Adaptation and Maladaptation of the Heart in Obesity
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Obesity appears to be a major cause of hypertension and associated cardiovascular pathophysiology, including cardiac dysfunction. However, obesity may lead to abnormal cardiac function through mechanisms that are independent of, or that act in concert with, hypertension. One hypothesis of obesity-induced cardiac dysfunction is that an oversupply of substrates leads first to adaptive changes and eventually to contractile dysfunction of the heart. We reason that increased supply of nonesterified fatty acids, together with metabolic dysregulation in obesity, including an inadequate activation of fat oxidation, results in the accumulation of toxic lipid byproducts and subsequent contractile dysfunction. Although the phenomenon may have already been known to Virchow when he described “fatty metamorphosis” of the heart, the concept of cardiac “lipotoxicity” re-emerged only recently with its description in the heart of the obese Zucker diabetic fatty rat. The concept is, however, still a hypothesis rather than an established physiological principle. In spite of the many investigations performed in rodent models, the mechanism(s) responsible for impaired contractile function of the heart is still obscure, and it is uncertain whether lipid metabolites contribute to “obesity cardiomyopathy” in humans. Our brief review is an attempt to understand the chronic regulatory effects of changes in systemic metabolism on cardiac function. In other words, we discuss current concepts of cardiac adaptation and maladaptation to a deranged metabolic environment.

Heart Muscle Disease in Human Obesity
Changes in cardiovascular function in the setting of clinically severe obesity were first reported in obese volunteers undergoing cardiac catheterization. The patients demonstrated reduced left ventricular (LV) compliance and a decrease in stroke work index in the presence of increased LV end diastolic pressure that correlated with the severity of obesity. There is a significant correlation between obesity and LV mass, even after controlling for age and blood pressure, and there is also a significant correlation between weight and impaired diastolic filling of the left ventricle. Both systolic and diastolic function are decreased in otherwise healthy obese young women. In the same population there is a decrease of cardiac efficiency. In severely obese patients with a body mass index >50, the serum concentrations of nonesterified fatty acid show a negative association with load-independent diastolic function. In addition to hemodynamic changes, obesity is also associated with increased risk of atrial fibrillation and ventricular ectopic activity.

The mechanisms of cardiac remodeling with obesity are complex. A major obstacle in any attempt to characterize “obesity cardiomyopathy” is the prevalence of comorbid disorders and confounding variables, such as the metabolic syndrome, insulin resistance, hypertension, type 2 diabetes, and physical inactivity. It is of note that both increased blood pressure and increased body mass index are independently associated with increased LV mass in obese individuals; the effects of hypertension seem to amplify those of sleep apnea and more severe obesity. In type 2 diabetes, hepatic steatosis coexists with myocardial insulin resistance and endothelial dysfunction. Liver and heart share the characteristic of “first-pass” organs into which fatty acids drain from a visceral adipose depot (the intra-abdominal and the epicardial fat). Not surprisingly, a cross-sectional study performed on a small cohort of healthy men has shown an association between circulating free fatty acids levels and myocardial fat.

Another line of reasoning refers to structural and functional changes of the heart in type 2 diabetes. Metabolic remodeling, or sustained changes in flux through a metabolic pathway, may precede functional and structural remodeling of the heart, including in insulin-resistant states. We have observed intramyocardial lipid accumulation in the failing heart of obese or diabetic patients. Intracytoplasmic lipid in cardiomyocytes of type 2 diabetic patients is accompanied by considerable loss of myofibrils. In patients without heart failure, increased myocardial triglycerides were associated with either impaired glucose tolerance or type 2 diabetes. Thus, impaired metabolism of energy-providing substrates and myocardial lipid accumulation are early events found in obese and insulin-resistant individuals.

Obesity and Heart Failure
After correction for hypertension and other risk factors for heart failure, obesity still increases the risk of heart failure ∼2-fold. At the same time, overweight patients with symptomatic heart failure have a better prognosis than nonobese individuals. In essence, obesity is a risk factor for developing heart failure, but after the onset of heart failure,
obesity is a positive predictor for survival.

Although visceral fat is considered a defining feature of the metabolic syndrome, a potential cardioprotective effect of perivascular and epicardial white adipose tissues has been proposed. The existence of this “obesity paradox” has led physicians to question whether obesity should be treated when associated with heart failure.

Obesity doubles the risk of premature death and increases the risk of death from cardiovascular disease 5-fold. In contrast to drug therapies and weight loss programs, bariatric surgery seems to offer a more effective therapy for severely obese patients. It has been suggested that bariatric surgery improves heart function and survival, even in patients with cardiomyopathy. Interestingly, weight reduction is a better predictor of changes in LV structure (decreased wall thickness and mass) than the concomitant decrease in blood pressure for patients undergoing bariatric surgery. More studies are needed to determine whether the surgery is feasible, safe, and effective for heart failure patients.

**Adipokines as Possible Causes for Cardiac Lipotoxicity**

Dysregulation of adipokine signaling is likely to play a role in the maladaptation of the heart and skeletal muscle to a high-fat environment. Under normal conditions, white adipose tissue protects nonadipose organs from lipid overload by storing the excess of nonesterified fatty acid in the form of triglycerides. Adipose tissue also protects nonadipose organs by leptin-regulated central and peripheral effects. A state of lipotoxicity may, thus, be promoted by the state of leptin resistance associated with obesity.

Adiponectin has beneficial effects on the vasculature and cardiac hypertrophy and regulates overall energy homeostasis. In liver, adiponectin improves insulin sensitivity, decreases nonesterified fatty acid uptake while increasing oxidation, and reduces neoglucogenesis. In skeletal muscle, adiponectin stimulates both glucose and fatty acid use. Whether adiponectin directly regulates cardiac metabolism is not clear, although in vitro experiments suggest that adiponectin can accelerate fatty acid oxidation in the heart. However, decreased adiponectinemia in the state of obesity is likely to promote insulin resistance, which will consequently affect heart metabolism.

Another adipokine, serum retinol-binding protein-4, is correlated with the severity of insulin resistance in human subjects. Interestingly, retinol-binding protein-4, like leptin and adiponectin, is related to ectopic fat accumulation, but a putative action of retinol-binding protein-4 on cardiac metabolism is unknown. Other adipokines, also linked to insulin resistance, like resistin or visfatin, still need to be investigated for their possible involvement in cardiac adaptation or maladaptation to obesity. Lastly, proinflammatory cytokines released by adipose tissue in the state of obesity may have the ability to promote tissue synthesis of ceramide, a critical molecule in the lipotoxic process. The appreciation of adipokine signaling and direct effects of adipokines on cardiac metabolism, especially leptin and adiponectin, are well established, but the pathways of adipocyte-heart cross-talk are still under investigation.

**Lipotoxicity in Rodent Models of Obesity**

Although the role of adipokines in the development of lipotoxicity is still debated, there is already good evidence for cardiac dysfunction in rodent models of obesity. Most models, such as the ob/ob mouse or the Zucker diabetic fatty rat, are the result of single gene mutations, which alter leptin signaling. Other models rely on the cardiac-specific overexpression of key regulatory enzymes of either fatty acid metabolism or fatty acid partitioning. Several studies in rodents have used an excess supply of dietary calories (usually in the form of fat) to define metabolic changes in the heart. But, whereas the hearts of genetically engineered animals are prone to maladaptation, it is more difficult to define why a normal heart fails to adapt to a chronic change in its metabolic environment. The situation is complicated by discrepancies among studies. The composition of the diet is of importance: a Western diet (high-fat and high-carbohydrate meal) seems detrimental for cardiac function, whereas a high-fat diet is not. A brief recapitulation of myocardial fatty acid metabolism will help us to understand why an unmitigated oversupply of lipids may adversely affect cardiac function.

**Fatty Acid Uptake and Activation**

Free fatty acids enter the myocardial cell via diffusion or via fatty acid–specific transporters like fatty acid translocase. Fatty acid uptake seems critical because fatty acid translocase deficiency is sufficient to reverse the lipotoxic phenotype in myosin heavy chain α–peroxisome proliferator-activated receptor (PPAR)-α mice. Inside the cell, free fatty acids bind to fatty acid–binding proteins are activated to fatty acyl-coenzyme A (CoA) and directed into different metabolic pathways: β-oxidation, binding to transcription factors, cellular signaling (via direct interaction with signaling proteins), conversion to lipid-based signaling molecules (eg, diacylglycerol), posttranslational modification of proteins, or storage in the form of triglycerides. Because the heart has a very limited capacity to store triglycerides and because increased fatty acid supply results in increased fatty acid uptake, the heart is subject to increased susceptibility to “spillover” of toxic lipid byproducts.

**Fatty Acid Metabolites Upstream of β-Oxidation**

The transgenic overexpression of fatty acyl-CoA synthetase-1 in mice results in dramatic triglyceride accumulation within the cardiomyocyte and systolic dysfunction followed by death. In contrast, systolic cardiac function is preserved in mice with the transgenic overexpression of the fatty acid transport protein FATP1 (another model of increased fatty acid uptake), whereas the mice develop impaired cardiac diastolic function and show a decreased density of the repolarizing voltage-gated K+ current and prolonged corrected Q-T interval on ECG. Fatty-acyl CoAs have been demonstrated as modulators of potassium currents mediated...
by $K_{ATP}$ in the heart. Thus, lipids are mediators of both systolic and diastolic dysfunction.

Much has been learned about lipotoxicity from studies on the $\beta$-cell of the pancreas, which show exquisite accumulation of triglycerides and long-chain fatty-acyl CoA, $\beta$-cell insulin resistance, impaired glucose-sensitive insulin secretion, and, ultimately, apoptosis. One of the central pathways that mediates this effect is the accumulation of ceramide. In the $\beta$-cell of the Zucker diabetic fatty rat, there is increased expression of the enzyme serine palmitoyltransferase, which catalyzes the first step in de novo ceramide biosynthesis. Ceramide can induce reactive oxygen species (ROS) generation, as well as apoptosis, and can inhibit insulin signaling at the Akt/protein kinase B complex. Another lipotoxic pathway is the activation of protein kinase C by diacylglycerol. The isoforms of protein kinase C are thought to confer repression of insulin signaling by serine/threonine phosphorylation of the insulin receptor or the insulin receptor substrates. Increased intramyocellular fatty acids and increased protein kinase C activity are present in insulin-resistant skeletal muscle.

### Regulation and Dysregulation of Fat Metabolism by Nuclear Receptors

A major mechanism by which the heart adapts to a high-fat environment is ligand activation of the PPARs transcription factor by fatty acids. In a complex “feed-forward” system, PPAR activation enhances the expression of multiple enzymes in the pathways of fatty acid use to prevent the accumulation of toxic lipid species. Animals fed a high-fat diet usually increase myocardial fatty acid oxidation and maintain near normal cardiac function, whereas reduced mitochondrial oxidative capacity and increased mitochondrial uncoupling impair myocardial energetics in ob/ob mice.

PPAR is not the only regulator of fatty acid oxidation in the heart. It seems likely that the divergence in the gene cassettes activated to a specific metabolic challenge is mediated through coactivators of the PPAR/retinoic X receptor complex. The PPAR$\gamma$ coactivator-1$\alpha$ (Figure 1) is a master regulator of mitochondrial biogenesis in multiple tissues, including the heart. Peroxisome proliferation-activated receptor $\gamma$ coactivation-1$\alpha$ also serves to integrate signaling outcomes of the p38 mitogen activated kinase, $\beta$-adrenergic, NO, AMP kinase, and Ca$^{2+}$-calmodulin kinase signaling pathways to define the energy requirements of the cell.

Two other PPAR isoforms exist, PPAR$\beta/\delta$ and PPAR$\gamma$. Like PPAR$\alpha$, PPAR$\beta/\delta$ is also highly expressed in the heart. However, in contrast to mice with cardiac overexpression of PPAR$\alpha$, myosin heavy chain $\alpha$–PPAR$\beta$ mice do not develop lipotoxic cardiomyopathy. Although both nuclear receptors induce expression of genes involved in mitochondrial fatty acid oxidation, PPAR$\beta/\delta$ preferentially induces glucose use. PPAR$\gamma$, which is critical for adipocyte differentiation and lipogenesis, is expressed at relatively low levels in the heart and has, therefore, been ignored for a long time. Although a PPAR$\gamma$ agonist treatment reverses lipotoxic cardiomyopathy, mice overexpressing cardiac PPAR$\gamma$ develop a dilated cardiomyopathy associated with increased lipid and glycogen stores. In conclusion, the transcriptional regulation of enzymes for fatty acid metabolism is a likely site of dysregulation. When considering ATP-requiring tissues like heart muscle, it is likely that an inadequate mitochondrial activity contributes to the activation of the above-mentioned lipotoxic pathways.

### Mitochondrial Dysfunction

Mitochondria are the site for $\beta$-oxidation of fatty acids. It is known for some time that impaired $\beta$-oxidation because of depletion of carnitine induces “fatty degeneration” of the heart. More recently, impaired oxidative phosphorylation has been demonstrated in patients with certain forms of genetic cardiomyopathies. Today several mouse models of impaired mitochondrial function exist that mimic human disease.

A potential cause of lipotoxicity is the accumulation of products of incomplete (or inefficient) $\beta$-oxidation, such as acylcarnitines and ROS. Studies by Koves et al have demonstrated an increase in acylcarnitines in skeletal muscle in a model of diet-induced obesity. The same group suggested the existence of a mitochondria-derived signal that couples incomplete $\beta$-oxidation with insulin resistance. The authors propose that physical inactivity may be a major contributor of the maladaptive metabolic remodeling of myocytes in response to overnutrition. Overexpression of peroxisome proliferation-activated receptor $\gamma$ coactivation-1$\alpha$ (which promotes increased mitochondrial biogenesis and function) improves the ratio of complete to incomplete oxidation of fatty acids in L6 myoblasts, whereas feeding a high-fat diet to mice overexpressing PPAR$\alpha$ or activating PPAR$\alpha$
cardiac hypertrophy results in contractile dysfunction.\(^{67,79}\) These results suggest that cardiac maladaptation in obesity may be because of fatty acid–enhanced \(\beta\)-oxidation in the absence of increased energy demand.

An increased reliance on \(\beta\)-oxidation, coupled with a decreased oxidative phosphorylation capacity, is likely to promote the formation of ROS.\(^{80}\) As a consequence of mitochondrial dysfunction, there is excess ROS production and incapacity of mitochondria to reduce superoxide.\(^{81}\) Superoxide is generated from the transfer of an electron from the electron transport chain to molecular oxygen (or via reduced nicotinamide adenine dinucleotide phosphate oxidase) and has multiple deleterious consequences for the cell.\(^{82}\) The enzymatic scavenging pathways to reduce superoxide are contained in the mitochondria (and in the cytosol to some extent).\(^{83}\) ROS, in turn, impair \(\text{Ca}^{2+}\) homeostasis in isolated cardiomyocytes treated with palmitate.\(^{83}\) The hearts of ob/ob mice exhibit decreased oxidative capacity and decreased protein content of the complexes of the electron transport chain.\(^{49}\) The defects in mitochondria are also present in skeletal muscle of mice with diet-induced obesity.\(^{77}\) Interestingly, oxidative stress is believed to be a major cause of mitochondrial alterations in the skeletal muscle of fed a high-fat, high-sucrose diet.\(^{84}\) There is, therefore, a noxious feed-forward mechanism in which inadequately enhanced \(\beta\)-oxidation favors the generation of ROS, which will, in turn, worsen mitochondrial dysfunction.

### Uncoupling and Futile Cycles

The heart may have a way to protect itself, at least temporarily, from the deleterious consequences of a high fat supply. We have proposed mitochondrial uncoupling and futile cycling as major adaptive mechanisms of the heart in the setting of high-fat feeding.\(^{54}\) One hypothesis is that uncoupling proteins (UCPs) function as fatty acid anion exporters that preferentially export those fatty acids that have entered the mitochondrial matrix by a flip-flop mechanism across the inner mitochondrial membrane.\(^{85}\) Because the mitochondrial matrix does not contain acyl-CoA synthetase isoforms, the negative charge of fatty acid anions would add to the proton gradient (Figure 2). To dissipate this electric charge, fatty acid anions are exported by UCPs and, thus, reduce the proton motive force with a net result in the tighter coupling of oxidative phosphorylation with a subsequent decrease in oxidative stress.\(^{85,86}\)

Similarly, Himms-Hagen and Harper\(^{87}\) propose that fatty acyl-CoA derivatives are hydrolyzed by mitochondrial thioesterase-1 in the mitochondrial matrix to release a fatty acid anion and coenzyme ASH. The coenzyme ASH released would be required for other metabolic processes in states of increased oxidation, such as reactions needed to maintain fatty acid oxidation (ie, pyruvate dehydrogenase, ketoglutarate dehydrogenase, and 3-ketoacyl-CoA thiolase)\(^{87}\) (Figure 2). Mitochondrial thioesterase-1 may also promote fatty acid export from cardiac mitochondria. The expression of the mitochondrial thioesterase-1 protein and its activity are enhanced in diabetes and by PPAR\(\alpha\) activation.\(^{88,89}\) However, the regulation of UCP3 expression by diabetes in these studies is less clear.\(^{88,89}\) Transcription of \(ucp3\) is fatty acid responsive,\(^{90}\) suggesting that fatty acids induce their own futile cycling.

Adenine nucleotide translocase (ANT) has also been proposed to mediate fatty acid efflux from the mitochondrial matrix.\(^{91}\) Fatty acid-induced uncoupling is inhibited by carboxyatractyloside in rat hearts, which correlated with ANT protein content.\(^{92}\) In ANT1-deficient mice, the proton conductance is decreased by \(\leq 50\%\).\(^{93}\) The dissipation of proton motive force and decrease in cytosolic ATP by palmitate were shown to be regulated by ANT using metabolic control analysis.\(^{93}\) The respective importance of ANT and UCP3 in futile cycling of fatty acids needs to be determined.

### Uncoupling and Generation of ROS

In line with the above observations we have postulated that the inadequate activation of PPAR\(\alpha\) responsive genes is a potential mechanism for the development of contractile dysfunction with a Western diet.\(^{54}\) These findings extend previous reports that obese Zucker rat hearts are unable to respond to increased fatty acid availability, showing contractile dysfunction.\(^{46}\) As with the deposition of neutral triglyceride in the heart, there is debate regarding whether futile cycling–uncoupling is adaptive or deleterious to cardiac contractile function. Diabetes is known to increase ROS and mitochondrial uncoupling in the heart, and it has been proposed that uncoupling may explain the reduced cardiac efficiency that is...
measured in diabetes. However, contractile function is preserved with a high-fat diet, where induction of uncoupling components is likely to occur to a greater extent than with a Western diet. It is possible that mitochondrial uncoupling is another example of an adaptive mechanism that may, in particular circumstances, become maladaptive.

Conclusions

It is clear that the metabolic dysregulation of obesity is accompanied by adaptive and by maladaptive responses of the heart. The control and regulation of fat or carbohydrate oxidation in the heart is linked to the complex flux of intermediates through distinct pathways that converge at important regulatory complexes or “nodal points” of metabolism. How exactly obesity affects the sites of metabolic regulation in the heart is not completely understood. Likewise, the conditions triggering lipotoxic mechanisms in the heart, as well as the role that these mechanisms might have in the development of contractile dysfunction, need better definition. A case in point for adaptation and maladaptation is insulin resistance in the heart. Insulin resistance may be adaptive when it is protecting the heart from excess fuel uptake or maladaptive when it is associated with ROS formation and activation of signaling pathways of programmed cell death. The present literature reflects an extraordinary complexity of the heart’s metabolic, functional, and structural changes in obesity.

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None.

References

1. Virchow R. Cellular Pathology as Based Upon Physiological and Pathological Histology. London, United Kingdom: John Churchill; 1860:325.


40. Barger PM, Kelly DP. PPAR signaling in the control of cardiac energy metabolism. Trends Endocrinol Metab. 2002;13:118–126.


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