Mechanoreflex Mediates the Exaggerated Exercise Pressor Reflex in Heart Failure

Scott A. Smith, PhD; Jere H. Mitchell, MD; R. Haris Naseem, MD; Mary G. Garry, PhD

Background—In heart failure, exercise elicits excessive increases in mean arterial pressure (MAP) and heart rate (HR). Using a novel rat model, we previously demonstrated that this exaggerated cardiovascular responsiveness is mediated by an overactive exercise pressor reflex (EPR). Although we previously determined that abnormalities in the group IV afferent neuron population (associated with the metabolic component of the reflex) initiate the development of the exaggerated EPR in heart failure, these fibers do not mediate the enhanced circulatory responses to exercise. Therefore, we hypothesized that the augmentation in EPR activity is primarily mediated by the mechanically sensitive component of the reflex (mediated predominately by activation of group III afferent fibers).

Methods and Results—Male Sprague-Dawley rats were divided into 3 groups: sham (control), dilated cardiomyopathic (DCM), and neonatal capsaicin-treated animals (NNCAP, group IV afferent fibers ablated). Activation of the EPR by electrically induced static muscle contraction of the hindlimb resulted in larger increases in MAP and HR in DCM and NNCAP compared with sham animals. In all groups, administration of gadolinium (a selective blocker of mechanically sensitive receptors) within the hindlimb attenuated the MAP and HR responses to contraction. However, the magnitude of this reduction was greater in DCM and NNCAP compared with sham animals.

Conclusions—From these data, we conclude that the muscle mechanoreflex mediates the exaggerated EPR that develops in heart failure. Moreover, these findings suggest that mechanoreflex overactivity in heart failure may be a compensatory response to functional alterations in group IV fibers. Given these findings, the muscle mechanoreflex may serve as a novel target in the treatment of the abnormal circulatory responses to exercise in heart failure. (Circulation. 2005;112:2293-2300.)

Key Words: nervous system, autonomic □ blood pressure □ cardiomyopathy □ exercise □ heart failure

In heart failure, exercise elicits excessive increases in sympathetic nerve activity, vascular resistance, heart rate (HR), and arterial blood pressure (BP). These abnormal elevations in circulatory hemodynamics may contribute to reductions in exercise capacity as well as increase the risk for adverse cardiac events during physical activity. Recent evidence from our laboratory and others suggests that the exercise pressor reflex (EPR) a circulatory reflex originating from skeletal muscle contributes significantly to the generation of this exaggerated cardiovascular responsiveness. However, the mechanism mediating this EPR overactivity in heart failure is currently unclear. Exercise-induced signals that compose the afferent arm of the EPR are generated by activation of mechanically (skeletal mechanoreflex) and metabolically (skeletal metaboreflex) sensitive skeletal muscle receptors. Activation of these receptors and their associated afferent fibers reflexively increases BP and HR during physical activity. As such, both the mechanoreflex and the metaboreflex serve as potential candidates for the EPR dysfunction that develops with heart failure.

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Within skeletal muscle, the metaboreflex is activated by stimulation of chemically sensitive receptors that primarily excite group IV afferent fibers. Attempts to quantify the contribution of this reflex to EPR overactivity in human heart failure have resulted in conflicting observations. More recently, in a novel rat model to assess EPR function, it has been demonstrated that the cardiovascular response to selective activation of metabolically sensitive group IV afferent neurons is reduced in cardiomyopathic animals. Furthermore, expression of mRNA for the transient receptor potential vanilloid-1 (TRPv1) protein, a marker of group IV afferent fibers, is downregulated in the dorsal root ganglia and soleus muscle of heart failure animals, indicating a possible reduction in group IV fiber density and/or sensitivity. These findings suggest that the muscle metaboreflex may be blunted in heart failure despite an overall exaggeration of EPR activity. Moreover, selective ablation of group IV afferent fibers may reduce the magnitude of the metabolic component of EPR responses in heart failure.
fibers in healthy rats recapitulates the exaggerations in EPR activity noted in heart failure. Collectively, these findings suggest that the withdrawal or desensitization of group IV afferent neurons (the primary mediators of the muscle metaboreflex) are important to the development of EPR overactivity but do not themselves drive this overactivity.

The skeletal muscle mechanoreflex is activated by stimulation of mechanically sensitive receptors that primarily excite group III afferent fibers. Several elegant studies in humans suggest that muscle mechanoreflex activity may be exaggerated in heart failure patients. However, isolation of this reflex is difficult in these studies owing to the limitations inherent in human investigation. Using a novel rat preparation to circumvent these limitations, we recently demonstrated that passively stretching skeletal muscle (a stimulus designed to preferentially activate mechanically sensitive receptors) induces augmented increases in BP and HR in heart failure animals. This finding suggests that the mechanoreflex may drive the EPR overactivity manifest in heart failure. However, it is currently unclear whether this is true during physiological contraction of skeletal muscle during exercise.

This study was designed, therefore, to determine the contribution of the muscle mechanoreflex to EPR overactivity in heart failure during physiological contraction of skeletal muscle. To make these determinations in sham control and heart failure rats, hindlimb muscle contractions were performed before and after pharmacological blockade of mechanically sensitive skeletal muscle receptors with the trivalent lanthanide gadolinium. Hayes and Kaufman have previously shown gadolinium to significantly attenuate the activity of mechanically sensitive group III afferent neurons in cats. In an attempt to understand the evolution of EPR overactivity in heart failure, additional studies were conducted to determine the contribution of the muscle mechanoreflex to the exaggerated EPR previously noted in animals deficient in group IV afferent fibers. Given that it appears that the mechanoreflex is overactive in heart failure, we hypothesized that gadolinium would attenuate the reflex cardiovascular response to muscle contraction to a greater degree in cardiomyopathic rats compared with sham control animals.

Methods
Experiments were performed in age-matched, male, Sprague-Dawley rats (Harlan, Indianapolis, Ind) divided into the following experimental groups: sham treated (sham), dilated cardiomyopathic (DCM), and neonatal capsaicin treated (NNCAP). The procedures outlined were approved by the institutional Animal Care and Use Committee of the University of Texas Southwestern Medical Center at Dallas.

Animal Models
Sham and DCM
To generate DCM rats and their sham-treated experimental controls, animals within the weight range of 150 to 175 g underwent thoracic surgery. Initially anesthesia was induced with isoflurane (2% to 5% in 100% O2). Animals were intubated and ventilated. A thoracotomy was performed and the heart exposed. In DCM animals, the left anterior descending coronary artery was ligated to produce a myocardial infarction, as described previously. In sham animals, a ligature was placed around the left anterior descending coronary artery but was not tied. Postoperatively, buprenorphine (20 μg/kg) was administered for analgesia. Nine weeks after surgery, transthoracic echocardiography (Vivid 7 Pro, GE Medical Systems) was performed in both DCM and sham animals to quantify left ventricular function, as previously described.

Neonatal Capsaicin-Treated Animals
The selective and chronic destruction of group IV primary afferent neurons in rats is induced by treatment of neonates with capsaicin. To generate this experimental model, a 50 mg/kg SC injection of capsaicin was administered to 2-day-old neonatal rat pups. Six weeks after treatment, a 0.01% capsaicin solution was applied to the cornea to confirm the efficacy of the procedure. Rats displaying 30 or fewer protective eye wipings were considered capsaicin-insensitive and designated as NNCAP animals. We have previously confirmed that neonatal capsaicin treatment ablates the capsaicin receptor TRPV1 in the L4 to L6 dorsal root ganglia, indicative of a reduction in group IV fiber density. In adult NNCAP animals, echocardiographic testing was performed at time points and ages matched to sham and DCM animals.

Acute Surgical Procedures
General Surgery
Rats were initially anesthetized with isoflurane gas and instrumented as previously described. In brief, animals were intubated for mechanical ventilation and cannulated with jugular venous and carotid arterial catheters. BP was recorded by connecting the arterial catheter to a pressure transducer (model DTX plus-DT-NNIZ, Ohmeda). Mean arterial pressure (MAP) was obtained by integrating the arterial signal with a time constant of 1 to 4 seconds. HR was derived from the BP pulse wave with use of a biotachometer (Gould Instruments).

Limb Vascular Surgery
To administer drugs into the arterial supply of skeletal muscle within the right hindlimb, the circulation of the hindlimb was isolated. A catheter was placed in the left common iliac artery and its tip advanced to the bifurcation of the abdominal aorta. As a result, injected substances first entered the circulation of the hindlimb via the right common iliac artery. To limit drug delivery to the right hindlimb, a reversible ligature was placed around the right common iliac vein emptying the hindlimb.

Spinal Surgery
A laminectomy exposing the lower lumbar portions of the spinal cord (L2 to L6) was performed, and stimulating electrodes were placed around the cut peripheral ends of the L4 and L5 ventral rootlets. The calcaneal bone of the right hindlimb was cut, and the Achilles’ tendon was connected to a force transducer (FT-10, Grass Instruments). After completion of these surgical procedures, animals were rendered insentient by precollicular decerebration. After forebrain transection and aspiration, gas anesthesia was discontinued.

Experimental Protocol
In these experiments, gadolinium was used to acutely and selectively block the firing of group III primary afferent neurons in the hindlimb of sham (n = 10), DCM (n = 8), and NNCAP (n = 9) animals. To begin, electrically induced static contraction of the gastrocnemius and soleus muscles of the right hindlimb was used to activate both the mechanically and metabolically sensitive components of the EPR (ie, group III and IV afferent fibers, respectively). With constant-current stimulation (3 times motor threshold, 0.1-ms pulse duration, 40 Hz), 30-second contractions were produced by excitation of the L4 and L5 ventral roots, with the peak MAP, force development, and HR responses recorded. These stimulation parameters elicit maximal static muscle contractions in the rat. After a 15-minute recovery period, preferential activation of mechanically sensitive afferent fibers...
was achieved by passively stretching the hindlimb muscles with a rack-and-pinion system (Harvard Apparatus, Inc). Care was taken to generate the same magnitude and pattern of muscle tension developed during electrically induced contractions. Collectively, these procedures cause increases in MAP and HR that have been shown to be caused by selective stimulation of skeletal muscle primary afferent fibers in this rat model.17 Subsequently, gadolinium (10 mmol/L, 0.25 mL) was injected directly into the arterial supply of the right hindlimb via the right common iliac artery. On injection of gadolinium, the reversible ligature around the right common iliac vein was tightened for 15 minutes to trap the injectate in the leg. Sixty and 120 minutes after entrapment of gadolinium, contraction and stretch maneuvers were repeated. The dose and time frame of gadolinium administration were based on previous studies by Hayes and Kaufman.22 As a control, this protocol was repeated in a subset of sham animals (n = 8) with isotonic saline (the vehicle for gadolinium) administered into the circulation of the right hindlimb. In all animals, the heart was excised and weighed on completion of physiological experimentation. In addition, the lungs and tibia were harvested, weighed, and measured.

**Data Acquisition and Statistical Analyses**

All cardiovascular and contractile force data were acquired, recorded, and analyzed with hardware and software for the CED micro 1401 system (Cambridge Electronic Design). Baseline values were determined with 30 seconds of data before a given maneuver. The peak response was defined as the greatest change from baseline elicited during a contraction or stretch. On all data sets, statistics were performed by ANOVA, with repeated measures as appropriate. A Student-Newman-Keuls post hoc test was used when significance within or between groups was determined by ANOVA.

### Results

**Morphometric and Hemodynamic Measurements**

Morphometric and baseline hemodynamic characteristics for each experimental group of animals are presented in Table 1. DCM rats displayed significant increases in indices of heart failure, such as ratios of heart weight to body weight, heart weight to tibial length, and lung weight to body weight compared with sham and NNCAP animals. It is important to note that baseline hemodynamic measurements (ie, MAP and HR) were not different among groups.

**Echocardiographic Measurements**

As determined by transthoracic echocardiography (Figure 1), DCM rats exhibited marked left ventricular dysfunction compared with sham and NNCAP animals. For example, both left ventricular end-diastolic and end-systolic dimensions were greater in DCM (0.82±0.03 and 0.59±0.05 cm, respectively) than in sham (0.72±0.02 and 0.40±0.02 cm, respectively) or NNCAP (0.69±0.02 and 0.39±0.02 cm, respectively) animals. Commensurate with these findings, left ventricular fractional shortening (an index of ventricular function, was significantly reduced in DCM. *Significance from sham and NNCAP, P<0.05.

**Gadolinium Reduces the Cardiovascular Response to Contraction and Stretch**

Consistent with our previous observations,7,10 baseline cardiovascular responses to static muscle contraction be-

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**TABLE 1. Morphometric and Baseline Hemodynamic Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Sham (n=16)</th>
<th>DCM (n=8)</th>
<th>NNCAP (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>388±12</td>
<td>412±7</td>
<td>376±9</td>
</tr>
<tr>
<td>Heart weight/body weight, mg/g</td>
<td>2.8±0.1</td>
<td>3.2±0.1*</td>
<td>2.8±0.1</td>
</tr>
<tr>
<td>Lung weight/body weight, mg/g</td>
<td>7.2±0.4</td>
<td>10.1±0.4*</td>
<td>6.9±0.4</td>
</tr>
<tr>
<td>Heart weight/tibial length, mg/mm</td>
<td>27.1±0.7</td>
<td>33.4±0.8*</td>
<td>27.1±0.8</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>113±8</td>
<td>112±13</td>
<td>112±11</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>355±18</td>
<td>384±20</td>
<td>348±12</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *Significance from sham and NNCAP, P<0.05.
fore administration of gadolinium were exaggerated in both DCM and NNCAP animals when compared with sham rats (Figure 2). Sixty minutes after administration of gadolinium, MAP and HR responses to contraction were significantly reduced in sham, DCM, and NNCAP animals. At 120 minutes after gadolinium administration, the cardiovascular response to contraction began to return to baseline levels in all groups. Similar results were observed in response to passive stretch (Figure 3). In contrast to gadolinium, isotonic saline had no effect on the cardiovascular response to either muscle contraction or stretch. A representative example of this finding is presented in Figure 4.

Effects of Gadolinium Are More Pronounced in DCM and NNCAP Than Sham

To determine the relative contribution of group III afferent neurons to the cardiovascular response elicited by contraction and stretch in all animal groups, we calculated both absolute and percentage changes in MAP and HR responses to these maneuvers before and after administration of gadolinium. First, we plotted the absolute differences in MAP and HR responses to contraction and stretch after administration of gadolinium from those obtained before administration of gadolinium (Figure 5). Although gadolinium reduced MAP and HR responses to both contraction and stretch in sham controls, the effect of gadolinium was more pronounced in
DCM and NNCAP animals. Second, we calculated the contraction- and stretch-induced percentage increases in MAP (Table 2) and HR (Table 3) from baseline BP and HR values, respectively, before and after administration of gadolinium. Again, although gadolinium significantly reduced the percentage increase in both MAP and HR in response to contraction and stretch, the difference between the pregadolinium percentage increase and the postgadolinium percentage increase was consistently larger in DCM and NNCAP than in sham animals. It should be noted, however, that when expressed as a percentage change from baseline, changes in MAP were markedly larger than changes in HR in all groups.

Discussion

Overview

The results of this study provide direct evidence that mechanosensitive afferent neurons primarily mediate the exaggerated EPR observed in heart failure. These data are clinically relevant because exaggerations in EPR function are well correlated with morbidity and mortality in heart failure patients. These data suggest that blockade of group III mechanosensitive afferent neurons may be a useful target for normalizing the enhanced cardiovascular responses to exercise in heart failure patients. It is feasible that successfully normalizing the EPR in heart failure may improve patient survival by eliminating recurring, intermittent, excessive elevations in MAP and HR in response to the performance of normal, daily tasks and ambulation. Such treatment holds the potential for a reduction of the increased peripheral vascular resistance and end-organ damage that are observed in heart failure.

Contribution of Mechanoreflex to EPR Activity in Healthy Animals

Our observation that the mechanoreflex contributes to the EPR under normal conditions is consistent with the findings of Hayes and Kaufman. For example, in decerebrate cats, those authors determined that static muscle contraction increased MAP by 110% from baseline BP under control conditions but only by 10% after administration of gadolinium into the circulation of the hindlimb. Likewise, in the current study, static contraction increased MAP by 18% from baseline in healthy sham animals before administration of gadolinium within the hindlimb but only by 10% afterward. In heart failure, however, we have observed that the mechanoreflex contribution to the EPR is significantly increased. For example, gadolinium reduced the increase in MAP in response to muscle contraction by 9 mm Hg in sham animals. In DCM rats, the elevation in MAP in response to contraction was attenuated by 18 mm Hg by administration of gadolinium within the hindlimb. These data indicate that although the mechanoreflex is an important component

Figure 4. BP response to activation of the EPR in representative sham animals before (pre) and 60 minutes after (post) administration of saline (A) or gadolinium (B) into the arterial supply of the hindlimb. Note that saline (the vehicle for gadolinium) had no effect on the pressor response to muscle contraction, whereas gadolinium significantly attenuated the contraction-induced increase in MAP. Saline control experiments were conducted in 6 sham animals.
of the EPR under normal conditions, it becomes more significant during heart failure.

TABLE 2. Contraction- and Stretch-Induced Percentage Increases in MAP Before (Pre-Gad) and After (Post-Gad) Administration of Gadolinium in the Hindlimb

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-Gad, % Increase From Baseline MAP</th>
<th>Post-Gad, % Increase From Baseline MAP</th>
<th>Difference, % Reduction by Gadolinium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Static contraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>18±3</td>
<td>10±3†</td>
<td>−8±2</td>
</tr>
<tr>
<td>DCM</td>
<td>38±5*</td>
<td>22±6†</td>
<td>−16±3*</td>
</tr>
<tr>
<td>NNCAP</td>
<td>32±6*</td>
<td>14±7†</td>
<td>−18±4*</td>
</tr>
<tr>
<td>Passive stretch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>12±2</td>
<td>6±3†</td>
<td>−6±2</td>
</tr>
<tr>
<td>DCM</td>
<td>20±3*</td>
<td>7±2†</td>
<td>−13±3*</td>
</tr>
<tr>
<td>NNCAP</td>
<td>20±2†</td>
<td>7±3†</td>
<td>−13±2*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. DCM n=8; NNCAP n=9.
*Significance from sham (n=10).
†Significance from pre-gad response, P<0.05.

Contribution of Mechanoreflex to EPR Activity in Heart Failure

Our data are also consistent with previous studies that suggest that the mechanoreflex is exaggerated in heart failure patients. For example, Middlekauff and colleagues (Negrao et al1 and Middlekauff et al20) reported that muscle mechanoreceptor control of muscle sympathetic nerve activity was exaggerated in heart failure. Moreover, they also determined that the muscle mechanoreceptor control of reflex renal vasoconstriction was exaggerated in heart failure patients.2,19 These results agree with previous findings in cardiomyopathic rats, which suggest that the EPR is exaggerated in response to passive stretch.10,18 In the present study, we extended these findings performed in humans by offering a direct evaluation of the contribution of group III afferent neurons to the EPR in both healthy and cardiomyopathic animals.

Contribution of Mechanoreflex to EPR Activity in NNCAP-Treated Animals

In heart failure, left ventricular dysfunction triggers a cascade of events that result in a peripheral disease state that may contribute to an exaggerated EPR.5,23,25–30 In an attempt to isolate the mechanisms responsible for mediating these enhanced cardiovascular responses to exercise, we performed selective ablation of capsaicin-sensitive (predominately group IV) afferent neurons in normal rats (ie, NNCAP animals). Previously, it was determined that this treatment recapitulates the abnormal cardiovascular responses to exercise observed in heart failure.7 In the present study, it was further determined that there was a greater contribution of the mechanoreflex to EPR activity in NNCAP-treated rats when compared with sham-treated animals. These data indicate that withdrawal of group IV primary afferent neurons can promote an exaggerated cardiovascular response to exercise mediated by the activation of group III afferent neurons. Previously, it was also observed that TRPV1 mRNA levels (which mark group IV afferent neurons in the periphery) were reduced in the
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patients, because the exaggerated sympathetic activation in
the debate about the prescription for exercise in heart failure
inhibition. Although such treatment would prevent sympathetic overac-
tivation in response to exercise, it might also avoid the
effects of chronic blockade of group III afferent neurons.
We hypothesize that is a critical event that initiates a
series of changes that ultimately result in a hypersensitive
mechanoreflex and EPR overactivity. We predict that
mechanoreflex overactivity develops as a compensatory
mechanism for the reduction in group IV afferent neuron
activity. Although this compensatory mechanism main-
tains the EPR in heart failure, we hypothesize that it is not
well regulated and that it results in an exaggerated EPR.
Further studies are under way to elucidate the cascade of
events that mediate the exaggerated EPR observed in heart
failure.

Issues Surrounding Sympathetic Blockade in Heart Failure
Increased sympathetic activation is a hallmark of heart
failure. The EPR is a multisynaptic reflex involving (1)
primary afferent neurons, (2) second-order spinal neurons, (3)
neurons in medullary centers, and (4) sympathetic and para-
sympathetic efferent neurons. The exaggerated EPR ac-
tivity that we previously reported in cardiomyopathic rats7,10
and the mechanoreflex overactivity described in the current
investigation are known to result in increased sympathetic
activation during exercise. Although the benefit of sympa-
thetic blockade has been established in heart failure patients,
physicians remain hesitant to prescribe such therapy for the
treatment of heart failure because it is believed that long-term
activation of the sympathetic nervous system provides com-
ensatory support for the failing heart.2 Our findings suggest
that selective blockade of group III afferent neurons may hold
potential as a novel therapy in the treatment of heart failure.
Although such treatment would prevent sympathetic overac-
tivation in response to exercise, it might also avoid the
negative side effects associated with chronic sympathetic
inhibition.

In addition, group III afferent blockade may reinvigorate
the debate about the prescription for exercise in heart failure
patients, because the exaggerated sympathetic activation in
response to exercise would be eliminated. Studies evaluating
the effects of chronic blockade of group III afferent neurons
are currently under way in our laboratory. Because group III
afferent neurons are also involved in the transmission of both
noxious and innocuous sensory information from both
cutaneous and deep tissues, it will be important to determine
the effect of chronic blockade on these processes as well.

Summary
In conclusion, this study provides direct evidence that group
III mechanosensitive afferent neurons are responsible for the
exaggerated EPR observed in heart failure. These studies
indicate that development of therapeutic agents targeted at
this afferent neuron population may be a novel and effective
treatment to increase the quality of life and improve prognosis
in heart failure patients.

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Robledo and Martha Romero for their expert technical assistance.

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**CLINICAL PERSPECTIVE**

It is well established that patients with heart failure experience abnormal increases in blood pressure and heart rate in response to mild forms of exercise. Although such abnormalities contribute to a poor clinical prognosis, the mechanisms controlling these cardiovascular responses are incompletely understood. Increased sympathetic activation is a hallmark of heart failure. The exercise pressor reflex is a multisynaptic reflex involving (1) primary afferent neurons, (2) second-order spinal neurons, (3) neurons in medullary centers, and (4) sympathetic and parasympathetic efferent neurons. The exaggerated exercise pressor reflex activity previously reported in cardiomyopathic rats and the mechanoreflex overactivity described in the current investigation are known to result in increased sympathetic activation during exercise. Although the benefit of sympathetic blockade has been established in heart failure patients, some physicians remain hesitant to prescribe such therapy for treatment of heart failure, particularly in high-risk patients, because it is believed that long-term activation of the sympathetic nervous system provides compensatory support for the failing heart. Our findings suggest that selective blockade of the mechanoreflex may hold potential as a novel therapy in the treatment of heart failure. Such therapy could selectively prevent sympathetic overactivation in response to exercise while avoiding the potentially negative effects associated with chronic sympathetic inhibition.
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