Abnormal Muscle Metaboreflex Control of Sympathetic Activity in Never-Treated Hypertensive Subjects


Background: Muscle metaboreflex control in hypertensive subjects has not been described yet. We investigated the integrity of muscle metaboreflex control of muscle sympathetic nerve activity (MSNA) and blood pressure (BP) in never-treated hypertensive subjects.

Methods: Eighteen hypertensive (42 ± 1 years) and 22 normotensive subjects (38 ± 1 years) were studied. The MSNA was measured by microneurography and forearm blood flow (FBF) by venous occlusion plethysmography. The BP was noninvasively monitored.

Results: Baseline MSNA was significantly increased in hypertensive subjects when compared with normal subjects (34 ± 2 v 22 ± 2 bursts/min, P < .001). Baseline FBF was significantly decreased in hypertensive subjects (2.66 ± 0.2 v 2.05 ± 0.1 mL/min/100 mL, P = .04). During moderate handgrip exercise (30% maximal voluntary contraction), MSNA levels were significantly higher in hypertensive subjects. However, MSNA responses were significantly lower in hypertensive subjects (1 ± 3 v 10 ± 2 bursts/100 heart beats, P = .001). Similarly, FBF responses were significantly lower in hypertensive subjects when compared with normotensive subjects (0.70 ± 0.19 v 1.60 ± 0.36 mL/min/100 mL, P = .04). During the postexercise circulatory arrest, when the metaboreflex control is isolated, MSNA levels returned toward baseline in hypertensive subjects (58 ± 4 v 55 ± 3 bursts/100 heart beats, P = .98). In contrast, in normotensive subjects, MSNA levels remained significantly elevated when compared with baseline (48 ± 3 v 35 ± 1 bursts/100 heart beats, P < .001).

Conclusions: These findings suggest an association between hypertension and decreased muscle metaboreflex control of MSNA. Am J Hypertens 2006;19:951–957 © 2006 American Journal of Hypertension, Ltd.

Key Words: Hypertension, sympathetic nervous system, muscle metaboreflex control, vasodilatation, exercise.
mand and muscle mechanoreceptors by means of circula-

tory arrest of the active limb. During this maneuver, 

metabolites trapped in skeletal muscles activate muscle 

receptors that reflexively maintain MSNA and BP above 

control levels until circulation is restored.11–13 

Although some investigators have reported that BP 

responses to moderate handgrip exercise is preserved in 

hypertensive subjects, they provide no information on the 

isolated muscle metaboreflex control of MSNA and 

BP.14,15 Thus, the integrity of muscle metaboreflex control 

in hypertensive subjects is unknown. It has been reported 

that sympathetic discharge and BP levels in response to 

exercise are coupled with muscle intracellular pH 

level.16,17 In addition, some investigators have described 

that, despite of the normal resting pH level, hyperten-

sive patients have decreased skeletal muscle acidifica-

tion and increased pH rate during acid load induced by 

exercise.18 These findings raise the possibility that 

muscle metaboreceptor stimulation is decreased in human 

hypertension.

To test the integrity of muscle metaboreflex control of 

MSNA and BP in human hypertension, never-treated hy-

pertensive subjects were submitted to: 1) moderate hand-

grip exercise, when sympathetic activation is mediated by 

central command and muscle mechanoreceptors; and 2) postexercise muscle circulatory 

arrest, when the metaboreceptors can be isolated from 

central command and mechanoreceptors.

Methods

Study Population

After the Ethical Committee for Human Research Protocols of the University of São Paulo, Medical School, 

approved the study, 18 never-treated hypertensive subjects and 22 normotensive control subjects were enrolled in the study. Hypertensive and normotensive subjects were paired by age, weight, height, and body mass index (BMI). The subjects were selected according to the following characteristics: age <55 years old, metabolic profile in the normal range, and no renal vascular hypertension, cerebral ischemic disease, or obstructive coronary artery disease at the time of the evaluation. No participant had ever been treated with antihypertensive drugs. In addition, the subjects took no medication 3 months before the study.

Measurements and Procedures

Clinic Blood Pressure Reading of clinic BP were obtained in the left arm of the subjects while seated, after 5 min of quiet rest, with a mercury sphygmomanometer. A minimum of three BP readings was taken on two separate occasions. Systolic and diastolic BP were recorded at the first appearance (phase I) and the disappearance (phase V) of Korotkoff sounds. The subjects were classified as hypertensive if the average of the systolic and diastolic BP levels were ≥140 or 90 mm Hg.19

Table 1. Studied population characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normotensive subjects (N = 22)</th>
<th>Hypertensive subjects (N = 18)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td><strong>Physical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gender, man/women</td>
<td>14/8</td>
<td>9/9</td>
<td>.08</td>
</tr>
<tr>
<td>Age (y)</td>
<td>38 ± 1</td>
<td>42 ± 1</td>
<td>.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73 ± 3</td>
<td>77 ± 3</td>
<td>.001</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.69 ± 0.02</td>
<td>1.68 ± 0.03</td>
<td>.75</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 1</td>
<td>27 ± 1</td>
<td>.14</td>
</tr>
</tbody>
</table>
| Maximal voluntary contrac.

tion (kg) | 34 ± 2                         | 36 ± 2                         | .50     |
| **Metabolic profile**    |                                 |                                |         |
| Glucose (mg/dL)          | 93 ± 2                          | 96 ± 3                         | .29     |
| Total cholesterol (mg/dL)| 196 ± 7                         | 189 ± 6                        | .50     |
| HDL-cholesterol (mg/dL)  | 47 ± 2                          | 50 ± 4                         | .60     |
| LDL-cholesterol (mg/dL)  | 127 ± 7                         | 119 ± 6                        | .43     |
| Triglycerides (mg/dL)    | 108 ± 15                        | 100 ± 15                       | .73     |
| **Hemodynamics**         |                                 |                                |         |
| Clinic systolic BP (mm Hg)| 122 ± 1                        | 150 ± 2                        | <.001   |
| Clinic diastolic BP (mm Hg)| 77 ± 1                        | 98 ± 2                         | <.001   |
| Clinic mean BP (mm Hg)   | 93 ± 1                          | 116 ± 2                        | <.001   |
| Automatic mean BP (mm Hg)| 88 ± 2                          | 107 ± 2                        | <.001   |
| Baseline FBF (mL/min/100 mL)| 2.66 ± 0.2                   | 2.05 ± 0.1                     | .048    |
| Baseline FVC (units)     | 2.98 ± 0.2                      | 1.94 ± 0.1                     | <.001   |
| Baseline HR (beats/min)  | 65 ± 3                          | 64 ± 2                         | .84     |
| **Neural**               |                                 |                                |         |
| Baseline MSNA (bursts/min)| 22 ± 1                         | 34 ± 2                         | <.001   |
| Baseline MSNA (bursts/100HB)| 34 ± 2                   | 52 ± 3                         | <.001   |

Values are mean ± SE.

BP = blood pressure; FBF = forearm blood flow; FVC = forearm vascular conductance; HR = heart rate; MSNA = muscle sympathetic nerve activity.
Muscle Sympathetic Nerve Activity  Muscle sympathetic nerve activity was recorded directly from the peroneal nerve using the technique of microneurography, as described elsewhere.20,21 All recordings of MSNA met previously established and described criteria.21 Muscle sympathetic bursts were identified by visual inspection by a single investigator (MUR), and were expressed as burst frequency (bursts/min) and burst incidence (bursts/100 heart beats).

Forearm Blood Flow  Forearm blood flow was measured by venous occlusion plethysmography as described elsewhere.11–13 Forearm blood flow (in milliliters per minute per 100 milliliters) was determined on the basis of a minimum of four separate readings.

Blood Pressure and Heart Rate  Baseline BP was monitored noninvasively by a finger photoplethysmography device (Finapres 2300, Ohmeda, Englewood, CO) on a beat-to-beat basis [AT/MCA-CODAS and WINDAQ(EX) DATAQ Instruments, Inc., OH] at a frequency of 500 Hz. During handgrip exercise, BP was monitored noninvasive and intermittently from an automatic and oscillometric cuff (Dixtal, DX 2710, Manaus, Brazil) placed on the ankle with cuff width adjusted to ankle circumference. The cuff inflated every minute. Heart rate was monitored continuously through lead II of the electrocardiogram (ECG).

Experimental Protocol

Baseline Measurements  All studies were performed at approximately 9:00 AM with the subjects lying supine in a quiet air-conditioned room (22° to 24°C). After obtaining an adequate microneurographic nerve recording site in the leg, and positioning the arm for venous occlusion plethysmography, all participants rested for 15 min. After this interval, MSNA, forearm blood flow, BP, and heart rate were monitored for a baseline period of 5 min.

Mild Sustained Handgrip Exercise  The purpose of this experiment was to determine the magnitude of change in MSNA, BP, forearm blood flow, and heart rate during activation of central command and mechanoreceptors in normotensive and hypertensive subjects. After obtaining maximal voluntary contraction (MVC), all participants rested for 15 min. After this period, baseline MSNA, forearm blood flow, mean BP, and heart rate were recorded for 3 min. Handgrip exercise was then performed with the dominant arm at the intensity of 10% MVC for 3 min. The subjects were instructed to breathe normally during exercise to avoid inadvertent performance of a Valsalva maneuver.

Moderate Sustained Handgrip Exercise  The purpose of this experiment was to determine the magnitude of change in MSNA, BP, forearm blood flow, and heart rate during activation of central command, mechanoreceptors,
and metaboreceptors in normotensive and hypertensive subjects. After a 15-min interval, baseline MSNA, forearm blood flow, mean BP, and heart rate were recorded for 3 min. Handgrip exercise was then performed with the dominant arm, at the intensity of 30% MVC for 3 min. The subjects were instructed to breathe normally during exercise to avoid inadvertent performance of a Valsalva maneuver.

**Muscle Metaboreflex Control** The purpose of this experiment was to determine the magnitude of change in MSNA and BP during isolated metaboreflex activation in normotensive and hypertensive subjects. Ten seconds before the release of 30% MVC during handgrip exercise, the circulation to the exercising forearm was arrested by inflating the upper arm occlusion cuff (240 mm Hg) for 2 min.

**Statistical Analysis**

Data are presented as mean ± SE. Studied population characteristics and baseline data were subjected to the Student paired t test for intergroup comparisons. The handgrip exercise responses and the posthandgrip circulatory arrest responses of normotensive and hypertensive subjects were compared by an analysis of variance (ANOVA) for repeated measurements. When significance was found, the Scheffé’s post hoc comparison test was applied. Significant differences were assumed to be at P < .05.

**Results**

**Baseline Measurements**

Baseline physical, metabolic, hemodynamic, and neural characteristics of normotensive and hypertensive subjects are shown in Table 1. There was no significant difference in age, BMI, MVC, and metabolic profile between normotensive and hypertensive subjects. The MSNA burst frequency and burst incidence were significantly higher in hypertensive subjects. In contrast, forearm blood flow and forearm vascular conductance were significantly lower in hypertensive subjects. Heart rate was similar between groups.

**Mild Sustained Handgrip Exercise**

The interaction of time and group effects showed that there were no significant differences in MSNA burst frequency between hypertensive subjects and normotensive subjects (P = .10; Fig. 1A). Similarly, MSNA burst incidence was not significantly different between groups (interaction effects, P = .13; Fig. 1C). With regard to BP, there were no significant differences in systolic and diastolic BP during mild exercise between hypertensive and normotensive subjects (interaction effects, P = .67 and P = .83, respectively; Table 2). Heart rate presented no significant differences between groups (P = .23; Table 2). The interaction of time and group effects showed no significant differences in forearm blood flow and forearm vascular conductance...
between hypertensive and normotensive subjects \((P = .68\) and \(P = .97\); Fig. 2A,C, respectively).

**Moderate Sustained Handgrip Exercise**

The interaction of time and group effects showed that MSNA burst frequency was significantly different between hypertensive and normotensive subjects \((P < .001; \text{Fig. 1B})\). Similarly, MSNA burst incidence was significantly different between the studied groups \((P < .05; \text{Fig. 1D})\). The analysis of BP showed no significant differences in systolic, diastolic, and mean BP between hypertensive and normotensive subjects (interaction effects, \(P = .66\), and \(P = .79\), respectively; Table 2). There was no significant difference in heart rate between groups \((P = .32; \text{Table 2})\). With regard to muscle blood flow, we found that forearm blood flow was significantly lower in hypertensive subjects when compared with normotensive subjects (interaction effects, \(P = .04; \text{Fig. 2B})\). Although the interaction effects showed no significant difference in forearm vascular conductance between the studied groups \((P = .09\)), the group effect showed that hypertensive subjects had significantly lower forearm vascular conductance than normotensive subjects \((P < .001)\).

**Muscle Metaboreflex Control**

During the postmild exercise period with circulatory arrest, MSNA burst frequency and burst incidence were not significantly different from baseline in both hypertensive and normotensive subjects (interaction effects, \(P = .81\) and \(P = .13\), respectively). Similarly, during the postmild exercise period with forearm circulatory arrest, mean BP levels were not significantly different from baseline in both hypertensive and normotensive subjects (interaction effects, \(P = .45\)).

During the postmoderate exercise with forearm circulatory arrest, when the muscle metaboreflex control was isolated, MSNA burst frequency and burst incidence levels remained significantly elevated in relation to baseline in normotensive subjects. In contrast, in hypertensive subjects, MSNA burst frequency and burst incidence were not significantly increased when compared with baseline (interaction effects, \(P < .001\) and \(P = .004; \text{Fig. 3})\). Further analysis showed that MSNA burst frequency and burst incidence levels at 2 min of forearm circulatory arrest were similar to those found at 3 min of moderate handgrip exercise in normotensive subjects (Fig. 1B,D). In hypertensive subjects, MSNA burst frequency levels at 2 min of forearm circulatory arrest were significantly lower than those found at 3 min of handgrip exercise (Fig. 1B). With regard to MSNA burst incidence, no significant difference was found between the second minute of forearm circulatory arrest and the third minute of moderate handgrip exercise (Fig. 1D).
MSNA responses in hypertensive subjects when compared with normotensive subjects, the absolute levels of MSNA during exercise were significantly higher in hypertensive subjects. On the other hand, we cannot rule out the possibility that the vascular smooth muscle hypertrophy as a consequence of hypertension limits the vasodilatory response in hypertension.23,24

Muscle Metaboreflex Control
The mechanisms involved in the muscle metaboreflex dysfunction in hypertension are beyond the scope of the present study. Nevertheless, previous findings bring about some possible candidates to explain the muscle metaboreflex alteration in our hypertensive subjects. First, the lowered skeletal muscle acidification and the increased pH rate during exercise in hypertension18 may favor a decrease in muscle metaboreceptor stimulation during this physiologic maneuver in humans with hypertension. Second, the reduction in glucose metabolism in hypertension may attenuate muscle acidosis during exercise and, as a consequence, muscle metaboreceptor stimulation in our hypertensive subjects. A previous study demonstrated that glucose uptake during sympathetic-mediated vasoconstriction was impaired in spontaneously hypertensive rats.25

Possible Limitations
Someone could raise the question that our experimental strategy did not discriminate between the effects of cuff inflation and muscle acidosis during circulatory arrest. Thus, the MSNA and BP responses during circulatory arrest could be due to cuff inflation, not necessarily to muscle acidosis. To eliminate this possible confounding variable, all participants underwent a 2-min circulatory arrest after 3 min in a quiet resting position (data not shown). The results of this study showed no significant difference in MSNA and mean BP between circulatory arrest and baseline in both normotensive and hypertensive subjects. In addition, five normotensive subjects underwent the same exercise protocol with no circulatory arrest. In this additional study, no significant difference in MSNA and BP levels between the second minute of recovery and baseline were found (P = .31 and P = .57, respectively).

Someone could argue that the difference between the two groups studied could simply reflect an attenuated metaboreflex response in women, as there are more women in the hypertensive group than in the normotensive group. This interpretation is unlikely because an additional statistical analysis showed no significant differences in MSNA and BP responses during the postexercise circulatory arrest when gender was taken into consideration (P = .28 and P = .72, respectively).

We recognize a distortion between clinic BP and ankle BP during exercise. However, it was impossible to perform arm BP measurements during exercise because the dominant arm was used for handgrip exercise, and the

Discussion
The main finding of the present study is the decrease in MSNA levels during postmoderate exercise with circulatory arrest of the active skeletal muscle in never-treated hypertensive subjects. These findings suggest an association between hypertension and impaired muscle metaboreflex control of MSNA in humans.

Neurovascular Control during Handgrip Exercise
In healthy subjects, muscle vasodilatation during exercise depends on the nitric oxide-mediated vasodilatory force and sympathetic-mediated vasoconstrictor force. We have recently reported that sympathetic activation restrains the endothelial-mediated muscle vasodilation during physiologic maneuvers in patients with heart failure.22 These previous findings led us to suspect that the blunted forearm vasodilation during exercise in our hypertensive subjects is due to a disequilibrium favoring the sympathetic-mediated vasoconstrictor force. In fact, despite of the lowered...
nondominant arm was used for forearm blood flow measurements.

Finally, the fact that MSNA recordings were not analyzed blindly may be considered a limitation in our study.

Perspectives

The clinical implications of the decreased muscle metaboreflex control of MSNA in hypertensive patients are unknown. However, we can suspect that it is involved in the constellation of hemodynamic alterations in human hypertension, especially during physiologic maneuvers when the blood flow distribution is needed. This is an interesting challenge for future investigations in hypertension.

References