Postexercise hypotension is mediated by reductions in sympathetic nerve activity

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Kulics, Jennifer M., Heidi L. Collins, and Stephen E. DiCarlo. Postexercise hypotension is mediated by reductions in sympathetic nerve activity. Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H27–H32, 1999.—Mean arterial pressure (MAP), the product of cardiac output (CO) and total peripheral resistance (TPR), is reduced below preexercise levels after a single bout of mild to moderate dynamic exercise. Thus acute, dynamic exercise may be used as a safe, therapeutic approach to reduce MAP. However, the mechanisms responsible for the postexercise hypotension (PEH) are unknown. We tested the hypothesis that PEH is associated with reductions in TPR and sympathetic nerve activity (SNA). Two experimental protocols were designed to test this hypothesis in male spontaneously hypertensive rats (SHR). In protocol 1 (n = 9), CO and TPR were determined before, during, and after exercise. In protocol 2 (n = 7), lumbar SNA (LSNA) was recorded before and after exercise. Rats in protocol 1 were chronically instrumented with left carotid arterial catheters and ascending aortic Doppler ultrasonic flow probes. Rats in protocol 2 were chronically instrumented with left carotid arterial catheters and electrodes around the lumbar sympathetic trunk. Dynamic treadmill exercise (9–12 m/min, 10% grade for 40 min) resulted in a postexercise reduction in MAP (from 143 ± 5 to 128 ± 4 mmHg, P < 0.05). Associated with the PEH was a reduction in TPR (from 28 ± 3 to 19 ± 2 mmHg/kHz; P < 0.05) and an elevation in CO (from 5.7 ± 0.4 to 7.2 ± 0.5 kHz; P < 0.05). The reductions in arterial pressure and TPR were associated with a decrease in LSNA (from 98 ± 3 to 49 ± 6%; P < 0.05). These results suggest that PEH is mediated by reductions in TPR and SNA.

METHODS
Design

Sixteen male SHR were weaned at 4 wk of age and housed in standard cages at all times. At 12 wk of age, nine rats were instrumented for measurements of AP, HR, and CO (protocol 1). Seven additional rats were instrumented for the measurements of AP, HR, and LSNA (protocol 2). All surgical and experimental procedures were performed in accordance with the guidelines established by the institutional animal care and use committee.

Surgical Procedures

Protocol 1. All instrumentation was performed using aseptic procedures. Rats were anesthetized with an intramuscular injection of xylazine (8 mg/kg), chlorpromazine hydrochloride (4 mg/kg), and ketamine hydrochloride (40 mg/kg). Supplemental doses were administered as needed. A right thoracotomy was performed through the third intercostal space. The sleeve of the pericardium that extends onto the ascending aorta was dissected free of surrounding tissue. A 3.0-mm epoxy-type Doppler ultrasonic flow probe was positioned around the vessel. The flow probe wires were tunneled subcutaneously and exteriorized at the back of the neck. The animals were allowed at least 7 days to recover from the surgery. During the recovery period, animals were carefully monitored for signs of infection and weight loss, familiarized with running on a motor-driven treadmill, and trained to rest quietly in a large Plexiglas box. At the end of the recovery period, all animals were healthy and gaining weight. At this time, the rats were anesthetized as described above, and a Teflon catheter was inserted into the ascending aorta via the left common carotid artery for measurements of AP and HR. The catheter was tunneled beneath the skin and exteriorized at the back of the neck. The arterial catheter was flushed daily with heparinized saline, filled with heparin (1,000 units/mL, 100 units/kg), and connected to an in-line heparinization device. All rats were allowed to recover for at least 7 days before measurements were taken.

Results

For results obtained in animal models of PEH to have clinical significance, the hemodynamic responses in hypertensive animals must be similar to the responses in hypertensive individuals. Furthermore, the overall hemodynamic responses and how they are mediated must be similar. These are important considerations because if postexercise hemodynamic responses are similar in hypertensive individuals and animals, then the animal model provides a situation where invasive manipulation of the autonomic nervous system can be performed to acquire new information, to test hypotheses, and to develop interventions designed to prevent the morbidity and mortality associated with hypertension.

Arterial pressure (AP) is reduced below preexercise levels after a single bout of low-intensity, short-duration, dynamic exercise (10, 20). The postexercise hypotension (PEH) has been demonstrated in hypertensive individuals (1, 11, 12) and animals (4, 5, 9, 21). In hypertensive individuals, PEH is most often associated with elevations in cardiac output (CO) as well as reductions in peripheral resistance (15) and sympathetic nerve activity (SNA) (11, 15). It is important to note, however, that the hemodynamic factors mediating PEH have not been determined in hypertensive animals.

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U/ml), and plugged with a paraffin-filled obturator. The animals were allowed at least 4 days to recover from the surgery. During the recovery period, animals were again monitored for signs of infection and weight loss.

Protocol 2. Rats were anesthetized with pentobarbital sodium (45 mg/kg ip), and a Teflon catheter was placed into the descending aorta as described for protocol 1. Subsequently, the lumbar sympathetic trunk was approached between L3 and L5 by a ventral abdominal approach. The aorta was reflected ventrally, and the left psoas muscle was reflected laterally to expose the sympathetic trunk. The sympathetic trunk lies on the quadratus lumbarum muscle located under the aorta. To avoid touching the nerve, we removed a small portion (5–10 mm) of the surrounding muscle, creating a pocket around the nerve. After the pocket was filled with warm saline, bipolar electrodes were placed around the isolated lumbar sympathetic trunk for the recording of LSNA. The nerve was not touched by the surgical instruments, and therefore it maintained its connective tissue and blood supply. Each electrode was constructed of a multistranded stainless steel Teflon-coated wire (part no. 316 SS 7/44T, Medwire, Mount Vernon, NY) with the exposed end wound into a single loop. Silicone gel (Wacker Sil-Gel 604) was used to isolate the electrodes from the surrounding tissue and to ensure contact with the nerve. A surgical steel suture was used to close the abdominal muscle and to serve as the ground electrode. The recording electrodes and ground electrode were tunneled beneath the skin and exteriorized at the back of the neck. The experiments were performed either 1 or 2 days after surgery.

Experimental Measurements

AP was determined by connecting the arterial catheter to a Gould P23 XL pressure transducer that was coupled to a MacLab BRIDGE Amplifier. HR was determined with a Gould electrocardiogram/biotach that was triggered from the Dopp-er flow-dimension system with 20-MHz high-velocity modules (Baylor College of Medicine). The Doppler flow-dimension system measures blood flow velocity in kilohertz of Doppler shift, which is directly proportional to absolute blood flow as determined with an electromagnetic system. Doppler flow and AP analog signals were digitized at 400 samples/s by a MacLab 8 analog-to-digital converter and laboratory computer for calculation of real-time HR and for subsequent mean AP (MAP) analysis.

SNA signals were initially amplified (1,000–5,000 ×) with a Grass P511 differential preamplifier and high-impedance probe (HIP 511GA, West Warwick, RI). The probe, amplifier, and animal were located inside a shielded Faraday cage. The low- and high-pass filters were set at 30-, 100-, and 1,000 Hz. The action potentials were displayed on an oscilloscope (Tektronix 5111A, Beaverton, OR) and monitored with a Grass AM8 audio monitor. Whole nerve activity was obtained by rectifying and integrating the action potentials with a root mean square (RMS) integrator, which was coupled to a Gould RS3600 (Cleveland, OH) recorder. Mean nerve activity was derived electronically using a low-pass filter with a time constant of 3.2 s. All data were displayed on a physiograph (model RS3600, Gould Instruments) and were sampled by a data-acquisition system and laboratory computer (MacLab 8 analog-to-digital converter and Macintosh computer, Milford, MA) for subsequent analysis. Background noise for LSNA was determined on the day of the experiment at the end of the postexercise period, after the animal was killed. Postmortem noise was subtracted from the raw LSNA recording before analysis. Extreme care was taken to distinguish LSNA from an electromyogram or movement artifact. Artifacts were identified as a distinctive change in the audible signal or changes in the average burst height and/or shape. Only data sections free of artifacts were analyzed.

Experimental Procedures

On the day of the experiment, rats were placed unrestrained in a large Plexiglas box. The animals were allowed to acclimate for 60 min before we proceeded with the collection of preexercise data. After the 60-min adaptation period, CO or LSNA, AP, and HR were measured at 10-min intervals for 30 min. The total time of the preexercise period was 90 min (60 min of adaptation plus 30 min of data collection). After the preexercise period, the rats ran on the treadmill at 9.0–12.0 m/min, 10% grade, for 40 min. Measurements of CO, AP, and HR were recorded at 10-min intervals during the single bout of dynamic exercise. After exercise, the rats were returned to the Plexiglas box. During the postexercise period, CO, OR, LSNA, AP, and HR were recorded at 10-min intervals for 60 min.

Evaluation of LSNA

Resting LSNA was recorded over 30 min while the rats were in the large Plexiglas box immediately before they commenced exercise. This value averaged over the 30 min was set at 100%. Values obtained at 10-min intervals during the 30 min before exercise were expressed as a percentage of the control value. Increases in LSNA after exercise were also expressed as a percentage of this control value and thus reflect changes from the resting level. This normalization allowed for the direct evaluation of the capability of a single bout of dynamic exercise to decrease SNA.

Data Analysis

All data are expressed as means ± SE. A one-way ANOVA with repeated measures was used to evaluate differences in AP, CO, and HR before, during, and after exercise, and differences in LSNA before and after exercise. Differences observed over time were further evaluated with a test of simple effects post hoc. An α-level of 0.05 was used to determine statistical significance.

RESULTS

Effect of Exercise on MAP and HR

Ten-second recordings of LSNA, AP, and HR in the preexercise and postexercise conditions are presented in Fig. 1. After a single bout of dynamic exercise, LSNA and AP were reduced below preexercise values. MAP before, during, and after exercise was determined during two experimental protocols. MAP responses for protocol 1 and protocol 2 did not differ significantly (P > 0.05); therefore, MAP responses were averaged and are presented in Fig. 2A. MAP increased from 143 ± 5 mmHg before exercise (0 min) to 165 ± 5 mmHg during exercise (10 min, P < 0.05). At 40 min of exercise, MAP was 147 ± 4 mmHg. MAP decreased to 128 ± 4 mmHg after exercise (10 min, P < 0.05). Thus MAP decreased by 15 ± 4 mmHg after exercise (10 min) compared with the preexercise value and remained lower throughout the postexercise period.

HR before, during, and after exercise was determined during two experimental protocols. HR responses for protocol 1 and protocol 2 did not differ significantly (P > 0.05); therefore, HR responses were averaged and
are presented in Fig. 2B. HR was 347 ± 14 beats/min before exercise (0 min) and increased to 497 ± 7 beats/min during exercise (10 min, P < 0.05). At 40 min of exercise, HR was 494 ± 5 beats/min. Ten minutes after exercise, HR decreased to 386 ± 11 beats/min. The steady-state HR after exercise was not significantly different from the preexercise HR.

**Effect of Exercise on CO and TPR (Protocol 1)**

Figure 3 illustrates CO (Fig. 3A) and TPR (Fig. 3B) before, during, and after exercise. CO increased from 5.7 ± 0.4 kHz before exercise (0 min) to 7.8 ± 0.4 kHz during exercise (10 min, P < 0.05). At 40 min of exercise, CO was 8.2 ± 0.4 kHz. Ten minutes after exercise, CO was 7.2 ± 0.5 kHz, an increase of 1.5 ± 0.4 kHz compared with the preexercise value. Postexercise CO remained elevated above preexercise values for the entire postexercise period.

TPR decreased from 28 ± 3 mmHg/kHz before exercise (0 min) to 22 ± 2 mmHg/kHz during exercise (10 min, P < 0.05). At 40 min of exercise, TPR was 18 ± 1 mmHg/kHz. TPR remained decreased (19 ± 2 mmHg/kHz) after exercise (10 min, P < 0.05). Thus TPR was decreased by 8.8 ± 2 mmHg/kHz 10 min after exercise and remained significantly lower than preexercise values for the entire postexercise period.

**Preexercise and Postexercise LSNA (Protocol 2)**

Figure 4 presents LSNA before and after a single bout of dynamic exercise. LSNA decreased from 98 ± 3% before exercise (0 min) to 49 ± 6% after exercise (10 min, P < 0.05). Thus LSNA was decreased by 48 ± 5% after exercise (10 min, P < 0.05) and remained reduced throughout the entire postexercise period.

**DISCUSSION**

Results from this study demonstrate that after a single bout of dynamic exercise, AP, SNA, and TPR are reduced while CO is elevated above preexercise levels. These results suggest that the postexercise reductions in AP are due, in part, to reductions in TPR. Furthermore, the reductions in TPR are due, in part, to reductions in SNA. The PEH was not due to reductions in CO because CO remained elevated in the postexercise period. The design of this study did not include a postexercise recording period that was long enough to demonstrate that both SNA and blood pressure had returned to preexercise levels. A design that included monitoring these parameters until they had returned to preexercise baseline levels would have strengthened the results of this investigation.

The reduction in SNA in SHR after a single bout of dynamic exercise is supported in work by Thore´n and colleagues (26, 29). These investigators reported that renal (26) and mesenteric (29) SNA were reduced after prolonged stimulation of the sciatic nerve in SHR. The reduction in SNA may be due to a resetting of the operating point of the arterial baroreflex to a lower pressure (4, 7, 13, 14). It has also been proposed that postexercise sympathoinhibition may be mediated by a facilitation of inhibitory cardiopulmonary reflexes because cardiac afferent blockade attenuated the hypoten-
sive effect of a single bout of dynamic exercise (9), and other investigators (1, 6) have shown that the inhibitory influence of cardiac afferents on the circulation may be enhanced after exercise. The reduction in SNA may be beneficial for individuals with hypertension. For example, an increase in sympathetic activity and/or responsiveness is associated with the development and maintenance of hypertension (3, 19, 27). Furthermore, reductions in sympathetic activity may be important in the prevention of cardiac arrhythmias. It has been shown both experimentally and clinically that increases in sympathetic activity are involved in the development of ventricular fibrillation, a major cause of cardiac sudden death (2, 23–25). Therefore, any intervention that decreases SNA, such as mild-to-moderate dynamic exercise, may contribute to a reduction in AP and help to prevent cardiac arrhythmias. Our findings of a postexercise reduction in SNA support the findings of a number of studies in hypertensive individuals (6, 11).

The postexercise reduction in TPR may be due to the reduction in SNA and a decreased vascular responsiveness to α-adrenergic receptor activation. Recent evidence has shown that a single bout of dynamic exercise significantly attenuated the vasoconstrictor response to phenylephrine in an isolated aortic ring preparation (17) and in the intact conscious rabbit (18) and rat (22, 28). This suggests that the ability of the vasculature to respond to a change in SNA or a sustained catechol-
amine increase after exercise is significantly reduced. Because the vasculature is less responsive to an elevated plasma catecholamine concentration after exercise, a higher level of SNA may be required to maintain AP. However, a single bout of dynamic exercise sufficient to produce postexertional hypertension has been observed in lower postganglionic muscle SNA and plasma norepinephrine concentration (6, 10, 13). These effects could explain the significant postexercise reduction in TPR (6, 8). The reduction in TPR may be beneficial for individuals with hypertension in terms of lowering resting AP and improving overall cardiovascular function. Our findings of a postexercise reduction in TPR support the findings of studies in hypertensive individuals (6, 15).

The postexercise elevation in CO (Fig. 3A) is due to an increase in stroke volume inasmuch as preexercise and postexercise HR values were not different (Fig. 2B). An increased preload and/or myocardial contractility and decreased afterload may contribute to the increase in stroke volume. The elevation in CO may be beneficial for improving overall cardiovascular function. For example, it is generally accepted that there is an excess postexercise oxygen consumption. Therefore, an elevated CO may be required to facilitate this enhanced oxygen consumption. In addition, a postexercise elevation in CO would be beneficial in maintaining tissue perfusion and allowing adequate recovery from the metabolic demands of the exercise. Our findings of a postexercise elevation in CO are consistent with results from hypertensive individuals (6, 15).

In summary, results from this study demonstrate that a single bout of dynamic exercise reduces AP. The new finding is that the decrease in AP was associated with a decrease in SNA and TPR and an increase in CO in the SHR. Our results from hypertensive rats are consistent with previous results obtained from hypertensive individuals. Taken together, these data suggest that the SHR may be a useful and applicable model for understanding PEH in hypertensive individuals.

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