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The metabolic contribution to heart failure

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Obesity and diabetes are widely recognized as major risk factors for the development of heart failure [1, 2]. Heart failure in obese individuals and those with diabetes is characterized by the early development of left ventricular diastolic dysfunction, increased left ventricular mass, increased left ventricular wall thickness, and the eventual development of left ventricular systolic dysfunction [3–7]. This increased risk of developing heart failure in obese individuals and those with diabetes persists even after adjusting for independent factors including coronary artery disease and hypertension [3–7]. As a result, a considerable research effort has focused on the mechanisms responsible for the increased prevalence of heart failure in obesity and diabetes. Potential contributing factors identified include increased oxidative stress, development of cardiac autonomic neuropathies, accelerated apoptosis, accelerated inflammatory responses, accelerated fibrosis, altered cardiac Ca^{2+} and Na^{+} handling, production of advanced glycation end products and receptors for advanced glycation end product activation, increased polyol pathway activity, activation of NADPH oxidase, and increased O-linked β-N-acetylglucosamine. Alterations in cardiac energetics also occur in the failing heart, especially in the setting of obesity and diabetes, and are thought to contribute to the severity of heart failure. This issue of *Heart and Metabolism* focuses on the energy metabolic changes that occur in the setting of obesity and diabetes, and how these changes may contribute to the severity of heart failure.

In the article entitled “Is chronic heart failure a reversible metabolic syndrome?”, J. Eduardo Rame describes what metabolic adaptations are associated with heart failure and summarizes the reversible components that are amenable to therapeutic interventions that may reverse myocardial remodelling. One major pathway that is altered in obesity, diabetes and heart failure is cardiac energy metabolism [8]. Obesity results in dramatic changes in cardiac energy metabolism, which include an increase in fatty acid oxidation and a decrease in glucose oxidation. In the Refresher Corner article Lionel Opie discusses the energy metabolic changes that occur in the diabetic heart. He nicely describes the adverse metabolic effects of hyperglycemia, the metabolic syndrome, and the diabetic heart. In the article entitled “Inhibition of fatty acid oxidation as an approach to treat diastolic heart failure”, John Ussher and Jagdip Jaswal describe the changes in diastolic function that can occur in heart failure in obesity and diabetes, as well as the metabolic abnormalities in the myocardium that appear to be associated with the progression of diastolic dysfunction. They also describe how optimizing cardiac energetics, potentially through inhibiting myocardial fatty acid oxidation, may represent a novel target for improving diastolic function. This can be achieved with the fatty acid oxidation inhibitor, trimetazidine. In the article entitled “Use of trimetazidine to treat diabetes patients with heart failure”, Rui Yan and Dengfeng Gao discuss the use of trimetazidine to treat diabetes patients with heart failure. They provide evidence showing that trimetazidine can improve cardiac function and prognosis, as well as improve left ventricular dysfunction and heart failure.

Understanding what alterations in energy metabolism occur in heart failure in obese and/or diabetes patients requires sophisticated imaging techniques.

In the article entitled "Imaging metabolism and perfusion in patients with diabetes and heart failure", Patricia Iozzo and Maria Angela Guzzardi discuss some of the new approaches for imaging metabolism and perfusion in patients with diabetes and heart failure. The authors demonstrate that myocardial insulin resistance is a modifiable marker of fatty acid overload in the heart, and may contribute to cardiac dysfunction in cardiovascular disease. They also highlight how reducing fatty acid oxidation may be beneficial in this setting.

While studies have shown that obesity increases the incidence of heart failure, it is now becoming clear that obese patients with heart failure have better outcomes; known as the "obesity paradox" [9–12]. The clinical literature thus offers conflicting results with regard to the relationship between obesity and heart failure. In the article entitled "The metabolic basis for the obesity paradox in heart failure", Stephan von Haehling addresses the metabolic basis for the obesity paradox, and the potential reasons for differences in heart failure outcomes between obese and nonobese individuals. Interestingly, in the Case Report article by Vitantonio Di Bello and colleagues a clinical case is discussed as to how dramatic weight loss in an obese patient with heart failure can lessen the severity of diabetic cardiomyopathy.

While the heart can be impacted by a number of hormones, it is now becoming clear that the heart itself may actually also function as an endocrine organ. In the Hot Topics article, Andrew Swick discusses irisin, a novel myokine, and its potential role in obesity and diabetes. The author discusses how irisin may play a role in the regulation of energy expenditure and metabolism secondary to "browning" of subcutaneous white fat, resulting in increased energy expenditure and resistance to diet-induced obesity and diabetes.

Combined, the articles in this issue of *Heart and Metabolism* highlight the importance of considering the contribution of energy metabolic changes that occur in obesity and diabetes to the development of heart failure. These articles also emphasize that optimizing energy metabolism may be a promising approach to treating heart failure in this patient population. ■

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