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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Metabolic Impairment in Heart Failure

The Myocardial and Systemic Perspective

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JACC JOURNAL CME

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CME Objective for This Article: Metabolic aspects, comorbidities, and maladaptation in HF patients will be explained as intrinsic features of HF pathophysiology. Metabolic failure in heart failure is emerging as an important facet in HF pathophysiology that may complement the neuroendocrine activation as therapeutic target.

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ABSTRACT

Although bioenergetic starvation is not a new concept in heart failure (HF), recent research has led to a growing appreciation of the complexity of metabolic aspects of HF pathophysiology. All steps of energy extraction, transfer, and utilization are affected, and structural metabolism is impaired, leading to compromised functional integrity of tissues. Not only the myocardium, but also peripheral tissues and organs are affected by metabolic failure, resulting in a global imbalance between catabolic and anabolic signals, leading to tissue wasting and, ultimately, to cachexia. Metabolic feedback signals from muscle and fat actively contribute to further myocardial strain, promoting disease progression. The prolonged survival of patients with stable, compensated HF will increasingly bring chronic metabolic complications of HF to the fore and gradually shift its clinical presentation. This paper reviews recent evidence on myocardial and systemic metabolic impairment in HF and summarizes current and emerging therapeutic concepts with specific metabolic targets. (J Am Coll Cardiol 2014;64:1388–400) © 2014 by the American College of Cardiology Foundation.

Despite therapeutic advances in heart failure (HF) therapy, the disease remains a major challenge. Between 1979 and 2004, the number of HF hospitalizations in the United States tripled, with more than 80% of cases among patients age 65 years or older (1). The neuroendocrine activation paradigm is the cornerstone of current pathophysiological understanding of HF, and most current medical therapies that impact survival block neuroendocrine activation (**Central Illustration**). However, evidence is mounting that this does not fully explain the complexity of HF pathophysiology. Additional mechanisms, such as inflammatory activation and metabolic impairment, are increasingly the focus of research for novel therapeutic concepts.

Metabolic failure as an important underlying mechanism is neither a new nor an exclusive concept for HF, but is a typical adaptive biological response to injury. In HF, the metabolic perspective is usually attributed to the myocardium. (See the Online Appendix for an overview of current concepts of myocardial metabolic and energetic failure.)

Beyond myocardial metabolic failure, systemic (peripheral) metabolic regulation is increasingly recognized as contributing both to major symptoms (muscle weakness, fatigue, exercise limitation, and dyspnea) and to disease progression. Along with prolonged patient survival in a stable, recompensated state, new clinical features and comorbidities of long-term disease progression, such as the development of insulin resistance, anemia, hyperuricemia, and cardiac cachexia, are coming to the fore. The growing complexity of HF pathophysiology will increase the need for treatment strategies tailored to specific characteristics of patient subgroups.

This review focuses on current bioenergetic concepts in HF, with particular emphasis on involvement of peripheral tissues and organs in the complex imbalance of energy metabolism and hormonal and inflammatory regulation and on current and emerging therapeutic concepts. Targeting the metabolic aspect of HF with novel, specific interventions may emerge as a new frontier in HF therapy, complementary to the neuroendocrine paradigm.

PERIPHERAL METABOLISM IN HF

Because of increased recognition of the metabolic perspective, HF is currently appreciated as a systemic and multiorgan syndrome (**Central Illustration**). Activated feedback signals from peripheral reflex circuits (2), systemic dysregulation of several hormonal pathways (3), and global metabolic imbalance (4) are intrinsic features of HF pathophysiology. Systemic metabolic concepts have pathophysiologic and therapeutic implications. Signals, such as inflammation, insulin resistance, anabolic blunting, and oxygen radical accumulation, not only affect the myocardium, but exert detrimental effects on a systemic level. These peripheral metabolic derangements contribute to the major symptoms and disease progression of HF. Moreover, specific metabolic therapeutic concepts to improve substrate utilization and energetic efficiency will affect both myocardial and peripheral tissues, namely skeletal muscle (**Figure 1**).