Role of Cardiac Steatosis and Lipotoxicity in Obesity Cardiomyopathy

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The pandemic of obesity is a devastating health problem and contributes to premature morbidity and mortality. Results from clinical and experimental studies have identified a variety of unfavorable consequences of obesity including cardiovascular diseases, pulmonary diseases, cancer, and sleep disorders. An obesity-triggered parallel increase in the prevalence of type 2 diabetes mellitus is also expected to add to the overall cardiovascular burden of obesity. Components of metabolic syndrome such as dyslipidemia, hyperglycemia, insulin resistance, and hypertension are thought to play pivotal roles in obesity-associated sequelae responsible for atherosclerosis, cardiac hypertrophy, and ventricular dysfunction. The presence of 1 or more of these metabolic syndrome components can adversely affect multiple metabolic pathways resulting in alterations in glucose and lipid metabolism, fatty acid (FA) transport/storage/oxidation, oxygen consumption, redox status, and high-energy phosphate metabolism. Although the precise mechanism(s) of action responsible for metabolic derangement-induced cardiac abnormalities in obesity remains poorly understood, 1 theory that has received pivotal roles in obesity-associated sequelae responsible for atherosclerosis, cardiac hypertrophy, and ventricular dysfunction. The presence of 1 or more of these metabolic syndrome components can adversely affect multiple metabolic pathways resulting in alterations in glucose and lipid metabolism, fatty acid (FA) transport/storage/oxidation, oxygen consumption, redox status, and high-energy phosphate metabolism. Although the precise mechanism(s) of action responsible for metabolic derangement-induced cardiac abnormalities in obesity remains poorly understood, 1 theory that has received increasing attention focuses on lipid transport and storage, excessive FA oxidation (FAO), and lipotoxic injury to the heart. When energy intake exceeds expenditure, fat is stored as triacylglycerol (TG) in adipose tissue. In turn, once fat levels exceed the storage capacity of adipocytes, a variety of neutral lipids are released and accumulated in other cells and tissues including the heart. The presence of lipid inclusions within cardiomyocytes, a condition referred to as cardiac steatosis, has been confirmed in obesity and diabetes. Although recent evidence indicates that cardiac steatosis, increased availability of FA and excess FAO contribute to cardiac anomalies associated with obesity and type 2 diabetes, it has also been suggested that cardiac steatosis may be a compensatory mechanism used to neutralize FAs and their metabolites through esterification to neutral lipids.

Generation of ATP for normal cardiac contractile function depends on a fine balance in the use of FA and carbohydrate as substrates. However, onset and development of obesity and type 2 diabetes result in an increased availability of FA, a concomitant overreliance on FA as an energy source, and accelerated FAO. In consequence, cardiomyocyte FA uptake often exceeds mitochondrial oxidative capacity, and cardiac steatosis ensues, leading to a build-up of lipotoxic intermediates such as ceramide and acylcarnitine. Collectively these events favor oxidative stress and apoptosis, and mitochondria become damaged further compromising ATP production and cardiac contractile function. FA uptake exceeding FAO results in increased FA storage as TG and the accompanied cardiac contractile dysfunction. Myocardial TG accumulation may either protect the heart by “storing away” the detrimental lipid intermediates (eg, diacylglycerol, long-chain fatty acyl-CoA esters, and ceramide), or elicit severe lipotoxicity thereby compromising cardiac function. Meanwhile, the insulin-resistant heart in obesity and type 2 diabetes is unable to fully use glucose, forcing the heart to rely on FA for energy demand and thus prompting a vicious cycle of increased cardiomyocyte FA uptake, oxidation, and TG accumulation, all of which are hallmarks of lipotoxic cardiomyopathy. Whereas the pathophysiology of lipid accumulation on cardiac function has been defined, the clinical value of cardiac steatosis remains elusive in obesity and type 2 diabetes. Impaired glucose tolerance is accompanied by cardiac steatosis in humans and precedes the onset of type 2 diabetes and systolic dysfunction. Evidence from genetically modified mice with overexpression or targeted gene deletion of FA uptake protein (eg, cardiac-specific lipoprotein lipase [LpL], acyl-CoA synthetase, and FA transport protein [FATP]) or that prevent lipid turnover (deletion of adipose triglyceride lipase gene [ATGL]) has revealed cardiomyocyte lipid deposition associated with cardiac dysfunction (Figure). For example, hearts from mice overexpressing LpL, the principal enzyme that hydrolyzes circulating TG and liberates free FAs to be used as energy, were dilated and exhibited systolic dysfunction. Increased free FA uptake with FATP1 overexpression contributes to early cardiomyocyte FA accumulation and subsequently increased cardiac FA metabolism. In this model, perturbation of cardiomyocyte lipid homeostasis leads to cardiac dysfunction with pathophysiological findings reminiscent of those seen in diabetes in the absence of systemic metabolic disturbances. These findings support the concept that cardiac-restricted steatosis may directly prompt cardiac anomalies independent of systemic obesity. In addition, overexpression of peroxisome proliferator-activated receptor (PPAR)α and PPARγ using the α-miosin heavy chain (MHC) promoter led to overt cardiac lipid accumulation and cardiomyopathy. The pathophysiology behind cardiomyopathy with PPARα and PPARγ overexpression is unclear.
but has been speculated to be associated with excess FAO and/or cardiac steatosis. In a recent study from the Kelly laboratory, cardiac function in cardiac-specific MHC-PPARα mice bred into a CD36 or LpL-deficient background (PPARα/hsLpLko and PPARα/CD36ko models) was evaluated. Preserved cardiac function was found in these mice against PPARα overexpression in association with the improved mitochondrial ultrastructure and reactivation of transcriptional regulators of mitochondrial function. Deficiency of CD36, a sarcolemmal protein required for FA uptake into cardiomyocytes, reduced uptake of free and lipoprotein-derived FA. This finding is consistent with the notion that overtly increased expression of CD36 is present in diabetes, insulin resistance and cardiac steatosis.

In this issue of *Hypertension*, Glenn et al created a new transgenic model of cardiac lipid accumulation using forced expression of diacylglycerol acyl transferase (DGAT)1 in cardiomyocytes. Over time, the DGAT1 transgenic mice exhibited increased cardiomyocyte lipid accumulation, cardiac fibrosis, ventricular remodeling, and cardiac contractile dysfunction and decreased mitochondrial biogenesis in the absence of obesity, insulin resistance or systemic dyslipidemia. These findings favor the notion that isolated cardiac steatosis compromises cardiac function independent of effects accrued from generalized adiposity or dyslipidemia. Their findings support the concept that cardiac-restricted steatosis may be directly responsible for cardiac anomalies in obesity independent of systemic metabolic derangements. Accordingly, focusing on cardiac steatosis as a potential therapeutic target in the management of lipotoxic cardiomyopathy in obesity and type 2 diabetes may have merit. DGAT is a microsomal enzyme expressed in mammalian tissues that catalyzes the esterification of 1,2-diacylglycerol with fatty acyl CoA to form TG. In contrast to their findings, an earlier study using the same model demonstrated that DGAT1 expression increases heart TG content but rather ameliorates lipotoxicity. As Glenn et al rightfully pointed out, this apparent paradox in the disparate DGAT1 overexpression-induced cardiac responses is time-dependent. DGAT1-dependent TG synthesis can be cardioprotective in acute or subacute FA-overload situations, but over time, accrual of TG leads to lipotoxicity. Interestingly, a recent report from the Goldberg group suggested that PPARα deficiency mitigates PPARγ-induced cardioliopotoxicity including diluted cardiolipotoxicity, endoplasmic reticulum stress, and apoptosis despite increased FA uptake gene expression, FAO, and increased lipotoxic ceramide levels. The preserved cardiac function in the PPARα-deficiency/PPARγ-crossed mice was accompanied by larger lipid droplet size and decreased levels of the toxic intermediate acylcarnitine. More surprisingly, mRNA expression was increased for genes governing lipid uptake, transport, and storage including Cd36, Atgl, and Dgat in PPARα-deficiency/PPARγ mice with lessened cardiac dysfunction, oxidative stress, and apoptosis. These findings seem to contradict a role of cardiac steatosis in the pathogenesis of lipotoxic cardiomyopathy. However, these authors argued that partitioning of lipid into storage and oxidation (redistribution) can reverse cardioliopotoxicity despite increased levels of diacylglycerol and ceramide, thus suggesting a mechanism for shunting FAs into lipid droplets and then allowing TG hydrolysis into oxidative substrates. Given the apparent controversies between cardiac steatosis and cardiac function, the jury is still out with regard to the precise role of cardiac steatosis (in particular, macro- versus microsteatosis) in lipotoxic cardiomyopathy in obesity. Last but not least, several of the seminal studies involving genetic modification of lipid uptake or turnover proteins used the Cre-loxP system to study the physiological effects of gene knockout. However, an observation from the Hall laboratory found that cardiac-specific Cre-recombinase may trigger a transient reduction in cardiac systolic function, although such transient reduction in cardiac function may not have a long-term impact on cardiac function. Nonetheless, caution should be taken in lipotoxic cardiomyopathy derived from the Cre-loxP–based genetic models. Because of the potential involvement of DGAT1 in disorders associated with TG metabolism and pathogenesis of a variety of diseases including obesity, insulin resistance, type 2 diabetes, and dyslipidemia, this molecule has received attention as a potential new target for the treatment of obesity. The pharmacological profile of a series of small molecule DGAT1 inhibitors such as RO-6036 is becoming available with several DGAT1-selective inhibitors in preclinical research. Observation based on DGAT1 genetic deletion and inhibition has confirmed that the reduced DGAT1 activity leads to improved insulin sensitivity, lowered plasma glucose, loss in either body weight or body weight gain, improved plasma lipid profiles (eg, nonesterified FAs, TG, and cholesterol), reduced hepatic steatosis, and altered secretion of gastrointestinal peptides. Moreover, a number of DGAT1 inhibitors, such as BAY-74-4113, PF-04620110, and LCQ-908 from Bayer, have entered clinical trials. Thus, a new spectrum of DGAT1 inhibitors may be used to reconcile cardiac steatosis–induced cardiac remodeling and contractile dysfunction in obesity and other cardiovascular diseases.

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