Gadolinium does not blunt the cardiovascular responses at the onset of voluntary static exercise in cats: a predominant role of central command

Kanji Matsukawa, Tomoko Nakamoto, and Atsushi Inomoto

Department of Physiology, Graduate School of Health Sciences, Hiroshima University, Hiroshima, Japan

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Address for reprint requests and other correspondence: K. Matsukawa, Dept. of Physiology, Graduate School of Health Sciences, Hiroshima Univ., Kasumi 1-2-3, Minami-ku, Hiroshima 734-8551, Japan (e-mail: matsuk@hiroshima-u.ac.jp).

The Autonomic Nervous System controls the cardiovascular adaptation at the beginning of voluntary exercise in humans and conscious animals, e.g., rapid increases in heart rate (HR) and arterial blood pressure (AP). There are two fundamental mechanisms responsible for autonomic regulation of the rapid cardiovascular adaptation (19, 30, 44). One is feedforward control by direct descending signal from higher brain centers, which appears in association with the voluntary type of exercise and is able to adjust the cardiovascular system immediately before and at the beginning of exercise. The other is feedback control by activation of mechanosensitive and metabosensitive afferents in the contracting skeletal muscles (termed exercise pressor reflex). Muscle mechanosensitive afferents are activated at once from the start of muscle contraction, whereas stimulation of muscle metabosensitive afferents develops slowly during contraction (20, 21). Therefore, either central command or the muscle mechanoreflex is considered as a candidate mechanism responsible for the initial cardiovascular adaptation at the onset of exercise. We have reported that cardiac and renal sympathetic effenter nerve activities abruptly increase immediately before or at the onset of voluntary muscle excursion, suggesting that central command has a predominant role in regulating the cardiovascular system during exercise (23–25). On the other hand, passive mechanical stretch of skeletal muscle, which is assumed to predominantly stimulate mechanoreceptors, increases HR, AP, and respiration in anesthetized animals and humans (8, 39). Furthermore, passive stretch increases cardiac and renal sympathetic nerve activities (27–29) but decreases cardiac parasympathetic nerve activity (33). Once voluntary exercise starts, it is difficult to discriminate the roles of the two mechanisms on the cardiovascular responses. It remains uncertain as to what extent each of the two mechanisms contributes to the rapid cardiovascular adaptation at the onset of voluntary exercise.

A variety of ion channels sensitive to mechanical stimuli has been identified to serve many physiological functions, such as mechanosensation in specialized sensory cells and local control of blood flow and cellular volume in nonsensory cells (4, 6, 12, 15, 16, 40, 42). Mechanical perturbation influences mechanosensitive ion channels in their conductive state, leading to a change in membrane potential and triggering Ca2+ entry with a subsequent cascade of intracellular reactions (11, 35, 38). Since gadolinium, a trivalent lanthanide, is known to block cation-selective mechanosensitive channels, gadolinium has emerged as a commonly used tool to identify phenomena dependent on cation-selective stretch-activated ion channels (1, 3, 16, 45). Recently, Hayes and Kaufman (18) investigated the effect of gadolinium on the exercise pressor reflex in both decerebrate and chloralose-anesthetized cats to determine the role played by mechanosensitive thin fiber afferents in evoking the exercise pressor reflex. They found that gadolinium attenuated the reflex pressor response to static contraction of the triceps surae muscles and to stretch of calcaneal tendon but had no effect on the pressor response to arterial injection of capsaicin. Furthermore, they found that gadolinium attenuated the responses of group III afferents, many of which are mechanosensitive, to both static contraction and to tendon stretch, whereas gadolinium had no effect on the responses of group IV afferents, many of which are metabosensitive, to either static...
contraction or the capsaicin injection. Their findings (18) suggested that mechanical stimuli arising in contracting skeletal muscles contribute to the elicitation of the exercise pressor reflex and that gadolinium might exert its effect on group III skeletal muscle mechanoreceptors by blocking stretch-activated ion channels in vivo animal experiments.

Accordingly, we used gadolinium in this study to determine whether either central command or a muscle mechanoreflex arising from contracting skeletal muscles contributes to the rapid cardiovascular adaptation at the onset of voluntary static exercise in conscious cats. We hypothesized that if gadolinium might blunt the initial cardiovascular adaptation, the muscle mechanoreflex would have a predominant role in evoking the cardiovascular responses at the onset of voluntary static exercise. Otherwise, central command would be responsible for autonomic control of the initial cardiovascular adaptation. To confirm the effect of gadolinium on skeletal muscle receptors, the cardiovascular responses to passive mechanical stretch of a fore- or hindlimb were compared before and after administration of gadolinium in anesthetized cats.

METHODS

The present study was conducted by using ten cats (weighing 3.3 ± 0.3 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. The experimental protocols were approved by the Committee of Research Facilities for Laboratory Animal Science, Natural Science Center for Basic Research and Development, Hiroshima University.

Static Exercise Training

The cats were operantly conditioned to perform static exercise as previously described in detail (5, 9, 22, 24, 26). They were trained to sit quietly in a transparent plastic box (width 35 × height 40 × depth 50 cm) with a small window (width 5 × height 7 cm), extend a forelimb through the window, and press a bar for 10–40 s while maintaining a sitting posture. As long as the cats pressed the bar, a sound of a buzzer was emitted as an audiofeedback. If the animal completed static exercise, food was given as a reward. The training was conducted over a period of 2–4 mo (5 days/wk).

Implantation Surgery

After the training procedure was completed, surgery was conducted to implant catheters. After an overnight fast, atropine sulfate (0.1–0.2 mg/kg im) was given as a preanesthetic drug to reduce salivation and bronchial secretion. Anesthesia was introduced by inhalation of a mixture of 4% halothane (Fluothane, Takeda Chemical Industries, Osaka, Japan), N2O (0.5 l/min), and O2 (1.0 l/min), and an endotracheal tube was inserted. Subsequently, the cats inhaled the halothane-N2O-O2 mixture through the endotracheal tube. ECG, HR, rectal temperature, and respiration were continuously monitored. To maintain an appropriate level of surgical anesthesia, the concentration of halothane was usually present in a range of 1.0–1.5% but was increased to 2.0–2.5% if an increase in HR and/or respiration and/or withdrawal of a limb in response to noxious pinch of the paw and/or a surgical procedure was observed. Rectal temperature was maintained at 36.5–37.5°C with a heating pad. Polyethylene catheters were inserted into the left external jugular vein to administer drugs and into the left carotid artery to measure AP. The arterial and venous catheters were tunneled subcutaneously and brought to the exterior in the interscapular region. After implantation surgery was completed, antibiotics (benzylpenicillin potassium, 20,000 U/kg im) were injected, and the cats were housed in their cages. Antibiotics (benzylpenicillin benzathine, Bicillin tablets, 100,000 U, Banyu Pharmaceutical, Tokyo, Japan) were orally given for 5–7 postoperative days.

Data Measurement

AP was measured through the carotid artery catheter connected to a pressure transducer (DPTIII, Baxter, Tokyo, Japan). Systolic AP (SAP), mean AP (MAP), and diastolic AP (DAP) were calculated every pulse. HR was derived from AP pulse by a tachometer (model 1321, GE Marquette Medical Systems, Tokyo, Japan). The actual force that the cats applied to the bar was measured with strain gauges (HG-2N, 120, Kyowa Electronic Instruments, Tokyo, Japan) affixed on the bar. The onset and offset of static exercise were defined from the force development. Timing at the start of forelimb movement was manually marked with an electric switch. AP, HR, force, and the timing signal for the start of forelimb movement were simultaneously recorded on an eight-channel pen-writing recorder (8M14, GE Marquette Medical Systems) and were also stored in a computer via an analog-to-digital converter (MP100, BIOPAC Systems, Santa Barbara, CA) at a sampling frequency of 400–500 Hz.

Experimental Protocols

Voluntary static exercise in conscious cats. When the cats were in good condition and were able to perform static exercise voluntarily, the experiments were conducted. On a day of the experiments, each cat was put into the transparent plastic box. A period of more than 30 min was allowed to establish that the animal was quiescent and the cardiovascular variables became stable. When sitting quietly, the cat voluntarily extended the forelimb through the window and pressed the bar while maintaining the sitting posture. HR, AP, and force applied to the bar during voluntary static exercise were measured. A typical example of the data during voluntary static exercise is shown in Fig. 1. The increase in HR at the onset of exercise lasted for about 10 s, and the HR then returned to the control level. After a total of 40 static exercise trials in four cats were repeatedly performed and the cardiovascular responses to exercise to exercise were identified, gadolinium was intravenously injected. Then a total of 46 static exercise trials [n = 14 (at 1–10 min), n = 15 (at 11–20 min), and n = 17 (at 21–30 min after injection of gadolinium)] were repeatedly evoked until 30 min following administration of gadolinium, and the cardiovascular responses to voluntary static exercise were identified in the presence of gadolinium. The duration of voluntary static exercise performed before and after gadolinium was 18 ± 0.4 s. As a time control, static exercise (n = 75 trials) was repeatedly evoked for more than 30 min in the absence of gadolinium in five cats, of which two were used in the voluntary exercise protocol with gadolinium.

Passive mechanical stretch of a limb in anesthetized cats. Seven cats, most of which had been instrumented with arterial and venous catheters, were anesthetized with pentobarbital sodium (25–40 mg/kg iv or ip). Four of the seven cats were used in the voluntary exercise protocol with gadolinium. Rectal temperature was maintained at 36.5–37.5°C with a heating pad. ECG, AP, HR, rectal temperature, and respiration were continuously monitored throughout the experiments. In two cats, a Doppler blood-flow probe (internal diameter, 2 mm) was implanted on the femoral artery and connected to a Transonic flowmeter (T206, Transonic System) to measure femoral blood flow. Femoral vascular resistance was calculated as a ratio of MAP and femoral blood flow.

The anesthetized cats were placed in the lateral posture with normal joint angles, avoiding any fixation of the body trunk and limbs. Passive stretch of a hindlimb was performed by holding the knee and ankle joints and manually extending the hip and knee joints and dorsiflexing the ankle joint for 1 min. When femoral blood flow was recorded, the contralateral hindlimb was passively stretched. During the hindlimb stretch, the hip and knee joints were extended by 20 ± 5° and 40 ± 9°, respectively, and the ankle joint was dorsiflexed by 32 ± 20°. It is estimated from the changes in joint angles that the
GADOLINIUM AND THE CARDIOVASCULAR RESPONSES TO STATIC EXERCISE

Effect of Gadolinium on the Cardiovascular Responses at the Onset of Voluntary Static Exercise

The effects of gadolinium on the baseline values in HR and AP in conscious cats are summarized in Table 1. Baseline HR, SAP, MAP, and DAP did not change significantly following intravenous injection of gadolinium, except an increase in HR at the 31- to 40-min period. The effect of gadolinium on the initial increases in HR and AP at the onset of voluntary static exercise is exemplified in Fig. 1. In the absence of gadolinium, HR began to increase immediately before a bar was pressed and reached the peak value of 153 beats/min from the control value of 117 beats/min at 1.5 s from the onset of exercise (Fig. 1A). Thereafter, HR returned to the preexercise level, although static exercise was not ended. AP increased from 89 mmHg to 104 mmHg at the onset of static exercise, and the rise in SAP persisted throughout static exercise. Gadolinium did not apparently affect the initial increases in HR and AP at the onset of static exercise.

Table 1. Baseline changes in HR, SAP, MAP, and DAP after administration of gadolinium

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>1–10 min</th>
<th>11–20 min</th>
<th>21–30 min</th>
<th>31–40 min</th>
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<tr>
<td>Conscious cats</td>
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<td>151±22</td>
<td>168±21</td>
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<td>SAP, mmHg</td>
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<td>70±7</td>
<td>73±5</td>
<td>72±5</td>
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<tr>
<td>Anesthetized cats</td>
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<td>194±16</td>
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<tr>
<td>HR, beats/min</td>
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<td></td>
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<tr>
<td>SAP, mmHg</td>
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<td>125±6</td>
<td>130±6</td>
<td>134±6*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
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<td>103±5</td>
<td>106±5</td>
<td>109±4</td>
<td>113±6*</td>
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<tr>
<td>DAP, mmHg</td>
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<td>82±5</td>
<td>85±5</td>
<td>89±5</td>
<td>91±6*</td>
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</tbody>
</table>

Values are means ± SE; n, number of cats. HR, heart rate; SAP, systolic arterial blood pressure; MAP, mean arterial blood pressure; DAP, diastolic arterial blood pressure. *P < 0.05, significant difference from control value before administration of gadolinium.
which was 0.57 ± 0.14 kg before gadolinium, tended to reduce following gadolinium. When a comparison is made of the initial increases in HR and MAP and the peak force before and at 21–30 min after injection of gadolinium (Fig. 3), the magnitudes of the increases in HR and MAP were the same before and after gadolinium, whereas the peak force decreased to 65% of the level before gadolinium. No significant effect of gadolinium on the increases in HR and MAP was confirmed by statistically analyzing the grouped data over exercise trials at each of the four periods before and after gadolinium. Essentially, the increases in HR and MAP were the same throughout the period examined, and the peak force was not deteriorated.

As time control of the data, the increases in HR and MAP and the peak force at the onset of static exercise were repeatedly measured for more than 30 min in the absence of gadolinium (n = 5 cats). As a matter of fact, the increases in HR and MAP were the same throughout the time period, and the peak force was not deteriorated (Figs. 2 and 3).

**Effect of Gadolinium on the Cardiovascular Responses During Mechanical Stretch of a Limb**

The effects of gadolinium on the baseline values in HR and AP in anesthetized cats are summarized in Table 1. Baseline HR, SAP, MAP, and DAP did not change significantly following intravenous injection of gadolinium in the anesthetized condition, as well as the conscious condition, except an increase in AP at the 31- to 40-min period. Figure 5 exemplifies the effects of gadolinium on the reflex increases in HR and AP in response to passive mechanical stretch of a fore- or hindlimb. HR increased from 217 to 227 beats/min during passive stretch of a forelimb; SAP increased from 129 to 159 mmHg during the passive stretch. The reflex increases in HR and AP were also produced during passive mechanical stretch of a hindlimb. Gadolinium obviously blunted the reflex responses in HR and AP during passive stretch of either forelimb or hindlimb (Fig. 5).
The time course of the average increases in HR and MAP to passive mechanical stretch of a forelimb or hindlimb following administration of gadolinium is shown in Fig. 6. Before gadolinium, passive mechanical stretch of either limb significantly increased HR and MAP (HR, 17 ± 5 beats/min for forelimb and 19 ± 5 beats/min for hindlimb; and MAP, 22 ± 3 mmHg for forelimb and 30 ± 5 mmHg for hindlimb). These cardiovascular responses to passive mechanical stretch were significantly blunted by gadolinium. These increases in HR and MAP in response to passive stretch of either limb. *P < 0.05, significant difference before and after gadolinium.

Fig. 4. The time courses of the average changes in HR and MAP during voluntary static exercise are compared among the 4 periods before and after gadolinium. The grouped data were obtained over exercise trials at each period. Gadolinium did not significantly affect the time courses of the increases in HR and MAP during static exercise.

Fig. 5. Responses in HR and AP during passive mechanical stretch of a forelimb (A) or hindlimb (B) before and 21–26 min after intravenous administration of gadolinium in an anesthetized cat. The increases in HR and AP during passive stretch of either limb were blunted by gadolinium.

Fig. 6. The average increases in HR and MAP during passive stretch of a forelimb or hindlimb before and over a period of 40 min after intravenous administration of gadolinium. Gadolinium significantly blunted the increases in HR and MAP in response to passive stretch of either limb. *P < 0.05, significant difference before and after gadolinium.
cantly and progressively blunted by gadolinium. At 21–30 min after gadolinium, the increase in HR in response to passive mechanical stretch of either limb was decreased to 50–54% of the control response before gadolinium, and the rise in MAP was decreased to 60–73% of the control response (Fig. 7).

**Effect of Gadolinium on the Femoral Blood Flow Response During Hindlimb Mechanical Stretch**

Femoral blood flow decreased to 6.6 ± 1.1 ml/min during passive stretch of the contralateral hindlimb from the control value of 7.5 ± 1.8 ml/min in two anesthetized cats; calculated femoral vascular resistance increased by 28% (from 15 ± 5 to 19 ± 6 mmHg·ml⁻¹·min). The increase in femoral vascular resistance, which was thought to be induced by the muscle mechanoreflex due to the passive stretch, was virtually abolished by administration of gadolinium; femoral vascular resistance did not change during hindlimb passive stretch (from 20 ± 6 to 20 ± 6 mmHg·ml⁻¹·min at 21–30 min after gadolinium and from 17 ± 6 to 17 ± 5 mmHg·ml⁻¹·min at 31–60 min after gadolinium).

**DISCUSSION**

We have studied the effect of gadolinium, a blocker of stretch-activated ion channels, on the increases in HR and MAP at the beginning of voluntary static exercise in conscious cats to understand whether either central command or muscle mechanoreflex played a major role in the initial cardiovascular adaptation during static exercise. Although gadolinium blocked stretch-activated ion channels and thereby attenuated the muscle mechanoreflex responses to passive stretch of a fore- or hindlimb in anesthetized cats, gadolinium did not blunt the initial increases in HR and MAP at the beginning of voluntary static exercise. We inferred from the present findings that the initial cardiovascular adaptation during voluntary static exercise was induced predominantly by central command descending from higher brain centers but not by the muscle mechanoreflex, at least in the presence of gadolinium.

**Limitations**

Several potential limitations are involved in this study. The finding that gadolinium did not affect the initial cardiovascular responses during voluntary static exercise in conscious cats needed careful consideration. First of all, the size of central command might be altered in the course of the experiments. Since the peak tension during static exercise reduced ~35% following gadolinium, a greater activation of central command may have occurred during exercise in the presence of gadolinium and may elicit greater responses in HR and MAP. If so, the present findings do not always imply the major role of central command in the initial cardiovascular adaptation during static exercise in the normal condition. However, augmented central command may not be sufficient to produce full force development if any. Furthermore, if there is an occlusive nonlinear summation of the cardiovascular responses between central command and muscle mechanoreflex, it is difficult to clarify a role of one mechanism by a simple destructive intervention to interrupt the other mechanism. These possibilities remain to be solved. Second, since the number of the conscious cats used in the voluntary exercise protocol was small, the obtained results were lacking in statistical power. However, the same tendency that gadolinium had no effects on the responses in HR and MAP during voluntary exercise was observed in all cats. In addition, when analyzing the changes in MAP and HR over 14–40 exercise trials at each period, we confirmed no significant effect of gadolinium on the magnitude and time course of the cardiovascular responses (Fig. 4). Taken together, it is unlikely that the insignificant effect of gadolinium on the increases in HR and MAP during voluntary static exercise was derived from the small sample size. Third, the maximal voluntary force that the cats could produce during static exercise was uncertain. The peak force during static exercise in conscious cats corresponded to ~17% of their body weight. Since the maximally developed force was nearly 1.0 kg in the present and previous studies (5, 9, 24, 26), the cats seemed to produce ~60% of the maximal voluntary force at the most, and the intensity of static exercise appeared mild or moderate. Thus the exercise intensity might be insufficient to initiate the muscle mechanoreflex, the contribution of which remains to be studied with a higher intensity of static exercise. Fourth, it is possible that plasma concentration of free gadolinium ions might not be enough to affect mechanosensitive receptors in skeletal muscle, because gadolinium may be bound with negatively charged ions in plasma and become inactive (3). Moreover, Hayes and Kaufman (18) noticed that the effect of intraarterially injected gadolinium on the cardiovascular responses during static con-

Fig. 7. Comparison in the increases in HR and MAP during passive stretch of a forelimb or hindlimb before and 21–30 min after intravenous administration of gadolinium. Gadolinium significantly blunted the increases in HR and MAP in response to passive stretch of either limb. *P < 0.05, significant difference before and after gadolinium.
traction and mechanical tendon stretch peaked 60 min after the injection. In this study, the effect of gadolinium on the cardiovascular responses during static exercise was examined for 30 min after administration of gadolinium in most cats, because it was difficult for the cats to perform voluntary static exercise repeatedly over a longer period. For these reasons the effect of gadolinium on muscle mechanosensitive receptors might not be developed fully within the observation period. However, such a possibility seems unlikely because the same dose of gadolinium significantly attenuated the increases in HR and MAP in response to passive stretch of a fore- or hindlimb in the anesthetized condition. Furthermore, if gadolinium may inhibit primary (group Ia) and secondary (group II) afferent activity from muscle spindles, stretch reflex will be attenuated by gadolinium, leading to decreased force development during static exercise. Activity of group Ia and II spindle afferents of a finger extensor muscle is known to show increased firing during voluntary isometric contraction in humans (7, 37). In this study the peak tension during voluntary static exercise was gradually attenuated following gadolinium. Gadolinium administered systemically in the present study seemed effective on muscle mechanosensitive afferents.

No Significant Effects of Gadolinium on the Baseline Hemodynamics

Since arterial baroreceptors in the cardiovascular system are mechanosensitive and spontaneously active, gadolinium may influence mechanoelectrical transduction in arterial baroreceptors. Indeed, gadolinium inhibited mecanoelectrical transduction in rabbit and cat carotid sinus baroreceptors in the vascularly isolated in vivo preparation (13, 46) and in rat aortic baroreceptor neurons isolated from the nodose ganglia (41), although gadolinium did not block mechanoelectrical transduction of rat aortic baroreceptors in the isolated aortic arch preparation (2). If gadolinium decreases the ongoing activity of arterial baroreceptors, systemic administration of gadolinium may affect baseline hemodynamics; for example, decreased activity in arterial baroreceptors will cause an increase in sympathetic nerve activity and, in turn, raise HR and MAP. However, in this study gadolinium (55 μmol/kg iv) did not alter the baseline values of HR and MAP in both conscious and anesthetized cats, except for the last period of 31–40 min taken after the treatment. Similarly, it has been reported that a smaller dose of gadolinium (~20–40 μmol/kg iv) had no significant effects on baseline hemodynamics in anesthetized cats and dogs; however, a larger dose of gadolinium >75 μmol/kg produced hypotension and myocardial contractility impairment (1, 14, 36). Intravenous injection of gadolinium <55 μmol/kg, therefore, may not affect the ongoing activity of arterial baroreceptors, although previous studies (13, 46) reported that gadolinium (0.1–1 mM ia) inhibited activity of carotid sinus baroreceptors. This discrepancy may be partly explained by a difference in the drug injection method (intraarterial vs. intravenous) and, accordingly, by a difference in concentration of gadolinium in the carotid sinus and aortic regions.

Central Command, But Not the Muscle Mechanoreflex, Is Responsible for the Initial Cardiovascular Regulation at the Onset of Static Exercise

As mentioned before, the size of central command may be augmented following gadolinium. Furthermore, if there is an occlusive summation of the cardiovascular responses between central command and muscle mechanoreflex, it is difficult to estimate a functional role of the muscle mechanoreflex from the sole effect of gadolinium on the cardiovascular responses during exercise. Although these limitations must be taken into account, the present finding that gadolinium did not at all alter the time course and magnitude of the cardiovascular responses at the onset of voluntary static exercise in conscious cats suggests a role of central command in producing the initial cardiovascular adaptation at least in the presence of gadolinium. The central command hypothesis is supported by previous findings from Matsukawa and colleagues (24, 25, 43) demonstrating that cardiac and renal sympathic efferent nerve activity start to increase immediately before or at the onset of static and dynamic exercise, which in turn contributes to tachycardia and pressor response in several seconds. The rapid sympathetic nerve responses are hardly explained by the muscle mechanoreflex. Momen et al. (31, 32) recently reported that a 15-s bout of evoked static muscle contraction by percutaneous electrical stimulation increased renal vascular resistance in humans, suggesting that muscle mechanoreflex engagement was responsible for the increase in renal vascular resistance. Taken together, the muscle mechanoreflex may not work on the whole vascular system but may affect the renal vascular bed particularly. This is in agreement with an increase in renal sympathetic nerve activity at the onset of static contraction or during passive mechanical stretch of skeletal muscle in anesthetized cats, which caused renal vasoconstriction (27, 28).

An influence of conditioning and/or learning on the autonomic nerve and cardiovascular responses during voluntary static exercise might be involved, because the cats were operantly trained for a long period to perform static exercise. To consider this issue, we compared the responses in renal sympathetic nerve activity, HR, and MAP during static exercise to their responses at the beginning of natural body movement, such as spontaneous postural changes, walking, and grooming (23, 24). The magnitude and time course of the increases in renal sympathetic nerve activity, HR, and MAP during static exercise were comparable with those during natural body movement. Furthermore, a buzzer sound emitted as audiofeedback in exercise training did not evoke any significant changes in renal sympathetic nerve activity, HR, and MAP. An influence of conditioning and/or learning in association with exercise training is unlikely to affect the autonomic nerve and cardiovascular responses during static exercise. We feel that central command, generated for feedforward regulation of the cardiovascular system in association with voluntary exercise in daily life, also occurs immediately before or at the onset of voluntary static exercise.

Central command has an important role not only in determining sympathetic outflows at the beginning of voluntary static exercise but also in interacting with the arterial baroreflex circuit in the brainstem. Matsukawa and colleagues (22, 26, 34) have recently provided clear evidence that central command acts upon the arterial baroreflex circuit within the brainstem and modulates its central property at the start of static exercise. The baroreflex bradycardia elicited by aortic nerve stimulation was blunted immediately before static exercise in conscious cats, even in the absence of muscular exertion, and at the onset of spontaneous muscle contraction in decerebrate cats; in contrast, the depressor response to aortic nerve stimulation was
not affected by static exercise (22, 34). It is likely that central command inhibits selectively the cardiac component of the arterial baroreflex at the onset of exercise, which, in turn, induces an abrupt increase in HR. Central command, therefore, has a predominant role in interacting with the cardiac limb of the arterial baroreflex circuit in the brainstem.

**Stimulation of Mechanosensitive Afferents Causes Increases in HR and MAP**

The present finding that gadolinium attenuated the reflex increases in HR and MAP in response to passive stretch of either forelimb or hindlimb in the anesthetized condition is in good agreement with the previous study by Hayes and Kaufman (18) demonstrating that gadolinium attenuated the cardiovascular responses during tendon stretch of the hindlimb triceps surae muscle in anesthetized or decerebrate cats. They also found that gadolinium attenuated the responses of group III afferents from the triceps surae muscle to tendon stretch, suggesting that gadolinium might exert its effect on group III skeletal muscle mechanoreceptors by blocking stretch-activated ion channels (18). Taken together, passive mechanical stretch of a forelimb as well as a hindlimb stimulates muscle mechanosensitive receptors, which is able to cause significant increases in HR and MAP in the anesthetized or decerebrate condition.

It is surprising that gadolinium did not attenuate the cardiovascular responses during voluntary static exercise in conscious cats, because the muscle mechanoreflex caused the cardiovascular and autonomic nerve responses in the anesthetized or decerebrate condition. Indeed, passive stretch of the hindlimb triceps surae muscle increased HR by 6–11 beats/min and MAP by 14–46 mmHg in anesthetized cats (27–29, 39) or decerebrate cats (33); passive stretch of the forelimb triceps brachii muscle increased HR by 16 beats/min and MAP by 38 mmHg in anesthetized cats (17). Moreover, passive stretch increased cardiac sympathetic efferent nerve activity by ~40–50% (29, 33) and renal sympathetic efferent nerve activity by ~20% (27, 28) in anesthetized or decerebrate cats and decreased cardiac vagal efferent nerve activity by ~30% (33). Since the cardiovascular variables and autonomic nerve activities responded depending on the extent of passive muscle stretch, some muscle mechanoreflex-induced responses would be expected during voluntary static exercise, even though the exercise intensity appeared mild or moderate. Gadolinium, however, did not blunt the cardiovascular responses at the onset of voluntary static exercise in this study. Thus we hypothesize that the muscle mechanoreflex, which can produce the cardiovascular responses in the anesthetized or decerebrate condition, appears to be inhibited in the conscious condition.

In conclusion, gadolinium did not blunt the cardiovascular responses at the beginning of voluntary static exercise in conscious cats, whereas it blunted the reflex cardiovascular responses during passive muscle stretch in the anesthetized condition of the same cats. Therefore, the cardiovascular adaptation at the onset of voluntary exercise in conscious cats is induced by feedforward control due to central command but not by feedback control due to the muscle mechanosensitive reflex. Furthermore, gadolinium can be used as a tool for identifying the reflex component originated from muscle mechanosensitive afferents stimulated during exercise.

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