Muscle mechanosensitive reflex is suppressed in the conscious condition: effect of anesthesia

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Matsukawa K, Nakamoto T. Muscle mechanosensitive reflex is suppressed in the conscious condition: effect of anesthesia. J Appl Physiol 104: 82–87, 2008. First published October 25, 2007; doi:10.1152/japplphysiol.00938.2007.—To test the hypothesis that a muscle mechanosensitive reflex is suppressed in the conscious condition, we examined the effect of anesthesia on the cardiovascular responses to passive mechanical stretch of the hindlimb triceps surae muscle in six conscious cats. The triceps surae muscle was manually stretched for 30 s by extending the hip and knee joints and subsequently by dorsiflexing the ankle joint; the lateral gastrocnemius muscle was lengthened by 19 ± 2.6 mm. Heart rate (HR) and mean arterial blood pressure (MAP) did not change significantly during passive stretch of the muscle in the conscious condition. At 10–40 min after intravenously administering pentobarbital sodium (20–25 mg/kg), the identical passive stretch of the triceps surae muscle was able to induce the cardiovascular responses; HR and MAP were increased by 14 ± 1.3 beats/min and 14 ± 1.4 mmHg, respectively, and the cardiovascular responses were sustained throughout the passive stretch. In contrast, stretching skin on the triceps surae muscle evoked no significant changes in HR and MAP in the anesthetized condition. When anesthesia became light 40–90 min after injection of pentobarbital and the animals started to show spontaneous body movement, the cardiovascular response to passive muscle stretch tended to be blunted again. It is therefore concluded that passive mechanical stretch of skeletal muscle is capable of evoking the reflex cardiovascular response, which is suppressed in the conscious condition but exaggerated by anesthesia.

Muscle mechanosensitive receptors; mechanical stretch of skeletal muscle; cardiovascular response; pentobarbital anesthesia; conscious cats

NEURAL CONTROL OF THE CARDIOVASCULAR system during exercise is accomplished by feedback control from group III and IV thin fiber afferents in contracting skeletal muscles (termed exercise pressor reflex) as well as feed-forward control from the higher brain centers (termed central command) (25, 34). Group III muscle afferent fibers are mainly mechanosensitive and activated at once from the start of muscle contraction, whereas group IV muscle afferent fibers are mainly metabosensitive and slowly activated during contraction (10–12). Passive mechanical stretch of skeletal muscle causes stimulation of muscle mechanoreceptors, which increases heart rate (HR), arterial blood pressure (AP), and plasma epinephrine in anesthetized or decerebrate cats and rats (6, 21, 28, 30, 31). Direct assessment of autonomic outflows has revealed that passive muscle stretch increases cardiac and renal sympathetic nerve activities and decreases cardiac parasympathetic nerve activity (22, 23, 27), suggesting a possible role of the muscle mechanosensitive reflex in autonomic regulation of the cardiovascular adaptation during voluntary exercise. However, it was important to identify the role of the muscle mechanosensitive reflex in the cardiovascular adaptation, apart from the muscle metabosensitive reflex and central command.

Gadolinium, a trivalent lanthanide blocking cation-selective mechanosensitive channels, has emerged as a commonly used tool to identify phenomena dependent on stretch-activated ion channels (1, 2, 5, 36). Gadolinium blunted the renal sympathetic and cardiovascular responses to static muscle contraction and passive stretch of the triceps surae muscle in anesthetized or decerebrate cats and rats (7, 13, 18, 28, 30). Hayes and Kaufman (7) found that gadolinium attenuated activity of group III muscle afferents during static muscle contraction in anesthetized or decerebrate cats, suggesting that mechanical stimuli in the contracting skeletal muscles contributes to the elicitation of the exercise pressor reflex and gadolinium might exert its effect on group III skeletal muscle mechanoreceptors by blocking stretch-activated ion channels. Recently, our laboratory has examined using gadolinium whether the muscle mechanoreflex contributes to the cardiovascular adaptation at the onset of voluntary static exercise in conscious cats (18). If gadolinium might blunt the initial cardiovascular adaptation, the muscle mechanoreflex would have a predominant role in evoking the cardiovascular response at the onset of voluntary static exercise. Otherwise, central command would be responsible for autonomic control of the initial cardiovascular adaptation. Gadolinium did not blunt the cardiovascular response during voluntary static exercise, suggesting that the muscle mechanoreflex may not have a predominant role in evoking the cardiovascular adaptation during exercise (18). On the other hand, because gadolinium reduced force development during static exercise, central command may be augmented following gadolinium and a role of the muscle mechanoreflex on the cardiovascular response during exercise in the absence of gadolinium may not be ruled out (18). Nevertheless, the insignificant effect of gadolinium on the cardiovascular responses during voluntary static exercise was surprising because passive stretch of skeletal muscle induced the substantial sympathetic nerve and cardiovascular responses in anesthetized or decerebrate animals.

To explain the discrepancy, we hypothesized that the muscle mechanoreflex, which was able to elicit the cardiovascular response in the anesthetized or decerebrate condition, was suppressed in the conscious condition. This hypothesis was supported by the previous results that passive stretch of the triceps surae muscle evoked weak or insignificant changes in...
HR and mean AP (MAP) in humans (3, 32). The purpose of this study was to examine the augmenting effect of anesthesia on the cardiovascular response induced by the muscle mechanoreflex during passive mechanical stretch of the hindlimb triceps surae muscle in conscious cats.

**METHODS**

The present study was conducted using six cats weighing 3.3 ± 0.4 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.

**Implantation surgery.** Sterile surgery was performed 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. The cats were placed in a plastic box, and 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). Subsequently, an endotracheal tube was inserted, and the cats inhaled the halothane-N2O-O2 mixture through the endotracheal tube. Electrocardiogram (ECG), HR, rectal temperature, and respiration were continuously monitored. To maintain an appropriate level of surgical anesthesia, the concentration of halothane was usually preset 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 for administering drugs and into the left carotid artery for measuring AP. The arterial and venous catheters were tunneled subcutaneously and brought to the exterior in the interscapular region. After implantation surgery was finished, 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.

**Experimental protocols.** We trained the cats to remain quiet when holding them in the lateral posture and grasping the knee and ankle by hand with keeping normal joint angles, avoiding any fixation of the body trunk and limbs. Passive mechanical stretch of the triceps surae muscle of each hindlimb was performed by manually extending the hip and knee joints and subsequently by dorsiflexing the ankle joint for 30 s. The hip and knee joints were extended by 13 ± 2.9° and 40 ± 4.9°, respectively, and the ankle joint was dorsiflexed by 17 ± 4.2°. In this study we did not isolate any tendon and did not measure muscle tension during passive stretch to allow the animals to recover from anesthesia. Because the triceps surae muscle was gradually stretched at a slow speed not to move the body trunk and not to evoke active contraction, it took ~5 s to fully stretch the muscle. A stretch trial accompanying active contraction was disregarded and was not involved in the data collection. When the change in length of the lateral gastrocnemius muscle was verified by postmortem examination in other 10 cats, it was revealed that the resting muscle length of the lateral gastrocnemius muscle (130 ± 2.9 mm) was not altered by extending the hip and knee joints but was increased to 149 ± 3.4 mm by the subsequent dorsiflexion of the ankle joint, in agreement with previous studies (4, 27). Because the time taken to stretch the triceps surae muscle in this study was greater than that taken in previous studies (6, 7, 21–23, 31), it was possible that the difference in the rate of stretch might affect discharges of group III mechanosensitive afferents and thereby the cardiovascular responses during passive stretch. In fact, HR and MAP increased more slowly at the initial period of passive stretch in the anesthetized condition than those in the previous studies (as shown in Figs. 1, 2, and 4), although the peak values of the cardiovascular responses at the end of passive stretch were the same.

After the cardiovascular responses to passive stretch of the triceps surae muscle were determined, pentobarbital sodium (20–25 mg/kg) was intravenously injected. The animals kept breathing spontaneously. 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 anesthesia. The cardiovascular responses to the same passive stretch of the triceps surae muscle were repeatedly recorded at 10–40 min after administering pentobarbital.

To examine a possible influence of stimulation of cutaneous mechanoreceptors on the passive stretch-induced cardiovascular responses, skin on the triceps surae muscle was maximally stretched by hand. Thereafter the cardiovascular responses during passive mechanical were recorded again 40–90 min after administering pentobarbital, at which the animals started to show spontaneous body movement as a sign of light anesthesia.

**Data measurement.** AP was measured through the carotid artery catheter connected to a pressure transducer (DPTIII, Baxter, Tokyo, Japan). MAP was calculated every pulse. HR was derived from AP pulse by a tachometer (model 1321, GE Marquette Medical Systems).

**Fig. 1.** Responses in heart rate (HR) and arterial blood pressure (AP) to passive mechanical stretch of the left hindlimb triceps surae muscle in the conscious (A), anesthetized (B), and recovery (C) from anesthesia conditions in the same cat. Data in B were taken at 20 min after intravenous administration of pentobarbital sodium (20 mg/kg). Data in C were taken at 60 min after injection of pentobarbital.
Timings at the start and end of passive stretch were manually marked with an electric switch. AP, HR, and the timing signal were simultaneously recorded on an eight-channel pen-writing recorder (8M14, GE Marquette Medical Systems, Tokyo, Japan) and were also stored in a computer via an analog to digital converter (MP100, BIOPACK Systems, Santa Barbara, CA) at a sampling frequency of 400–500 Hz.

Statistical analysis. Passive mechanical stretch of the triceps surae muscle of each hindlimb was performed by manually extending the hip and knee joints and subsequently by dorsiflexing the ankle joint in an individual cat. Because the cardiovascular responses to passive stretch of the triceps surae muscle were virtually similar between both sides, we pooled the responses to passive stretch of the right or left triceps surae muscle and analyzed them together. Then the data in passive stretch trials of the triceps surae muscle were divided into three groups: 1) before \( n = 44 \) trials in 6 cats), 2) at 10–40 min \( n = 68 \) trials in 6 cats), and 3) at 40–90 min after administration of pentobarbital \( n = 20 \) trials in 4 cats). In addition, the responses to passive stretch of skin on the triceps surae muscle were examined in the anesthetized condition \( n = 8 \) trials in 3 cats). The peak values of the cardiovascular responses were compared among the groups by a one-way ANOVA with repeated measures. If a significant main effect was found, a Tukey post hoc test was performed to detect a difference between mean values. The time course data of the cardiovascular responses during passive stretch were also analyzed by an one-way ANOVA with repeated measures. If the main effect of time was significant, a Dunnett post hoc test was performed to detect a difference in the mean values at a given time from the control. The level of statistical significance was defined as \( P < 0.05 \) in all cases. The data are expressed as means \( \pm SE \) in the text and figures.

RESULTS

The baseline values of HR and MAP were 213 \( \pm 11 \) beats/min and 118 \( \pm 9 \) mmHg in the conscious condition, respectively. HR significantly decreased to 198 \( \pm 10 \) beats/min at 10–40 min after injection of pentobarbital, and MAP decreased to 95 \( \pm 5 \) mmHg. When anesthesia became light at 40–90 min after injection of pentobarbital and the cats started to show spontaneous body movement, HR and MAP were 199 \( \pm 11 \) beats/min and 99 \( \pm 7 \) mmHg, respectively. The effect of pentobarbital anesthesia on the reflex cardiovascular responses during passive mechanical stretch of the triceps surae muscle in an awake cat is shown in Fig. 1. HR and AP did not respond to passive stretch of the triceps surae muscle in the conscious condition before anesthesia. However, they considerably increased in response to the same passive stretch at 20 min after injection of pentobarbital. The increases in HR and AP became smaller thereafter, when anesthesia became light at 60 min after injection of pentobarbital.

The time courses of the average responses in HR and MAP during passive stretch of the triceps surae muscle are compared before and at 10–40 min after injection of pentobarbital in Fig. 2. Before anesthesia, the change in HR to passive muscle stretch was negligible and the increase in MAP to passive muscle stretch were small \( (4 \pm 0.7 \) mmHg, respectively); both of them were not statistically significant. In contrast, HR and MAP significantly increased by 14 \( \pm 1.3 \) beats/min and 14 \( \pm 1.4 \) mmHg, respectively, in response to passive stretch at 10–40 min after injection of pentobarbital. The increases in HR and MAP were sustained throughout the passive stretch (Fig. 2). As anesthesia became light at 40–90 min after injection of pentobarbital, the increases in HR and MAP in response to passive stretch tended to become smaller (Figs. 1 and 3). To examine a possible role of stimulation of cutaneous mechanoreceptors in evoking the passive stretch-induced cardiovascular response during anesthesia, stretching skin on the triceps surae muscle was conducted by hand (as shown in Fig. 4). Actually, the mechanical stimulation of skin evoked no significant cardiovascular changes.

DISCUSSION

It has been considered that passive manual stretch of the hindlimb triceps surae muscle causes chiefly stimulation of muscle mechanosensitive receptors within the physiological range, which in turn is able to elicit the reflex cardiovascular response via excitation of the sympathetic nervous system. The new finding of the present study was that the muscle mechanosensitive reflex elicited by passive mechanical stretch of the triceps surae muscle was suppressed in the conscious condition compared with the anesthetized condition. In other words, the cardiovascular response elicited by the muscle mechanoreflex was unmasked under anesthesia. The present findings cannot be simply applied to a mechanosensitive reflex during exercise, because passive stretch is not the same as a mechanical event of static muscle contraction. Nevertheless, if the muscle mechanosensitive reflex elicited by muscle contraction during exercise is also suppressed in the conscious condition, the present
finding supports the idea that the initial cardiovascular adaptation during voluntary exercise is not induced by the muscle mechanoreflex but predominantly evoked by central command descending from higher brain centers (15, 16, 18, 33).

We found that the identical passive stretch of the triceps surae muscle failed to increase HR and MAP, whenever the cats were conscious. Passive limb movement in humans also failed to induce the significant cardiovascular responses. Gladwell and Coote (3) and Tokizawa et al. (32) reported that sustained passive stretch of the triceps surae muscle for 1–2 min by dorsiflexion of the foot caused a significant but slight increase in HR of 4–5 beats/min with no significant changes in MAP and forearm blood flow in humans. Middlekauff et al. (24) also reported that rhythmic passive movement of the arm did not change muscle sympathetic nerve activity, HR, and MAP in humans. Nobrega et al. (29) and Williamson et al. (35) reported that passively induced cycling with a tandem bicycle caused a significant but slight shortening in R-R interval. Ishida et al. (9) reported that passive leg movement with rhythmic extension and flexion of the knee joint slightly increased HR by 4 beats/min and did not change stroke volume and cardiac output in humans, although it increased minute ventilation by ∼40% with increases in both tidal volume and respiratory rate. Taking the cardiorespiratory responses to passive stretch of a limb into consideration, it is likely that the muscle mechanosensitive reflex has diverse influences on the cardiovascular system and the respiratory system in the conscious condition. The mechanoreflex has a modest augmenting effect on the respiratory system, whereas it has a slight or insignificant effect on the cardiovascular system. However, it is possible as another diversity that an influence of the muscle mechanoreflex on the vascular system might be different among individual vascular beds, because electrically induced muscle contraction caused an immediate increase in renal vascular resistance, suggesting muscle mechanoreflex engagement (26).

When Ishida et al. (9) studied the effects of sleep on the cardiorespiratory responses to passive leg movement in humans, they found that the increases in minute ventilation, respiratory rate, and HR were more than doubled during stage 3 or 4 of sleep compared with the responses in the conscious state. This interesting result is in good agreement with the present finding that the cardiovascular responses elicited by the muscle mechanoreflex are exaggerated under anesthesia, even though the sleep stage may not be the same as the anesthetized state.

![Fig. 3. Average increases in HR and MAP during passive muscle stretch in the conscious, anesthetized, and recovery from anesthesia conditions in the same 4 cats. Data in the anesthetized condition were taken at 10–40 min after administration of pentobarbital. The data in the recovery from anesthesia condition were taken at 40–90 min after injection of pentobarbital. A significant difference (*P < 0.05) between mean values was obtained between the conscious and anesthetized or recovery conditions.](image)

![Fig. 4. Responses in HR and AP to passive mechanical stretch of either the left triceps surae muscle [in the conscious (A) and anesthetized (B) conditions] or skin on the muscle [in the anesthetized (C) condition] in the same cat. Mechanical stimulation of the triceps surae muscle increased HR and AP, whereas mechanical stimulation of skin evoked no significant cardiovascular changes. Data in B and C were taken at 35–40 min after intravenous administration of pentobarbital (20 mg/kg).](image)
Neural mechanisms for the augmenting effect of anesthesia on the muscle mechanoreflex will be discussed. Because pentobarbital reduces tonic cardiac sympathetic nerve activity (CSNA) and renal sympathetic nerve activity (RSNA) as well as MAP and HR (19, 20), an inhibition of tonic activity of sympathetic vasomotor centers may relate to the augmenting effect of anesthesia on the muscle mechanoreflex. However, this possibility is unlikely because the inhibition of tonic activity of sympathetic vasomotor centers would not enhance but blunt the cardiovascular responses to passive stretch. Next, an inhibition of arterial baroreflex by pentobarbital anesthesia is considered. Pentobarbital temporarily decreases the gains of the arterial baroreceptors-RSNA reflex and the arterial baroreceptors-CSNA reflex (19, 20). If pentobarbital anesthesia inhibits the arterial baroreflexes, which in turn may augment the cardiovascular responses to passive stretch because of a disinhibition of the arterial baroreflex. On the other hand, although chloralose anesthesia did not blunt the arterial baroreflex (19, 20), passive stretch of the triceps surae muscle evoked the unmasked sympathetic nerve and cardiovascular responses in the anesthetized condition with chloralose similar to those with pentobarbital. Thus the inhibition of the arterial baroreflex cannot fully explain the augmenting effect of anesthesia on the muscle mechanoreflex responses. Alternatively, it is possible that descending command from higher centers may interact with the input from muscle mechanosensitive receptors and suppress the mechanoreflex in the conscious condition. This speculation is supported by the results that the muscle mechanoreflex was able to cause the significant cardiovascular and autonomic nerve responses in the unanesthetized and decerebrate condition, whose decerebration was conducted at the precollicular or midcollicular level (6, 17, 27, 30). Moreover, the arterial baroreflex might not be inhibited in the decerebrate condition. A descending inhibitory system from the higher vasomotor centers above the decerebration level, such as the cerebral cortex and/or diencephalon including the hypothalamus, may interact with the input from muscle mechanosensitive receptors in the lower brain stem. The interaction may be inhibited by pentobarbital anesthesia or interrupted by decerebration, which in turn may exaggerate the muscle mechanoreflex.

The present findings cannot be simply applied to a mechanosensitive reflex during exercise, because passive stretch is not the same as a mechanical event of static muscle contraction. In fact, Hayes et al. (8) reported that different populations of group III afferents, which are primarily activated by mechanical stimuli, are excited by static contraction and by stretch. Even though the limitation remains to be solved, it is meaningful to discuss some new insights drawn from the present findings into the cardiovascular regulation during exercise. First, it is speculated that a muscle mechanoreflex during active muscle contraction may be also suppressed in the conscious condition. If so, the initial cardiovascular adaptation during voluntary static exercise will be induced predominantly evoked by central command descending from higher brain centers (15, 16, 18, 33). Second, the present findings imply that a central circuit of the muscle mechanoreflex will be modulated by a given intervention. The muscle mechanoreflex will be facilitated by anesthesia or decerebration. Recently it has been reported that the muscle mechanoreflex is exaggerated in human patients with heart failure and animal model with myocardial infarction (14, 24, 30). Although neural mechanisms responsible for the augmented mechanoreflex with heart failure have not been identified yet, central modulation of the reflex pathway may be involved in concert with peripheral modulation of activity of muscle mechanosensitive afferent fibers.

In conclusion, passive mechanical stretch of skeletal muscle is capable of evoking the reflex cardiovascular responses, which are suppressed in the conscious condition but exaggerated by anesthesia.

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