The role of serum lipids in cardiovascular disease risk is well established, and reduction of serum lipid levels is now a cornerstone in the treatment of coronary artery disease. Dysregulation of lipid metabolism is also thought to play a role in the development of heart failure, although the mechanisms behind this are incompletely understood.1 Under normal conditions, the heart is primarily dependent on energy production derived from the β-oxidation of fatty acids and, to a lesser extent, glycolysis. However, in heart failure, fatty acid use seems to be reduced.2

The decrease in fatty acid oxidation and subsequent reduction in energy availability have been proposed to contribute to decreased contractile function of the heart. On the other hand, there is growing evidence that overaccumulation of fatty acid or triglyceride in the heart may be directly toxic to the myocyte, contributing to a process called cardiac lipotoxicity.1

Because the heart depends on fatty acid oxidation for energy, the transport and storage of lipids in the myocyte are tightly regulated. Although precise quantification of lipid levels within the myocyte is technically difficult, triglyceride and free fatty acid levels are thought to be low under normal physiological conditions. As noted above, there is evidence to suggest that exaggerated accumulation of triglyceride or free fatty acid within the myocyte is linked to the development of cardiomyopathy (ie, cardiac lipotoxicity). In diabetic and obese patients with severe nonischemic heart failure, myocyte steatosis (ie, increased intramyocardial lipid accumulation) can be demonstrated.3 However, obesity and diabetes, as systemic disorders, may have complex effects on the heart. To circumvent this complexity, several animal models have been established to examine the direct role of fatty acid and/or neutral lipid accumulation in the myocyte.4–6 In most cases, genetic perturbation of fatty acid uptake or lipid metabolism is associated with cardiomyopathy. Several mechanisms have been postulated to play a role in the development of this cardiomyopathy, including increased production of the proapoptotic sphingolipid metabolite ceramide, generation of reactive oxygen species, and activation of selected isoforms of protein kinase C.7

To undergo β-oxidation and to generate ATP, long-chain fatty acids must be transported from the cytoplasm to the mitochondria, a process that depends on intracellular carnitine8 (Figure).

Carnitine is transported into the cell through an organic cation transporter, OCTN2, and subsequently conjugated to fatty acids by carnitine palmitoyl transferase I. Carnitine-conjugated fatty acids are transported into the mitochondria via the transporter, carnitine acylcarnitine translocase. Intramitochondrial carnitine is then cleaved from the fatty acid by carnitine palmitoyl transferase II and recycled back to the cytosol. The importance of this process is exemplified by the human disease, systemic carnitine deficiency, an autosomal recessive disorder characterized by the absence of functional OCTN2.9 Interestingly, humans lacking OCTN2 activity develop a dilated cardiomyopathy, which can be prevented by dietary carnitine supplementation. The frequency of this disorder is estimated to be ≈1 in 40,000 newborns in Japan.10

A spontaneous mutation in the OCTN2 gene associated with juvenile visceral steatosis (jvs) has been identified in the mouse. Mice homozygous for deletion of the OCNT2 gene display increased myocardial lipid accumulation and cardiomyopathy.9 In the article by Takahashi et al,11 published in this issue of Hypertension, the authors carry out an interesting experiment using the heterozygous jvs mouse (jvs/+). Although this mouse appears normal and without obvious cardiac phenotype, both serum and cardiac carnitine levels are decreased, suggesting that they may be at increased risk for the development of heart disease. To test this hypothesis, the authors subjected the jvs/+ mice to aortic banding, a maneuver that produces pressure overload of the left ventricle, and compared the resulting phenotype to wild-type mice that underwent the same banding procedure. Both groups developed cardiac hypertrophy; however, the jvs/+ phenotype was more severe, as assessed by a variety of gravimetric, morphological, and gene expression criteria. Inferentially, it appears that the jvs/+ mouse is at risk for developing a more severe cardiomyopathic phenotype than the wild-type mice subjected to similar hemodynamic stress. The authors suggest that humans heterozygous for the OCTN2 gene defect are similarly at an increased risk for cardiomyopathy, especially in the setting of additional risk factors, such as hypertension. Given the frequency of heterozygotes, which has been reported to be as high as 1% in Japan,10 additional assessment of this otherwise marginal metabolic dysfunction in contributing to “idiopathic” cardiomyopathy seems warranted.

In attempting to understand the underlying mechanism(s) responsible for the more severe phenotype seen in jvs/+ mice, the authors assessed myocardial energy reserve through measurement of the phosphocreatine/ATP ratio. In the jvs/+ mouse subjected to aortic banding, these levels are reduced, suggesting that decreased energy reserves may contribute to the cardiomyopathy and compromised heart function. Interestingly, when they examined myocardial triglyceride and diacylglycerol levels, they found that both were only slightly increased in the jvs/+
compared with the wild-type mouse; however, lipids decreased to near identical levels in both mouse lines after aortic banding. These results suggest that the phenotype in the heterozygote results from a decrease in the availability of fuel in the setting of increased demand and insufficient carnitine reserves. This stands in contrast to the markedly elevated levels of triglyceride and diacylglycerol, which have been implicated as the primary contributors to the observed cardiomyopathy in the homozygous jvs mouse (jvs/jvs). Thus, it seems that OCTN2 gene copy number and, inferentially, levels of carnitine in the myocardium are critically important for normal myocyte function. Severe carnitine deficiency results in lipid accumulation and likely lipotoxicity, whereas modest reductions seem to compromise energy metabolism and functional reserve, particularly in the setting of hemodynamic stress.

The results of Takahashi et al taken together with those collected from animal models of cardiac steatosis and dysfunctional energy use would suggest that a critical balance exists between lipid-sufficient and lipid-deficient states. Lipid excess within the myocyte may lead to a lipotoxic state and contribute to cardiomyopathy. In fact, pilot studies using inhibitors of fatty acid oxidation have been shown to improve heart failure. On the other hand, insufficient lipid availability may promote heart failure in certain contexts by depriving the myocyte of a preferred energy source. Inhibition of β-oxidation in this setting would obviously be detrimental from the standpoint of myocardial function. Thus, it appears that the heart tolerates neither feast nor famine when it comes to myocyte lipid levels.

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