Original Article

Mechanism behind Augmentation in Baroreflex Sensitivity after Acute Exercise in Spontaneously Hypertensive Rats

Naoyoshi MINAMI[1)], Nobuyoshi MORI[1)], Makoto NAGASAKA[1)], Osamu ITO[1)], Hajime KUROSAWA[1)], Masayuki KANAZAWA[1)], Ki KAKU[1)], Eigyoku LEE[1)], and Masahiro KOHZUKI[1)]

A single bout of dynamic exercise increases baroreflex sensitivity (BRS) in spontaneously hypertensive rats (SHR). We examined whether change in hemodynamics (increases in blood pressure and heart rate) associated with dynamic exercise contribute to the post-exercise modulation of BRS. SHR aged 12 weeks were chronically instrumented with a carotid artery catheter and jugular vein catheter. They were then allocated to three groups submitted to 40 min of 1) running on a treadmill at 12 m/min (Run), 2) concomitant infusion of isoproterenol and a relatively high dose of phenylephrine (Iso+Phe(high)), or 3) concomitant infusion of isoproterenol and a relatively low dose of phenylephrine (Iso+Phe(low)). Arterial pressure and heart rate were continuously recorded throughout the experiments. BRS estimated by heart rate responses to phenylephrine injection and systolic blood pressure–low frequency power amplitude (SBP-LFamp) evaluated by power spectral analysis of SBP, a marker of sympathetic activity, were examined before and after running (Run group), or administration of drugs (Iso+Phe(high) or Iso+Phe(low) groups). BRS increased significantly from 1.4 to 1.9 bpm/mmHg after running, but not after administration of Iso+Phe(high) or Iso+Phe(low). Blood pressure and SBP-LFamp significantly decreased in each of the Run, Iso+Phe(high) and Iso+Phe(low) groups. These results suggest that hemodynamic change alone does not contribute to post-exercise modulation of BRS, while hemodynamic change or sympathetic activation during exercise contributes to post-exercise hypotension associated with a reduction of sympathetic activity. (*Hypertens Res* 2006; 29: 117–122)

***Key Words*: baroreflex sensitivity, blood pressure, exercise, heart rate, sympathetic activity**

Introduction

It has been well demonstrated that exercise training lowers blood pressure (*1*, *2*) and increases baroreflex sensitivity (BRS) (*1*) in hypertensive subjects. Apart from these chronic effects of exercise, a single bout of dynamic exercise is known to induce hypotension in the post-exercise period in hypertensive subjects (*3*) and spontaneously hypertensive rats (SHR) (*4–6*). Post-exercise hypotension (PEH) is associated with no change or a reduction of heart rate (HR) (*7*, *8*) and a reduction in cardiac (*9*) and peripheral sympathetic nerve activity (*10*, *11*). The reduction in blood pressure without a baroreflex-mediated compensatory tachycardia or sympa-

From the [1)]Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Sendai, Japan.

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 14570633).

Address for Reprints: Naoyoshi Minami M.D., Ph.D., Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, 1–1 Seiryo-cho, Aoba-ku, Sendai 980–8574, Japan. E-mail: minaoyo@mail.tains.tohoku.ac.jp

Received August 19, 2005; Accepted in revised form December 13, 2005.

thetic excitation suggests that a single bout of dynamic exercise resets the operating point of the arterial baroreflex to a lower pressure (*5*). PEH is also associated with a reduction in cardiac vagal tone (*5*, *12*). However, BRS in response to blood pressure elevation, which is predominantly determined by augmentation in cardiac vagal activity, increases after an acute bout of exercise (*13*). These observations suggest that the tonic and phasic reflex activity in cardiac vagal nerves are differently modulated in the post-exercise period.

The arterial baroreceptor cardiovagal baroreflex gain is determined by two components: mechanical gain, reflecting the transduction of pressure into arterial wall stretch, and neural gain, reflecting the transduction of arterial diameter changes into HR responses *via* central integration. There are several possible mechanisms by which dynamic exercise modulates these components. Arterial pressure and HR increase during dynamic exercise. These hemodynamic changes could influence the viscoelastic properties of the arterial wall where arterial baroreceptors are located (*14*). Actually, Studinger *et al*. (*15*) have demonstrated that an index of carotid arterial distensibility is altered in parallel with BRS during the post-exercise period. Hemodynamic changes associated with dynamic exercise could also lead to alternations in central baroreflex processing by arterial baroreceptors (*5*) or cardiac mechanoreceptor stimulation (*4*). Alternatively, dynamic exercise may modulate central baroreflex integration by triggering increased discharge from mechanosensitive afferent nerve fibers arising from contracting skeletal muscle (*16*). It is not known, however, what changes associated with dynamic exercise contribute to the post-exercise modulation of BRS. To address this question, in the present study BRS was measured in SHR before and after running on a treadmill or concomitant infusion of isoproterenol and phenylephrine, a combination known to increase blood pressure and HR.

Methods

All experimental procedures were performed in accordance with institutional guidelines.

Animal Care

Male SHR were obtained from Charles River, Astugi, Japan. The rats were fed standard laboratory chow and water ad libitum while housed at a controlled temperature (23°C) with a 12-h light-dark cycle. At the age of 11 weeks, all rats were submitted to 10-min periods of exercise on the motor treadmill at 10 m/min on a 0 grade incline every day for 1 week to become accustomed to the experimental procedures.

Surgical Procedures

At the age of 12 weeks, under ether anesthesia, an arterial catheter (tapered PE 100 on one end) and venous catheter (PE 20) were implanted into the left carotid artery and right jugular vein, respectively. The free ends of these catheters were brought subcutaneously to the back of the neck. The catheters were then filled with heparinized saline (100 IU/ml), and their ends were occluded. The rats were returned to individual cages and allowed to recover for 2 days after surgery.

Measurement of Arterial Pressure

Arterial pressure was monitored from the arterial catheter with a strain-gauge transducer (LIFE KIT DX-360; Nihon Kohden, Tokyo, Japan) and amplifier (MacLab Bridge Amp ADInstruments Pty Ltd., Castle Hill, Australia). Phasic pressure, mean arterial pressure (MAP) and HR were recorded at a sampling rate of 200/s by a data acquisition system and laboratory computer (MacLab 8 analog-to-digital converter and Macintosh computer).

Wavelet Transformation (WT)

Arterial pressure data were also stored on a magneto-optical disk (LX-10 RECORDING UNIT; TEAC, Tokyo, Japan), and the WT was computed using software running on a personal computer (Fluclet; Dai-nippon Pharmaceutical, Osaka, Japan). This software performs the spectral analysis of systolic blood pressure (SBP) fluctuation based on WT and provides a description of the spectral parameters every s. The reliability of this analytical method has been reported elsewhere (*17*). In the present study, the spectral component, the low frequency (LF; 0.26–0.74 Hz) of SBP, was calculated at every 1-s interval with continuous wavelet transform. The magnitude of the LF component was expressed as amplitude rather than power (area under the curve obtained by spectral analysis). The mean amplitude was obtained as follows: mean amplitude = $(2 \times \text{power})^{1/2}$. A secondary infinite impulse response Butterworth digital filter was used for smoothing of the amplitudes. The cut-off frequency was 0.05 Hz. The LF amplitude of SBP (SBP-LFamp) was determined as the mean of the filtered LFamp values obtained over each successive 5 s. Of these data, mean of three successive SBP-LFamp before and 20 to 30 min after running or concomitant infusion of isoproterenol and phenylephrine, at which the rat was quiet, was used as an index of sympathetic activity (*18*).

Experimental Protocols

The rats were assigned to three groups that were subjected to 40 min of 1) running on a motor-driven treadmill at 12 m/min at a 0 grade incline (Run) ($n=6$), 2) concomitant infusion of isoproterenol and a relatively high dose of phenylephrine (Iso+Phe(high)) ($n=8$), or 3) concomitant infusion of isoproterenol and a relatively low dose of phenylephrine (Iso+Phe(low)) ($n=5$). All rats were moved from individual cages to the treadmill and allowed to habituate to the experimental conditions for at least 1 h, while the catheters were

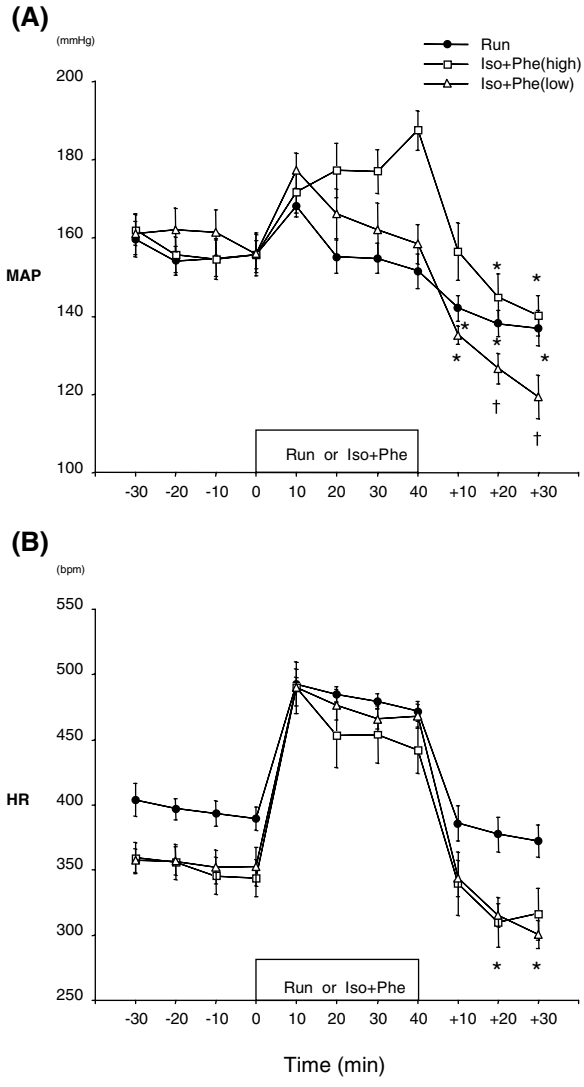

Fig. 1. *Mean arterial pressure (MAP) (A) and heart rate (HR) (B) before, during, and after treadmill exercise (Run) or concomitant infusion of isoproterenol and a relatively high dose of phenylephrine (Iso+Phe(high)), or a relatively low dose of phenylephrine (Iso+Phe(low)).* *p < *0.05,* †p < *0.01, time 0* vs. *post-Run or Iso+Phe.*

being connected for measurements. After the adaptation period, 30-min baseline data on arterial pressure and HR were obtained. Subsequently, intravenous injections of phenylephrine were given through a jugular vein catheter to produce increases in MAP (15 to 30 mmHg). The mean of at least three ratios of changes in HR to changes in MAP was taken as the BRS. Following measurements of BRS, rats were submitted to 40-min running, or administration of Iso+Phe(high) or Iso+Phe(low). The rats submitted to Iso+Phe(high) received concomitant infusion of isoproterenol (200 ng/kg/min) and phenylephrine (40 μg/kg/min) for 40 min at a volume of 0.73 ml/h. The rats submitted to Iso+Phe(low) received the same infusion as the rats in the Iso+Phe(high) group during the first 10 min, and then the infusion rate of phenylephrine was decreased to ~20 μg/kg/min so that the blood pressure changes resembled those in the rats during exercise. The rats in the Run group received a saline infusion at the same infusion rate. Thirty min after exercise or administration of Iso+Phe(high) or Iso+Phe(low), and an additional 60 min after administration of Iso+Phe(low), BRS was evaluated as described above.

Data Analysis

All results were expressed as the means±SEM. Values of MAP and HR during and after exercise or drug administration were compared with baseline data (time 0) in each group using a paired *t*-test. Values of BRS and SBP-LFamp before and after exercise or drug administration were also compared using a paired *t*-test. Differences were considered significant when $p<0.05$.

Results

MAP and HR

Figure 1 shows the values of MAP and HR before, during, and after the Run, Iso+Phe(high) or Iso+Phe(low) period. In Run rats, MAP had significantly increased by 10 min after the start of running but thereafter returned to the baseline level. Ten min after the cessation of exercise, MAP had significantly decreased compared with the baseline level, and this hypotension persisted for the duration of the post-exercise period. In Iso+Phe(low) rats, MAP changes during infusion period and post-infusion period resembled to those of Run, although MAP decreased more profoundly during post-infusion period in the Iso+Phe(low) group than in the Run group. In Iso+Phe(high) rats, MAP significantly increased throughout the infusion period, and 20 and 30 min after cessation of the infusion, MAP was significantly lower than the baseline level. In Run, Iso+Phe(high) and Iso+Phe(low) rats, HR significantly increased throughout the exercise or infusion period. After exercise, HR returned to the baseline level in Run rats, while in the Iso+Phe(high) and Iso+Phe(low) rats, 20 and 30 min after cessation of the infusion, HR was slightly but significantly decreased compared with the baseline level.

BRS

Figure 2 shows BRS before and 30 min after exercise or drug administration. BRS in Run rats was significantly increased (from 1.4±0.2 to 1.9±0.2 bpm/mmHg, $p=0.0003$, paired *t*-test). No significant changes in BRS were observed in Iso+Phe(high) and Iso+Phe(low) rats (from 1.4±0.1 to 1.5±0.2 bpm/mmHg, $p=0.6831$ and from 1.25±0.13 to 1.2±0.12 bpm/mmHg, $p=0.4900$, respectively, paired *t*-test). In Iso+Phe(low) rats, BRS at 60 min after termination of

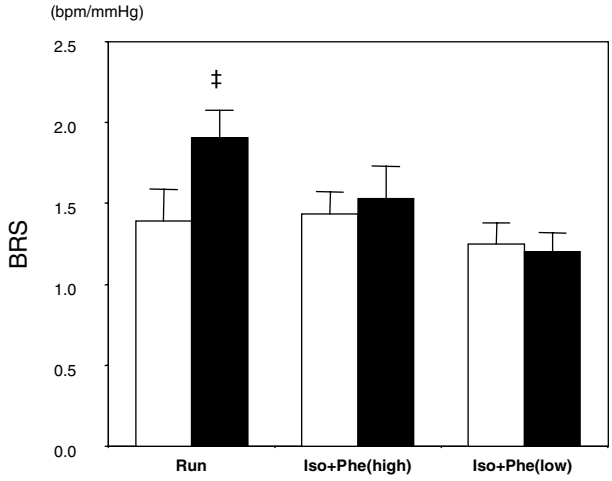

Fig. 2. *Baroreflex sensitivity (BRS) before (open column) and after (filled column) the Run, Iso+Phe(high), or Iso+Phe(low) period.* ‡$p < 0.001$, *pre-Run* vs. *post-Run.*

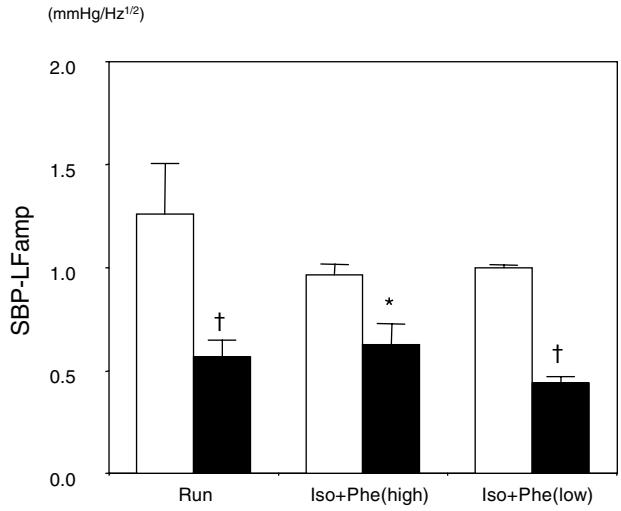

Fig. 3. *SBP-LFamp, a marker of sympathetic activity, before (open column) and after (filled column) the Run, Iso+Phe(high) or Iso+Phe(low) period.* *$p < 0.05$, †$p < 0.01$, *pre-Run* vs. *post-Run or pre-Iso+Phe* vs. *post-Iso+Phe.*

infusion was also unchanged (1.20±0.09 bpm/mmHg, $p=0.6157$, paired *t*-test).

SBP-LFamp

Figure 3 shows SBP-LFamp before and after exercise or drug administration. SBP-LFamp was significantly decreased in Run, Iso+Phe(high) and Iso+Phe(low) rats (from 1.26±0.24 to 0.57±0.08 mmHg/Hz$^{1/2}$, $p=0.0099$, from 0.97±0.05 to 0.62±0.10 mmHg/Hz$^{1/2}$, $p=0.0139$, and from 1.00±0.01 to 0.44±0.03 mmHg/Hz$^{1/2}$, $p=0.0001$, respectively, paired *t*-test).

Discussion

It has been well demonstrated that BRS increases after a single bout of dynamic exercise (*13*, *19*, *20*). However, the mechanism responsible for the acute increase in BRS after exercise remains unclear. The results of the present study demonstrated that in SHR, BRS significantly increased after running on a treadmill but not after administration of Iso+Phe(high) or Iso+Phe(low), and the latter drug combination induced hemodynamic changes similar to those during exercise. These results suggest that hemodynamic change during exercise alone does not contribute to the post-exercise augmentation of BRS in SHR.

One component determining arterial baroreceptor cardiovagal baroreflex gain is mechanical gain, which reflects the transduction of pressure into arterial wall stretch. It has been shown that increases in arterial pressure and HR could influence the viscoelastic properties of the arterial wall (*14*). Actually, Chapleau *et al*. (*21*) have demonstrated that increase in pulse pressure and HR similar to those that are induced by exercise can sensitize baroreceptors. However, arterial distensibility and BRS seem to be altered in the post-exercise period. Studinger *et al*. (*15*) have demonstrated that carotid artery distensibility is reduced immediately after stopping exercise but gradually increases thereafter, and exceeds the control level at 60-min post-exercise. Analogous with these time-dependent changes in arterial distensibility, BRS is reduced immediately post-exercise period, and increases 30–60 min post-exercise (*22*, *23*).

Although the mechanisms behind these phenomena are not clear, several explanations are possible. Elevated arterial pressure during exercise may induce a strong myogenic response in the carotid smooth muscle (*24*), and when exercise is terminated and arterial pressure suddenly drops, the myogenic smooth muscle contraction would be left unopposed, causing a transient decrease in carotid artery distensibility. Following this, as observed after chronic exercise training (*25*), increased production of endothelial-derived relaxing factors such as nitric oxide, which is induced by factors associated with exercise, such as an increases in blood flow (*26*, *27*) and catecholamines (*28*), may relax vascular smooth muscle, leading to an increase in arterial distensibility. Alternatively, increase in vasa vasorum blood flow may contribute to increased aortic distensibility during the post-exercise period (*29*). However, these speculations are based on the observations obtained in normotensive animals or men. In the present study, BRS did not change at 30 min or even 60 min after the infusion period in Iso+Phe(low) rats. It is possible that 40-min increases in arterial pressure and HR could not alter arterial distensibility, and thus BRS in SHR, although chronic exercise training seems to increase arterial distensibility (*30*) and aortic baroreceptor gain sensitivity (*31*) in SHR.

Chandler and DiCarlo (*5*) have demonstrated that sinoaortic denervation prevents post-exercise reductions in arterial pressure and sympathetic tonus. Cardiac afferent blockade also attenuates PEH (*4*). These observations suggest that hemodynamic change during exercise stimulates arterial baroreceptors or cardiac mechanoreceptors, which resets the arterial baroreflex control of sympathetic nerve activity (SNA) to a lower operating point by modulating central baroreflex processing. In support of this, it has been shown that resting SNA and gain of baroreflex SNA control are reduced after prolonged elevations of arterial pressure (*32*). Consistent with the results of previous studies (*10*, *11*, *32*, *33*), in the present study SBP-LFamp, a marker of SNA (*18*), decreased in association with a reduction of arterial pressure after exercise as well as Iso+Phe infusion. On the other hand, BRS, which is predominantly determined by augmentation in cardiac vagal activity, increased after exercise but not after cessation of Iso+Phe infusion. These results suggest that afferent input(s) from some source other than arterial baroreceptors or cardiac mechanoreceptors contributes to increase BRS after acute exercise in SHR.

During dynamic exercise, muscle afferents are stimulated (*34*). These somatic afferent fibers project to the nucleus tractus solitarii (NTS) (*35*), a medullary region at which arterial baroreceptor messages are first integrated (*36*). Following pressure increases, second-order neurons in the NTS are stimulated and excite the parasympathetic neurons in the nucleus ambiguous and dorsal motor nucleus of the vagus (DMV), resulting in an increased vagal outflow to the heart and bradycardia. Thus muscle afferent stimulation during exercise may directly alter the discharge properties of NTS neurons, resulting in an increased BRS in the post-exercise period. Although the NTS contains an abundance of neurotransmitters (*37*), it has been demonstrated that muscle afferent stimulation releases substance P in the NTS (*38*). However, at the present time it is still not clear whether or how substance P in the NTS is involved in modulating the arterial baroreceptor reflex (*39*). Alternatively, muscle afferent stimulation may indirectly modulate the baroreflex function by changing the activities of other sites of the central nervous system. It is known that the NTS projects to the paraventricular nucleus (PVN) and other hypothalamic nuclei as well as to the amygdala and cortex (*40–42*), all of which reciprocally project to the NTS (*43*). Among these feedback control loops, the relation between the NTS and PVN may be of importance in terms of central adaptation to exercise. Braga *et al*. (*44*) have demonstrated that oxytocinergic projections from the PVN to the NTS are stimulated when rats exercise. In addition, Higa *et al*. (*45*) have shown that oxytocinergic projections to the NTS/DMV area act to increase BRS, thereby facilitating the vagal outflow to the heart, during blood pressure elevations. However, since stimulation of oxytocinergic projections to the NTS during exercise occurs only in trained animals (*44*), it is not clear whether this system is responsible for the augmentation of BRS observed during the post-exercise period in non-trained SHR.

In conclusion, our data suggest that somatic afferent stimulation from skeletal muscle during exercise, rather than hemodynamic change, plays an important role in the post-exercise augmentation of BRS in SHR. Further studies are needed to clarify the possible central mechanisms by which muscle afferent stimulation modulates BRS.

References

1. Somers VK, Conway J, Johnston J, Sleight P: Effects of endurance training on baroreflex sensitivity and blood pressure in borderline hypertension. *Lancet* 1991; **337**: 1363–1368.
2. Moriguchi J, Itoh H, Harada S, *et al*: Low frequency regular exercise improves flow-mediated dilatation of subjects with mild hypertension. *Hypertens Res* 2005; **28**: 315–321.
3. Halliwill JP: Mechanisms and clinical implications of post-exercise hypotension in humans. *Exerc Sports Sci Rev* 2001; **29**: 65–70.
4. Collins HL, DiCarlo SE: Attenuation of postexertional hypotension by cardiac afferent blockade. *Am J Physiol* 1993; **265**: H1179–H1183.
5. Chandler MP, Dicarlo SE: Sinoaortic denervation prevents postexercise reductions in arterial pressure and cardiac sympathetic tonus. *Am J Physiol* 1997; **273**: H2738–H2745.
6. Chen C-Y, Munch PA, Quail AW, Bonham AC: Postexercise hypotension in conscious SHR is attenuated by blockade of substance P receptors in NTS. *Am J Physiol* 2002; **283**: H1856–H1862.
7. Overton JM, Joyner MJ, Tipton CM: Reductions in blood pressure after acute exercise by hypertensive rats. *J Appl Physiol* 1988; **64**: 748–752.
8. Shyu BC, Thorén P: Circulatory depression following spontaneous muscle exercise in normotensive and hypertensive rats. *Acta Physiol Scand* 1986; **128**: 515–524.
9. Chen Y, Chandler MP, DiCarlo SE: Acute exercise attenuates cardiac autonomic regulation in hypertensive rats. *Hypertension* 1995; **26**: 676–683.
10. Halliwill JR, Taylor JA, Eckberg DL: Impaired sympathetic vascular regulation in humans after acute dynamic exercise. *J Physiol* 1996; **495**: 279–288.
11. Kajekar R, Chen C-Y, Mutoh T, Bonham AC: $GABA_A$ receptor activation at medullary sympathetic neurons contributes to postexercise hypotension. *Am J Physiol* 2002; **282**: H1615–H1624.
12. Chen Y, Chandler MP, DiCarlo SE: Acute exercise attenuates cardiac autonomic regulation in hypertensive rats. *Hypertension* 1995; **26**: 676–683.
13. Silva GJJ, Brum PC, Negrão CE, Krieger EM: Acute and chronic effects of exercise on baroreflexs in spontaneously hypertensive rats. *Hypertension* 1997; **30**: 714–719.
14. Glaser E, Lacolley P, Boutouyrie P, *et al*: Dynamic *versus* static compliance of the carotid artery in living Wistar-Kyoto rats. *J Vasc Res* 1995; **32**: 254–265.
15. Studinger P, Lénárd Z, Kováts Z, Kocsis L, Kollai M: Static and dynamic changes in carotid artery diameter in humans during and after strenuous exercise. *J Physiol* 2003; **550**: 575–583.

16. Thoren P, Floras JS, Hoffman P, Seals DR: Endorphins and exercise: physiological mechanisms and clinical implications. *Med Sci Sports Exerc* 1990; **22**: 417–428.
17. Nagai R, Nagata S: New algorithms for real-time, 24 hr continuous and noise-adjusted power spectral analysis of heart rate and blood pressure fluctuations in conscious rats. *Jpn J Pharmacol* 1996; **72**: 355–364.
18. Brown DR, Brown LV, Patwardhan A, Randall DC: Sympathetic activity and blood pressure are tightly coupled at 0.4 Hz in conscious rats. *Am J Physiol* 1994; **267**: R1378–R1384.
19. Convertino VA, Adams WC: Enhanced vagal baroreflex response during 24 h after exercise. *Am J Physiol* 1991; **260**: R570–R575.
20. Halliwill JR, Taylor JA, Hartwig TD, Eckberg AD: Augmented baroreflex heart rate gain after moderate-intensity, dynamic exercise. *Am J Physiol* 1996; **270**: R420–R426.
21. Chapleau MW, Johnson SL, Hajduczok G, Abboud FM: Relative contribution of pulse amplitude and frequency to post-pulsatile pressure sensitization of baroreceptors. *Physiolgist* 1988; **31**: A198 (Abstract).
22. Somers VK, Conway J, LeWinter M, Sleight P: The role of baroreflex sensitivity in post-exercise hypotension. *J Hypertens* 1985; **3** (Suppl): S129–S130.
23. Piepoli M, Coats AJ, Adamopoulos S, *et al*: Persistent peripheral vasodilation and sympathetic activity in hypotension after maximal exercise in human. *J Appl Physiol* 1993; **75**: 1807–1814.
24. Olesen HL, Mitchell JH, Friedman DB, Iversen HK, Secher NH: Reduced arterial diameter during static exercise in humans. *Acta Physiol Scand* 1994; **153**: 335–341.
25. Sugawara J, Inoue H, Hayashi K, Yokoi T, Kono I: Effect of low-intensity aerobic exercise training on arterial compliance in postmenopausal women. *Hypertens Res* 2004; **27**: 897–901.
26. Cooke JP, Stamler J, Andon N, Davies PF, MeKinley G, Loscalzo J: Flow stimulates endothelial cells to release a nitrosovasodilator that is potentiated by reduced thiol. *Am J Physiol* 1990; **259**: H804–H812.
27. Maeda S, Tanabe T, Otsuki T, *et al*: Moderate regular exercise increases basal production of nitric oxide in elderly women. *Hypertens Res* 2004; **27**: 947–953.
28. Pegoraro AA, Carretero OA, Sigmon DH, Beierwaltes WH: Sympathetic modulation of endothelium-derived relaxing factor. *Hypertension* 1992; **19**: 643–647.
29. Stefanidis C, Vlachopoulos C, Karayannacos P, *et al*: Effect of vasa vasorum flow on structure and function of the aorta in experimental animals. *Circulation* 1995; **91**: 2669–2678.
30. Hagg U, Andersson I, Naylor AS, *et al*: Voluntary physical exercise-induced vascular effects in spontaneously hypertensive rats. *Clin Sci* 2004; **107**: 559–560.
31. Brum PC, Silva GJJ, Moreira ED, Ida F, Negrão CE, Krieger EM: Exercise training increases baroreceptor gain sensitivity in normal and hypertensive rats. *Hypertension* 2000; **36**: 1018–1022.
32. Undesser KP, Jing-Yun P, Lynn MP, Bishop VS: Baroreflex control of sympathetic nerve activity after elevations of pressure in conscious rabbits. *Am J Physiol* 1985; **248**: H827–H834.
33. Kulics JM, Collins HL, DiCarlo SE: Postexercise hypotension is mediated by reductions in sympathetic nerve activity. *Am J Physiol* 1999; **276**: H27–H32.
34. Tibes U: Reflex inputs to cardiovascular and respiratory centers from dynamically working canine muscles: some evidence for involvement of group III or IV nerve fibers. *Circ Res* 1977; **41**: 332–341.
35. Nyberg G, Blomqvist A: The central projection of muscle afferent fibers to the lower medulla and upper spinal cord: an anatomical study in the cat with transganglionic transport method. *J Comp Neurol* 1984; **230**: 99–109.
36. Spyer KM: Central nervous mechanisms contributing to cardiovascular control. *J Physiol* 1994; **474**: 1–19.
37. Pilowsky PM, Goodchild AK: Baroreceptor reflex pathways and neurotransmitters: 10 years on. *J Hypertens* 2002; **20**: 1675–1688.
38. Potts JT, Fuchs IE, Li J, Leshnower B, Mitchell JH: Skeletal muscle afferent fibers release substance P in the nucleus tractus solitarii of anesthetized cats. *J Physiol* 1999; **514**: 829–841.
39. Helke CJ, Seagard JL: Substance P in the baroreceptor reflex: 25 years. *Peptides* 2004; **25**: 413–423.
40. Sved AF, Gordon FJ: Amino acids as central neurotransmitters in the baroreceptor reflex pathway. *News Physiol Sci* 1994; **9**: 243–246.
41. Sawchenko PE, Swanson LW: Central noradrenergic pathways for the integration of hypothalamic neuroendocrine and autonomic responses. *Science* 1981; **214**: 685–687.
42. Palkovits M: Neuronal circuits in central baroreceptor mechanism. in Saito H, Parvez H, Parvez S, Nagatsu T (eds): Progress in Hypertension, Vol 1. Utrecht, VSP, 1988, pp 387–409.
43. Whitehead MC, Bergula A, Holliday K: Forebrain projections to the rostal nucleus of the solitary tract in the hamster. *J Comp Neurol* 2000; **422**: 429–447.
44. Braga DC, Mori E, Higa KT, Morris M, Michelini LC: Central oxytocin modulates exercise-induced tachycardia. *Am J Physiol* 2000; **278**: R1474–R1482.
45. Higa KT, Mori E, Viana FF, Morris M, Michelini LC: Baroreflex control of heart rate by oxytocin in the solitary-vagal complex. *Am J Physiol* 2002; **282**: R537–R545.