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Obesity and Cardiac Metabolism in Women

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Obesity is a vexing problem for the clinician and for the cardiovascular physiologist alike. Although we tend to blame an "obesogenic" environment, nobody really knows the cause for the current obesity epidemic. Is it the environment? Is it genes? Or is it the environment acting on certain genes? Currently about 6% of the American population is clinically severely obese (1) and it is well documented that obesity reduces life expectancy (2). Death and disability from heart disease feature prominently in obesity. Most importantly, the dysregulated lipid metabolism in obesity does not stop in the arterial wall. Obesity is, for example, an independent risk factor for heart failure, as defined by criteria of the Framingham Study (3). The data also show that women are more likely to develop heart failure than men (14% vs. 11%). It is tempting to speculate that the gender difference can be traced to the metabolism of energy providing substrates.

The study by Peterson et al. in this issue of the Journal (4) suggests that this might be the case. In a series of elegantly performed tracer kinetic experiments, complemented by extensive metabolic and hemodynamic profiling, the investigators found that a pre-existing increase in myocardial blood flow (MBF) and oxygen consumption (MVO_2) in women was further amplified by obesity. Furthermore, both MBF and MVO_2 were directly related to BMI in women, but not in men. In spite of greater cardiac work, the heart's efficiency (defined as cardiac work/ MVO_2) was less in women than in men. Because energy can neither be created nor destroyed, the results suggest impaired coupling of fatty acid oxidation to ATP production or futile cycling of substrates (5) in the heart of obese women. The authors imply uncoupling proteins (UCPs) as the mediators for reduced cardiac efficiency. This is a reasonable speculation, although it needs to be considered that there is also a cardioprotective role for UCPs. We have speculated that UCPs reduce the formation of reactive oxygen species (5,6) and lessen the consequences of oxidative stress on the heart.

Circulatory dysfunction in massively obese people associated with cardiac enlargement (during life and at autopsy) was first suggested in the "Munich beer heart" at the beginning of the last century (7) and in a study on adiposity of the heart in the 1930s (8) . It has long been appreciated that obesity is associated with an increase in blood volume and cardiac output which are proportional to body weight and duration of obesity (9). There are also significant negative correlations between the ratio of stroke work index to the left ventricular and diastolic pressure and the amount of excess weight (10) as well as left ventricular diastolic function and plasma free fatty acid concentrations (11).

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In the normal mammalian heart free fatty acids provide the bulk of energy providing substrates (12), although the heart exhibits a great amount of metabolic flexibility (13). This flexibility seems to be compromised when the heart is flooded with fatty acids and when the heart becomes less responsive to insulin. Although the mechanisms underlying impaired glucose uptake in the presence of fatty acids are complex, the inhibition of glucose oxidation by fatty acids at the level of the pyruvate dehydrogenase complex is undisputed. Nature seems to find ways to protect the heart muscle cell from an oversupply of fuel in the form of carbohydrate and also in the form of fatty acids. While the mechanisms for the inhibition of glucose metabolism are relatively well understood, the heart's response to excess fatty acids is more complex. Although fatty acids contain more than twice the amount of chemical energy (by weight) than carbohydrates, the amount of usable ATP produced from oxidation of fatty acids is less than the amount of ATP derived from oxidation of glucose (14). Also, the "uncoupling" effect of fatty acid oxidation is not an entirely new observation. Earlier studies, one of them *in vitro* (15), and the other *ex vivo* (16) readily explain the increased MVO_2 and decreased cardiac efficiency (4).

The question remains: Are the increase in fatty acid oxidation and the decrease in cardiac efficiency cause or consequence for the presumed increased death and disability from heart failure in obese women? The question is also: Is the increase in cardiac mass in obese subjects the result of true hypertrophy (synthesis of contractile proteins) or "metabolic hypertrophy" (increase in mitochondrial mass and/or endogenous substrates)? Figure 4 of the study by Peterson et al. (4) seems to suggest the latter. It would also be of interest to know how to reconcile the present findings with those of animal models of obesity which suggest the opposite gender effects, i.e. predominance of fatty acid metabolism in hearts from male rather than female animals (17). Furthermore, the variability in body composition between the obese male and female is significant in fat mass, percent fat, and fat-free mass, as well as a relatively larger waist circumference in women. While these differences are consistent with the pattern of change of obesity in women (a shift from subcutaneous to visceral adiposity), should this be taken into consideration when comparing obese and non-obese women as well as men, which have a more consistent pattern of visceral adiposity throughout life? Also, visceral adiposity in women is associated with decreased skeletal muscle uptake of free fatty acids (18) and impaired left ventricular remodeling compared to that of men (19). These factors may contribute to the gender differences in myocardial fatty acid oxidation and cardiac function. Lastly, the readers would probably like to know whether the observed changes are reversible with weight loss.

In short, there is still much to be learned about the "woman's heart." It is, however, exciting to see that the tools of metabolic imaging are now sophisticated enough to address these questions. In other words: After nearly three decades of assessing regional differences, metabolic imaging with positron labeled tracers is now reaching deeper and deeper into cardiac physiology and biochemistry.

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