Chronic Heart Failure
A Reversible Metabolic Syndrome?

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Heart failure is a progressive clinical syndrome marked by venous congestion and maladaptive neurohormonal activation in the setting of left ventricular dysfunction. More recently, another face of this syndrome is beginning to emerge involving metabolic derangements implicating other organs—adipose tissue, skeletal muscle—and the endocrine systems of leptin, adiponectin, insulin, and insulin-like growth factor—regulating their mass and function. The metabolic abnormalities which have been described thus far include the following: (1) Systemic and myocardial insulin resistance; (2) Mitochondrial dysfunction; (3) Progressive weight loss leading to cardiac cachexia in the more advanced stages; and (4) Myocardial energetic failure associated with a downregulation of fatty acid uptake and oxidation resulting in a rigid shift from fatty acid to glucose as the primary energy source for maintenance of ATP flux in the heart—a preferential switch to a fetal-like gene program regulating cardiac energetics. Despite the important advances to date, our understanding of the metabolic phenotype of chronic heart failure in humans is certainly incomplete, if not rudimentary.

In the current issue of Circulation, Chokshi et al1 provide some definitive insight into the underlying mechanisms of a cardinal feature in the metabolic syndrome associated with heart failure—myocardial insulin resistance. Before their study, the state of knowledge on this subject can be summarized briefly: (1) Heart failure is associated with increased systemic and myocardial insulin resistance. (2) Independent of diabetes mellitus, chronic heart failure patients identified to have decreased insulin sensitivity have a worse prognosis. (3) Advanced heart failure patients with diet-induced obesity or diabetes mellitus have increased intramyocardial triglyceride levels at the time of cardiac transplantation—a phenotype that has been recapitulated in several animal models of obesity and diabetes mellitus. By distinguishing neutral lipid species such as triacylglycerides from toxic lipid intermediates such as diacylglycerols and ceramides in the myocardium of patients with end-stage heart failure, the study by Chokshi et al1 was able to demonstrate a decrease in triacylglycerides and an increase in the lipotoxic diacylglycerols and ceramide species in comparison with nonfailing controls. This finding alone constitutes a significant contribution, providing yet another mechanism which may be playing a role in the progression of human heart failure—namely the role of lipotoxic stress in the failing heart. The authors also identified decreased activation of insulin signaling in the myocardium of end-stage human heart failure and postulated that the accumulation of these toxic lipid intermediates could be playing a role, via increased activation of protein kinase C, in the development of impaired insulin signaling which has been associated with chronic heart failure. This mechanism of fatty acid–induced insulin resistance driven by the accumulation of fatty acid metabolites (fatty acyl coenzyme A, diacylglycerols, ceramides) in skeletal muscle has been proposed for obese patients with increased circulating fatty acids.2 Moreover, the authors provide proof that these metabolic derangements are associated with myocardial failure by demonstrating that both impaired insulin signaling and the accumulation of lipotoxic species in the heart are reversible components of this metabolic syndrome after a period of mechanical unloading with a long-term left ventricular assist device. After a period of mechanical circulatory support, the study identified improved myocardial insulin signaling, decreased cardiac lipotoxicity, and a decrease in systemic insulin resistance as measured by the homeostatic model assessment (HOMA-IR).

What are the implications of this landmark study in the broader context of lipid metabolism in humans? The work by Chokshi et al1 is the first to link the established mechanisms of end-organ dysfunction including insulin resistance in the metabolic syndrome of diet-induced obesity with this emerging metabolic phenotype of chronic heart failure in humans (Figure). The link appears to be lipotoxicity—the hypothesis that intracellular lipid accumulation will render the heart and other organs susceptible to various forms of injury including cellular apoptosis and, ultimately, end-organ failure.3,4 In the metabolic syndrome of diet-induced obesity, increased weight gain is associated with hyperinsulinemia and the resistance to insulin at the level of the fat cell results in an increase in circulating lipid species, including strikingly elevated free fatty acid levels without a commensurate increase in fatty acid oxidation. The end-organ toxicity that results from the dysregulated lipid metabolism in obesity includes nonalcoholic fatty liver disease, cardiomyopathy, increased intramyocardial lipid accumulation in skeletal muscle with impaired insulin signaling, and pancreatic β-cell dysfunction and apoptosis progressing to diabetes mellitus (Figure). Besides hyperinsulinemia, hyperleptinemia has been associated with the metabolic syndrome of obesity, and the increase in circulating levels of leptin—an adipocytokine

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which has been shown to increase fatty acid transport and oxidation—has been proposed as an antilipotoxic (lipid detoxifying) effect for the protection of end-organs from lipid excess. In animal models of heart failure, the development of myocardial and systemic insulin resistance has also been demonstrated with a decrease in the translocation of the glucose transporter, Glut4, to the sarcolemma as a downstream consequence of decreased activation of Akt. The current study by Chokshi et al not only extends this observation to humans but is the first to link the mechanism of lipotoxicity implicated in the metabolic syndrome of obesity with the presence of myocardial insulin resistance in chronic human heart failure.

Thus, a metabolic syndrome of chronic heart failure is emerging, and its cardinal features include (Figure) the following: (1) A spectrum of weight loss with cardiac cachexia in the more advanced stages; (2) Myocardial and systemic insulin resistance linked to lipotoxicity; (3) Altered levels of circulating adipocytokines, including leptin and adiponectin (increased as a result of functional adiponectin resistance); and (4) The potential for reversibility of these metabolic derangements with mechanical unloading in patients on long-term left ventricular assist device support.

Whereas the accumulation of toxic intermediate lipid species in the failing heart may explain the development of myocardial insulin resistance, several questions remain for future investigation in this area. (1) What is the mechanism behind the increased accumulation of these lipotoxic species in the myocardium of end-stage heart failure? The authors suggest that decreased fatty acid oxidation coupled with mitochondrial dysfunction would result in a diversion of the lipid storage pools to the intermediate lipotoxic species diacylglycerols and ceramides. In both A and B, impaired insulin signaling will result in a further enhancement of lipolysis, setting up a vicious cycle of dysregulated lipid metabolism linked to the disease progression of diet-induced obesity and, most likely, chronic heart failure. Both systemic and myocardial insulin resistance improve with left ventricular assist device support, raising the possibility that this metabolic phenotype in human heart failure is reversible. LVD-CHF indicates left ventricular dysfunction – congestive heart failure.
hydrolysis of glycerolipids by adipocyte triglyceride lipase and hormone sensitive lipase in adipocytes. The increase in circulating fatty acids (analogous to what is observed in diet-induced obesity and non-insulin dependent diabetes mellitus) could result in the accumulation of toxic and neutral lipid species in the myocardium, especially when fatty acid oxidation is decreased in heart failure. (2) What is the link, if any, between insulin resistance and weight loss in human heart failure? If proven, can sustained and possibly dysregulated lipolysis connect these two cardinal features of the metabolic phenotype in human heart failure by implicating fat as well as muscle wasting in this syndrome? (3) What is the mechanism of systemic insulin resistance in heart failure, and can it be tightly coupled to the accumulation of intramyocellular lipids in skeletal muscle, as has been demonstrated in obesity and type II diabetes mellitus? (4) Can left ventricular mechanical assist device support alone improve the myocardial insulin resistance and energetics of the right ventricle in end-stage human heart failure? If not, is there a role for the development and testing of therapies targeting cardiac metabolism to protect the vulnerable right ventricle for short- and long-term success after implantation of a left ventricular assist device? Irrespective of where these questions may lead us in the future, the case has been made by Chokshi, et al for lipotoxicity and dysregulated lipid metabolism in the pathogenesis of insulin resistance in human heart failure as the components of this metabolic syndrome in chronic CHF are emerging.

Disclosures

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References

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