Protein catabolism and impairment of skeletal muscle insulin signalling in heart failure

P. Christian SCHULZE
Division of Cardiology, New York-Presbyterian Hospital, Columbia University Medical Center, New York, NY 10032, U.S.A.

Abstract

Derangements in systemic and local metabolism develop in patients with CHF (chronic HF (heart failure)) and contribute to the progression of the disease. Impaired skeletal muscle metabolism, morphology and function leading to exercise intolerance are hallmarks of the syndrome of CHF. These changes result in abnormal glucose and lipid metabolism, and the associated insulin resistance, which contribute to progression of skeletal muscle catabolism and development of muscle atrophy in patients with advanced HF. In the present issue of Clinical Science, Toth and co-workers demonstrate the impairment of skeletal muscle protein metabolism in patients with HF and specifically show an impaired anabolic response in the skeletal muscle of these patients following a period of nutritional deficiency.

The syndrome of CHF (chronic HF (heart failure)) is a complex multi-organ response mechanism to the primary inability of the heart to provide a cardiac output needed for the metabolic needs of the body. Although acute decompensated HF is characterized by the sudden onset of cardiac failure with resulting haemodynamic compromise and impaired peripheral organ perfusion, patients with CHF are able to maintain everyday activities for sustained periods of time until deterioration of functional status. This period during which patients maintain functional capacity and the associated decline in exercise tolerance has been the focus of multiple studies. Patients with CHF have various levels of exercise tolerance only partially explained by ‘central’ cardiac dysfunction [1]. Of note, the ability to exercise is primarily defined by so called ‘peripheral factors’, including muscle metabolism and function [2], insulin resistance [3] and vascular endothelial function [4].

In HF, abnormalities in several endocrine systems contribute to structural and functional impairment of skeletal muscle. These include systemic and local inflammation [5,6], development of insulin resistance [3] and impaired GH (growth hormone)/IGF-1 (insulin-like growth factor-1) signalling [7–10]. Skeletal muscle function and metabolism in HF has been studied by various groups elucidating changes in mitochondrial metabolism [11], local inflammation [5], enhanced oxidative stress [12], changes in muscle fibre distribution from type I oxidative to type II glycolytic fibres [11], and muscle fibre atrophy [10].

Peripheral muscle metabolism is a complex interplay of anabolic and catabolic factors and signalling pathways. The resulting balance of muscle growth or atrophy is a result of mechanisms controlling protein synthesis and degradation. In the present issue of Clinical Science, Toth and co-workers [13] demonstrate the impairment of skeletal muscle protein metabolism in patients with HF. They specifically show an impaired anabolic response in skeletal muscle of patients with HF following a period of nutritional deficiency. Of note, the authors did not find differences in the fasting amino acid balance, but a strong reduction in the anabolic response (>50%) to insulin and amino acid infusion (hyperinsulinaemic–hyperaminoacidaemic condition) in patients with HF [13]. Protein degradation was directly related to the impaired anabolic response in patients with HF and the impaired response to insulin correlated with circulating levels of the pro-inflammatory cytokine IL-6 (interleukin-6). Although the study cohort is small, the study by Toth et al. [13] is an interesting and valid

Key words: amino acid, cachexia, heart failure, inflammation, insulin, proteolysis, sarcopenia.

Abbreviations: GH, growth hormone; HF, heart failure; CHF, chronic HF; IGF-1, insulin-like growth factor-1.

Correspondence: Dr P. Christian Schulze (email pcs2121@columbia.edu).
contribution to the current literature of impaired skeletal muscle metabolism in HF. The novel finding of the study by Toth et al. [13] is that patients with HF exhibit an impaired muscle protein anabolism after a brief period of nutritional deficiency, which may contribute to muscle wasting.

Muscle wasting has been demonstrated to be of prognostic significance in patients with HF [6,14], as well as other disease states [15]. The relationship between muscle wasting in HF and impaired growth factor signalling is well documented, including reduced GH/IGF-1 and insulin signalling [7–10]. Insulin resistance and inflammation, in fact, are directly linked to morbidity and mortality in HF [14,16]. It is, however, unclear how these different mechanisms are linked to each other and whether a causative relationship exists. One might speculate that local inflammation uncouples anabolic signalling through direct or indirect interaction with insulin/IGF-1 receptors or their secondary signalling molecules. On the other hand, increased proteolytic breakdown of both structural and functional proteins in skeletal muscle has been shown to be regulated by inflammatory molecules [10]. The study by Toth et al. [13] argues for an alternative mechanism that impairs the anabolic response of skeletal muscle after a period of starvation. One might hypothesize that this reduced metabolic flexibility can be explained by insulin resistance leading to impaired anabolism due to the absence of anabolic growth factor signalling. It will be interesting to see whether this pathological phenomenon can be corrected by an intervention such as exercise training or other positive anabolic intervention (e.g. testosterone or GH application). In addition, further studies should examine the role of toxic metabolic intermediates, such as lipids, that might accumulate in skeletal muscle in a chronic catabolic state. Finally, to address the question of whether local skeletal muscle catabolism in HF is reversible, studies should be designed to investigate muscle metabolism in patients with haemodynamic correction after ventricular-assist device placement or cardiac transplantation. These attempts might be able to shed light into the molecular causes and clinical progression of exercise intolerance in patients with advanced HF.

REFERENCES


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