Cardiovascular and Respiratory Response to Static Exercise in the Newborn Kitten

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ABSTRACT. Muscle contraction produces a reflex increase in blood pressure, heart rate, and minute ventilation in adults. To evaluate the role of this reflex in newborns, we compared the blood pressure, heart rate, and ventilatory responses to static contraction of the hindlimb muscles in sedated newborn and adult felines. The reflex response to muscle contraction was compared with the baroreflex, the chemoreceptor reflex, and the response to maximal stimulation of sciatic nerve afferents. With muscle contraction, newborn systolic blood pressure increased by $8.5 \pm 2.6\%$, which was significantly less than the adult response of $15.9 \pm 1.8\%$ ($p < 0.025$). Heart rate response to muscle contraction was less in newborns compared with adults, increasing by 1.4 ± 0.5 and $8.3 \pm 1.3\%$, respectively ($p < 0.025$). In contrast to heart-rate and blood-pressure responses, ventilatory responses to muscle contraction were similar in both age groups, increasing by 34 ± 20 and $34 \pm 10\%$ in newborns and adults, respectively. With stimulation of sciatic nerve afferents and with hypoxemia, blood pressure and heart rate increased similarly in both newborns and adults. When the baroreflex was elicited, heart rate decreased similarly in both age groups. We conclude that newborn cats have a reduced heart rate and blood pressure response to muscle contraction compared with the adult. We speculate that the postnatal development of this reflex is due to maturation of integrative and modulatory mechanisms in the CNS. (*Pediatr Res* 30: 95-99, 1991)

Blood pressure, heart rate, and minute ventilation increase reflexively during exercise (1). Chemically and mechanically sensitive unmyelinated (C) and lightly myelinated (A- δ) nerves form the afferent limb of this reflex arc (2). Brainstem autonomic centers integrate the afferent input and activate the efferent portion of the reflex arc (3, 4).

Although this reflex has been studied in adult mammals (5), including humans (6, 7), there is no information about the reflex in the immature animal. Clinical studies have shown that the hemodynamic response to exercise is more variable in children than in adults (8). Similarly, the ventilatory response at the onset of exercise is smaller in children for a given hypoxic stimulus (9). These findings suggest that there are important maturational changes in the reflex responses to exercise. We know nothing, however, about the reflex cardiovascular effects of muscle activity in neonates. It is possible that spontaneous muscle activity is an important factor regulating blood pressure in the newborn. However, teleologic thinking leads us to speculate that there is little need for a pressor reflex in immature animals when activity of

large muscle groups is quite disorganized. Therefore, we hypothesized that the reflex response to static muscle contraction would be muted or absent in newborns. To explore this hypothesis, we compared the blood pressure, heart rate, and ventilatory responses to static contraction of the hindlimb muscles in newborns with those in adult felines. In addition, the reflex response to muscle contraction was compared with the baroreflex, the chemoreceptor reflex, and the reflex responses evoked by maximal stimulation of sciatic nerve afferents.

MATERIALS AND METHODS

Surgical preparation. Nine newborn (less than 1 wk of age) and eight adult cats (more than 6 mo of age) were sedated initially with ketamine, 25 mg/kg, s.c. The right external jugular vein, carotid artery, and trachea were cannulated, and α -chloralose, 25 to 50 mg/kg, was given i.v. for additional anesthesia. The carotid line was attached to a Statham P23 pressure transducer (Statham, Cambridge, MA) and the tracheal cannula to a pneumotach for continuous recording of arterial pressure and minute ventilation, respectively. Heart rate was calculated beat to beat with a Gould Biotach (Gould, Inc., Oxnard, CA). Arterial blood gases were measured periodically (Radiometer ABL-3, Radiometer America, Inc., Westlake, OH), and acid-base status was maintained in the normal range with i.v. sodium bicarbonate.

Cats were placed in a Kopf spinal unit (David Kopf Instruments, Tyunga, CA) to stabilize the hips and spine. The left calcaneal tendon was sectioned and attached to a force transducer. The right sciatic nerve was exposed and protected in a pool of 37°C mineral oil.

In half of the animals from each age group, a lumbosacral laminectomy was performed. After exposing the lumbosacral spinal cord and roots, the area was maintained in a 37°C mineral oil pool to prevent drying. Ventral roots L7 and S1 on the left side (muscle efferents) were sectioned, and the distal ends were placed on a stimulating electrode.

The animals without a laminectomy had the left sciatic nerve exposed. All visible branches of the nerve were cut except those supplying the triceps surae muscles. The nerve was placed on a stimulating electrode and protected by a pool of warm mineral oil.

Protocols. After a 30- to 60-min recovery period, during which heart rate, blood pressure, and minute ventilation stabilized, each animal underwent five experimental procedures. Twenty to 30 min elapsed between each procedure to permit the animal to restabilize.

First, we tested the cardiovascular and ventilatory responses to static muscular contraction as well as the reproducibility of these responses. Initially, and 20 min later, the triceps surae muscles were statically contracted for 60 s by electrically stimulating the left sciatic nerve or the L7-S1 ventral roots. The ventral roots were stimulated with current voltages two to three times motor threshold, a frequency of 30 to 40 Hz, and a pulse duration of 0.1 ms. The parameters for stimulating the left sciatic nerve

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(1.5 to 2.5 times motor threshold, 30 to 40 Hz, 0.025 ms) have been shown to be too weak to activate electrically group III and IV fibers (10, 11). Before stimulation, the triceps surae muscles were stretched to a resting tension from which maximal peak tension could be developed. Blood pressure, heart rate, and ventilation were monitored continuously for 60 s before, during, and after the contraction.

For the second protocol, we abolished afferent input from the contracting triceps surae muscle to the CNS by sectioning the L6, L7, and S1 left dorsal roots. For those animals in which contraction was produced by stimulating the left sciatic nerve, this nerve was sectioned proximal to the stimulating electrode. Contractions were evoked by using the aforementioned stimulation parameters.

In protocol 3, we assessed the cardiovascular and ventilatory responses evoked by high-intensity electrical stimulation of the cut end of the sciatic nerve. The right sciatic nerve was sectioned, and the proximal end attached to a stimulating electrode. After 1 min of baseline recording, the nerve was stimulated with a frequency of 20 Hz, pulse duration of 0.75 ms, and voltage of 7 mA. This was at least 100 times the motor threshold and is known to activate both myelinated and unmyelinated fibers (12).

For protocol 4, we evaluated the cardiovascular effects of hypoxic stimulation of chemoreceptors. After 1 min of baseline measurements, taken while the animals were breathing room air, the animals were switched to a gas mixture of 95% nitrogen and 5% oxygen for 1 min. Arterial blood gases were measured before and at the end of the hypoxic episode.

Finally, the effects of baroreceptor stimulation were assessed. Phenylephrine was infused rapidly into the jugular vein, and blood pressure, heart rate, and ventilation were recorded. Adults were given a dose of 10 μ g/kg. Because newborns are less responsive to this drug (13), a dose of 20 μ g/kg was used for this age group.

Statistical analysis. During the intervention protocols, heart rate, blood pressure, and minute ventilation were recorded continuously for 60 s before each stimulus (baseline recording) and for another 60 s during each stimulus (stimulus recording). To summarize responses, peak heart rate and blood pressure were noted for each 60-s period. Ventilatory volumes were integrated, and the total inspired volume during each 60-s period was noted (minute ventilation). All values are reported as means $\pm$ SEM. Between group and within group comparisons were performed using analysis of variance with a mixed design (one between and one within) (14). When significant differences were found, Tukey's test was used for post-hoc testing (15). A p value of less than 0.05 was chosen as indicative of significant differences between means.

RESULTS

Baseline data. Table 1 contains descriptive information for the newborn kittens and adult cats. Also shown in Table 1 are control values for protocol 1 measurements of muscle tension, blood pressure, heart rate, and ventilation. Similar control measurements were obtained with each protocol. As noted in Table 1, the adult body weight was approximately 25 times more than the newborn body weight, whereas the triceps surae muscles were over 80 times heavier in the adults than in newborns. When resting and developed muscle tension were divided by the weight of the muscle, newborns had significantly greater values. This suggests that newborn muscle performed significantly more work during the min of contraction than the adult muscle. However, because adult triceps were more hypertrophied than newborn muscle, we also show the muscle tensions as a percentage of body weight. Looked at this way, resting and developed tension were not significantly different between the age groups. Control resting and developed tensions were not significantly different between protocols 1 and 2.

The stability of the preparation is documented by the lack of

Table 1. Baseline measurements

	Newborn (n = 9)	Adult (n = 8)
Age (d)	1.6 $\pm$ 0.4	>6 mo*
Body wt (g)	141 $\pm$ 11	3776 $\pm$ 340*
Triceps surae wt (g)	0.43 $\pm$ 0.04	37.97 $\pm$ 4.15*
Triceps surae wt (% body wt)	0.305 $\pm$ 0.012	0.994 $\pm$ 0.41*
Resting tension (g/g triceps)	46.5 $\pm$ 5.6	20.9 $\pm$ 2.4†
Resting tension (g/g body wt)	0.167 $\pm$ 0.032	0.204 $\pm$ 0.015
Developed tension (g/g triceps)	450 $\pm$ 90	137 $\pm$ 16†
Developed tension (g/g body wt)	1.39 $\pm$ 0.30	1.34 $\pm$ 0.14
Systolic pressure (mm Hg)	70 $\pm$ 3	169 $\pm$ 7*
Diastolic pressure (mm Hg)	51 $\pm$ 3	133 $\pm$ 5*
Mean pressure (mm Hg)	57 $\pm$ 3	145 $\pm$ 6*
Heart rate (bpm)	262 $\pm$ 21	209 $\pm$ 10†
Minute ventilation (mL/min)	77 $\pm$ 15	709 $\pm$ 115*

* $p < 0.001$.

† $p < 0.05$.

change in baseline measurements throughout the various protocols. For newborns, mean blood pressure was 57 $\pm$ 3.0 mm Hg at the beginning of the experiment (protocol 1) and 51 $\pm$ 3.3 mm Hg at baseline in protocol 5 ($p = 0.07$). For the adults, mean blood pressure was 141 $\pm$ 8 and 144 $\pm$ 6 mm Hg, respectively ($p = 0.58$). Newborn heart rate was 262 $\pm$ 22 for protocol 1 and 250 $\pm$ 26 for protocol 5 ($p = 0.23$). Adult heart rates were 206 $\pm$ 11 and 200 $\pm$ 10 ($p = 0.38$). Newborn minute ventilation was 77 $\pm$ 15 and 79 $\pm$ 17 mL/min ($p = 0.84$). Minute ventilation in the adults was 703 $\pm$ 128 and 593 $\pm$ 133 mL/min ($p = 0.24$).

Muscle contraction. Two muscle contractions were performed in each animal before severing the muscle afferents. Because the responses to these two muscle contractions were not significantly different, the results were pooled for the purposes of analysis. In response to muscle contraction, systolic blood pressure increased by 8.5 $\pm$ 2.6% in newborns and 15.9 $\pm$ 1.8% in adults. Although this was a significant change from baseline for both groups, the newborn increase was less than that of the adult group ($p < 0.025$). After afferent input from the muscle was abolished (protocol 2), systolic blood pressure did not change significantly in the newborn group during muscle contraction (1.6 $\pm$ 1.8%) and increased only slightly in the adults (3.7 $\pm$ 1.7%; $p =$ not significant, newborns *versus* adults). For both groups, the blood-pressure response after severing muscle afferents was significantly less than the response with an intact reflex arc. Similar age-dependent differences were found when mean blood pressure (mm Hg) was analyzed (Fig. 1A). Thus, newborn blood pressures changed very little during muscle contraction, and this was significantly different from the response seen in the adults.

Heart rate response to muscle contraction is summarized in Figure 1B, displayed as bpm. Although heart rate increased slightly in the newborn (1.4 $\pm$ 0.5%, $p < 0.05$), this was not significantly different from the response after abolition of muscle afferents (1.0 $\pm$ 1.1%). In the adult, heart rate increased by 8.3 $\pm$ 1.3% during contraction. This was significantly different from the newborn response ($p < 0.025$) and was different from the heart rate response after severing the muscle afferents (3.0 $\pm$ 2.0%, $p < 0.01$).

Ventilatory responses to muscle contraction are summarized in Figure 1C. Both age groups showed significant increases in minute ventilation during muscle contraction, and these increases were abolished after severing muscle afferents. There was no differences between the age groups.

Sciatic stimulation. The response of systolic blood pressure to sciatic stimulation is summarized in Figure 2 and is compared with the systolic pressure changes with muscle contraction. Maximal sciatic nerve stimulation produced significantly greater increases in blood pressure and heart rate than did muscle contraction. However, unlike muscle contraction, there were no significant differences between newborns and adults during sciatic

Fig. 1. Increases in blood pressure, heart rate, and minute ventilation are displayed for the control contraction (protocols 1 and 2) and for the contraction after muscle afferents were severed (protocol 3). Values are displayed as means $\pm$ SEM. C, contraction; *, different from newborn group ($p < 0.05$); †, different from control contraction ($p < 0.05$).

Fig. 2. Increase in systolic blood pressure as a percentage of change from the baseline value is shown for the control contraction (protocols 1 and 2) and for the maximal sciatic nerve stimulation (protocol 4). Values are displayed as means $\pm$ SEM. C, contraction; Stim, stimulation; *, different from newborn group ($p < 0.025$); †, different from sciatic stimulation ($p < 0.01$).

stimulation. Heart rate (not shown) increased by 9.5 ± 3.9 and $12.3 \pm 4.2\%$ in newborns and adults, respectively ($p = \text{NS}$, newborn versus adult). Minute ventilation increased by $47 \pm 21\%$ in newborns and by $58 \pm 34\%$ in adults ($p = \text{NS}$, newborn versus adult).

Hypoxemia (chemoreceptor stimulation). Breathing 5% oxygen for 1 min, both newborns and adults achieved similar levels of arterial hypoxemia with no acidosis [$\text{PO}_2 = 22 \pm 2$ torr (2.9 kPa) and 24 ± 1 torr (3.2 kPa) in newborn and adult groups, respectively]. This hypoxemia produced significant increases in blood pressure in both age groups, and there was no significant difference between newborns and adults (Fig. 3). Although newborns appeared to have a decrease in heart rate with hypoxemia (Fig. 3), there was no statistically significant change from baseline and no difference between newborns and adults. As shown in Figure 4, hypoxemia produced significant increases in minute ventilation in adults but not in newborns.

Baroreceptor stimulation. Phenylephrine injection produced similar increases in blood pressure in newborns and adults (Fig. 5). The 25% increase in mean blood pressure after phenylephrine infusion was similar to the increase in mean pressure produced by muscle contraction in the adult group in protocols 1 and 2. The decrease in heart rate after phenylephrine infusion was significant for both groups ($-40 \pm 7\%$ in newborns and $-55 \pm 6\%$ in adults, $p = \text{NS}$, newborns versus adults). Only the adult group achieved a significant decrease in minute ventilation compared with baseline values, although comparison of the percentage of change showed no significant difference between the two age groups (Fig. 5).

Fig. 3. Blood pressure and heart rate response to hypoxemia is shown as a percentage of change from the baseline value (protocol 5). Values are displayed as means $\pm$ SEM. BP, blood pressure; HR, heart rate; *, different from the normoxic baseline ($p < 0.05$).

Fig. 4. Ventilatory response to hypoxemia is shown as a percentage of change from the baseline value (protocol 5). Values are displayed as means $\pm$ SEM. *, different from the normoxic baseline ($p < 0.05$); †, different from the newborn group ($p < 0.05$).

Fig. 5. Blood pressure, heart rate, and ventilatory response to phenylephrine infusion is shown as a percentage of change from the baseline value (protocol 6). Values are displayed as means $\pm$ SEM. BP, blood pressure; HR, heart rate; Vent, minute ventilation; *, different from the predrug baseline ($p < 0.05$).

DISCUSSION

We evaluated the reflex cardiorespiratory responses to skeletal muscle contraction in newborn and adult cats. We also compared the effects of muscle contraction with the following interventions: 1) direct stimulation of the sciatic nerve afferents, 2) hypoxemia, and 3) phenylephrine infusion. The efferent arm of the exercise pressor reflex is mediated by the sympathetic nervous system, as is the response to sciatic nerve stimulation and to hypoxemia. The efferent limb of the baroreceptor reflex is mediated by the parasympathetic system. We found that newborns had a reduced pressor and heart rate response to muscle contraction compared with the adults, but minute ventilation increased similarly in both groups. There were no differences between the groups regarding stimulation of sciatic afferents or with phenylephrine infusion; hypoxemia was different only in that it stimulated ventilation in the adult much more than in the newborn.

Several mechanisms should be considered as we try to understand our results. Immaturity of this exercise-pressor reflex arc might occur at any one of three levels: 1) the afferent limb; 2) the efferent limb; or 3) the central integration and processing of the reflex.

Skoglund (16) studied reflexes arising from muscle afferents in the immature kitten. He evaluated proprioceptive and stretch reflexes and found that these mature postnatally because of the development of their afferent links. At birth, peripheral nerves are poorly myelinated, and conduction velocities are consequently quite slow. With time, the nerves become progressively more myelinated, conduction velocities increase, and the simple stretch and proprioceptive reflexes mature (17). However, the increasing conduction velocity in these studies is probably due to myelination of group I and II afferents. Rapid conduction over these afferents is essential for the development of stretch reflexes, but the exercise pressor reflex is mediated by slowly conducting group III and IV afferents. There is little information available about the maturity of these group III and IV muscle afferents at birth.

Downing (18) has recorded nerve activity from A- δ - and C-fiber afferents from the carotid sinus of the newborn rabbit. He found that, despite low resting blood pressures, the afferents responded to increases in blood pressure in a fashion similar to adult nerves. It is therefore reasonable to speculate that group III and IV muscle afferents (A- δ and C fibers) function normally at birth, but additional investigations will be needed to test this hypothesis.

Data from the current study supports the idea that the afferent arm of the exercise pressor reflex arc is intact in the newborn. Although the blood pressure and heart rate response to muscle contraction was muted in the newborn, the ventilatory response

was virtually identical to that of the adult. This suggests that the afferent limb of the reflex arc is intact, eliciting a normal ventilatory response, but immaturity of the efferent arm or of the central integration of afferent information prohibits a mature pressor and heart rate response. Furthermore, we found no significant age-related differences in the baroreflex, which is also mediated by A- δ - and C-fiber afferents. This suggests that these small afferent nerves can be mature at birth.

Many studies support the idea that the efferent arm of this pressor reflex could be impaired at birth. Boatman *et al.* (19) found that sympathetic control of vascular smooth muscle was decreased in the newborn dog. Others have found that adrenergic innervation develops at varying rates in different vascular beds but is generally poor at birth (20). Rockson *et al.* (21) discovered impaired adrenergic responsiveness in neonatal dog myocardium. In humans, as well as other species, adenylate cyclase activity of the myocardium is decreased at birth and increases with maturity (22). Despite these concerns about the integrity of the efferent limb of the pressor reflex arc, our own data suggest that this does not account for the age-related differences in blood pressure response. Because we observed no age-related differences in the blood pressure response to hypoxemia and sciatic nerve stimulation, we speculate that the muted blood pressure response during muscle contraction is not due to immaturity of the efferent limb of the reflex arc.

Our finding of a muted pressor response to muscle contraction in the newborn is best explained by an immaturity of the CNS. Kalia (23) came to a similar conclusion when she evaluated the J reflex in newborn kittens. Kalia found a disparity between the rate of maturation of the somatic and the visceral components of this reflex. She felt that this disparity implied an immaturity in the CNS. Pathologic studies have demonstrated a relatively simple axonal architecture in the cortex (24) and spinal gray matter (25) of kittens. In addition, potential central modulators of reflex pressor responses (substance P and opioid receptors) (26) have been found to be immature at birth and continue to develop postnatally (27, 28).

Although chemoreceptor and baroreceptor reflexes seemed similar in newborns and adults, we did note one important difference. Newborns had no significant ventilatory response to hypoxia, whereas adults did increase minute ventilation. This disparity between newborns and adults in response to hypoxia has been recognized and reported in the past (29, 30) and probably reflects immaturity of the respiratory control centers.

Methodologic issues should be considered when evaluating our data. The triceps weight in our kittens was significantly less than that of the adults when expressed as a percentage of body weight (Table 1). This suggests that the attenuation of the pressor reflex might have been due to the lesser muscle mass in newborns. However, if fewer afferents were being stimulated in the newborn muscles because of the lesser mass, we might expect an attenuation of the ventilatory component of the reflex as well. Because ventilation was not attenuated in the newborn, we believe that the afferent arm of the reflex was probably similar in the two age groups.

Another methodologic consideration in this model is the intensity of the muscle contraction. The muscle contraction in this model is probably several times longer and more intense than any naturally occurring muscle contraction in the newborn. Because kittens had a muted response to this stimulus, we suspect that spontaneous movements of newborns play little role in the control of blood pressure. We cannot rule out age-related differences in the response to anesthesia or to the surgical preparation; however, we would have expected any differences in response to these portions of the model to impact on all of the reflexes studied.

Generalization of these results to other animals or humans may be inappropriate, because maturation of cardiovascular reflexes has previously been shown to be quite model-specific (31). In general, newborn kittens are probably less mature at

birth than humans. Kittens have less noradrenaline in the adrenal gland at birth than humans (32). They are also less responsive to dopamine at birth than many other species (33).

In summary, we found that newborn cats have a reduced heart rate and blood pressure response to muscle contraction compared with the adult. We conclude that the exercise pressor reflex plays little or no role in the control of blood pressure in the newborn feline. We speculate that the postnatal development of this reflex is due to maturation of integrative and modulatory mechanisms in the CNS.

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