Direct measurement of cardiac sympathetic efferent nerve activity during dynamic exercise

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The autonomic nervous system plays an important role in the regulation of cardiac adaptation during dynamic exercise. Cardiac sympathetic efferent nerve activity during dynamic exercise is a neurogenic response via the autonomic nervous system partly due to cardiac adaptation during exercise. Cardiac sympathetic efferent nerve activity (CSNA) was increased by measuring CSNA during treadmill exercise (speed, 10–60 m/min) for 1 min in five conscious cats. As soon as exercise started, CSNA and heart rate (HR) increased and mean arterial pressure (MAP) decreased; their time courses at the initial 12-s period of exercise were irrespective of the running speed. CSNA increased 168%–297% at 7.1 ± 0.4 s from the exercise onset, and MAP decreased 8–13 mmHg at 6.0 ± 0.3 s, preceding the increase of 40–53 beats/min in HR at 10.5 ± 0.4 s. CSNA remained elevated during the later period of exercise, whereas HR and MAP gradually increased until the end of exercise. After the cessation of exercise, CSNA returned quickly to the control, whereas HR was slowly restored. In conclusion, cardiac sympathetic outflow augments at the onset of and during dynamic exercise even though the exercise intensity is low to moderate, which may contribute to acceleration of cardiac pacemaker rhythm.

Keywords: cardiac vagal efferent; tachycardia; central command; cardiovascular adaptation; arterial baroreflex

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exercise capacity, there was a 10-fold increase in cardiac norepinephrine spillover, which accounted for 9% of the total systemic norepinephrine spillover (12). This result suggests that sympathetic drive to the heart is considerably augmented during the moderate intensity of dynamic exercise. Recently, renal and lumbar sympathetic nerve activities have been measured during dynamic or static exercise in cats (11, 15, 16), rats (6), and rabbits (26). Unlike the delayed response of muscle sympathetic nerve activity in humans, renal and lumbar sympathetic nerve activities were increased rapidly at the onset of treadmill or overground locomotion and voluntary static exercise. Although a species difference in the response of the sympathetic nervous system cannot be neglected, sympathetic outflows to various organs are likely to be controlled separately and differently during exercise. Indeed, it has been shown that skin sympathetic nerve activity starts to increase at the onset of static exercise in humans, dissimilarly to the delayed increase in muscle sympathetic nerve activity (32, 42). Thus cardiac sympathetic outflow cannot be extrapolated from data of muscle sympathetic nerve activity so that it was important for the understanding of neural regulation of the cardiac adaptation during dynamic exercise to directly measure cardiac sympathetic efferent nerve activity (CSNA).

Ninomiya et al. (23, 24) have developed a novel technique for recording CSNA in conscious cats. We found using this technique that CSNA increased during light body movement performed voluntarily, and the increase in CSNA occurred immediately before or simultaneously with the onset of body movement before an increase in HR (14, 24). On the basis of these observations, we hypothesized that sympathetic outflow to the heart is stimulated during whole body dynamic exercise even though the exercise intensity is low to moderate, which in turn contributes to exercise-induced tachycardia. The present study was, therefore, undertaken to 1) directly identify the response in CSNA during treadmill exercise in conscious cats and 2) examine the relative contributions of cardiac sympathetic and parasympathetic outflows responsible for autonomic control of cardiac pacemaker rhythm during dynamic exercise. We directly investigated the first goal using measurements of cardiac sympathetic discharge. The second goal was indirectly assessed from similarity or dissimilarity between the responses in CSNA and HR during exercise, although cardiac parasympathetic outflow was not directly recorded in this study.

METHODS

The present study was conducted in five cats weighing between 2.5 and 3.5 kg in accordance with the “Guiding Principles for the Care and Use of Animals in the Fields of Physiological Sciences” approved by the Physiological Society of Japan and by the Institutional Animal Experimental Committee, Hiroshima University Faculty of Medicine.

Implantation surgery. All animals were trained at least over 5 wk (4 days/wk) to get accustomed to running on a motor-driven treadmill. The training session consisted of five exercise bouts for 1–3 min at the running speed of 10–60 m/min at 0% grade. After the training was completed, surgery for implantation of recording electrodes and catheters was performed. After an overnight fast, atropine sulfate (0.1–0.2 mg/kg im) was given as a preanesthetic medication to reduce salivation and bronchial secretion. The cats were anesthetized by inhalation of a gas mixture of 4% halothane (Fluothane, Takeda Chemical Industries; Osaka, Japan), N2O (0.5 l/min), and O2 (1.0 l/min). Each cat was intubated with an endotracheal tube. ECG, HR, rectal temperature, and respiration were continuously monitored during surgery. To maintain an appropriate level of surgical anesthesia, the concentration of halothane was adjusted in a range of 1.0–2.5% if an increase in HR and/or respiration and/or withdrawal of the limb in response to noxious pinch of the paw and/or a surgical procedure was observed. Rectal temperature was maintained at 37–38.5°C with a heating pad. Polyvinyl catheters were inserted into the left external jugular vein for administration of drugs and into the left carotid artery for measurement of AP. After the cat was placed in the lateral position under anesthesia, a left thoracotomy was performed. The third or fourth intercostal space was opened. A branch of the inferior cardiac nerve that innervated the left side of the heart was carefully isolated from surrounding connective tissue near the aortic arch with aid of an operating microscope (OME, Olympus Optical; Tokyo, Japan). The left inferior cardiac nerve contained no vagal nerve component (23). A pair of silver wire electrodes (bare diameter, 0.1 mm) insulated with Silastic silicone tubing (SF3M-1050, SF Medical; Hudson, MA) was carefully wound on the cardiac nerve branch for bipolar recording of cardiac sympathetic discharge, and the electrode-nerve complex was covered with silicone gel. The cardiac nerve was left intact. Another silver wire electrode was placed as a ground electrode under the skin of the back. The lead wires of the recording electrodes and arterial and venous catheters were tunneled subcutaneously and were brought to the exterior in the intrascapular region. During the exercise experiments, the wires were connected to a recording instrument by a light lead cable.

After the implantation surgery was finished, antibiotics (20,000 U/kg im benzylpenicillin potassium) were injected, and the cats were housed in their cages and warmed with a heating pad and an external lamp. They were able to stand up, walk, and eat food on the next day after the surgery. Antibiotics (benzylpenicillin benzathine, Bicillin tablets, 100,000 units, Banyu Pharmaceuticals; Tokyo, Japan) were orally given for 5–7 postoperative days.

Recording of CSNA. The original CSNA was amplified by a differential preamplifier (S-0476, Nihon Kohden; Tokyo, Japan). The amplified output was fed into a bandpass filter between 150 and 3,000 Hz. Sympathetic discharges were converted into standard pulse trains using a digital technique that detected the peaks of the original neural spikes (17, 23). The pulse trains were integrated continuously with the aid of a digital integrator to reduce salivation and bronchial secretion. The cats were anesthetized by inhalation of a gas mixture of 4% halothane (Fluothane, Takeda Chemical Industries; Osaka, Japan), N2O (0.5 l/min), and O2 (1.0 l/min). Each cat was intubated with an endotracheal tube. ECG, HR, rectal temperature, and respiration were continuously monitored during surgery. To maintain an appropriate level of surgical anesthesia, the concentration of halothane was adjusted in a range of 1.0–2.5% if an increase in HR and/or respiration and/or withdrawal of the limb in response to noxious pinch of the paw and/or a surgical procedure was observed. Rectal temperature was maintained at 37–38.5°C with a heating pad. Polyvinyl catheters were inserted into the left external jugular vein for administration of drugs and into the left carotid artery for measurement of AP. After the cat was placed in the lateral position under anesthesia, a left thoracotomy was performed. The third or fourth intercostal space was opened. A branch of the inferior cardiac nerve that innervated the left side of the heart was carefully isolated from surrounding connective tissue near the aortic arch with aid of an operating microscope (OME, Olympus Optical; Tokyo, Japan). The left inferior cardiac nerve contained no vagal nerve component (23). A pair of silver wire electrodes (bare diameter, 0.1 mm) insulated with Silastic silicone tubing (SF3M-1050, SF Medical; Hudson, MA) was carefully wound on the cardiac nerve branch for bipolar recording of cardiac sympathetic discharge, and the electrode-nerve complex was covered with silicone gel. The cardiac nerve was left intact. Another silver wire electrode was placed as a ground electrode under the skin of the back. The lead wires of the recording electrodes and arterial and venous catheters were tunneled subcutaneously and were brought to the exterior in the intrascapular region. During the exercise experiments, the wires were connected to a recording instrument by a light lead cable.

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Experimental protocols. When the cats were in good condition and were able to run on the motor-driven treadmill, the present experiments were started at least 3–4 days after the implantation surgery and conducted for ~6–7 days. On the experimental day, each cat was put into a transparent plastic box (size, 65 × 20 × 35 cm) placed on the treadmill. A
period of >30 min was allowed to establish that the animal was quiescent and that the cardiovascular variables had become stable. To determine the changes in CSNA, HR, and mean AP (MAP) during treadmill exercise and the effects of exercise intensity on their responses, a series of exercise trials was performed in five cats for 1 min at 0° incline with different treadmill speeds (10, 20, 30, 40, 50, and 60 m/min). A rest for 10–30 min between trials of exercise was taken depending on the exercise intensity. When the cats stood quietly, treadmill exercise was started. The belt speed of the treadmill was gradually raised so as not to disturb body trunk posture and limb movements of the animals. It took 6.6 ± 0.3 s for the speed of treadmill to reach from zero to a steady-state level. We observed that all cats began to walk as soon as treadmill was started and that the time lag between the treadmill onset and the start of locomotion seemed to be <1–2 s. At a given treadmill speed, a total of 5–12 trials was performed by the cats. We attempted to randomize the order of the trials as much as possible. To test whether anticipation might evoke the sympathetic and cardiovascular responses at the onset of exercise, a visual and audio cue was given 30 s before the exercise onset by tapping a switch in front of the cats.

**Data and statistical analyses.** AP was measured through the carotid artery catheter connected to a pressure transducer (DPTIII, Baxter; Tokyo, Japan). HR was derived from the AP pulse by a tachometer (model 1321, GE Marquette Medical Systems; Tokyo, Japan). Timings at the start and end of treadmill exercise were manually marked with an electric switch. The CSNA, AP, HR, ECG, and marking signal were simultaneously recorded on an eight-channel pen-writing recorder (Recti-8K, GE Marquette Medical Systems) and stored in a computer with an analog-to-digital converter (MP100, BIOPAC systems; Santa Barbara, CA) at a sampling frequency of 2 kHz. Mean CSNA was obtained by performing a moving average of the CSNA data over neighbouring 2,000 points. Concomitantly, the same original data were acquired at 400 Hz with the other analog-to-digital converter (Cordat II, Data Integrated Scientific Systems; Pinckney, MI) to store the beat-to-beat values of CSNA, HR, MAP, and their corresponding average values over 1 s on a hard disk for off-line analysis.

In the data analysis, the onset and offset of exercise were determined using the marking signal while showing the data of CSNA, HR, and MAP in a given trial of exercise on a computer display screen. The data obtained for >25 s before the onset of exercise were defined as the baseline value. Because the absolute level of CSNA varied among the animals, the average of the preexercise baseline values was defined 100% and the relative percent changes in CSNA from the average baseline value were sequentially calculated before, during, and after treadmill exercise. The absolute changes in HR and MAP from the baseline values were also calculated in the same manner. The changes in CSNA, HR, and MAP were then aligned at the onset of exercise and further averaged over all trials. When the time course and magnitude of the responses during exercise among different running speeds were compared, the data obtained at the speeds of 50 and 60 m/min were pooled because some animals did not run at 60 m/min.

The responses in CSNA, HR, and MAP during exercise were statistically analyzed by one-way ANOVA with repeated measures. When a significant *F*-value in the main effect of time was present, a Dunnett post hoc test was performed to detect the significant difference between mean values obtained in the baseline control and at a given time. For an individual parameter, the effects of the running speed on the initial peak response and the response during the last 20-s period of exercise were examined by a linear regression analysis. The level of statistical significance was *P* < 0.05 in all cases. Data are expressed as means ± SE.

**RESULTS**

**Activation of CSNA during dynamic exercise.** CSNA showed characteristic grouped discharges synchronous with cardiac cycle and respiratory movement (Fig. 1). CSNA markedly reduced on administration of norepinephrine (0.5–1.0 μg/kg iv), and the grouped nerve discharges almost disappeared, as shown in Fig. 1. Intravenous administration of a ganglionic blocker (3 mg/kg hexamethonium bromide) also decreased CSNA remarkably. Both synchronized grouped discharges and the baroreflex-induced inhibition of CSNA were observed over 7–10 days after the implantation surgery. The baseline value of CSNA was 54 ± 12 impulses/s in five cats; HR and MAP were 186 ± 10 beats/min and 103 ± 5 mmHg, respectively.

A typical example of the responses in HR, AP, CSNA, and mean CSNA during exercise at the speed of 40 m/min is represented in Fig. 2. When a visual and audio cue was given as a prediction 30 s before the exercise (as indicated by an arrow), two of five cats frequently took a preparatory posture immediately after the cue, such as standing up from the sitting posture. However, the predictive stimulus induced no significant changes in CSNA, HR, and MAP; slight, brief increases in CSNA and HR were observed over 7–10 days after the implantation surgery. The baseline value of CSNA was 54 ± 12 impulses/s in five cats; HR and MAP were 186 ± 10 beats/min and 103 ± 5 mmHg, respectively.

The same data as shown in Fig. 2 are demonstrated with a faster time sweep in Fig. 3. Before exercise, grouped bursts of CSNA synchronized with the cardiac and respiratory rhythms appeared intermittently. The incidence rate of synchronized grouped bursts of CSNA during exercise was markedly enhanced compared with that before exercise, whereas the magnitude of the synchronized bursts seemed to increase slightly. Immediately after exercise, the incidence rate and magnitude of the bursts of CSNA quickly decreased to the resting levels, although HR and systolic AP remained elevated.

**Time courses of changes in CSNA, HR, and MAP during exercise.** The time courses of the average responses in CSNA, HR, and MAP during treadmill exercise at the speed of 40 m/min are summarized in Fig. 4. CSNA significantly increased at 3 s from the onset of exercise. This increase in CSNA reached the maximum value of 276 ± 50% at 6 s. HR began to increase...
significantly at 7 s from the exercise onset, and the initial peak response (50 ± 10 beats/min) was observed at 11 s. MAP decreased initially by 8 ± 3 mmHg at 6 s and then increased gradually by 24 ± 6 mmHg until the end of exercise. Immediately after the end of exercise, CSNA quickly recovered within 1 s, whereas HR remained elevated for 12 s. It took >30 s for HR to return to near the resting level. MAP decreased to a level above the resting value and was sustained at that level at least for 30 s.

**Effect of running speed on initial and late responses in CSNA, HR, and MAP.** The effect of running speed on the average responses in CSNA, HR, and MAP are compared in Fig. 5. At the initial period of exercise (up to ~12 s from the exercise onset), the time courses of the changes in CSNA, HR, and MAP were quite similar irrespective of the running speed. During the initial period, CSNA reached the peak value of 168–297% with the time interval of 7.1 ± 0.4 s (range, 6.6–8.5 s) from the exercise onset at all running speeds. HR showed an initial increase and MAP showed a transient decrease; the time intervals from the exercise onset to the responses were 10.5 ± 0.4 s for HR (range, 10.0–12.5 s) and 6.0 ± 0.3 s for MAP (range, 5.7–6.2 s), respectively. The increase in CSNA always preceded the increase in HR by 3.5 ± 0.3 s. Thereafter, CSNA remained elevated throughout the exercise, whereas HR and MAP were gradually increased until the end of exercise. The responses of HR and MAP reached the maximum values of 45–73 beats/min and 10–24 mmHg during the last 20-s period of exercise. After the cessation of exercise, CSNA returned quickly to the baseline level with the same time course irrespective of the running speed. However, HR recovered much more slowly than CSNA at all running speeds; the slope of the HR recovery was 2.3–2.9 beats·min⁻¹·s⁻¹ among...
the exercise speeds. On the other hand, MAP decreased to a level above the resting within 10 s after exercise and remained at that level for >20 s.

When the initial peak responses in CSNA, HR, and MAP were plotted against the running speed, the response in CSNA was increased in proportion to the running speed, whereas the responses in HR and MAP were independent of the speed (Fig. 6). On the other hand, all responses of CSNA, HR, and MAP during the last 20-s period (40–60 s from the exercise onset) were dependent on the running speed; the faster the running speed was, the greater the responses were evoked. From these time-course and magnitude data of the cardiac sympathetic and circulatory responses, it appeared that the cardiovascular adaptation at the beginning and during the later period of exercise was induced by different mechanisms.

The effect of running speed on the relationship between the average changes in CSNA and HR before, during, and after exercise is represented in scatter diagrams in Fig. 7. There was a remarkable anticlockwise hysteresis relationship between CSNA and HR. During the initial period of exercise, a rightward shift was abruptly induced on the relationship curves, indicating that an increase in CSNA preceded tachycardia. During the mid to late period of exercise (13–60 s from the onset), both CSNA and HR were elevated. After the end of exercise, a leftward shift was abruptly induced, indicating that a rapid drop in CSNA preceded a decrease in HR. Thereafter, a downward shift was observed, implying a gradual decrease in HR with no changes in CSNA. The

Fig. 2. Responses in HR, AP, CSNA, and mean CSNA during treadmill exercise at speed of 40 m/min. An audio and visual cue signal was given 30 s before the exercise onset as a prediction (indicated by the arrow). *Initial responses in HR, AP, and mean CSNA at the onset of exercise.

Fig. 3. Discharge pattern of CSNA before (A), during (B), and immediately after treadmill exercise (C). The same data of the responses in HR, AP, and CSNA as shown in Fig. 2 are presented with a faster chart speed.
size of the hysteresis curves became greater in proportion to the running speed, although the fundamental characteristics of the curves were the same.

**DISCUSSION**

A role of cardiac sympathetic outflow in regulation of cardiac pacemaker rhythm during dynamic exercise has been indirectly estimated from the response in muscle sympathetic nerve activity during dynamic exercise in humans (33, 34, 40, 41) and the effect of β-adrenergic or muscarinic blockade on the exercise-induced tachycardia in humans and dogs (1, 29). On the basis of these results, it has been proposed that cardiac sympathetic outflow does not increase during low to moderate intensity of dynamic exercise and that the exercise-induced tachycardia at those levels of exercise is predominantly controlled by withdrawal of cardiac parasympathetic nerve activity (29, 30). However, such data gave little information about the dynamic response in cardiac sympathetic outflow that alters from moment to moment during exercise. As another substantial problem, it was difficult to extrapolate cardiac sympathetic outflow from sympathetic nerve activity to a peripheral vascular bed such as skeletal muscles. It was therefore necessary for better understanding of autonomic regulation of the cardiac adaptation to dynamic exercise to directly identify the response of CSNA. We have succeeded for the first time in recording CSNA during treadmill exercise in conscious cats. The major finding of the present work is that cardiac sympathetic nerve discharge increased during whole body exercise in proportion to a running speed of 10–60 m/min. As opposed to the generally considered assumption (29, 30), we propose that cardiac sympathetic outflow is stimulated during dynamic exercise even though the intensity of exercise is low to moderate, in concert with cardiac parasympathetic withdrawal. Furthermore, the time-course analysis of the CSNA response revealed that CSNA rapidly increased at the onset of dynamic exercise, preceding the tachycardia by 3.5 s; it remained elevated throughout the exercise and returned promptly to the control within 1 s immediately after the cessation of exercise. The rapid increase in CSNA at the onset of dynamic

Fig. 4. Time course of the average responses in CSNA, HR, and mean AP (MAP) during treadmill exercise at a speed of 40 m/min. The changes in CSNA, HR, and MAP from the preexercise control levels in an individual trial are aligned at the onset of exercise (time = 0) and then averaged (n = 6 trials). Values are means ± SE.

*Significant difference from the preexercise level (P < 0.05).

Fig. 5. Effects of exercise speed on the average responses in CSNA, HR, and MAP. The time course and magnitude of their average responses around the onset and offset of exercise (as shown by vertical dotted lines) are compared among different speeds (10, 20, 30, 40, and 50–60 m/min).
exercise and its rapid withdrawal after the end of exercise suggest that a central feedforward mechanism (central command) is likely to produce the stimulation of CSNA, which is one of the important causes of tachycardia during dynamic exercise.

Sympathetic efferent nerve discharge to the heart. Ninomiya et al. (23) reported that no action potential was evoked in the left inferior cardiac nerve of the cat when the cervical vagal nerve trunk was electrically stimulated, indicating that the inferior cardiac nerve contains neither vagal efferents nor afferents. Because the cardiac nerve was left intact in this study, it cannot be denied that the CSNA might involve an activity of cardiac sympathetic afferents. However, this possibility is unlikely because CSNA was almost completely inhibited by administration of norepinephrine or hexamethonium. The nerve discharges recorded from the feline inferior cardiac nerve, therefore, are considered to originate from sympathetic postganglionic efferent fibers. We found that the cardiac sympathetic nerve is tonically active in the conscious state, but it is very susceptible to anesthesia (17); its firing rate in mass discharge is relatively high (54 ± 12 impulses/s). Obviously this result indicates an existence of basal cardiac sympathetic outflow in the resting condition of conscious cats. Cardiac sympathetic nerve is also ac-

Fig. 6. Effects of exercise speed on the initial peak values and the last 20-s values of the changes in CSNA (A), HR (B), and MAP (C) during exercise. Left, initial peak values of the changes in CSNA, HR, and MAP at the beginning of exercise plotted against the running speed; right, respective values during the last 20-s period of exercise plotted against the running speed. The relationship between the individual values (○) and running speed was analyzed by a linear regression. When a significant relationship (\( P < 0.05 \)) was observed, the correlation coefficient \( r \) is shown. n.s., Not significant; ■, mean value of the individual data obtained at a given exercise speed. Values are means ± SE.
tive in humans because baseline cardiac spillover of norepinephrine has been observed (9, 12). To assess the effect of baseline cardiac sympathetic outflow on the cardiac pumping function, β-adrenergic blockade has been utilized. Propranolol reduced baseline HR by 8–20% in the human and dog (13, 29, 38) and reduced stroke volume by 16–22% in the dog (1, 38); consequently, propranolol decreased cardiac output by 18–35% (13, 38). With these results taken into consideration, the ongoing discharge of the cardiac sympathetic nerve possesses a substantial influence on both cardiac pacemaker rhythm and ventricular contractility so as to raise HR and stroke volume and thereby cardiac output.

**New explanation for the role of cardiac sympathetic outflow during exercise.** Our novel findings about cardiac sympathetic outflow during dynamic exercise is contradictory to the generally considered assumption that sympathetic outflow to the heart does not increase during the low to moderate intensity of exercise and that exercise-induced tachycardia at those levels of exercise is predominantly controlled by withdrawal of cardiac parasympathetic nerve activity (29, 30). This discrepancy might be explained by a species difference in cardiac parasympathetic and sympathetic balance, because it has been thought that cardiac parasympathetic tone is higher in the human and perhaps in the dog rather than the cat. However, respiratory arrhythmia, which is known to reflect cardiac parasympathetic activity, is usually observed in the conscious cat, as shown in Figs. 1 and 2. As a matter of fact, cardiac parasympathetic nerve activity has been recorded in the decerebrate or chloralose-anesthetized cat (4, 21), indicating that substantial cardiac parasympathetic tone exists in the cat. Therefore, additional factors except the species difference should be taken into account as follows. First, it is fundamentally difficult to extrapolate CSNA from the data of muscle sympathetic nerve activity, because the sympathetic nervous system possesses a widespread regional difference. Second, muscle sympathetic nerve activity was recorded in humans during rhythmic or dynamic exercise with a relatively small muscle mass but not during treadmill exercise with whole body mass utilized in this study. The difference in muscle mass may also affect the response of the sympathetic nervous system. Finally, with respect to the effects of pharmacological autonomic blockade on exercise-induced tachycardia, it cannot be ignored that autonomic blockade shifts baseline HR, which may modify the size of the HR response to exercise. Moreover, it is possible that cardiac sympathetic outflow and its response during exercise are influenced by a given autonomic blockade itself. From these reasons, the data of muscle sympathetic nerve activity and/or the effects of autonomic blockade on the tachycardia are limited as an estimate of the response in cardiac sympathetic outflow during dynamic exercise. Instead, the present evidence obtained by direct measurement of CSNA suggests that not only withdrawal of cardiac parasympathetic nerve activity but also stimulation of CSNA is important for accelerating cardiac pacemaker rhythm and increasing cardiac output as fast as possible, even though the exercise intensity is low to moderate.

**Comparison between the CSNA response and tachycardia.** It has been believed that the HR response to sympathetic nerve stimulation is characterized by slow development with a time constant of 10–20 s (43). If so, the initial tachycardia at the beginning of exercise observed in this study can be hardly explained by the
increase in CSNA, which preceded the increase in HR by 3.5 s. However, it is likely that the development of the response in HR, followed by stimulation of the cardiac sympathetic nerve is much faster than that considered previously, because Mokrane and Nadeau (20) reported that the time constant of the tachycardia obtained by electrical stimulation of the right ansa subclavia or the right stellate ganglion in anesthetized dogs is 2.1 s with an initial delay time of 0.7 s from the onset of sympathetic stimulation. That is, HR is able to respond within 3 s to a sharp increase in sympathetic nerve traffic. The difference in the time constant of the tachycardia may be due to a difference in the stimulation protocol, because Mokrane and Nadeau (20) used an initial brief pulse train at a frequency of 50 Hz followed by pulses at 0.5–4 Hz. The initial train pulses, which resembled the abrupt increase in CSNA at the beginning of exercise, seemed to accelerate the HR response. The initial activation of cardiac sympathetic outflow is, therefore, capable of producing the cardiac acceleration at the onset of dynamic exercise. In the hysteresis relationship between CSNA and HR (Fig. 7), a rightward shift was abruptly induced during the initial period of exercise, indicating that an increase in CSNA preceded tachycardia. It is of interest that the initial trajectory seems to be independent of the running speed.

During the mid to late period of exercise (13–60 s from the onset), CSNA remained elevated, suggesting that the sustained augmentation of CSNA contributes to the tachycardia during the later period of exercise as well (Fig. 7). However, HR tended to increase gradually throughout the exercise, whereas CSNA remained elevated at the initial peak level or decreased slightly from that level (Figs. 4 and 5). Such a gradual increase in HR was also observed during the later period of exercise in cardiac denervated dogs and heart transplant recipients, which was blunted by β-adrenergic blockade (3, 39). Taken together, the excess development of tachycardia during the later period of exercise seems to be mediated by a humoral factor such as circulating plasma epinephrine and/or a progressive withdrawal of cardiac parasympathetic nerve activity.

In contrast to the exercise period, CSNA seems to be less involved in the regulation of HR during the recovery period. HR decayed more slowly after treadmill exercise in cardiac transplant recipients than normal subjects (35), suggesting that the cardiac autonomic nerves control the recovery process of HR. In this study, CSNA returned promptly to the resting level within 1 s after the end of exercise, whereas HR decreased slowly for >30 s (Figs. 4 and 5). The hysteresis relationship between CSNA and HR (Fig. 7) showed a downward shift, indicating a gradual decrease in HR without any changes in CSNA. Thus CSNA seems to be less involved in regulation of HR after dynamic exercise. The higher-frequency component of the power spectrum of R-R interval variability, which is considered as an index of cardiac parasympathetic nerve activity, is depressed during exercise and returns to the control after exercise with the similar time course as that of the HR recovery (37). In agreement with this result, respiratory arrhythmia diminished during exercise and was gradually restored after the end of exercise (Fig. 2). The recovery of HR after exercise is, therefore, more likely to be controlled by a gradual restoration of cardiac parasympathetic nerve activity than by a rapid withdrawal of CSNA.

Neural mechanisms responsible for stimulation of CSNA at the onset of exercise. Several neural mechanisms producing the rapid response in CSNA at the onset of dynamic exercise have been considered (19): 1) a feedback control by the exercise pressor reflex from mechanoreceptors in the exercising skeletal muscles, 2) a feedforward control by central command descending from the higher central nervous system, and 3) an interaction with the arterial baroreflex. The immediate activation of CSNA at the beginning of exercise and the rapid withdrawal of CSNA after the end of exercise (Figs. 4 and 5) are in favor of either the skeletal muscle mechanoreflex or central command as a candidate mechanism. Because static contraction or passive stretch of the hindlimb triceps surae muscle produces an increase of ~50% in CSNA in anesthetized or decerebrate cats (18, 21), the muscle mechanoreceptor reflex is capable of increasing CSNA during exercise. In the case of whole body dynamic exercise, it cannot be denied that the muscle mechanoreflex with a large amount of muscle mass may cause a profound increase in CSNA, as observed in the present study. As another possibility, central command may preset the initial responses in CSNA, HR, and MAP at the onset of dynamic exercise, because the time courses of the initial responses were quite similar irrespective of the running speed (Figs. 5 and 7). When we observed CSNA during voluntary body movement such as walking, turning, and grooming, CSNA started to increase immediately before or simultaneously with the onset of body movement, suggesting that this increase in CSNA is probably produced by central command originating from the higher central nervous system (14, 24). The magnitude of the CSNA increase observed at the onset of dynamic exercise in the present study is the same as that at the onset of voluntary movement. Moreover, renal and lumbar sympathetic nerve activities and AP increased during spontaneous fictive locomotion in decerebrate cats, in which a feedback control from muscle mechanoreceptors and metaboreceptors was not operative (11). We propose, therefore, that the rapid increase in CSNA at the onset of dynamic exercise is more likely to be induced by central command, although a more comprehensive study will be needed to determine which neural mechanism is responsible for stimulation of CSNA during dynamic exercise.

Because MAP decreased concomitantly with the increases in CSNA and HR at the onset of exercise, it is possible that the initial depressor response may elicit increased in CSNA and HR through the arterial baroreflex. From our previous studies (17, 22), the arterial baroreflex sensitivity of CSNA is 1.4–2.3%/mmHg during resting in conscious cats. It has been considered that the sensitivity of the arterial barore-
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Flex is attenuated during exercise or it does not alter during exercise, although the functional curve of the arterial baroreflex is shifted toward a higher level of AP (28). However, it has never been reported that the arterial baroreflex sensitivity is enhanced during exercise. When a baroreflex increase in CSNA due to the initial decline of ~10 mmHg in MAP is calculated from the baroreflex sensitivity of CSNA during resting, it will provide an overestimated value; even so, the estimated increase in CSNA is 14–23%, much less than the initial increase of 168–297% observed at the onset of exercise. Therefore, the arterial baroreflex mechanism elicited by the initial depressor response at the onset of exercise is not sufficient to explain the increase in CSNA. Indeed, when the increase in renal sympathetic nerve activity and pressor response were observed during locomotion in decerebrate cats, the responses were exaggerated or were not influenced by sinoaortic denervation (11, 16, 31).

Recently we observed an interesting finding: that the tachycardia at the onset of spontaneous overground locomotion in decerebrate cats is blunted by sinoaortic denervation, whereas the pressor response becomes exaggerated, implying a modulation of the cardiac component of the arterial baroreflex at the beginning of locomotion (16, 31). We hypothesize that central command may modify the cardiac component of the arterial baroreflex system in the brain stem, which may in turn evoke a rapid increase of CSNA and thereby contribute to the initial tachycardia at the beginning of dynamic exercise in intact animals. As to an interaction between central command and the arterial baroreceptors-HR reflex, it is conceivable that the sensitivity of the baroreflex relationship is blunted or the functional curve of the baroreflex relationship is reset toward a higher level of AP without changes in the baroreflex sensitivity. It has been reported that the resetting of the arterial baroreflex is more likely to occur during exercise (28). However, we feel that the dynamic characteristics of the arterial baroreflex at the initial period of exercise remain to be solved, because the previous studies compared only the baroreflex function before and the later period of exercise.

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