Genetic Deletion of Myostatin From the Heart Prevents Skeletal Muscle Atrophy in Heart Failure

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Background—Cardiac cachexia is characterized by an exaggerated loss of skeletal muscle, weakness, and exercise intolerance, although the cause of these effects remains unknown. Here, we hypothesized that the heart functions as an endocrine organ in promoting systemic cachexia by secreting peptide factors such as myostatin. Myostatin is a cytokine of the transforming growth factor-β superfamily that is known to control muscle wasting.

Methods and Results—We used a Cre/loxP system to ablate myostatin (Mstn gene) expression in a cell type–specific manner. As expected, elimination of Mstn selectively in skeletal muscle with a myosin light chain 1f (MLC1f)-cre allele induced robust hypertrophy in all skeletal muscle. However, heart-specific deletion of Mstn with an Nkx2.5-cre allele did not alter baseline heart size or secondarily affect skeletal muscle size, but the characteristic wasting and atrophy of skeletal muscle that typify heart failure were not observed in these heart-specific null mice, indicating that myocardial myostatin expression controls muscle atrophy in heart failure. Indeed, myostatin levels in the plasma were significantly increased in wild-type mice subjected to pressure overload–induced cardiac hypertrophy but not in Mstn heart-specific deleted mice. Moreover, cardiac-specific overexpression of myostatin, which increased circulating levels of myostatin by 3- to 4-fold, caused a reduction in weight of the quadriceps, gastrocnemius, soleus, and even the heart itself. Finally, to investigate myostatin as a potential therapeutic target for the treatment of muscle wasting in heart failure, we infused a myostatin blocking antibody (JA-16), which promoted greater maintenance of muscle mass in heart failure.

Conclusions—Myostatin released from cardiomyocytes induces skeletal muscle wasting in heart failure. Targeted inhibition of myostatin in cardiac cachexia might be a therapeutic option in the future. (Circulation. 2010;121:419-425.)

Key Words: atrophy ■ heart failure ■ hypertrophy ■ muscle, skeletal ■ myocardium

In 2005, >5 million people were estimated to suffer from heart failure in the United States.1 Heart failure is associated with high rates of morbidity and mortality that are comparable to many forms of cancer. Similar to cancer, body wasting occurs in heart failure that affects skeletal muscle, fat, and bone tissues.2 Strikingly, the presence of body wasting in heart failure was recently identified as a strong independent risk factor for mortality.3 Skeletal muscle atrophy occurs in up to 68% of patients with heart failure and is thought to contribute to the muscle weakness and low exercise tolerance typically observed in this disease.4 Despite recent progress in the therapies for heart failure, an effective treatment strategy for wasting is currently lacking.

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Plasma levels of inflammatory cytokines such as tumor necrosis factor-α or neurohormones such as epinephrine, norepinephrine, and cortisol are upregulated in heart failure patients and hence could contribute to the general catabolic state observed in this disease.5 However, a direct causal association between increased neurohormones and total body wasting has not been established, nor does this association hold true in all heart failure patients. Therefore, we hypothesized that an atrophy-inducing factor such as myostatin, a cytokine of the transforming growth factor-β superfamily that functions as a potent inhibitor of skeletal muscle growth, might be released directly from the myocardium in heart failure,6,7 Indeed, myostatin is upregulated in the heart after infarction injury and volume overload injury and in transgenic mice with diseased hearts because of Akt overexpression.8–12 In the absence of pathology, myostatin is expressed predominantly in skeletal muscle, although some weak expression is observed in the heart and adipose tissue.7,9,10,13 Myostatin uniquely functions to control skeletal muscle mass; loss of this gene in mice, cattle, and dogs leads to

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profound increases in size that result from both hypertrophy and hyperplasia of muscle.6,7 Deletion of myostatin specifically in adult mice with a tamoxifen-inducible Cre/loxP strategy still resulted in a 25% increase in skeletal muscle weight mainly through the development of muscle fiber hypertrophy rather than hyperplasia.14 Consistent with these observations, systemic overexpression of myostatin (such as injection of myostatin producing Chinese hamster ovary cells) in adult mice resulted in cachexia with a significant reduction in individual skeletal muscle weight.15 These data demonstrate the effectiveness of myostatin in the modulation of skeletal muscle mass in adulthood.

We demonstrate here that myostatin from cardiomyocytes plays a crucial role in the development of muscle wasting in a mouse model of heart failure. We also show that systemic myostatin inhibition with a blocking antibody might be a valuable approach for the treatment of heart failure–associated skeletal muscle atrophy.

Methods

Animals and Animal Procedures

The generation of Myostatin (Mstn) loxP site–targeted (fl/fl) embryonic stem cells and mice was described previously.16 Mice carrying an Nkx2.5-cre knock-in allele and mice expressing cre recombinase under the control of the myosin light chain 1f (MLC1f) genomic locus (knock-in) were described previously.17,18 The Mstn fl/fl, the Nkx2.5-cre, and the MLC-cre mice were all maintained in the C57Bl/6j genetic background. Myostatin transgenic mice (FVBN MLC-cre, and the Nkx2.5-cre fl/fl, the Mstn fl/flMLC-cre mice were all maintained in the C57Bl/6j genetic background. Myostatin transgenic mice (FVBN MLC-cre, and the Nkx2.5-cre fl/fl, the Mstn fl/flMLC-cre lines) were used to generate mice in which the third exon is flanked by loxP sites (Nkx2.5-cre MLCK1f-cre line) or in which the Nkx2.5-cre or Mstn fl/fl mice were crossed to the Mstn-cre line to generate Mstn fl/flMLC-cre or Nkx2.5-cre Mstn fl/fl mice, respectively (Figure 1A). At 2 months of age, Mstn fl/flMLC-cre mice showed a large increase in total skeletal muscle mass (normalized to tibia length) compared with Mstn fl/fl control mice, as specifically quantified from quadriceps, gastrocnemius, and soleus (Figure 1B through 1D).

Figure 1. Genetic deletion of Mstn in skeletal muscle produces hypertrophy. A, Schematic of the crosses performed to delete the Mstn gene in skeletal muscle with the MLC1f-cre line or in heart with the Nkx2.5-cre line. Muscle weight (MW) normalized to tibia length (TL) of the quadriceps (B), gastrocnemius (C), and soleus (D) from the indicated groups of mice at 2 months of age. The number of mice per group is indicated in the bars. E, Western blots for myostatin protein from the plasma of wild-type (WT) or global Mstn−/− mice. Recombinant myostatin protein is shown as a control. F, Western blots for myostatin protein in the plasma of the indicated mice after 2 weeks of TAC stimulation or a control sham procedure. Mstn−/− plasma is shown as a control. *P<0.01 vs control.

Antibody Administration

The monoclonal anti-myostatin blocking antibody (clone JA-16, Wyeth Research, Collegeville, Pa) inhibits the binding of myostatin to its receptor ActRIIB. Mice were treated with weekly intraperitoneal injections of JA-16 at 60 mg/kg or mouse control antibody for 6 weeks starting at 8 weeks after TAC or sham surgery.20

Semiquantitative Reverse-Transcription PCR

RNA was prepared from quadriceps muscles and hearts with TRizol reagent (Invitrogen, Carlsbad, Calif) according to the manufacturer’s instructions. Complementary DNA was generated through reverse transcription (RT) with the SuperScript III first-strand synthesis system (Invitrogen) following the protocol provided by the manufacturer. Myostatin complementary DNA was amplified by PCR (34 cycles) with the following primers: 5′-agctacgcaacagga3′ and 5′-ctgtcgctgaggattaca-3′. L7 was used as a control and was amplified with the following primers: 5′-agaagctctatgagagcg-3′ and 5′-aagagagagctcagaa3′.

Western Blotting

Protein concentration from mouse plasma samples was determined with the DC protein assay (Bio-Rad, Hercules, Calif). Plasma and homogenized protein tissue samples supplemented with Laemmli loading buffer were boiled, subjected to electrophoresis on 16% Tris-Tricine gels, and Western blotted with rabbit anti-myostatin antibody (Millipore, Billerica, Mass). Protein extracts from tissues were obtained by homogenization in RIPA buffer (10 mmol/L Tris/HCl at pH 7.5, 150 mmol/L NaCl, 4% glycerol, 1% Triton X-100, 0.1% Na deoxycholate, 0.05% SDS, 1 mmol/L DTT, Halt protease inhibitors cocktail [Thermo Scientific, Waltham, Mass], and phosphatase cocktail inhibitors I and II [Calbiochem, San Diego, Calif]). Insoluble material was precipitated by centrifugation at 14,000 rpm for 30 minutes at 4°C.

Statistics

All values are presented as means±SEM. The unpaired Student t test was used to analyze differences between 2 groups in Figures 1 and 3. Statistical differences for multiple comparisons in Figures 2 and 4 were determined with 2-way ANOVA followed by the Holm-Sidak posthoc test. Nongaussian-distributed data were analyzed by Kruskal-Wallis test followed by the Dunn posthoc test for the data shown in Figure 2G. A 2-tailed value of P<0.05 was considered significant.

Results

Genetic Deletion of Mstn in Skeletal Compared With Cardiac Muscle Cells

Although myostatin is expressed primarily in skeletal muscle, some expression is observed in heart muscle; its function there remains unknown. Here, we used Mstn gene–targeted mice in which the third exon is flanked by loxP sites (Mstn fl/fl) to permit tissue-specific deletion with an appropriate cre-expressing line. Skeletal muscle– and cardiac muscle–specific deletion was achieved separately by crossing mice containing an MLC1f-cre or Nkx2.5-cre knock-in allele, respectively (Figure 1A). At 2 months of age, Mstn fl/flMLC-cre mice showed a large increase in total skeletal muscle mass (normalized to tibia length) compared with Mstn fl/fl control mice, as specifically quantified from quadriceps, gastrocnemius, and soleus (Figure 1B through 1D).
Previous reports have shown that myostatin mRNA and protein are upregulated in the heart after injury or induction of hypertrophy and heart failure.\(^8\)–\(^{12}\) Given the known role of myostatin as a muscle atrophy factor, the hypothesis arose that myostatin secretion from the injured or failing heart could alter skeletal muscle mass. First, we confirmed that myostatin protein could be detected in mouse plasma by using the global \(Mstn^{-/-}\) mouse as a control for the antibody, as well as recombinant myostatin protein. The data show that myostatin protein is easily detected in the plasma of wild-type mice but is absent in plasma from \(Mstn^{-/-}\) mice (Figure 1E).

More important, plasma harvested from mice subjected to cardiac injury by TAC-induced pressure overload exhibited a 2- to 3-fold increase in circulating myostatin levels (Figure 2).

Figure 2. \(Mstn\) deletion from heart prevents skeletal muscle atrophy in heart failure. A, Representative RT-PCR analysis of myostatin and L7 (control) in heart and quadriceps from control and \(Mstn^{-/-}\) mice. B, RT-PCR analysis of myostatin and L7 (control) in the quadriceps from \(Mstn^{-/-}\) mice 12 weeks after sham or TAC surgery. C, RT-PCR analysis of myostatin and L7 (control) in the heart from control and \(Mstn^{-/-}\) mice 12 weeks after sham or TAC surgery. D, Western blot from quadriceps from \(Mstn^{-/-}\) mice 12 weeks after sham or TAC surgery as a control, the last lane shows loss of prepromyostatin from quadriceps in \(Mstn^{-/-}\) mice. As a control, the last lane shows loss of prepromyostatin from quadriceps in \(Mstn^{-/-}\) mice. E, PCR (30 cycles) from quadriceps genomic DNA isolated from \(Mstn^{-/-}\) mice 12 weeks after sham surgery to assay for the recombinated allele (Δ, top) or the unrecombinated allele (Wt, bottom). The last lane shows recombination of the \(Mstn\) locus in \(Mstn^{-/-}\) mice from quadriceps and negative control without Cre in the adjacent lane. F, Fractional shortening (FS) determined by echocardiography in control and \(Mstn^{-/-}\) mice 12 weeks after sham (Sh.) or TAC surgery. *\(P<0.05\) vs sham. G, Heart weight normalized to body weight (HW/BW) in control and \(Mstn^{-/-}\) mice 12 weeks after sham or TAC surgery. *\(P<0.05\) vs sham control; #\(P<0.05\) vs TAC control. The number of mice per group in F through K is indicated in the bars.

Figure 3. Cardiomyocyte-specific overexpression of myostatin reduces cardiac and skeletal muscle mass. A, Representative RT-PCR analysis of myostatin and L7 (control) expression in cardiac muscle from nontransgenic (NTG) mice and lines 15 and 27 transgenic (TG) mice. B, Western blot for myostatin protein in plasma of wild-type (WT) and myostatin transgenic mice. Recombinant myostatin protein is shown as a migration control. C through F, Muscle weight (MW) or heart weight (HW) normalized to tibia length (TL) from 3-month-old nontransgenic and transgenic mice (Line 27). The number of mice per group is indicated in the bars. *\(P<0.01\) vs nontransgenic.
myostatin in the plasma (Figure 1F). However, this increase in circulating myostatin after 2 weeks of TAC was blocked in Mstn fl/flNkx2.5-cre mice, suggesting that the heart was producing this increased level of myostatin in the plasma (Figure 1F).

Next, we analyzed mice with cardiomyocyte-specific Mstn deletion (Mstn fl/flNkx2.5-cre), Myostatin mRNA levels were quantified from quadriceps and hearts of Mstn fl/flNkx2.5-cre mice by RT-PCR, showing that myostatin was markedly deleted in the heart but not the quadriceps, indicating that the Cre allele was effective and specific to the heart (Figure 2A). To evaluate our hypothesis that myostatin from the heart could affect skeletal muscle mass in cachexia, we subjected Mstn fl/flNkx2.5-cre and control mice to 12 weeks of TAC stimulation to induce heart failure. Controls consisted of either Mstn fl/fl mice or Nkx2.5-cre mice because each showed no difference in their response to TAC over 12 weeks. Importantly, myostatin mRNA levels in the quadriceps did not change after TAC in Mstn fl/flNkx2.5-cre mice (Figure 2B). In the heart, myostatin mRNA levels were still essentially absent in Mstn fl/flNkx2.5-cre mice after TAC compared with controls (Figure 2C). We also examined myostatin protein levels in the quadriceps of Mstn fl/flNkx2.5-cre mice to ensure that this Cre allele was not expressed outside the heart at baseline or after TAC. The data show no loss of prepro-myostatin protein from skeletal muscle of Mstn fl/flNkx2.5-cre mice (Figure 2D), nor was there detectable recombination of the Mstn genetic locus by PCR compared with abundant recombination in Mstn fl/flMLC-cre control mice (Figure 2E).

After 12 weeks of TAC, echocardiography revealed a significant reduction in left ventricular function (measured as fractional shortening) in both control and Mstn fl/flNkx2.5-cre mice, suggesting equivalent dysfunction in both groups (Figure 2F). Measurements of heart weight normalized to body weight and lung weight normalized to body weight showed equivalent hypertrophy and edema, respectively, in each group (Figure 2G and 2H). Other parameters of decompensation such as left ventricular dilation and wall thinning were also similarly affected in control mice and mice lacking myostatin in their hearts (data not shown). Analysis of skeletal muscle weights revealed a reduction in muscle mass in control mice after TAC in quadriceps, gastrocnemius, and soleus muscles compared with sham-operated mice (Figure 2I through 2K). However, this decrease in muscle mass after TAC was blocked in Mstn fl/flNkx2.5-cre mice (Figure 2I through 2K). Analysis of the gastrocnemius (Figure 2J) showed a trend toward significance in the prevention of atrophy with a 2-way ANOVA, although a pairwise analysis between the control and deleted TAC groups did produce significance. Skeletal muscle weight did not differ in any group of mice subjected to sham operation. These results indicate that deletion of Mstn from the heart mitigates skeletal muscle atrophy during long-term pressure overload stimulation.

Cardiomyocyte-Specific Overexpression of Myostatin Induces Muscle Wasting in Mice

To complement our results observed in Mstn fl/flNkx2.5-cre mice with respect to muscle wasting in heart failure, we specifically overexpressed myostatin within cardiomyocytes to determine its ability to affect skeletal muscle through the blood. Here, we generated heart-specific myostatin–overexpressing transgenic mice using the mouse α-myosin heavy chain cardiac-specific promoter. Two independent lines (lines 15 and 27) were obtained and shown to produce similar levels of myostatin overexpression in the heart at 3 months of age by RT-PCR (Figure 3A). Western blotting from heart protein extracts of these transgenic mice showed abundant expression of the prepro-myostatin peptide (data not shown). More important, line 27 transgenic mice showed 3- to 4-fold more myostatin in the plasma compared with wild-type mice, mimicking the known enhancement in circulating myostatin levels in response to cardiac injury (Figure 3B).

Myostatin transgenic mice of both lines were viable and fertile and did not show any obvious signs of disease. However, skeletal muscle showed a significant reduction in mass that was apparent in both transgenic lines compared with nontransgenic control mice (data from line 27 are presented in Figure 3C through 3E). Interestingly, the heart weight normalized to tibia length was also significantly, albeit subtly, reduced in both transgenic lines (data from line 27 are presented in Figure 3F). These data indicate that myostatin produced in cardiomyocytes alone is sufficient to inhibit cardiac and skeletal muscle growth.
Myostatin Blocking Antibody (JA-16) Maintains More Muscle in Preexisting Heart Failure

Next, we wanted to examine whether pharmacological inhibition of myostatin in preexisting heart failure could be therapeutically effective in mice. For this purpose, we performed TAC or sham procedures in 2-month-old mice (C57Bl/6 background) and started treatment with a myostatin-blocking antibody (JA-16) or a control antibody 8 weeks after surgery. Cardiac performance was evaluated by echocardiography at multiple time points throughout the procedure, and equivalent pressure gradients across the aortic constrictions were observed after TAC in the beginning of the protocol (Figure 4A). Echocardiography revealed markedly reduced left ventricular function after 8 weeks of TAC in mice of both treatment groups, even before control antibodies were administered (Figure 4B). During the 6 weeks of treatment, the mortality rate was 64.3% in the control antibody TAC group and 60% in the JA-16 TAC group. Echocardiography at the end of treatment demonstrated similar reductions in left ventricular performance in both TAC treatment groups, indicating that the inhibition of myostatin during heart failure did not improve survival or cardiac performance over this period of time (Figure 4C). However, inhibition of myostatin with JA-16 maintained muscle weight (quadriceps and gastrocnemius) during heart failure at values observed in sham mice without treatment (Figure 4D and 4E). Although JA-16 treatment also increased muscle weight in sham-operated mice compared with control antibody, anti-myostatin antibody nonetheless prevented atrophy as defined by a change from a baseline value of muscle mass observed in sham control mice (Figure 4D and 4E). Thus, systemic inhibition of myostatin maintains more muscle mass in a mouse model of heart failure because of pressure overload, preventing frank muscle cachexia.

Discussion

In this study, we identified cardiac myostatin as an important mediator of muscle atrophy in heart failure. Myostatin is highly and almost exclusively expressed in skeletal muscle where it strongly inhibits myoblast proliferation before birth, as well as muscle fiber hypertrophy before birth and in adulthood. Although myostatin is generated in skeletal muscle where it acts in an autocrine manner, it is also present in the plasma, implying a systemic role of this transforming growth factor-β family member protein and the possibility that it is made and secreted by other organs. Indeed, myostatin is also expressed in heart and fat tissue, which could serve as another source of this factor and contribute to total plasma levels.

Our analysis of gene-targeted mice suggests that it is the local production of myostatin within skeletal muscle itself that dominantly regulates developmental growth and hypertrophy in adulthood, which is a novel finding not previously reported. For example, deletion of Mstn only in skeletal muscle with the MLC1f-cre knock-in allele resulted in a robust 72% increase in the weight of the quadriceps at 2 months of age. Before this work, another group crossed Mstn-loxP–targeted mice with transgenic mice expressing cre under the muscle creatine kinase promoter, which similarly induced skeletal muscle hypertrophy. However, the muscle creatine kinase promoter is also expressed in the heart, so this approach did not unequivocally prove that deletion of Mstn from skeletal muscle is the reason for hypertrophy induction.

Our data suggest that heart myostatin expression at baseline does not dominantly affect skeletal muscle mass. For example, cardiomyocyte-specific deletion of Mstn with the Nkx2.5-cre allele did not increase skeletal muscle mass in adult mice, suggesting that local production of myostatin within skeletal muscle is the primary regulator of myofiber growth and that the heart does not secrete enough myostatin under normal physiological conditions to affect skeletal muscle. However, myostatin production is induced in the heart by pathological insults, which may then significantly contribute to plasma levels to secondarily affect skeletal muscle mass. Indeed, TAC stimulation in wild-type mice, but not in heart-specific Mstn-deleted mice, enhanced circulating myostatin levels. The simplest interpretation of this observation is that the heart secretes myostatin, causing or contributing to an increase in total plasma levels after injury or prolonged cardiac stress stimulation. Myostatin protein expression is also induced in cultured cardiomyocytes in response to cyclic stretching. Thus, cardiac stress likely induces physiologically meaningful myostatin expression or release, which can have an effect on skeletal muscle. Indeed, α-myosin heavy chain–myostatin transgenic mice showed skeletal muscle wasting and atrophy, indicating that cardiac production is competent to regulate muscle mass through an endocrine-like mechanism. From a teleological perspective, it might be beneficial to rarify skeletal muscle during heart failure to secondarily reduce total circulatory burden on the heart, although too much rarefaction likely becomes maladaptive, leading to excessive morbidity.

Many patients with heart failure present with skeletal muscle atrophy, reductions in fiber strength normalized to cross-sectional area, and a disproportionate loss of exercise tolerance. Indeed, patients in advanced heart failure showed an ≈10% to 30% reduction in limb muscle weight estimated by dual x-ray absorptiometry. Here, we showed that induction of heart failure in mice, by applying long-term pressure overload, similarly led to muscle wasting. More specifically, we observed a 10%, 13%, and 26% reduction in the weight of the gastrocnemius, quadriceps, and soleus muscles, respectively, in wild-type mice 12 weeks after TAC. Thus, although this degree of muscle wasting is not highly robust, it is similar to clinically observed cachexia in heart failure. Remarkably, cardiomyocyte-specific deletion of Mstn with Nkx2.5-cre completely prevented skeletal muscle atrophy after 12 weeks of TAC, indicating that cardiac-generated myostatin influences skeletal muscle mass in heart failure. However, the function of myostatin proposed here does not preclude a role for inflammatory cytokines like tumor necrosis factor-α or neurohormones like epinephrine, norepinephrine, and cortisol in contributing to muscle wasting in heart failure. Indeed, we identified a significant increase in local tumor necrosis factor-α from the quadriceps after TAC-induced heart failure, although JA-16 antibody treatment did not reduce this expression (data not shown).
Beside its inhibitory effect on skeletal muscle growth, Mstn<sup>−/−</sup> mice were shown to develop significantly more cardiac hypertrophy in response to phenylephrine infusion, suggesting that it can also mildly affect heart growth. Consistent with these results, we observed that cardiac overexpression of myostatin results in a small but significant reduction in heart weight. Similarly, transgenic mice with muscle creatine kinase promoter–driven myostatin overexpression also showed a small reduction in heart weight. Together, these data indicate that although myostatin is primarily a regulator of skeletal muscle mass, it can negatively influence cardiac muscle hypertrophy.

Genetic deletion of Mstn from the heart appeared to be more effective in combating muscle wasting in heart failure than JA-16 antibody treatment (compare Figures 2 and 4). However, the genetic approach rendered the heart without Mstn from the onset of the TAC experiment, whereas JA-16 antibody treatment began after the induction of heart failure by TAC. This might suggest that early inhibition of myostatin is more effective or simply that JA-16 antibody results in only partial inhibition of myostatin, especially given the increased plasma levels produced in heart failure. Regardless of this issue, we demonstrate that systemic inhibition of myostatin with a blocking antibody in preexisting heart failure in mice can maintain overall muscle weight at values of sham-operated control mice. The effectiveness of JA-16 had previously been reported in the treatment of some forms of muscular dystrophy, where antibody-mediated inhibition of myostatin increased muscle weight and strength and reduced fibrosis. Although drugs commonly used for the treatment of heart failure can reduce muscle atrophy (angiotensin-converting enzyme inhibitors, for example, reduce the risk of cachexia in heart failure by 19%), a targeted and more efficient treatment for cardiac cachexia is needed. Interestingly, although muscle weight was increased in our study, this effect did not correlate with an improvement in mortality or cardiac function after long-term TAC. Thus, even though combating muscle atrophy in heart failure may improve the quality of life in patients, it remains to be determined whether it will ultimately extend lifespan.

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**Disclosures**

The JA-16 antibody was obtained from Wyeth Pharmaceuticals for a previous study. The authors report no other conflicts.

**References**


The prevalence of chronic heart failure is steadily increasing in our population. Individuals suffering from this disease face high rates of mortality (which were reported to be as high as 50% in 5 years) and dire symptoms like dyspnea, edema, exercise intolerance, and muscle loss. Skeletal muscle atrophy occurs in up to 68% of patients with heart failure and has been identified as a strong independent risk factor for mortality. Despite these facts, the cause of muscle wasting in heart failure is unclear, and a targeted treatment option is lacking. In this study, we show that the mouse heart, when exposed to pathological hemodynamic burden consistent with heart failure, releases the protein myostatin, a well-known inhibitor of skeletal muscle growth, into the systemic circulation. Genetic ablation of myostatin specifically in the heart prevented skeletal muscle atrophy when heart failure was induced. Antithetically, genetically modified mice with enhanced myostatin expression in the myocardium showed skeletal muscle rarefaction, indicating that cardiac myostatin is sufficient to induce skeletal muscle wasting. Therapeutically, injection of a myostatin-blocking antibody in mice with preexisting heart failure preserved muscle mass. Thus, myostatin inhibition might be a medically relevant avenue for the treatment of muscle wasting in heart failure.
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