Impaired Modulation of Sympathetic Vasoconstriction in Contracting Skeletal Muscle of Rats With Chronic Myocardial Infarctions
Role of Oxidative Stress

Gail D. Thomas, Weiguo Zhang, Ronald G. Victor

Abstract—Skeletal muscle perfusion during exercise is impaired in heart failure, but the underlying mechanisms are poorly understood. One possibility is that sympathetic vasoconstriction is enhanced in exercising muscle in heart failure as a result of impaired counterregulatory mechanisms that normally act to attenuate vasoconstrictor responses. In healthy animals, sympathetic vasoconstriction in contracting skeletal muscle is attenuated by endogenously produced nitric oxide (NO). Because the NO pathway may be dysfunctional in heart failure, we hypothesized that reduced NO in contracting muscle would result in enhanced sympathetic vasoconstriction. In sham rats and rats with chronic myocardial infarctions (MIs) produced by coronary artery ligation, we measured arterial pressure and femoral artery blood flow responses to sympathetic nerve stimulation (1, 2.5, and 5 Hz) in resting and contracting hindlimb. In resting hindlimb, sympathetic stimulation decreased femoral vascular conductance similarly in sham and MI rats. In contracting hindlimb, these vasoconstrictor responses were attenuated to a greater extent in sham than in MI rats. NO synthase inhibition enhanced sympathetic vasoconstriction in contracting hindlimb of sham, but not MI, rats. Conversely, infusion of L-arginine or a superoxide scavenger, tempol or tiron, attenuated sympathetic vasoconstriction in contracting hindlimb of MI rats. NO synthase expression was similar, but malondialdehyde (a marker of free radical damage) was greater in skeletal muscle from MI than from sham rats. These data suggest that impaired metabolic modulation of sympathetic vasoconstriction in contracting skeletal muscle of MI rats is a consequence of superoxide-mediated disruption of the NO pathway. (Circ Res. 2001;88:816-823.)

Key Words: vasoconstriction ■ oxidant stress ■ nitric oxide ■ skeletal muscle ■ heart failure

Activation of the sympathetic nervous system plays an essential role in the cardiovascular response to exercise. Sympathetic activation causes vasoconstriction in regions such as the renal and splanchnic circulations, which redistributes cardiac output to the exercising muscles. Sympathetic activation also occurs in exercising muscle, but the vasoconstrictor response appears to be blunted in part by local metabolic products of contraction. Such metabolic modulation is particularly evident in the small resistance arterioles of the muscle microcirculation, which may serve to optimally distribute blood flow within the active muscle.

Nitric oxide (NO) is thought to be one of the key substances produced in contracting skeletal muscle that effectively opposes sympathetic vasoconstriction. Although both the endothelial and neuronal isoforms of NO synthase (eNOS and nNOS, respectively) are expressed in skeletal muscle, nNOS appears to be an important source of NO production during contraction as demonstrated by the impaired modulation of α-adrenergic vasoconstriction in the contracting hindlimb of nNOS knockout mice. This impairment also is evident in boys with Duchenne muscular dystrophy (DMD) and in mdx mice, a model of DMD in which a primary deficiency of the cytoskeletal protein dystrophin results in a secondary reduction of skeletal muscle nNOS. Recurrent ischemia caused by unopposed sympathetic vasoconstriction in the nNOS-deficient muscles of DMD patients may contribute to exercise intolerance in this rare disease. Whether a similar mechanism might contribute to the exercise intolerance observed in a much more common condition such as heart failure is unknown.

Increasing evidence suggests that NO-mediated vasodilation is impaired in heart failure. During exercise, NO production is reduced in heart failure patients compared with healthy controls. Additionally, NOS inhibition reduces blood flow to exercising muscles in healthy rats and humans, but not in those with heart failure. The reasons for the apparent NO deficiency in these studies were not investigated. One possibility is that NOS expression is reduced.
however, this has not been a consistent finding.\textsuperscript{15,16} Another possibility is that NO bioavailability, rather than production, is limited in heart failure. Reactive oxygen species, in particular superoxide anion (O$_2^-\$), are known to rapidly inactivate NO. Recent studies in animals and humans have shown that oxidative stress is increased in heart failure, as evidenced directly by increased myocardial and aortic production of reactive oxygen species\textsuperscript{16,17} and indirectly by circulating markers of free radical–induced cellular damage.\textsuperscript{18–20} Whether heart failure also increases oxidative stress in skeletal muscle and how this might impact muscle blood flow regulation are currently unknown.

On the basis of these observations, we hypothesized that metabolic modulation of sympathetic vasoconstriction in skeletal muscle is impaired in chronic heart failure. We further hypothesized that this impairment is mediated in part by NO deficiency caused by decreased skeletal muscle NOS expression and/or O$_2^-\$-mediated disruption of the NO pathway. To test these hypotheses, we performed studies in anesthetized rats with chronic myocardial infarctions (MIs) produced by coronary artery ligation to determine whether the vasoconstrictor responses to sympathetic nerve stimulation were enhanced in contracting hindlimb and whether these responses could be normalized by experimental interventions that increased NO or decreased O$_2^-\$.

**Materials and Methods**

All methods and protocols were approved by the Institutional Animal Care and Research Advisory Committee at the University of Texas Southwestern Medical Center.

**Coronary Artery Ligation Model**

Female Sprague-Dawley rats were anesthetized with methohexital sodium (50 mg/kg IP), intubated, and ventilated. A thoracotomy was performed to expose the heart, and the left coronary artery was ligated. Sham operations followed the same procedure without coronary ligation. Studies were performed 6 to 20 weeks after coronary ligation. On completion of each experiment, the heart was excised and myocardial infarct size was estimated as described by Chien et al.\textsuperscript{21}

**Experimental Preparation**

Rats were anesthetized with ketamine (80 mg/kg IP) and α-chloralose (60 mg/kg IV) and instrumented as previously described.\textsuperscript{4} Briefly, artificially ventilated rats were instrumented with jugular vein and carotid artery catheters, a Doppler flow probe (Crystal Biotech) on the left femoral artery, and stimulating electrodes around the left lumbar sympathetic chain and left sciatic nerve. The left hindlimb was connected to a force-displacement transducer (FT-10, Grass Instruments).

**Protocol 1: Comparison of Sympathetically Mediated Vasoconstriction in Resting and Contracting Hindlimb of Sham and MI Rats**

Arterial pressure and femoral blood flow responses to lumbar sympathetic nerve stimulation (1-ms pulses of 5 V each at 1, 2.5, or 5 Hz) were measured in resting and contracting hindlimb. Contractions were produced by sciatic nerve stimulation at 2 to 3 times motor threshold voltage with 100-ms trains of pulses at a rate of 60 trains/min.

**Protocol 2: Effect of Perturbation of the NO System on Sympathetic Vasoconstriction in Skeletal Muscle of Sham and MI Rats**

Responses to lumbar nerve stimulation were measured in resting and contracting hindlimb before and after (1) NOS inhibition with N-nitro-L-arginine methyl ester (L-NAME; 5 mg/kg IV) or (2) infusion of the NOS substrate l-arginine (300 mg/kg IV).

**Protocol 3: Effect of Superoxide Scavenging on Sympathetic Vasoconstriction in Skeletal Muscle of Sham and MI Rats**

Responses to lumbar nerve stimulation were measured in resting and contracting hindlimb before and after infusion of the membrane-permeable O$_2^-\$ scavenger tempol (Sigma; 4,5-dihydroxy-1,3-benzene-disulfonic acid; 1 g/kg per hour IA) or tiron (Sigma; 4,5-dihydroxy-1,3-benzene-disulfonic acid; 1 g/kg per hour IA). To determine whether NO inhibition prevented the effect of O$_2^-\$ scavenging, this protocol was repeated in additional rats pretreated with L-NAME. The specificity of the scavengers for O$_2^-\$ was assessed by measuring the hindlimb vasodilator response to local intra-arterial injection of acetylcholine (3 μg/kg) alone, during infusion of an O$_2^-\$-generating solution of xanthine (X)/xanthine oxidase (XO) (X, 1 mmol/L; XO, 1 U/mL; 0.02 mL/min IA), and during coinfusion of X+XO and tempol or tiron.

**Western Blot Analysis**

Gastrocnemius muscle samples were frozen in liquid nitrogen and stored at −80°C until analyzed as previously described.\textsuperscript{4} NOS was detected using rabbit polyclonal antibodies raised against the N-terminus of nNOS (1:4000) or inducible NOS (iNOS; 1:4000) or mouse monoclonal anti-eNOS (1:1000; Transduction Laboratories). Protein concentrations were determined using a Bio-Rad DC Protein Assay kit.

**Malondialdehyde (MDA) Assay**

Gastrocnemius muscle samples were homogenized in 10 vol of 20 mMol/L Tris-HCl (pH 7.4) and centrifuged at 3000g for 10 minutes at 4°C. The supernatant was assayed for MDA according to kit instructions (Calbiochem).

**Data and Statistical Analysis**

Homodynamic and hindlimb force data were acquired and analyzed using MacLab hardware and software (ADInstruments). Statistical analyses of hemodynamic and force data were performed by repeated-measures ANOVA with the Dunnett test for within-group comparisons or the Scheffé test for between-group comparisons. Biochemical data were compared by unpaired Student $t$ tests. All data are presented as mean±SE.

**Results**

Twenty sham operations and 104 coronary artery ligations were performed. Sixty-one rats with the latter treatment survived, 23 with infarcts <35% of the left ventricle (LV) and 38 with infarcts >35%. Only data from rats with infarcts >35% are included in this study. Experiments in 2 sham and 4 MI rats were aborted because of technical difficulties. At the time of study (14.5±0.8 weeks after surgery), MI rats exhibited significant ventricular hypertrophy and LV dysfunction characterized by elevated LV diastolic pressures and depressed LV systolic pressures and contractility (Table 1). Although all of the MI rats exhibited LV dysfunction, they were not yet decompensated as evidenced by the lack of visible ascites and hemodynamics comparable with those of sham rats (Table 2).

**Metabolic Attenuation of Sympathetic Vasoconstriction Is Impaired in Contracting Hindlimb of MI Rats**

In sham rats, sympathetic nerve stimulation increased arterial pressure and decreased femoral blood flow and vascular conductance in resting hindlimb (Figures 1 and 2). These
sympathetically mediated decreases in blood flow and conductance were significantly attenuated in contracting hindlimb of sham rats (Figures 1 and 2). In MI rats, sympathetic nerve stimulation elicited responses in resting hindlimb similar to those observed in sham rats (Figures 1 and 2). The hyperemic response to hindlimb contraction alone and the force generated by the contracting muscles also were similar in MI and sham rats (Table 2). In contrast, the vasoconstrictor responses to sympathetic nerve stimulation were significantly greater in the contracting hindlimb of MI than in that of sham rats, indicating impaired modulation of sympathetic vasoconstriction (Figures 1 and 2).

NOS Inhibition Reproduces the MI Phenotype in Sham Rats

The NOS inhibitor L-NAME increased arterial pressure in both groups of rats, although the mean increase was greater in the sham (+50±9 mm Hg) than in the MI (+32±6 mm Hg) rats. In resting hindlimb, the vasoconstrictor responses to sympathetic nerve stimulation at 2.5 Hz were not altered by L-NAME in either group of rats (Figure 3). In the contracting hindlimbs of sham rats, sympathetic vasoconstriction was enhanced after L-NAME administration, producing a phenotype resembling that of the MI rats (Figure 3). In contrast, L-NAME had no additional effect on the already enhanced sympathetic vasoconstriction in the contracting hindlimbs of the MI rats (Figure 3). Similar results were obtained with sympathetic nerve stimulation at 1 or 5 Hz (data not shown).

Exogenous L-Arginine Reproduces the Sham Phenotype in MI Rats

Infusion of L-arginine significantly reduced arterial pressure in MI rats by 14±6 mm Hg but had only a minor effect on blood pressure in sham rats. In resting hindlimb, L-arginine attenuated the vasoconstrictor responses to sympathetic nerve stimulation at 2.5 Hz in resting hindlimb to a similar extent in both groups (Figure 3). In the contracting hindlimbs of MI rats, sympathetic vasoconstriction was further attenuated after L-arginine infusion, producing a phenotype resembling that of the sham rats (Figure 3). In contrast, L-arginine had no additional effect on the greatly attenuated sympathetic vasoconstriction in the contracting hindlimbs of sham rats (Figure 3). Similar results were obtained with sympathetic nerve stimulation at 1 or 5 Hz (data not shown).

Skeletal Muscle NOS Expression Is Not Altered in MI Rats

There were no significant differences in eNOS or nNOS immunoreactivity in gastrocnemius muscle homogenates

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LV indicates left ventricle; RV, right ventricle; SP, systolic pressure; and EDP, end-diastolic pressure.

*P<0.05 vs sham.

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<th>TABLE 2. Hemodynamics in Response to Unilateral Hindlimb Contraction in Untreated Sham and MI Rats</th>
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MAP indicates mean arterial pressure; HR, heart rate; FBF, femoral blood flow; and FVC, femoral vascular conductance. Not included in these data are 4 sham and 6 MI rats pretreated with L-NAME.

*P<0.05 vs sham.
Immunoreactivity to iNOS was not detected in any of the muscle homogenates (data not shown).

MDA, a Marker of Oxidative Stress, Is Increased in Skeletal Muscle of MI Rats

MDA, an end product derived from the peroxidation of polyunsaturated fatty acids and related esters, was increased 3-fold in gastrocnemius muscle homogenates from MI rats (0.63 ± 0.15 nmol/mg protein) compared with sham rats (0.21 ± 0.06 nmol/mg protein; \( P < 0.05 \) vs MI).

Superoxide Scavenging Reproduces the Sham Phenotype in MI Rats

In normal rats, acetylcholine injected into the hindlimb increased femoral blood flow by 2.32 ± 0.22 kHz (n=6). Responses to acetylcholine were reduced by 66±8% in the presence of the \( \text{O}_2^- \)-generating solution of X+XO (Figure 5A). Coinfusion of tempol or tiron prevented this effect of X+XO, indicating effective \( \text{O}_2^- \) scavenging by these drugs (Figure 5A).

Tempol and tiron had no significant effects on baseline hemodynamics in either sham or MI rats, with the exception of an increased femoral blood flow in MI rats after tempol infusion (+0.95±0.22 kHz). In resting hindlimb, the vasoconstrictor responses to sympathetic nerve stimulation at 2.5 Hz were not altered by tempol in either sham or MI rats or by tiron in MI rats (Figure 5B). In the contracting hindlimbs of sham rats, tempol had no additional effect on the greatly attenuated sympathetic vasoconstriction (Figure 5B). In contrast, in the contracting hindlimbs of MI rats, sympathetic vasoconstriction was further attenuated after tempol or tiron infusion, producing a phenotype resembling that of the sham rats (Figure 5B). This effect of tempol in the MI rats was prevented completely by pretreatment with L-NAME (Δ

**Figure 2.** Effects of sympathetic nerve stimulation on femoral vascular conductance in resting and contracting hindlimb of sham and MI rats. In resting hindlimb, sympathetic vasoconstrictor responses were similar in sham and MI rats. Compared with responses in resting hindlimb, sympathetic vasoconstriction was attenuated in contracting hindlimb of both sham and MI rats. However, at each frequency of sympathetic nerve stimulation, the degree of attenuation was significantly smaller in MI rats. Sham, n=14; MI, n=28; \( *P < 0.05 \) vs sham.

**Figure 3.** Effects of L-NAME or l-arginine (L-Arg) on decreases in femoral vascular conductance (FVC) in response to 2.5-Hz sympathetic nerve stimulation in resting and contracting hindlimb of sham and MI rats. In resting hindlimb, sympathetic vasoconstriction was similar in sham and MI rats in all 3 conditions. In contracting hindlimb during control conditions (no drug), sympathetic vasoconstriction was attenuated to a greater degree in sham (n=10) than in MI (n=16) rats. After L-NAME, sympathetic vasoconstriction was enhanced in sham (n=5) but not in MI (n=10) rats. Conversely, after L-arginine infusion, sympathetic vasoconstriction was attenuated equally in sham (n=5) and MI (n=6) rats. \( *P < 0.05 \) vs sham; \( \dagger P < 0.05 \) vs no drug.

**Figure 4.** Expression of NOS isoforms in skeletal muscle homogenates from sham and MI rats. Top, Western blots showing eNOS and nNOS immunoreactivity of gastrocnemius muscle homogenates. Sham, Lanes 2, 5, and 8; MI, lanes 1, 3, 4, 6, and 7; positive control, lane 9. Bottom, Quantitative analysis of Western blots by densitometry showing equivalent expression of NOS isoforms in sham (n=13) and MI (n=25) muscles. iNOS was not detected in any samples (data not shown).
conductance in contracting hindlimb in response to sympathetic stimulation, 22763% before tempol and 22565% after tempol; n=6). Responses were similar in sham rats pretreated with L-NAME (Δ conductance in contracting hindlimb in response to sympathetic stimulation, 23463% before tempol and 22962% after tempol; n=4). Similar results were obtained with sympathetic nerve stimulation at 1 or 5 Hz (data not shown).

**Sympathetically Mediated Changes in Blood Flow Alter Hindlimb Contractile Function**

In both sham and MI rats, changes in blood flow elicited by sympathetic nerve stimulation resulted in directionally similar changes in force output of the contracting hindlimbs (Figure 6). In sham rats, blood flow to the contracting hindlimbs tended to increase during sympathetic nerve stimulation as a result of increased systemic arterial pressure coupled with locally attenuated hindlimb vasoconstriction. These increases in hindlimb blood flow were accompanied by increases in force output of the contracting muscles. In contrast, in MI rats blood flow to the contracting hindlimbs decreased during sympathetic stimulation, resulting in decreases in force output. These sympathetically mediated decreases in flow and force tended to be reversed after treatment with L-arginine (L-Arg), tempol, or tiron in the MI rats.

**Discussion**

Abnormal regulation of the peripheral circulation in heart failure may contribute to hypoperfusion and fatigue of exercising muscles, although the underlying mechanisms are not well defined. Our major new finding is that NO-mediated attenuation of sympathetic vasoconstriction in contracting skeletal muscle is impaired in rats with left ventricular dysfunction due to chronic MI. Our results further suggest that this impairment is mediated at least in part by increased oxidative stress in the contracting muscles. The reduced ability to modulate sympathetic vasoconstriction in contracting muscle of MI rats had significant functional consequences, given that sympathetically mediated decreases in blood flow resulted in decreased force production by the contracting muscles. Together these data suggest that free radical–mediated disruption of the NO system is an important mechanism underlying abnormal sympathetic regulation of skeletal muscle blood flow in heart failure.

We and others previously provided several lines of evidence that skeletal muscle nNOS is an important source of NO that modulates sympathetic vasoconstriction during exercise.4,5,22 Such modulation may constitute an important protective mechanism that serves to optimize blood flow distribution in contracting skeletal muscle. We now have shown that this protective mechanism is defective in a rat model of heart failure. The explanation does not involve decreased NOS expression, because neither eNOS nor nNOS was reduced in skeletal muscle of MI rats. Instead, defective NO-dependent modulation of sympathetic vasoconstriction may have been due to an O2 -mediated impairment of the NO pathway in the contracting muscles. This conclusion is
predicated on 2 findings. First, in MI rats contraction-induced attenuation of sympathetic vasoconstriction was normalized by tempol or tiron, each of which is a drug that we showed acts as an $O_2^-$ scavenger in this experimental model. Second, the effect of tempol to normalize responses in MI rats was prevented by pretreatment with L-NAME to inhibit NO production. Taken together, these experiments strongly suggest that the effect of tempol was due to the scavenging of $O_2^-$ and subsequent relief of NO inhibition rather than to some nonspecific effect of the compound.

Supporting evidence that oxidative stress was increased in skeletal muscle of MI rats was provided by a 3-fold greater MDA concentration in muscle homogenates from MI compared with sham rats. The reaction of oxygen free radicals with polyunsaturated fatty acids in cellular membranes leads to the formation of lipid hydroperoxides that are degraded to a variety of stable products, including MDA. Previous studies have reported increased MDA in plasma of patients with heart failure and in cardiac muscle of MI rats. Interestingly, in heart failure patients with elevated plasma MDA at rest, exercise elicited further increases in plasma MDA that were correlated inversely with peak oxygen consumption.

These data suggested that exercise-induced oxidative stress might contribute to exercise intolerance in heart failure. Our data further advance this concept by providing one potential mechanism by which oxidative stress mediates vascular dysregulation and subsequently impairs contractile function in exercising skeletal muscle of MI rats. Indeed, in our experiments sympathetically mediated decreases in blood flow resulted in decreased force production by the contracting hindlimbs of MI rats.

Oxygen free radicals are produced in the body by numerous pathways, including mitochondrial oxidases, membrane-bound oxidoreductases such as NAD(P)H oxidase, extracellular and cytosolic xanthine oxidases, heme oxygenases, NOS, cyclooxygenase, and lipoxygenase. In quiescent skeletal muscle, the production of free radicals is low and may play a role in cellular signaling. In contracting muscle, free radical production is accelerated mainly as a result of the marked increases in cellular metabolism and oxygen consumption. The antioxidant defenses in healthy skeletal muscle are usually adequate to cope with contraction-induced oxidative stress. However, in heart failure the fine balance between production of free radicals and endogenous scavenging mechanisms appears to be disrupted. This imbalance could be mediated by factors such as catecholamines, angiotensin II, or cytokines (eg, tumor necrosis factor-$\alpha$ or interleukin-1), which are known to be elevated in heart failure and have been shown to activate one or more of the free radical–generating pathways.

In addition, oxidative metabolism is impaired in heart failure, possibly because of decreased expression of oxidative enzymes or functional block of mitochondrial electron transport. Finally, antioxidant capacity also may be reduced in heart failure.

Coexistence of any of these conditions would greatly increase the propensity for free radical generation, particularly during metabolically stressful situations such as skeletal muscle contraction.

Free radical production could occur in a number of cellular sites in the contracting hindlimb of MI rats, including skeletal or vascular myocytes, endothelial cells, and neurons. The vascular endothelium and smooth muscle have been implicated as sites of free radical production in pathophysiological states such as hypertension, atherosclerosis, and heart failure. Recent studies using the rat coronary artery ligation model of heart failure have shown that endothelial dysfunction in large and small arteries studied in vitro can be attributed to increased oxidant stress and decreased bioavailability of NO. Because NO and $O_2^-$ undergo a rapid diffusion-limited reaction, excessive $O_2^-$ production in skeletal muscle of MI rats could reduce the functional impact of NO by decreasing its bioavailability.

Although direct inactivation of NO by $O_2^-$ is one possible explanation for the results of our study, other explanations also merit discussion. Plasma levels of the endogenous competitive NOS inhibitor asymmetric dimethylarginine (ADMA) have been reported to be elevated both in heart failure patients and in MI rats, raising the possibility that NO production is impaired. The mechanisms by which ADMA is elevated in heart failure are unknown, but perhaps oxidative stress is involved given that the enzyme that metabolizes ADMA, ADMA dimethylaminohydrolase, is inhibited by oxidized lipoproteins and cytokines. In addition, soluble guanylyl cyclase, which is the downstream effector of NO, may be inhibited directly by $O_2^-$. The fact that L-arginine normalized responses in MI rats when given acutely suggests a number of possibilities. L-Arginine may have increased NO production by reversing NOS inhibition caused by elevated ADMA or because of its antioxidant properties may have acted directly to reduce $O_2^-$ levels in contracting muscle. L-Arginine availability may be reduced in heart failure, possibly as a result of reduced plasma membrane arginine transport or increased activity of cellular arginases, which metabolize L-arginine as part of the urea cycle. The resultant L-arginine deficiency could contribute to oxidative stress not only by decreasing NO production but also by increasing $O_2^-$ production by NOS.

Impaired skeletal muscle blood flow responses to exercise in heart failure have been reported in numerous studies, although only a limited number have focused either on the role of the sympathetic nervous system or on the NO system in these abnormal responses. Sympathetic vasoconstriction has been implicated in the attenuated exercise hyperemia in 2 recent studies in heart failure patients, whereas NO deficiency has been implicated in one study in
MI rats and one in heart failure patients. Our study further advances these concepts by providing a novel unifying hypothesis that links enhanced sympathetic vasoconstriction with NO deficiency as a potential underlying mechanism contributing to hyperperfusion of exercising skeletal muscle in heart failure.

In conclusion, using the rat coronary artery ligation model of heart failure, we have shown that oxidative stress–mediated dysfunction of the NO system plays a key role in the impaired modulation of sympathetic vasoconstriction in contracting skeletal muscle. We suggest that this abnormal vascular regulation may contribute to hyperperfusion of skeletal muscle during exercise and thus may be a factor contributing to reduced exercise tolerance in heart failure. Because NO also has been proposed to modulate skeletal muscle metabolism and mechanics, O$_2^-$–mediated impairment of the NO system may have additional implications for skeletal muscle function in heart failure.

Acknowledgments

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References


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