The Metabolic Syndrome and Cardiac Function


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The metabolic syndrome includes obesity, insulin resistance, dyslipidemia, and type 2 diabetes mellitus. It increases the risk of developing cardiovascular diseases, including heart failure. Evidence is emerging that changes in energy metabolism might contribute to the development of cardiac myocyte contractile dysfunction. The focus of our laboratory is in understanding the potential molecular mechanisms for these abnormalities.

Over 40% of US citizens older than 60 years have metabolic syndrome and the prevalence of the metabolic syndrome parallels the global epidemic of obesity and diabetes.[1] What is unknown is the prevalence of the metabolic syndrome and/or type 2 diabetes in patients with pulmonary hypertension. More importantly, the impact that these comorbidities may have on right ventricular performance and patient outcomes is not known. The objective of this article is to review the cardiac effects of the metabolic syndrome and highlight possible areas for investigation in determinants of right ventricular dysfunction.

Metabolic Alterations

Obesity, insulin resistance and diabetes increase the risk of developing cardiovascular disease.[2-4] Many believe that the major determinant of cardiovascular complications in the metabolic syndrome is coronary artery disease. Our work suggests that the metabolic alterations that occur in obesity and type 2 diabetes can also affect cardiac structure and function independently of hypertension or coronary artery disease. In addition, after adjusting for age, blood pressure, weight, cholesterol, and coronary artery disease, obesity is associated with an increased risk of heart failure.[3,5,6] This "diabetic cardiomyopathy" is defined as ventricular systolic or diastolic dysfunction occurring in diabetic patients in the absence of coronary artery disease and hypertension.[7-9] Several studies have identified the presence of lipid material in the hearts of patients who are obese or have type 2 diabetes who have had nonischemic heart failure.[10,11] The transcriptional profile of these lipid-laden hearts is similar to that of the Zucker diabetic rat (ZDF), an animal model of lipotoxicity and contractile dysfunction, which suggests that dysregulation of fatty acid metabolism in failing human hearts may contribute to contractile dysfunction.

Most mechanistic insights into obesity-related cardiomyopathy and diabetic cardiomyopathy have come from rodent studies. The most widely investigated models are *db/db* mice (leptin receptor mutation), *ob/ob* mice (leptin deficiency), and ZDF rats (leptin receptor mutation). All of these models have obesity, insulin resistance, and hyperglycemia in common, although to varying degrees in each model.[12,13] These animals do not develop atherosclerosis, which allows an evaluation of the effects of obesity, insulin resistance, and type 2 diabetes in the heart that are independent of coronary artery disease.[13,14] Each of these animal models is associated with evidence of contractile dysfunction, both systolic and diastolic, which further supports the existence of an obesity-related and/or diabetic cardiomyopathy.[15-24]

Pathophysiology

Patients with type 2 diabetes have decreased whole-body aerobic capacity that may be related to decreased expression of mitochondrial proteins in skeletal muscle.[25-28] Mitochondrial function and morphology are also abnormal in prediabetic and diabetic states and include a reduction in overall mitochondrial size and content and a 30% reduction in ATP synthesis.[29-32] What is not clear is whether these skeletal muscle mitochondrial abnormalities represent a genetic predisposition to the metabolic syndrome or acquired defects.[33,34]

Cardiac muscle mitochondria have been less well studied. A few indirect studies suggest that myocardial mitochondrial function is altered in obesity and diabetes as evidenced by increased oxygen consumption and reduced cardiac efficiency.[35] Which are, in turn, associated with increased myocardial fatty acid use and impaired glucose tolerance. More direct evidence for cardiac mi-

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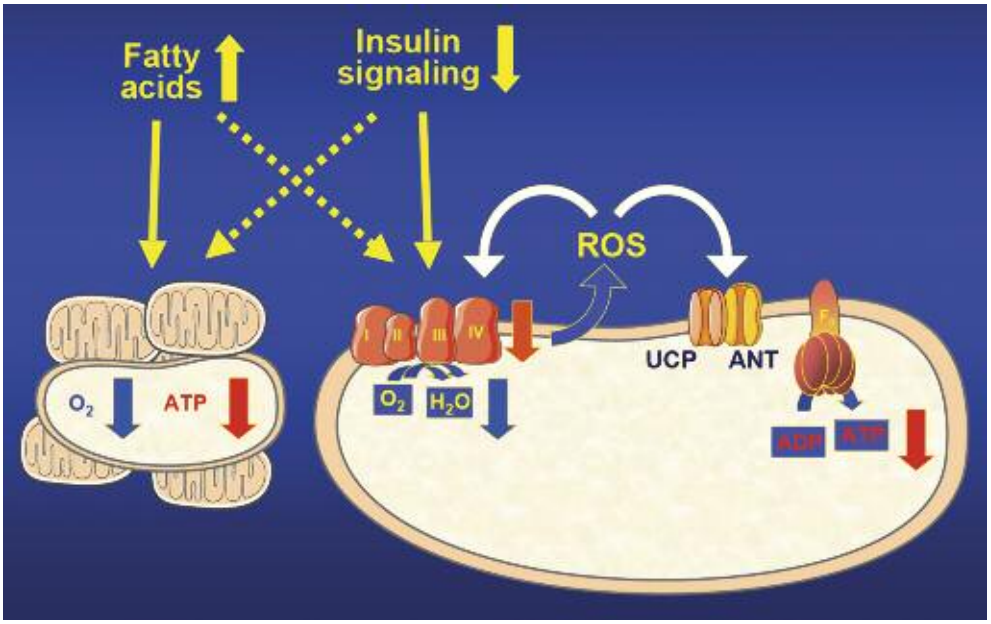

Figure. Model for Synergistic Effects of Insulin Resistance and FA Excess in Precipitating Mitochondrial Dysfunction in Hearts. FA, fatty acids; ROS, reactive oxygen species; UCP, uncoupling protein; ANT, adenine nucleotide translocase; ATP, adenosine triphosphate; ADP, adenosine diphosphate.

tochondrial dysfunction in patients with type 2 diabetes has come from studies using ^{31}P nuclear magnetic resonance (NMR) spectroscopy. Findings from these studies suggest that patients with type 2 diabetes have reduced cardiac phosphocreatine/adenosine triphosphate (ATP) ratios, and impaired high-energy phosphate metabolism and a cardiac energy deficit.[36,37] Phosphocreatine/ATP ratios are also decreased in failing hearts of other etiologies, which are associated with mitochondrial dysfunction.[38-40] In addition, plasma-free fatty acid concentrations were found to correlate negatively with phosphocreatine/ATP ratios in patients with diabetes.[37] This may be due to increased expression of uncoupling proteins (UCPs) that reduce the efficiency of ATP production and lead to reduced phosphocreatine/ATP ratios. Increased lipid deposition has been found in diabetic cardiomyopathy and may exceed mitochondrial fatty acid oxidative capacity. This results in increased lipid storage instead of oxidation and lipotoxic effect.[11]

In contrast with human studies, mitochondrial function has been directly investigated in several animal models of metabolic syndrome. Mitochondrial dysfunction is present in the type 2 diabetic rodent heart as demonstrated by reduced mitochondrial respiration and ATP synthesis.[41-43] Mitochondrial structural defects and abnormal mitochondrial proliferation also occur in *ob/ob* mice.[44-46]

The heart depends on continuous oxidative metabolism for ATP generation to maintain contractile function. Mitochondria account for approximately 40% of cardiomyocyte volume. The normal heart generates ATP mainly from the mitochondrial oxidation of fatty acids (60% to 70% of ATP generated) and to a lesser extent from glucose, lactate, and other substrates (30% to 40%).[19,20,23] The increased myocardial fatty acid oxidative capacity in obesity and diabetes are mediated, in part, by increased activity of peroxisome proliferator-activated receptors (PPARs) (in particular PPARα). PPARα has been shown to be a central regulator of fatty acid oxidation in the heart by increasing the expression of genes involved in virtually every step of cardiac fatty acid utilization.[47] Conversely PPARα reduces the expression of genes that regulate glucose use and thereby contribute to reduced glucose oxidation. Mice with cardiac overexpression of PPARα mimicked the metabolic phenotype of the diabetic heart, which implicates PPARα in the regulation of cardiac metabolism in the diabetic heart.

Theoretical calculations of the yield of ATP per oxygen atom consumed show that fatty acids are a less efficient fuel when compared with glucose.[48] It is calculated that shifting from 100% palmitate to 100% glucose would increase the ATP yield per molecule of oxygen consumed by 12% to 14%. Thus, increased fatty acid use in the diabetic heart may be energetically detrimental because of the higher oxygen cost to produce ATP. The higher oxygen cost and the decrease in cardiac efficiency may contribute to the development of contractile dysfunction in the metabolic syndrome. Cardiac energy depletion may become even more pronounced by the coexistence of hypertension (a common comorbidity in the metabolic syndrome), which increases the energy demand for the heart. In addition, these mechanisms may also contribute to the increased susceptibility to ischemic damage and poorer outcomes after myocardial infarction.

The mechanisms for increased myocardial oxygen consumption and decreased cardiac efficiency are incompletely understood. Our findings suggest increased mitochondrial uncoupling as one underlying mechanism.[43,49] Mitochondrial uncoupling increases oxygen consumption without proportionately increasing mitochondrial ATP production. The energy deficit that results may explain the lack of increase in cardiac contractile function and reduced cardiac efficiency.

One of the mechanisms leading to cardiac mitochondrial uncoupling in type 2 diabetes may be the increased expression of UCPs (**Figure**). These proteins allow the H+ generated from the transfer of electrons from oxygen to re-enter the mitochondrial intermembrane space without generation of ATP from adenosine diphosphate (ADP) thus uncoupling oxygen consumption from ATP generation. Several UCPs have been identified.[50-59] Both UCP2 and UCP3 are expressed in the heart, but their roles are still unclear.[60,61] Circulating free fatty acid levels correlate with the expression of UCP2 and UCP3 in the human heart, which suggests that plasma free fatty acid concentrations may regulate cardiac UCP expression, possibly through activation of PPARα-response elements in the UCP promoter regions.[61-65]

Proton leak via the adenine nucleotide translocator (ANT) may also lead to uncoupling (**Figure**). This protein was shown to mediate uncoupling by fatty acids and to lower mitochondrial membrane potential in heart and skeletal muscle.[66,67] Studies that used inhibitors of ANT suggest that the large part of mitochondrial uncoupling was mediated by UCPs, but that a small part of proton leak was also mediated by ANT activity.[49]

Another mechanism that may lead to decreased cardiac contractility is through generation of reactive oxygen species (ROS). Mitochondria are the principal source of ROS in cells. Normally, electrons are funneled through the redox carriers of the respiratory chain to molecular oxygen reducing O_2 to water. Even during nor-

mal metabolism, some electrons leak from the respiratory chain, which results in the generation of reactive incompletely reduced forms of oxygen, such as superoxide and hydroxyl anions. Increased electron delivery from increased glucose oxidation or increased fatty acid oxidation have been shown to increase mitochondrial ROS generation.[68,69]

ROS can severely harm the cell through oxidation of proteins, DNA (including mitochondrial DNA), and nitrosylation of proteins (through generation of reactive nitrogen species) and lead to improper protein function (**Figure**). Oxidative stress is widely accepted as a key player in the development and progression of diabetes and its complications, including cardiac pathologies.[70-74] In diabetes, ROS may be predominantly derived from mitochondria as opposed to cytosolic origins.[68,75,76] Mitochondria are not only the origin, but also the target of oxidative stress. In addition to the direct effects on proteins and DNA, ROS can also induce mitochondrial uncoupling.[49]

Most studies that investigate the effect of ROS on mitochondrial function in diabetic hearts have been performed in type 1 diabetic models. In these animal models, cardiac mitochondrial respiratory dysfunction has been demonstrated and, in some studies, improved antioxidant defense was able to at least partially, if not completely, restore mitochondrial respiratory function.[77-80] The possibility that the mechanisms by which ROS causes mitochondrial damage are similar in type 2 diabetes and is supported by several similar observations in type 2 diabetic models.[49,78,81-83]

A recent study suggests that mitochondrial ROS overproduction may play a greater role in impairing mitochondrial energetics in models of insulin resistance and obesity versus models of insulin deficiency and type 1 diabetes.[84] It appears likely that ROS plays a central role in impaired mitochondrial energy metabolism by participating in mitochondrial uncoupling (in type 2 diabetes and cardiac efficiency) thus directly damaging mitochondrial proteins. Both mechanisms probably contribute to a deficit in energy reserve and contribute to the development of contractile dysfunction.

Cardiac performance also depends on the influx of Ca2+. It exposes active sites on actin, which interact with myosin crossbridges in an energy-requiring reaction. At the end of the contraction, Ca2+ is rapidly removed from the cytosol. Ca2+ exchange between these subcellular compartments is believed to provide a mechanism for matching energy production to energy demand under physiological conditions or increased workload and is termed the "parallel activation model."[85]

Although some Ca2+ is exported via the sarcolemmal membrane, the bulk of Ca2+ is resequestered in the sarcoplasmic reticulum by the activity of sarcoplasmic/endoplasmic reticulum Ca2+-ATPase 2a (SERCA2a).[86-88] Contractile dysfunction in the diabetic heart has been proposed to be the consequence of abnormalities in sarcoplasmic reticulum Ca2+ handling and has been specifically attributed to the decreased expression of SERCA2a.[89-93]

It has recently been demonstrated that mitochondrial biogenesis occurs in hearts of obese and insulin resistant animals.[44,45] However, this was not associated with increased mitochondrial respiration or ATP generation. We have also observed increased mitochondrial density and DNA content in *ob/ob* and *db/db* mice despite impaired ADP stimulated respiration and ATP synthesis.[43,44,49] These observations raise the question whether mitochondrial biogenesis is adaptive or maladaptive in the metabolic syndrome.

Given that animal models of the metabolic syndrome exhibit insulin resistance the question arises whether cardiac insulin resistance may contribute to the development of contractile dysfunction. Since the animal models are characterized by systemic metabolic alterations, evaluation of the contribution of insulin resistance to cardiomyocyte contractile dysfunction is challenging. To approach this problem, we generated mice with a deletion of the insulin receptor (CIRKO mice) restricted to the cardiomyocyte.[94]

CIRKO mice have reduced insulin-stimulated glucose uptake and also have a modest decrease in contractile function, thereby insulin resistance may be a contributing factor in contractile dysfunction in the metabolic syndrome. This may be caused by decreased mitochondrial gene expression, which limits oxidative capacity and impairs mitochondrial energetics and contractile function in CIRKO mice. If this is correct, then CIRKO hearts may be more susceptible to injury when subjected to increased energy demands

CIRKO mice subjected to pressure overload through transverse aortic banding or following chronic β-adrenergic stimulation resulted in worse left ventricular dysfunction, left ventricular dilation, and interstitial fibrosis compared to controls.[95,96] These findings support the notion that insulin resistance may play a role in the development of contractile dysfunction in the metabolic syndrome, and impaired myocardial mitochondrial oxidative capacity due to reduced insulin action could be an underlying mechanism.

Conclusion

It is probable that no one single mechanism, but rather the combination of several mechanisms, leads to cardiac dysfunction in the metabolic syndrome. We propose that mitochondrial dysfunction compromises cardiac ATP generation and leads to contractile dysfunction. Novel treatments that target these abnormalities might lead to new therapeutic avenues for the prevention of cardiac dysfunction. What is not known is if the mechanisms of cardiac dysfunction outlined above can be extrapolated to the right ventricle.

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