commentary

Myocardial lipid accumulation and lipotoxicity in heart failure[1]

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The syndrome of chronic heart failure is a systemic disease state with primary cardiac dysfunction that subsequently affects multiple organ systems. After the primary cardiac insult, the clinical course of the patient is affected by comorbidities and the underlying type of cardiomyopathy. The most common cause of heart failure in the United States is coronary artery disease. This proportion is rising due to improved survival of patients after myocardial infarction secondary to the success of coronary revascularization procedures but also because of the increasing number of patients with cardiac risk factors such as obesity, diabetes, hypertension, and hyperlipidemia. The highly prevalent metabolic syndrome is a unifying clinical diagnosis that represents these abnormalities. Although the metabolic syndrome is a clinical constellation with higher risk for the development of cardiac disease, it also affects the clinical course of patients with established cardiac disease, e.g., coronary artery disease and heart failure.

Intrinsic cardiac metabolism of the adult heart depends primarily on the utilization of fatty acids for oxidative phosphorylation and generation of ATP (1). In contrast, the fetal heart preferably uses glucose for energy generation. After birth, for reasons still unknown, profound changes in the program of myocardial gene expression lead to increased expression of genes involved in fatty acid metabolism (1, 2). The myocardium, in response to stressors including hypertrophy, failure, and infarction, switches back to the fetal transcriptional program (1) with reduced expression of genes involved in fatty acid metabolism with relative increase in gene products involved in glucose metabolism (1). These changes result in the preferable utilization of glucose for energy generation. This change is, however, accompanied by altered substrate utilization and reduced myocardial production of ATP due to the lower number of ATP molecules generated during glycolysis compared with fatty acid oxidation. Notably, lipids accumulate in failing myocardium, in particular, in subjects with diabetes and obesity with increased levels of toxic intermediates leading to lipotoxicity (3). Toxic intermediate products may further worsen cardiac function and metabolism with development of progressive myocardial atrophy and protein breakdown (4). Although the hemodynamic improvement through unloading of the left ventricle by left ventricular assist device implantation partially corrects pathways of protein synthesis and degradation (5), no data are known regarding the impact of hemodynamic correction on lipid accumulation and markers of lipotoxicity.

Under physiologic conditions, most triglycerides are stored in adipocytes with only minimal accumulation of lipids in other tissues such as the liver or muscle. Increased stores of triglycerides are detectable in the myocardium of animals with obesity and diabetes (4). This finding has been reproduced in patients with heart failure and diabetes (3) and correlates with the degree of obesity (6, 7). It has been proposed that the amount and composition of lipids in the myocardium contributes to the development of cardiac dysfunction through so called "lipotoxic" effects. Although the underlying molecular pathways are only partially understood, several groups have reported animal models of cardiac lipotoxicity. The transcription factor sterol regulatory element binding-protein (SREBP)-1c controls lipogenesis and regulates the metabolism of glucose to fatty acids and triglycerides during the storage of excess energy (8). Activation of SREBP-1c in the liver induces hepatosteatosis and insulin resistance (9). Activation of the transcriptional coactivator peroxisome proliferator-activated receptor (PPAR)γ and the transcription factor SREBP-1c might be important molecular switches regulating lipid accumulation and lipotoxicity. Notably, transgenic mice overexpressing PPARγ in the myocardium show increased cardiac expression of fatty acid oxidation genes and increased lipoprotein triglyceride uptake. PPARγ transgenic mice also develop a dilated cardiomyopathy associated with increased lipid and glycogen stores and abnormal mitochondrial structure (10). These findings are well in line with the known detrimental effects of

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pharmacologic modulation through PPARγ agonists in patients with heart failure leading to fluid retention and cardiac decompensation.

In the current study by Marfella et al. (11), a group of patients with and without evidence of the metabolic syndrome was selected from a large cohort of patients undergoing aortic valve replacement. All patients underwent echocardiographic assessment of their cardiac function. During open heart surgery, myocardial samples were collected from those patients for molecular and histological analysis. Increased amounts of lipid deposits were found in the myocardium of patients with left ventricular hypertrophy and the metabolic syndrome compared with patients without the metabolic syndrome. Increased protein levels of SREBP-1c and PPARγ and lower levels of SERCA2a were also detectable in patients with the metabolic syndrome, suggesting activation of lipogenesis and impaired calcium handling in those patients. These changes correlated well with the degree of left ventricular dysfunction, suggesting a link between molecular markers of lipogenesis and abnormal calcium handling with impaired ventricular function. Notably, no differences in circulating total cholesterol or LDL cholesterol levels were noted in the presence of increased levels of triglycerides and HDL cholesterol. Not surprisingly, patients with the metabolic syndrome had a higher degree of insulin resistance. The degree of insulin resistance, however, did not correlate with the amount of lipid in failing myocardium.

Because all current studies in patients with and animal models of heart failure have only demonstrated the accumulation of lipids in the myocardium, it is not clear whether this results from increased uptake of fatty acids, increased lipogenesis, or impaired degradation of lipids. Future studies have to focus on these mechanisms in order to clarify the causative mechanism behind increased lipid stores in the failing myocardium. Further, although the phenotype of increased lipid accumulation in the failing myocardium, in particular in the setting of diabetes and the metabolic syndrome, has been established, it is not clear what specific type of lipid intermediates accumulates in the failing myocardium. The role of insulin resistance and impaired insulin signaling on myocardial lipid accumulation, as well as the specific lipid composition, is currently unclear. A systematic approach to characterize the lipid content in normal and different types of failing myocardium through lipidomics will help to clarify these issues. Finally, one might speculate that the intracellular compartmentalization of lipids are important for their potential cytotoxic role and a more specific characterization would be beneficial to better understand their functional significance.

Although it is known that toxic intermediates of lipid metabolism can cause cardiac dysfunction, the reversibility of this phenotype after correction of myocardial structure and morphology has never been shown. It is, therefore, possible that ectopic myocardial lipid deposits are just a sign of myocardial degradation during the progression of cardiac failure (as seen in Duchenne's muscular dystrophy). On the other hand, data on increased levels of toxic lipid intermediates that accumulate in failing myocardium suggest direct myocardial toxicity of impaired lipid metabolism in heart failure. It would, therefore, be interesting to see whether the pharmacologic modulation of lipid metabolism in the failing myocardium leads to changes in myocardial function and structure.

The current study is a valuable addition to the literature on cardiac abnormalities in heart failure and the metabolic syndrome. As is the case with most complex diseases, the novel and useful information reported in this study raises a number of new questions that need to be addressed in future studies. Most importantly, this study describes a distinct phenotype of abnormal cardiac structure and metabolism that might advance our knowledge on cardiac metabolism not only in cardiac failure but also in the normal myocardium. The once obscure finding of lipid accumulation in the failing myocardium has opened the door toward a better understanding of mechanisms of lipotoxicity in the failing myocardium with the potential of novel therapeutic interventions in patients with heart failure.

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