocardial fatty acid metabolism remained statistically significant after this subject was excluded from the analyses.
addition, hyperinsulinemia, which stimulates insulin-like growth factor-1 (IGF-1) receptors, is also likely involved in the pathogenesis of myocardial hypertrophy observed in obese women in the present study. However, obese subjects in the present study did not yet manifest clinical or echocardiographic evidence of contractile dysfunction, which suggests that more prolonged alterations in substrate metabolism and increased myocardial mitochondrial oxidative stress are needed to decrease LV contractility.

The mechanisms involved in the pathogenesis of the concentrically remodeled heart in obesity are fundamentally different from those of the concentrically remodeled heart in hypertension, even though the cardiac phenotypes are similar. Insulin resistance, increased adipokine production, and increased myocardial fatty acid metabolism are associated with the nonhypertensive obese heart phenotype, whereas increased LV wall stress and myocyte stretch in response to pressure overload and increased glucose metabolism are associated with the hypertensive heart phenotype.

Future studies are needed to determine the cardiac phenotype of subjects with the metabolic syndrome, who often have both hypertension and insulin resistance. In the present study, only 4 obese subjects met criteria for the metabolic syndrome, and only 1 of those had an elevated blood pressure by Adult Treatment Panel criteria.

The results of the present study differ from the results of 2 previous studies that used PET to evaluate myocardial fatty acid metabolism. In those studies, MFAUp and MFAO were not different between normal volunteers and subjects with impaired glucose tolerance. However, differences in study subject sex, age, and endogenous myocardial fat content and the choice of tracers between studies may have affected the results. Data from studies conducted in experimental animals suggest that estrogens increase MFAO. Therefore, it is possible that the alterations in fatty acid metabolism observed in young obese women in the present study may not apply to men studied previously by other investigators.

We found that MGU tended to be inversely associated with BMI and plasma glucose AUC, but the relationship was not statistically significant even though MFAUp, MFAU, and MFAO correlated significantly with BMI, plasma glucose AUC, or both. This pattern of substrate metabolism parallels that seen in obese animals that are studied early in the course of their progression from insulin resistance to type II diabetes and in isolated working rat heart models that are infused with leptin. The increases in MFAUp and MFAO in these models were not accompanied by a concomitant decrease in glucose oxidation.

Implications
The results of the present study have several important implications. Changes in myocardial fatty acid metabolism (increased MFAUp, MFAU, and MFAO) and efficiency observed in the young, adult obese women in the present study are consistent with the changes observed in animal models of myocardial lipotoxicity and mitochondrial oxidative stress and may ultimately lead to the contractile dysfunction and decreased LV performance associated with obesity.

In addition, the present data suggest that in obese women, the heart is an important sink for plasma fatty acids, helping to clear fatty acids from the circulation and perhaps preventing excessive and directly harmful delivery of fatty acids to other tissues, such as the pancreas. The heart, like the liver, is uniquely capable of disposing of fatty acids because of its high energy requirements and its ability to package and secrete fatty acids as VLDL. Nonetheless, prolonged excessive fatty acid delivery to the heart, as in the liver, could lead to intracellular lipid accumulation and lipotoxicity and/or oxidative stress.

Conclusions
In premenopausal women, obesity is an independent predictor of increased MV̇O2 and decreased efficiency, and impaired insulin resistance is an independent predictor of increased MFAUp, MFAU, and MFAO in young, otherwise healthy women. These changes mirror the initial metabolic changes observed in animal models of myocardial lipotoxicity and oxidative stress and suggest that future studies are needed to determine whether long-term alterations in myocardial substrate metabolism observed in obese women lead to cardiac dysfunction.

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