Exercise Training Restores Baroreflex Sensitivity in Never-Treated Hypertensive Patients


Abstract—The effects of exercise training on baroreflex control of sympathetic nerve activity in human hypertension are unknown. We hypothesized that exercise training would improve baroreflex control of muscle sympathetic nerve activity (MSNA) and heart rate (HR) in patients with hypertension and that exercise training would reduce MSNA and blood pressure (BP) in hypertensive patients. Twenty never-treated hypertensive patients were randomly divided into 2 groups: exercise-trained (n=11; age: 46±2 years) and untrained (n=9; age: 42±2 years) patients. An age-matched normotensive exercise-trained group (n=12; age: 42±2 years) was also studied. Baroreflex control of MSNA (microneurography) and HR (ECG) was assessed by stepwise intravenous infusions of phenylephrine and sodium nitroprusside and analyzed by linear regression. BP was monitored on a beat-to-beat basis. Exercise training consisted of three 60-minute exercise sessions per week for 4 months. Under baseline conditions (before training), BP and MSNA were similar between hypertensive groups but significantly increased when compared with the normotensive group. Baroreflex control of MSNA and HR was similar between hypertensive groups but significantly decreased when compared with the normotensive group. In hypertensive patients, exercise training significantly reduced BP (P<0.01) and MSNA (P<0.01 levels and significantly increased baroreflex control of MSNA and HR during increases (P<0.01 and P<0.03, respectively) and decreases (P<0.01 and P<0.03, respectively) in BP. The baseline (preintervention) difference in baroreflex sensitivity between hypertensive patients and normotensive individuals was no longer observed after exercise training. No significant changes were found in untrained hypertensive patients. In conclusion, exercise training restores the baroreflex control of MSNA and HR in hypertensive patients. In addition, exercise training normalizes MSNA and decreases BP levels in these patients. (Hypertension. 2007;49:1298-1306.)

Key Words: hypertension ■ baroreflex sensitivity ■ sympathetic nerve activity ■ exercise ■ blood pressure

There is accumulated evidence that arterial baroreflex plays an important role in the regulation of the cardiovascular system. During spontaneous variation of blood pressure (BP), stimulation or deactivation of the arterial baroreceptors located in the carotid sinus and aortic arch causes reflex bradycardia and tachycardia, respectively. At the vascular level, stimulation of the arterial baroreceptors results in sympathetic inhibition and, in consequence, reflex vasodilatation. In contrast, the deactivation of the arterial baroreceptors elicits sympathetic-mediated vasoconstriction.1 All of these responses work in concert to maintain the BP levels in the reference range.1

It has been described that arterial baroreflex sensitivity can be profoundly altered in some cardiovascular diseases.2,3 In hypertension, some investigators,4-6 but not all,7-9 observed that baroreflex control of heart rate (HR) and sympathetic nerve activity is significantly reduced. This autonomic dysfunction seems to correlate with an increase in sympathetic outflow and in BP levels.10 On the other hand, previous studies have demonstrated that regular exercise causes significant changes in baroreflex control of HR in experimental hypertension. Exercise training improves baroreflex control of HR during the increase and decrease of BP in spontaneously hypertensive rats.11,12 Furthermore, these studies indicate that the improvement in baroreflex sensitivity is, in part, mediated by the enhancement of the aortic depressor nerve sensitivity. In humans with hypertension, little information exists regarding the effects of exercise training on the baroreflex sensitivity. One of the few studies showed that exercise training caused a modest improvement in baroreflex bradycardia.13 Thus, the effects of regular exercise on the baroreflex control of sympathetic nerve activity in humans with hypertension are unknown.

It has been consistently shown that exercise training is a powerful nonpharmacological strategy to reduce BP levels in humans with hypertension.14-16 However, the mechanisms involved in the BP reduction after exercise training are still a matter of discussion. In the present study, we investigated the

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impact of regular exercise on muscle sympathetic nerve activity (MSNA) and BP levels in hypertensive patients. In addition, we sought to determine whether there was any relationship between the changes in MSNA and the changes in BP levels in exercise-trained hypertensive patients. Our hypotheses were as follows: (1) exercise training would improve baroreflex control of MSNA and HR during the increase and decrease of BP in never-treated hypertensive patients; (2) exercise training would reduce MSNA and BP in these patients; and (3) the changes in BP levels after exercise training would be associated with changes in MSNA.

Methods

Study Population
Twenty consecutive never-treated hypertensive patients were selected to participate in the study. An additional normotensive age-paired control group (N=12) was also enrolled in the study. They were <55 years old, had no evidence of metabolic disorders, renal vascular hypertension, cerebral ischemic disease, obstructive coronary artery disease, or musculoskeletal abnormality (eg, arthritis) and were not involved in regular exercise training for ≥6 months. In addition, the hypertensive patients had never been treated with antihypertensive drugs and were taking no medications 3 months before the study. Thereafter, the hypertensive patients were randomly divided into the exercise-trained group (n=11) and the untrained group (n=9). The normal control group was also submitted to exercise training. The study was approved by the University of São Paulo Medical School Ethical Committee for Human Research Protocols, and the participants gave their written informed consent.

Measurements and Procedures

Clinic BP
The clinic BP levels were obtained in the left arm of the sitting patient, after 5 minutes of quiet rest, with a mercury sphygmomanometer. A minimum of 3 BP readings was taken on 2 separate occasions. Systolic and diastolic BP were recorded at the first appearance of Korotkoff sounds. The subjects were classified as hypertensive if the average of the systolic and diastolic BP levels were >140 and/or 90 mm Hg, respectively.15

MSNA
MSNA was recorded directly from the peroneal nerve using the microneurography technique.17,18 Multunit postganglionic muscle sympathetic nerve recordings were made using a tungsten microelectrode (tip diameter: 3 to 15 μm). The signals were amplified by a factor of 50,000 to 100,000 and bandpass filtered (700 to 2000 Hz). For recordings and analysis, nerve activity was rectified and integrated (time constant: 0.1 seconds) to obtain a mean voltage display of sympathetic nerve activity that was recorded on paper. All of the recordings of MSNA met previously established and described criteria. MSNA was quantified as burst frequency (bursts per minute) and burst incidence (burst per 100 heart beats).

Miscellaneous Measurements
BP was monitored noninvasively by a finger photoplethysmography device (Finapres 2300, Ohmeda) on a beat-to-beat basis. HR was monitored continuously through lead II of ECG.

Arterial Baroreflex Measurements
Baroreflex sensitivity for control of MSNA and HR was studied by the technique of infusion of vasoactive drugs.2 Briefly, phenylephrine was infused incrementally through a cannula placed in the antecubital vein at doses of 0.4, 0.8, and 1.2 μg/kg/min to stimulate the baroreceptors. Sodium nitroprusside was also infused incrementally through a cannula placed in the antecubital vein at doses of 0.4, 0.8, and 1.2 μg/kg/min to deactivate the baroreceptors. The infusion of phenylephrine and sodium nitroprusside was maintained for 3 minutes per dose. Mean BP, MSNA, and HR were averaged for 3 minutes before infusion and every minute of each step infusion. Baroreflex sensitivity for control of MSNA and HR for each individual was estimated by the slope (“a”) of the linear regression equation generated by calculation of the absolute change in MSNA burst frequency and the absolute change in HR in relation to the absolute change in mean BP induced by phenylephrine and sodium nitroprusside infusion.19,20 The 9 points generated during the stepwise infusion (3 points for each dose) were used in the linear regression analysis.

Exercise Training Program
Subjects underwent exercise training under supervision at the Heart Institute. The 4-month training program consisted of three 60-minute exercise sessions per week. Each exercise session consisted of 5 minutes of stretching exercises, 40 minutes of cycling on an ergometer bicycle, 10 minutes of local strengthening exercises (sit-ups, push-ups, and pull-ups), and 5 minutes of cool down with stretching exercises. The exercise intensity was established by HR levels that corresponded with the anaerobic threshold up to 70% of peak oxygen uptake, obtained by a progressive cardiopulmonary exercise test. The anaerobic threshold was determined to occur at the point where there was a loss of linearity between oxygen uptake and carbon dioxide production or at the point where the ventilatory equivalent for oxygen or end-tidal oxygen partial pressure curves reached their respective minimum values and began to rise during the progressive exercise test. The peak oxygen uptake was considered at the end of the bicycle cardiopulmonary exercise test (ramp protocol with 10-, 15-, or 20-W increments every minute up to exhaustion) when the subject no longer maintained the bicycle velocity at 60 rpm. Untrained patients were instructed to avoid any regular exercise program (supervised or unsupervised) for 4 months.

Experimental Protocol
All of the studies were performed at ~7:30 AM, with the subjects lying in supine position in a quiet air-conditioned room (22°C to 24°C). After obtaining an adequate microneurographic nerve recording site in the leg and placing the cannula in the antecubital vein for drugs infusions, all of the participants rested for 15 minutes. The experimental protocol started with a 3-minute period of baseline measures of BP, MSNA, and HR (Figure 1). After this period, phenylephrine infusion was started and maintained for a 9-minute period. The end of the phenylephrine infusion was separated from the beginning of the sodium nitroprusside infusion by a recovery period. Mean BP, MSNA, and HR were continuously recorded throughout experimental protocols. Cardiopulmonary exercise test, clinic BP, and experimental protocol were repeated after 4 months in all of the groups. The second examination was performed 48 hours after the last exercise session.

Statistics
Data are presented as mean±SE. Unpaired t test was used to test the baseline differences between hypertensive patients and normotensive individuals. A χ² test was used to assess the gender differences between hypertensive patients and normotensive individuals. Pearson correlation coefficient was used to evaluate the correlation between the change in BP and the change in MSNA and the change in baroreflex sensitivity and the change in BP and MSNA. Two-way ANOVA with repeated measures was performed to test the differences among untrained hypertensive patients, exercise-trained hypertensive patients, and normal control individuals before and after intervention. When significant difference was found, Scheffé’s posthoc comparison test was used. Significant differences were assumed to be at P<0.05.
Baseline Measurements
Physical characteristics, hemodynamic and neural measurements, and functional capacity of the hypertensive patients and normotensive individuals are shown in Table 1. There were no significant differences in sex, age, height, weight, body mass index, HR, and functional capacity between hypertensive patients and normotensive individuals. Clinical systolic, diastolic, and mean BP levels were significantly higher in hypertensive patients than in normotensive individuals. MSNA burst frequency and burst incidence were also significantly higher in hypertensive patients than in normotensive individuals. The baroreflex control of MSNA during increase of mean BP, analyzed by the slope of the linear regression equation, was significantly lower in hypertensive patients when compared with normotensive individuals (Figure 2A and 2B). Similarly, the baroreflex control of MSNA during decrease of mean BP was significantly lower in hypertensive patients than in normotensive individuals (Figure 2A and 2B). The baroreflex control of HR during increase in mean BP, analyzed by the slope of the linear regression equation, was significantly lower in hypertensive patients than in normotensive individuals (Figure 2C and 2D). In addition, the baroreflex control of HR during decrease in mean BP was also significantly lower in hypertensive patients than in normotensive individuals (Figure 2C and 2D).

Effects of Exercise Training
Compliance with the exercise program was excellent, reaching an average of 96%±3% and 96%±3% of exercise sessions attended by both hypertensive patients and normotensive individuals, respectively. The effects of exercise training on hemodynamic measurements are shown in Table 2. Exercise training significantly reduced clinical systolic, diastolic, and mean BP levels in hypertensive patients. The comparison between hypertensive groups showed that exercise-trained hypertensive patients had clinical systolic, diastolic, and mean BP levels significantly lower than untrained hypertensive patients. Exercise training significantly decreased the baseline and standard 60-W workload HR in hypertensive patients and normotensive individuals. No significant changes were found in untrained hypertensive patients over the 4-month duration of the study. Exercise training significantly decreased MSNA burst frequency and burst incidence in hypertensive patients. Consequently,
MSNA burst frequency and burst incidence were significantly lower in exercise-trained hypertensive patients when compared with untrained hypertensive patients and similar when compared with normotensive individuals (Figure 3A and 3B). Further analysis showed a significant correlation between the changes in MSNA and the changes in mean BP (values measured after 4 months of study minus baseline) in exercise-trained and untrained hypertensive patients (Figure 2).
Of note, 1 patient who had a substantial increase in BP and MSNA was an untrained hypertensive woman. No significant changes in BP and MSNA were found in normotensive individuals over the 4-month exercise training period.

Examples of MSNA tracing and pulse pressure at baseline, both under phenylephrine and sodium nitroprusside infusion before and after intervention in 1 exercise-trained hypertensive patient are shown in Figure 5. Exercise training improved baroreflex control of MSNA and HR significantly in hypertensive patients (Figure 6A and 6B and 6C and 6D, respectively). Consequently, at the end of the 4-month intervention period, baroreflex sensitivity in exercise-trained hypertensive patients exceeded that observed in untrained hypertensive patients and was similar to that observed in normotensive control subjects. No significant changes were found in the baroreflex control of MSNA and HR in normotensive individuals over the 4 months of the exercise training period.

Exercise training significantly increased peak oxygen uptake in hypertensive patients (25 ± 2 vs 29 ± 3 mL/kg/min; \( P < 0.04 \)) and normotensive individuals (30 ± 2 vs 34 ± 2 mL/kg/min; \( P = 0.02 \)). No significant changes were found in untrained hypertensive patients over the 4-month duration of the study (26 ± 1 versus 25 ± 2 mL/kg/min; \( P = 0.90 \)).

**Discussion**

One of the major findings of the present study is that moderate exercise training improves the baroreflex control of MSNA and HR significantly in hypertensive patients (Figure 6A and 6B and 6C and 6D, respectively). Consequently, at the end of the 4-month intervention period, baroreflex sensitivity in exercise-trained hypertensive patients exceeded that observed in untrained hypertensive patients and was similar to that observed in normotensive control subjects. No significant changes were found in the baroreflex control of MSNA and HR in normotensive individuals over the 4 months of the exercise training period.

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**Figure 3.** MSNA burst frequency (A) and burst incidence (B) in exercise-trained hypertensive patients (n = 8), untrained hypertensive patients (n = 9), and exercise-trained normotensive individuals (n = 10). Note that exercise training significantly reduced MSNA burst frequency and burst incidence in hypertensive patients. *Significant difference vs normotensive individuals, \( P < 0.05 \); †Significant difference pre- vs postinterventions, \( P < 0.05 \); ‡Significant difference vs exercise-trained hypertensive patients, \( P < 0.05 \).

**Table 2.** Hemodynamic Measurements Preintervention and Postintervention in Hypertensive Patients and Normotensive Individuals

<table>
<thead>
<tr>
<th>Hemodynamic Measurements</th>
<th>Hypertensive Exercise-Trained (N=11)</th>
<th>Hypertensive Untrained (N=9)</th>
<th>Normotensive Exercise-Trained (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic systolic BP, mm Hg</td>
<td>Preintervention 145±2*</td>
<td>145±4*</td>
<td>117±2</td>
</tr>
<tr>
<td></td>
<td>Postintervention 130±5†*</td>
<td>146±6†</td>
<td>116±2</td>
</tr>
<tr>
<td>Clinic diastolic BP, mm Hg</td>
<td>Preintervention 94±2*</td>
<td>94±2*</td>
<td>78±1</td>
</tr>
<tr>
<td></td>
<td>Postintervention 84±3†</td>
<td>93±4†</td>
<td>78±2</td>
</tr>
<tr>
<td>Clinic mean BP, mm Hg</td>
<td>Preintervention 110±2*</td>
<td>110±2*</td>
<td>91±2</td>
</tr>
<tr>
<td></td>
<td>Postintervention 98±3†</td>
<td>112±4†</td>
<td>91±1</td>
</tr>
<tr>
<td>Baseline HR, bpm</td>
<td>Preintervention 80±5</td>
<td>72±3</td>
<td>78±4</td>
</tr>
<tr>
<td></td>
<td>Postintervention 70±4†</td>
<td>73±4</td>
<td>69±3†</td>
</tr>
<tr>
<td>60-W HR, bpm</td>
<td>Preintervention 114±4</td>
<td>119±6</td>
<td>121±6</td>
</tr>
<tr>
<td></td>
<td>Postintervention 102±4†</td>
<td>118±6†</td>
<td>106±5†</td>
</tr>
</tbody>
</table>

Values are mean±SE.

*Significant difference vs normotensive control subjects, \( P < 0.05 \).
†Significant difference preintervention vs postintervention, \( P < 0.05 \).
‡Significant difference vs exercise-trained hypertensive patients, \( P < 0.05 \).
baroreflex control of MSNA between normotensive and hypertensive subjects was apparent only in larger changes in BP (20 to 30 mm Hg; Figure 2). These large changes in BP were not achieved in other studies in which the baroreflex control of MSNA was similar between normotensive and hypertensive subjects. We cannot rule out the possibility that some methodologic differences explain the controversy among studies. We studied baroreflex sensitivity during increase and decrease of BP provoked by intravenous infusion of vasoactive drugs, whereas others studied baroreflex sensitivity during spontaneous fluctuation of BP. The drug infusion allows the investigation of the baroreflex control in a large range of BP variation, which rarely occurs during resting spontaneous BP variation. The hypertensive patients who participated in the study by Rea et al were younger than those involved in our study. In the study by Grassi et al, the normotensive individuals had higher BP and MSNA levels than those who took part in the present study. Grassi et al determined baroreflex control by calculating the percentage of change in MSNA in relation to the change in BP caused by each dose of phenylephrine and nitroprusside, the average ratio of percent changes in MSNA, and the corresponding

Figure 4. Relationship between the absolute changes (values after 4 months of training minus baseline) in MSNA and the absolute changes in mean BP (MBP) in exercise-trained (n=8, ○) and untrained (n=9, ▲) hypertensive patients.

Figure 5. Sympathetic neurograms and simultaneous recordings of BP in 1 exercise-trained hypertensive patient (male, 45 years old). A, MSNA and BP at baseline and during increase of BP by 1.2-µg kg⁻¹ min⁻¹ infusion of phenylephrine. B, MSNA and BP at baseline and during decrease of BP by 1.2-µg kg⁻¹ min⁻¹ infusion of sodium nitroprusside.
changes in BP. We studied the baroreflex control by calculating the linear regression equation between the absolute change in MSNA and the absolute change in BP induced by phenylephrine and sodium nitroprusside infusion.

The effect of exercise training on baroreflex control of HR has been described in animals and humans with hypertension. In spontaneously hypertensive rats, exercise training improves baroreflex bradycardia and tachycardia.11,12 In hypertensive patients, regular exercise enhances baroreflex bradycardia.13 Our study confirms that exercise training improves both baroreflex bradycardia and baroreflex tachycardia in hypertensive patients, but, for the first time, it demonstrates

Figure 6. Baroreflex control of MSNA and HR analyzed by the slope ("a") of the linear regression equation, in exercise-trained hypertensive patients, untrained hypertensive patients, and normotensive individuals. MBP indicates mean BP. *Significant difference vs postexercise normotensive and hypertensive individuals, $P<0.05$; †Significant difference vs normotensive individuals, $P<0.05$; ‡Significant difference pre- vs postinterventions, $P<0.05$; §Significant difference vs exercise-trained hypertensive patients, $P<0.05$. 
that regular exercise enhances baroreflex control of MSNA in hypertensive patients. The mechanism by which exercise training improves baroreflex sensitivity is out of the scope of the present study. However, it is conceivable to attribute the augmentation in baroreflex sensitivity, at least in part, to the aortic depressor nerve sensitivity. In a previous study, we found that the increase in baroreflex sensitivity in exercise-trained spontaneously hypertensive rats was associated with an improvement in aortic baroreceptor gain directly measured in an aortic baroreceptor multifiber preparation.12 This beneficial effect of exercise training may be mediated by an enhancement in arterial compliance that acts to increase stimulus transduction and afferent responsiveness.21 It has been described that a reduction in compliance of the large elastic arteries in which the arterial baroreceptors are located is a key mechanism underlying impairment in cardio-vagal baroreflex sensitivity in older subjects.22 On the other hand, 3 months of regular aerobic exercise significantly increases the carotid arterial compliance in previously sedentary middle-aged and older individuals.23,24 In addition, the age-related reduction in carotid artery compliance is significantly attenuated in endurance exercise-trained subjects when compared with sedentary healthy adults.23 But what are the possible explanations for the amelioration in arterial compliance after exercise training? So far, there is no definite information regarding this vascular change in hypertensive patients. However, further analysis in the present study may provide some hints for future investigations in this area. We found a significant correlation between the exercise-induced changes in baroreflex control of MSNA during increase and decrease of BP and changes in BP levels (r=0.72, P<0.01 and r=0.50, P<0.05, respectively). Thus, it is possible that the reduction in BP levels is implicated in the amelioration of arterial compliance after exercise training in hypertensive patients. We cannot exclude the possibility that the improvement in baroreflex control of MSNA is mediated by alterations in the central and efferent components of the baroreflex pathway. There is growing evidence that regular exercise normalizes plasma and central angiotensin II concentration and central angiotensin II type 1 receptor messenger RNA.25 A previous study demonstrated that long-term central infusion of angiotensin II reduced the gain of the cardiac baroreflex in rabbits, whereas long-term treatment with the angiotensin II type 1 receptor antagonist produced an increase in baroreflex gain.26

Another interesting piece of information in our study is that exercise training reverses the increased MSNA to normal levels in hypertensive patients. This remarkable effect of exercise has been described in other human syndromes, such as obesity and heart failure.27,28 Although we have no definitive information with regard to the mechanisms underlying the reduction in sympathetic nerve activity in humans, recent observations in animal models provide suggestive explanations for the reduction in MSNA after exercise training observed presently in hypertensive patients. Some investigators29 described that the reduction in basal renal sympathetic nerve activity after exercise training was associated with significant attenuation of chemoreflex-mediated sympathoexcitation in pacing-induced heart failure rabbits. The reduction in sympathetic nerve activity after exercise training has been attributed to a decrease in central angiotensin II concentration or an increase in central NO production by means of an enhancement in neuronal NO synthase expression.25 However, we cannot rule out the possibility that a reduction of sympathetic activity may occur with a loss of excitatory synapses. A reduced synaptic activity seems to correlate with structural neuroplasticity. Nelson et al30 observed that chronic exercise resulted in attenuated dendritic arborization of the cardiorespiratory and locomotor centers of the brain. In addition, a lower level of excitation of cardiorespiratory and locomotor centers of the brain for a given absolute workload during exercise has been also documented.31 It seems unlikely that the reduction in MSNA after training is associated with the improvement in arterial baroreflex sensitivity, because further analysis in the present study showed no significant correlation between the absolute changes in baroreflex control of MSNA and the changes in baseline MSNA in hypertensive patients (r=0.28, P value not significant, and r=0.38, P value not significant, respectively).

Confirming previous studies dealing with exercise training and hypertension,14 the present investigation clearly demonstrates that regular moderate dynamic exercise reduces systolic, diastolic, and mean BP in humans with high BP. Surprising was the fact that BP did not reach normal levels after exercise training. These findings raise the possibility that vascular changes caused by hypertension32,33 were not fully reversed by our exercise regimen. It is possible that a 4-month period of exercise training may be insufficient to reverse vascular structural alterations, which might explain the failure to completely normalize BP in our study. The decrease in both MSNA and BP after training could suggest a cause and effect relationship between these 2 parameters. However, the present results seem to be insufficient to support this concept. Despite the significant correlation between the changes in MSNA and the changes in BP (r=0.62; P<0.01), this association is weakened when only exercise-trained hypertensive patients are taken into consideration (Figure 4).

Both the decrease in resting HR and the improvement in peak oxygen uptake in the exercise-trained hypertensive patients and in normotensive control subjects clearly demonstrate the effectiveness of our exercise regimen. Resting bradycardia and increase in peak oxygen uptake are considered 2 important markers of exercise training adaptation in humans.34,35

Perspectives
The changes in baroreflex sensitivity and MSNA caused by exercise training have clinical implications. Previous observations demonstrated that reduction in baroreflex sensitivity is an independent risk factor for sudden death after acute myocardial infarction.36 Thus, it is reasonable to expect that the improvement in baroreflex sensitivity plays a protective role in hypertensive patients. In fact, the increase in baroreflex control of HR after regular exercise was associated with increased survival after a 10-year follow-up in patients with uncomplicated myocardial infarction.37 The sympathoinhibition after exercise training may improve prognosis in humans.
with hypertension. In preliminary studies, we found that increased MSNA was associated with mortality in heart failure patients. Finally, moderate dynamic exercise training is a unique nonpharmacological therapy for the treatment of human hypertension.

In conclusion, regular exercise restores baroreflex control of sympathetic nerve activity and HR in patients with hypertension. In addition, this nonpharmacological therapy provokes neurovascular inhibition and reduction in BP levels in human hypertension.

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Disclosures
None.

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