Cachexia in chronic heart failure (HF) is a major clinical problem that is still underestimated for its impact on morbidity, mortality, and healthcare expenditures. The pathophysiology of cardiac cachexia is characterized by a catabolic/anabolic imbalance. An important player in the development of muscle wasting and cachexia in HF may be myostatin.

Myostatin
Regulator of Muscle Wasting in Heart Failure and Treatment Target for Cardiac Cachexia

Jochen Springer, PhD; Volker Adams, PhD; Stefan D. Anker, MD, PhD

Myostatin, also known as growth differentiation factor-8 (GDF-8), is a member of the transforming growth factor-β superfamily and was identified in 1997.1 In humans, myostatin is expressed almost exclusively in skeletal muscle and is essential for normal regulation of muscle mass through its actions as a negative regulator of muscle bulk.2 Gene disruption, either natural or by targeted mutation, leads to a marked increase in muscle mass due to hypertrophy and hyperplasia.1 This was clearly evident in a child with a mutation in the myostatin gene who had the ability to hold two 3-kg dumbbells at the age of 4 years.3 Myostatin has been shown to be upregulated in human immunodeficiency virus– and cancer-associated cachexia,4 with advanced age,5 and in chronic HF.6 In each of these conditions, a loss of skeletal muscle mass occurs that leads to a disproportionate loss of exercise tolerance and an early increase in muscle fatigue.

Human cardiovascular studies concerning myostatin are generally lacking. Before the report by Heineke et al7 in this issue of Circulation, 2 animal studies reported increased myostatin expression in the peri-infarct zone in sheep8 and in a rat model of volume overload induced by an aortocaval shunt.9 Importantly, the expression remained increased after 4 weeks in the shunt model. In 2008, Hoenig10 presented a hypothesis that myostatin acts as a mediator of cardiac cachexia, insulin resistance, and osteoporosis in chronic HF. To date, it has been unclear how alterations in the myocardium of patients with HF influence gene expression and function of the peripheral skeletal muscle. It has been hypothesized that soluble factors secreted by the heart may be responsible for the observed skeletal muscle alterations. The data to support or refute this hypothesis have been missing thus far.

The article by Heineke et al7 in this issue aims to fill this gap by proposing that myostatin released from the failing heart induces skeletal muscle wasting in HF. Furthermore, their results suggest that myostatin inhibition may be a therapeutic option to counteract skeletal muscle wasting in HF. A loss of cardiac mass is reported in their model of HF. This is known to be a late event in human HF; skeletal muscle wasting and general loss of body weight (ie, development of body cachexia) precede the loss of cardiac mass.11 Although no data on actual animal body weight or body weight loss have been reported, the term “muscle cachexia” is used. This term is misleading, because a loss of muscle mass without actual body weight loss is not cachexia but muscle wasting. When muscle wasting occurs in the context of aging, it is termed “sarcopenia.”12 The term “cachexia,” however, describes a “complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass.”13 This statement is taken from a recent consensus definition of cachexia, which continues, “The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders).”13 We believe that when cachexia and muscle wasting are discussed, the use of precise language based on precise definitions is important. Otherwise, this new research area may suffer from misunderstandings and misleading conclusions.

Heineke et al7 did not find an increased expression of myostatin in skeletal muscle after transverse aortic banding. Knockout of myostatin expression in the heart but not in the skeletal muscle reduced transverse aortic banding–induced loss of lean body mass. This is somewhat contradictory to an earlier publication that used the left anterior descending coronary artery ligation model to induce HF, in which a robust induction of myostatin messenger RNA expression in skeletal muscle was observed that correlated with the protein level of myostatin.6 In that study, myostatin expression correlated with the expression of tumor necrosis factor-α, which suggests that tumor necrosis factor is a potent regulator of myostatin expression. Exercise reduced both tumor necrosis factor and myostatin expression in both heart and skeletal muscle.6 These differences could be due to the different models used to induce HF. When one looks at the relevance of the 2 models for human HF, the incidence of chronic HF due to aortic stenosis is rare, whereas development of chronic HF due to coronary artery disease is frequent.
These criticisms, however, should not detract from the importance of the report by Heineke et al. The results clearly suggest that myostatin inhibition is a potential therapeutic strategy for attenuating loss of muscle mass in cardiac cachexia. As many good studies do, this study triggers more questions than it answers. It remains to be shown that an improvement in muscle mass translates to an improvement in muscle function or, more importantly, to an improved survival. In addition, it appears necessary to investigate very carefully the potential cross-talk between 1 of the gold standard medication therapies for chronic HF (ie, the use of β-blockers) and myostatin inhibition. It has been demonstrated recently that myostatin inhibits basal and insulin-like growth factor–stimulated proliferation and differentiation in the heart. Knockout of myostatin induced eccentric hypertrophy and enhanced cardiac responsiveness to β-adrenergic stimulation owing to increased sarcoplasmic reticulum calcium release in vivo. Interestingly, the β2 antagonist formoterol negatively regulates myostatin expression and signaling in skeletal muscle.

Although a great deal of mechanistic insight has been generated by genetic modification of myostatin in mice, there have only been 2 experimental compounds targeting myostatin that have been tested in humans for safety and efficacy. These myostatin inhibitory antibodies/peptibodies are being developed for the treatment of muscular dystrophies. Wyeth’s myostatin antibody MYO-029 showed only minimal improvements in muscle strength and pathology in patients with muscular dystrophies, which resulted in the discontinuation of further development of this compound for dystrophies in 2008. No plans for MYO-029 development in other indications such as cardiac cachexia have been published so far.

The Amgen compound AMG 745 is presently listed in the company’s 2008 annual report as being in phase I development to be investigated for muscle-wasting disorders. Unfortunately, no further information on AMG 745 is available in the current literature, and none has been released directly by Amgen. A phase II study to investigate the use of AMG 745 in patients with cachexia was stopped just before its initiation, although ethics approval was available in some locations. More news on myostatin-targeting treatment approaches was to become available during the 5th Cachexia Conference that was scheduled to take place in Barcelona, Spain, from December 5–8, 2009 (see www.cachexia.org).

We are left with the question of whether the inhibition of myostatin is the “golden key” to treat cardiac cachexia, as Heineke et al suggest. Before we can definitively answer this question, several issues must be resolved. First, is an increased expression and secretion of myostatin the only relevant factor responsible for skeletal muscle atrophy, or are other pathways activated that also regulate muscle wasting? With respect to other pathways, the ubiquitin-proteasome pathway appears to regulate enhanced proteolysis and atrophy of skeletal muscle in various pathologic states. For example, MG132 and HWA488, both substances that influence proteasome activity, proved to be powerful inhibitors of muscle wasting in animal models. This raises the question of whether there is cross-talk between the myostatin and proteasome pathways or whether they are activated by other mechanisms. One potential candidate, which is also increased in most cases of muscle wasting, is tumor necrosis factor. At least in cell culture experiments, it has the ability to activate myostatin expression and to regulate the expression of important enzymes involved in ubiquitin-proteasome–mediated protein degradation. Furthermore, catalytic factors are not the only factors involved in the regulation of muscle homeostasis; factors involved in the regulation of appetite or muscle anabolism, such as melanocortin-4, ghrelin, growth hormone, and insulin-like growth factor-1, may also be relevant targets in cardiac cachexia.

In conclusion, the strength of the report by Heineke et al is the compelling evidence provided that a soluble factor—myostatin—secreted by the myocardium induces skeletal muscle wasting. Whether inhibition of myostatin to treat muscle wasting in chronic HF and to treat cardiac cachexia in general is a valid treatment option remains to be proven. The present report is a giant step forward in the quest to understand the mechanism(s) responsible for cardiac cachexia and to generate therapies for cardiac cachexia.

Disclosures

Dr Springer has been a consultant to Myotec Therapeutics. Dr Anker has been a consultant to Amgen Inc, Fresenius Kabi, Myotec Therapeutics, Professional Dietetics, and Vifor Pharma and received honoraria for speaking from Amgen Inc, Fresenius Kabi, and Vifor Pharma. Dr Adams reports no conflicts.

References


**Key Words:** Editorials ■ heart failure ■ muscles ■ myocytes ■ cachexia ■ wasting disease
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_Circulation_. 2010;121:354-356; originally published online January 11, 2010;
doi: 10.1161/CIR.0b013e3181d0ba8b

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/121/3/354

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