Prostaglandins Contribute to Cardiovascular Reflexes Evoked by Static Muscular Contraction

Charles L. Stebbins, Yuji Maruoka, and John C. Longhurst

The purpose of this study was to determine the contribution of prostaglandins to the reflex cardiovascular responses induced by static contraction of the hind limb in cats, i.e., the exercise reflex. To accomplish this, the cardiovascular responses to hind limb contraction induced by electrical stimulation of spinal cord ventral roots L4-7, and S1, were compared before and after inhibition of prostaglandin synthesis (indomethacin, 2–6 mg/kg i.v., n = 5, or sodium meclofenamate, 2–6 mg/kg i.v., n = 5) or after injection of prostaglandin E2 into the hind limb arterial blood supply. Treatment with indomethacin attenuated the contraction-induced increase in mean arterial pressure and left ventricular dP/dt by 76% and 86%, respectively. Heart rate and average developed triceps surae muscle tension were unchanged. After administering sodium meclofenamate, the reflex response was attenuated to a similar degree. In the indomethacin-treated animals, injection of exogenous prostaglandin E2 (PGE2) partially restored the pressor and myocardial contractile responses. In 6 animals, treatment with exogenous PGE2 without prior inhibition of prostaglandin synthesis did not significantly augment the contraction-induced cardiovascular response. Using the radioactive microsphere technique, we measured skeletal muscle blood flow during contraction before and after treatment with indomethacin (n = 6) to determine if an indomethacin-induced alteration in blood flow could account for the attenuated contraction-induced cardiovascular response. Blood flow during static muscle contraction was not significantly altered by indomethacin. We conclude that prostaglandins contribute to the exercise reflex through an action on afferent nerve endings rather than through a regional vascular effect. (Circulation Research 1986;59:645–654)

RESULTS of recent studies have shown that the release of prostaglandins from skeletal muscle increases during exercise.1-3 However, our understanding of the functional relevance of this phenomenon presently is incomplete. While it has been suggested that prostaglandins may contribute to prolonged vasodilation after exercise4 and possibly to hyperemia during dynamic exercise,5 their potential role in the reflex cardiovascular response to muscle contraction (the "exercise reflex") has not been investigated.

In this regard, evidence from neural recording studies of muscle afferents6 and studies of reflexes arising from abdominal viscera7 suggests that PGE2, PGE3, and PGI2 may enhance the responsiveness of chemosensitive afferent nerve endings associated with reflex excitation of the cardiovascular system. It is believed that this "prostaglandin effect" involves primarily a sensitization of afferent units associated with nociception.7,8 However, many nociceptive units are polymodal in that they respond also to non-nociceptive stimuli.9,10 As such, many of these units are capable of serving as "ergoreceptors."9,10 Since the sensitivity of these afferent units can be influenced by the presence of prostaglandins, it seems reasonable to assume that local production of prostaglandins during muscular contraction may be necessary for the full manifestation of the exercise reflex.

Recent evidence also suggests that bradykinin may contribute to the exercise reflex.11,12 However, the effects caused by bradykinin may be due, in part, to prostaglandins, since bradykinin stimulates their synthesis.13 Thus, it is possible that bradykinin may not be capable of causing an independent effect. Therefore, the purposes of this study were to investigate the contribution of prostaglandins to the exercise reflex and determine if bradykinin and prostaglandins independently influence this response. To this end, we proposed the following hypotheses: 1) Prostaglandins contribute to the exercise reflex originating from statically contracting muscle. 2) Both prostaglandins and bradykinin contribute to the exercise reflex in an independent manner.

Materials and Methods

Surgical Preparation

Adult cats of either sex (2.0–5.4 kg) were studied. All animals were anesthetized initially with ketamine (25–35 mg/kg, i.m.) and then maintained with α-chloralose (50–100 mg/kg, i.v.). The right femoral vein was cannulated for infusion of drugs and fluids. The right femoral artery was cannulated (tip positioned at level of renal artery) and the cannula attached to a pressure transducer for measurement of systemic arte-
rial blood pressure (Statham P23ID). Left ventricular blood pressure was measured with a catheter-tip pressure transducer (Millar Instruments PC 350) that was placed into the left ventricle through a carotid artery. The left ventricular pressure signal was processed by a differentiation amplifier (Gould 13-4615-71) to obtain dp/dt. Pulse rate was measured continuously with a cardiograph (Gould 13-4615-71) triggered by the arterial pressure signal. All measurements were recorded on an eight channel electrostatic recorder (Gould ES 1000B).

A lumbar laminectomy was performed to expose the L5-S1 spinal roots, and the animals then were placed in a Kopf spinal unit. The skin overlying the spine was sewn to two horizontal bars to form a pool that was filled with warm mineral oil. The left L5 and S1 ventral roots were isolated and transected near the spinal cord. The peripheral cut ends were placed on a shielded and grounded electrode that was attached to a stimulus isolation unit (Grass PS16U) and stimulator (Grass 588). The femur of the left hind limb was clamped in a fixed position. The left triceps surae was dissected in the region of the calcaneous and the Achilles tendon attached to an isometric force transducer (Grass FT10). Tension produced by contraction of the triceps surae was recorded as an index of overall hind limb contraction. Tension was expressed as average developed tension and was determined by planimetry of the area under the active tension curve. We expressed tension in this manner because it has been shown to correlate well with contraction-induced cardiovascularpressor and respiratory responses.14,15

A modified surgical preparation was used in those animals in which regional blood flow to the triceps surae was measured. A median sternotomy was performed. Catheters were placed in the left atrium for injection of microspheres and in the right femoral artery for withdrawal of reference arterial blood during microsphere injections. In this preparation, the catheter-tip pressure transducer was placed into the left ventricle through a stab wound in the apex of the heart. A carotid artery was cannulated to allow measurement of systemic arterial blood pressure. The chest then was closed with 2–3 large sutures and the animal placed in the spinal unit. The left leg was clamped in a fixed position. To induce hind limb contraction, the sciatic nerve was exposed, cut, and the peripheral end placed on a stimulating electrode. Tension of the triceps surae was measured in the same manner as described previously.

Triceps surae blood flow was measured by the distribution of 15 μm diameter microspheres ($^{51}$Sc, $^{99}$Nb, $^{111}$Sn, $^{103}$Ru, $^{141}$Ce, or $^{51}$Cr) injected into the left atrium according to the method described previously.16 In any single animal, only four of the six microsphere labels were used. The procedures for microsphere disaggregation, injection, reference sample collection, and calculation of energy overlap have been described previously.17 Reference blood was collected for 2 minutes at a withdrawal rate of 2–3 ml/min, starting just before microsphere injection. For these animals, 0.5–1.0 ml of microspheres was diluted with 10% dextran and a small amount of polysorbate (Tween 80) to a concentration of 1.5–2 × 10$^6$ spheres/ml. The spheres were agitated in a vortex mixer, injected, and then slowly flushed over 20 seconds with 2–4 ml of Ringer’s solution. During microsphere injection and flush, blood pressure, heart rate, and left ventricular dp/dt were monitored. Any animal that showed a significant change in any of these parameters was excluded from the study. Blood flow to the triceps surae, fore limb, and kidneys was determined by the reference sample method described by Archie et al.18 Only animals that showed a difference of less than 15% in blood flow to the left and right kidneys and/or to the left and right fore limbs were used for analysis of triceps surae blood flow. Individual tissue samples that yielded a count of less than 400 microspheres were excluded from evaluation.

Body temperature was monitored continuously using a telemeter (Yellow Springs Instruments) and maintained at 36–38°C by a heating pad and lamp.

In all animals, arterial blood gases and pH were measured periodically using an automated blood gas analyzer (Radiometer ABL-3). These variables were kept within normal limits by enriching the inspired oxygen supply and correcting the arterial pH by infusing a 1.5% solution of sodium bicarbonate. Body temperature was monitored continuously using a telemeter (Yellow Springs Instruments) and was maintained between 36 and 38°C by a heating pad and lamp.

Protocols

Blockade of prostaglandin synthesis. In 13 cats, ventral roots L5 and S1 were stimulated electrically to induce static hind limb contraction capable of producing sufficient tension to evoke a reflex cardiovascular response. This required ventral root stimulation at a voltage of 3–5 times motor threshold, a pulse duration of 0.1–0.2 milliseconds and a frequency of 40–50 Hz for 30 seconds. Resting tension in the triceps surae was adjusted to between 0.1–0.5 kg. Initially at least two separate stimulations were performed to establish that the cardiovascular responses were repeatable. Either indomethacin (Sigma Chemical Company, St. Louis, Mo.) (2–5 mg/kg, n = 7) or sodium meclofenamate (Warner-Lambert, Morris Plains, N.J.) (2–10 mg/kg, n = 6) then was administered intravenously to inhibit prostaglandin production by blocking the action of cyclooxygenase. Fifteen to 20 minutes after treatment with either indomethacin or sodium meclofenamate, the ventral roots again were stimulated at the same voltage, frequency, and pulse duration. If the cardiovascular response was attenuated, then 20–25 minutes later PGE$_2$ (Sigma Chemical Company, St. Louis, Mo.) (70–150 μg, n = 7) was injected intra-arterially through the catheter in the contralateral femoral artery. When arterial blood pressure returned to preinjection levels (2–5 minutes), the ventral roots were stimulated one last time. This was done to determine if the magnitude of the cardiovascular response to static contraction could be restored to the levels observed prior to
treatment with indomethacin. In five other control animals, ventral root stimulation was performed before and after administration of indomethacin and again 20–25 minutes later in the absence of exogenous PGE₂. This protocol was necessary to determine if there was any spontaneous restoration of the contraction-induced cardiovascular response (independent of any effect caused by exogenous PGE₂).

To demonstrate that indomethacin or sodium meclofenamate had effectively blocked prostaglandin synthesis, arachidonic acid (1–3 mg) was injected intravenously before and 15 minutes after treatment with indomethacin. If an attenuated depressor response to arachidonic acid was not observed following indomethacin treatment, one or two additional injections of indomethacin (2 mg/kg) or sodium meclofenamate (2 mg/kg) were performed.

Indomethacin was prepared daily by dissolving it in a 0.1 M Na₂CO₃ solution to a concentration of 10–25 mg/ml. Sodium meclofenamate was dissolved in distilled water to a concentration of 10–12 mg/ml and then diluted with an equal volume of Ringer’s solution. PGE₂ was stored at −10°C in an absolute ethanol stock solution (10 mg/ml). Prior to injection, it was diluted to a concentration of 100 μg/ml with a 0.2 M phosphate buffer solution.

Cardiovascular Response to Static Hind Limb Contraction Following Indomethacin and Captopril. In the cardiovascular response to hind limb static contraction was monitored before and after intra-arterial injection of PGE₂ (70–150 μg). Changes in arterial blood pressure, maximal dP/dt, and heart rate were recorded. At least two successive ventral root stimulations were performed before administration of PGE₂ to ensure that a repeatable cardiovascular response was present. PGE₂ was injected 20–25 minutes after the second ventral root stimulation. When blood pressure returned to baseline levels, the ventral roots were stimulated for a third time.

Cardiovascular Response to Static Hind Limb Contraction Following Treatment with PGE₂. In 6 cats, 8 cats, arterial blood pressure, maximal dP/dt, and heart rate were observed during electrically stimulated static hind limb contractions before and 15–20 minutes after treatment with indomethacin (2–5 mg/kg). Then, with prostaglandin synthesis inhibited, captopril (Squibb Laboratories, Princeton, N.J.) (2–3 mg/kg) was administered intravenously to block the action of converting enzyme (kininase II) and slow the degradation of bradykinin. Approximately 20 minutes after injection of captopril, static hind limb contraction was performed one more time while the relevant cardiovascular variables again were monitored. Captopril blockade was confirmed by the presence of an augmented depressor response to bradykinin injection (5 μg, i.v.) after captopril treatment. In every animal tested, the depressor response was augmented by at least 30%.

Measurement of Blood Flow in Triceps Surae Muscle. In 5 cats, radioactive microsphere injections were made during rest (no contractions) and during 45 seconds of sciatic nerve stimulation to induce hind limb contraction. These injections were performed prior to and 15 minutes after treatment with indomethacin (4–5 mg/kg). Injection of microspheres was performed 10 seconds after the onset of contraction.

Deletion of Animals. In all protocols, the cardiovascular responses to electrically stimulated hind limb contraction were compared only when the averaged developed tension was similar (≤ 10% difference among groups) throughout the entire protocol. This was necessary to control for the effects that large differences in developed tension could have on the magnitude of the reflex cardiovascular responses.

For this reason, the following number of animals from each protocol were not included in the statistical analysis: 2 indomethacin-treated cats, 1 animal treated with sodium meclofenamate, and 1 given captopril. In addition, one of the animals in the indomethacin control group did not show an attenuated cardiovascular response to contraction following two treatments with indomethacin. As a result, we were not able to complete the protocol, and this cat was not included in the data analysis. Finally, a second cat in the captopril protocol was excluded from statistical analysis because the animal became hypotensive (MAP < 50 mm Hg) following the treatment and subsequently demonstrated no reflex response to static hind limb contraction.

Statistics

The Student’s paired t test was used to determine statistical significance of differences between two means. When simultaneous comparisons of differences among means were made, the Bonferroni modification of the critical value for the modified Student’s t statistic was employed. Results are expressed as the mean ± standard error. Means were considered to be significantly different at p < 0.05.

Results

Blockade of Prostaglandin Synthesis

A total of 17 animals were treated with indomethacin to inhibit prostaglandin synthesis. This total includes animals that were subsequently treated with exogenous PGE₂ (n = 5), captopril (n = 6), and 6 control animals.

For purposes of statistical analysis, the results obtained from all 17 animals were pooled to help define the effects of indomethacin blockade on the pressor, contractile, and heart rate responses to static hind limb contraction. Prior to administration of indomethacin, mean arterial blood pressure increased by 34 ± 3 mm Hg during contraction from a control of 106 ± 7 mm Hg. Maximal dP/dt increased by 1670 ± 255 mm Hg/sec (control: 3805 ± 430 mm Hg/sec) while heart rate and average developed tension increased 15 ± 2 beats/minute (control: 196 ± 8 beats/min) and 4.5 ± 0.3 kg (control: 0.6 ± 0.06 kg), respectively. After treatment with indomethacin the increases in mean...
arterial blood pressure and dP/dt were significantly attenuated, rising only 13 ± 2 mm Hg (control: 103 ± 7 mm Hg) and 614 ± 171 mm Hg/sec (control: 3609 ± 414 mm Hg/sec), respectively. The change in heart rate was not significantly different from preindomethacin conditions (11 ± 2 beats/min; control: 174 ± 10 beats/min), but average developed tension was slightly larger (5.2 ± 0.3 kg; control: 0.6 ± 0.06 kg).

In the 5 animals treated with exogenous PGE₂, treatment with indomethacin attenuated the pressor and contractile responses to electrically stimulated static hind limb contraction (Figures 1 and 2). The heart rate response, however, was unchanged. The average developed tension was constant in all conditions. Following administration of PGE₂, the contraction-induced cardiovascular response was restored, in part, back toward its initial level (Figures 1 and 2). In this regard, the increases in mean arterial blood pressure and dP/dt after administration of PGE₂ were significantly greater than those observed immediately postindomethacin stimulation.

In the 6 control animals, attenuated hemodynamic responses to hind limb contraction were observed 15 and 45 minutes after injection of indomethacin (Figure 3). However, the pressor and contractile responses observed at 15 and 45 minutes were not significantly different.

Five animals treated with sodium meclofenamate showed attenuation of the contraction-induced reflex cardiovascular response (Figure 4). The pattern of response was similar to that observed following injection of indomethacin and included a reduced rise in mean arterial pressure and maximal dP/dt.

**Treatment With Exogenous PGE₂**

The hemodynamic response to electrically stimulated static hind limb contraction was augmented in only 3 of the 6 animals tested. In these animals the increases in mean arterial blood pressure and dP/dt were augmented from 27 ± 17 to 42 ± 20 mm Hg and 2317 ± 1326 to 3000 ± 1676. In the other 3 animals the reflex cardiovascular responses were unaltered after administration of PGE₂. Therefore, when the data from all 6 animals were analyzed statistically, there was no significant augmentation of the response.

**Treatment With Indomethacin and Captopril**

Following injection of indomethacin the contraction-induced pressor and contractile responses were reduced in 6 cats (Figures 5 and 6). As with the other indomethacin protocols, average developed tension was held constant. Treatment with captopril augmented the magnitude of the reflex increases in mean arterial blood pressure and dP/dt that had been observed subsequent to indomethacin treatment (Figures 5 and 6). Heart rate did not change and average developed tension was not different from that observed during the initial and postindomethacin stimulations. The initial untreated responses and final postcaptopril responses were not significantly different.

**Figure 1.** Original record of cardiovascular responses to electrically stimulated hind limb contraction (A) before indomethacin, (B) after indomethacin, and (C) after indomethacin + PGE₂.
Blood Flow in Triceps Surae Muscles

Blood flow at rest and during static hind limb contraction (at the same level of average developed tension) was not altered by administering indomethacin (Table 1). However, renal blood flow was reduced in both conditions following indomethacin treatment (Table 1).

Discussion

The results of this study indicate that prostaglandins play an important role in the reflex cardiovascular response to static muscular contraction. In this regard, we found that inhibition of prostaglandin synthesis resulted in an attenuated cardiovascular response to contraction, while subsequent treatment with exogenous prostaglandins (PGE2 in this case) partially restored the response. These observations suggest that the magnitude of the contraction-induced cardiovascular response is dependent on the local concentration of prostaglandins in contracting skeletal muscle.

However, since prostaglandin production was manipulated pharmacologically, our results must be interpreted cautiously. Consideration must be given to the possibility that nonspecific side effects were induced by our pharmacological interventions. Consequently, the responses we observed may have occurred independently of the intended action of the drugs. For example, it is possible that indomethacin, the primary drug used to inhibit prostaglandin synthesis, may have caused the attenuated cardiovascular response to static contraction as a result of either a central effect of the drug or inhibition of prostaglandin synthesis in areas other than the contracting muscle. Previous work in our laboratory has shown this to be an unlikely occurrence. In that study, stimulation of the central cut end of the sciatic nerve was performed as a control maneuver to induce a cardiovascular reflex. This was done to circumvent any stimulation of the muscle afferent nerve endings. The sciatic nerve was stimulated before and after intravenous injection of indomethacin, using doses comparable to those employed in the present study. No change in the magnitude of the cardiovascular response was observed, suggesting that the effect of indomethacin was limited primarily to the skeletal muscle.

As an additional control, in the present study, we compared the cardiovascular response to electrically stimulated hind limb contraction before and after administration of meclofenamate. Since this cyclooxygenase inhibitor is structurally different from indomethacin, it is unlikely that it would cause the same nonspecific side effects. Following administration of meclofenamate we observed an attenuated cardiovascular response to static contraction that was similar to that seen after treatment with indomethacin. Conse-
CHANGES IN MEAN ARTERIAL BLOOD PRESSURE

Initial Response  
Response Post-Indomethacin  
Response 45 min Post-Indomethacin

CHANGES IN LV dP/dt

Initial Response  
Response Post-Indomethacin  
Response 45 min Post-Indomethacin

CHANGES IN HEART RATE

Initial Response  
Response Post-Indomethacin  
Response 45 min Post-Indomethacin

CHANGES IN TRICEPS SURAE TENSION

Initial Response  
Response Post-Indomethacin  
Response 45 min Post-Indomethacin

CHANGES IN MEAN ARTERIAL BLOOD PRESSURE CHANGES IN LV dP/dt

Initial Response  
Response Post-Indomethacin  
Response 45 min Post-Indomethacin

Figure 3. Changes (mean ± SE) in mean arterial blood pressure, left ventricular dP/dt, heart rate, and average developed triceps surae muscle tension in response to electrically stimulated hind limb contraction before and after indomethacin (Indo) and 45 minutes after indomethacin (n = 6). Numbers below histograms represent control values. *p<0.05 initial response vs. post-Indo. †p<0.05 initial response vs. 45 minutes post-Indo.

quently, this finding further supports our contention that indomethacin acted by inhibiting prostaglandin synthesis rather than through a nonspecific side effect.

It has been suggested, however, that both indomethacin and meclofenamate may induce a nonspecific potentiation of the vasodilator response to static muscle contraction that is unrelated to any effect resulting from cyclooxygenase inhibition (i.e., reduction of prostaglandin-induced vasodilation). If this potentiation occurred after drug treatment in the present study, it could account for the attenuated cardiovascular responses we observed. Since accumulation of muscle metabolites during exercise is believed to play a major role in the exercise reflex, it is possible that a greater increase in muscle blood flow at the same level of contraction could cause an enhanced washout of these substances. The end result might be a reduced cardiovascular response to hind limb contraction. To test this possibility, we measured blood flow to the triceps surae during the same level of developed tension before and after treatment with indomethacin. No alterations in muscle blood flow were observed. The difference between our findings and those previously reported may be due to the intense level of static contraction we used (generally greater than 50% of maximal tension). It is known that contractions of this intensity severely restrict muscle blood flow due to nipping and compression of vessels between facial planes and contracting muscle fibers. In fact, we did not observe a significant increase in muscle blood flow even in the untreated condition. Due to these restrictions, we believe that under our experimental conditions indomethacin did not significantly alter muscle blood flow.

Injection of exogenous PGE₂ partially restored the magnitude of the contraction-induced cardiovascular response to levels observed prior to treatment with indomethacin. This restoration was not due merely to recovery from the effects of indomethacin since no significant restoration of the contraction-induced cardiovascular response was observed when animals performed static contraction without administering PGE₂. This observation further weakens the "washout" hypothesis since the vasodilator action of PGE₂ would be expected to enhance muscle blood flow. On the other hand, the fact that treatment with PGE₂ restored a portion of the cardiovascular response to hind limb contraction supports the idea that the attenuated response observed after administration of indomethacin was due to inhibition of prostaglandin production by the drug.

Since we did not measure local prostaglandin levels before and after administration of indomethacin, the effectiveness of cyclooxygenase inhibition might be questioned. However, it should be noted that we tested for effectiveness of blockade with arachidonic acid...
before and after treatment with indomethacin. If an attenuated depressor response to this prostaglandin precursor was not observed, then additional doses of indomethacin (2 mg/kg) were given. Additionally, the doses we used were similar or slightly greater than those used previously to abolish the release of prostaglandins from contracting skeletal muscle of the dog.28 Finally, it is known that a reduction in renal PGE\textsubscript{2} synthesis caused by indomethacin injections results in a reduction in renal blood flow.29 Examination of our regional blood flow data (Table 1) shows that administration of 2–5 mg/kg of indomethacin caused a decrease in renal blood flow of about 50%. Therefore, taken together, these findings provide strong evidence that the doses of indomethacin used in the present study were effective in inhibiting cyclooxygenase activity to reduce prostaglandin synthesis.

Our attempt to augment the contraction-induced cardiovascular response by treatment with exogenous prostaglandins yielded equivocal results. We saw an augmentation of the response in only half the animals tested. The remaining cats demonstrated no alterations in the degree of response. This observation suggests that prostaglandin production during static contraction in some animals may be sufficient to produce an optimal cardiovascular response that cannot be augmented by administration of additional prostaglandin.

A second major finding of this study concerns the relationship between prostaglandins and bradykinin and their contribution to the cardiovascular response to static hind limb contraction. Bradykinin has been shown previously to contribute to this reflex cardiovascular response.12 Using pharmacological interventions designed to manipulate either the synthesis or degradation of bradykinin, a predictable alteration in the magnitude of the contraction-induced cardiovascular response was achieved. However, because changes in local concentrations of bradykinin can influence the synthesis of prostaglandins,13 it was not known definitely if alterations in the reflex response were due to alterations in local concentrations of bradykinin, prostaglandin, or both. We have clarified this issue in the present study. Since indomethacin is not known to have any effect on bradykinin metabolism, we were able to establish an independent role for prostaglandins in the exercise reflex by attenuating the reflex response with this drug. Subsequently, after blockade of prostaglandin synthesis, we were able to augment the post-indomethacin response by treating the animals with captopril (given to potentiate the effects of bradykinin by decreasing its degradation and thus increasing local kinin concentrations9,30,31). Thus, we conclude that bradykinin and prostaglandins each are capable of independent contributions to the expression of the exercise reflex.

Furthermore, although treatment with captopril restored the magnitude of the reflex cardiovascular response to levels observed initially, the response was
not augmented above the initial response. Since intravenous administration of captopril can augment the exercise reflex when prostaglandin synthesis is not blocked, we suggest that prostaglandins make an important contribution to this reflex response at different levels of endogenous bradykinin formation.

It should be acknowledged that baseline arterial blood pressure was significantly lower after treatment with captopril when compared to the initial and post-indomethacin conditions. We were not able to correct this situation even after intravenous infusion of 10–15 ml of Ringer’s solution. Consequently, it is possible that the lower baseline blood pressure may have accounted for the differences in the magnitude of the cardiovascular response between the post-indomethacin and post-captopril conditions. We believe this to be an unlikely occurrence. Two of our cats had baseline mean arterial blood pressures that decreased by only 3–6 mm Hg after injection of captopril, and a greater cardiovascular response still was observed. Furthermore, in a previous study, as a control, we used electrical stimulation of the central end of the cat sciatic nerve to induce a pressor response before and after treatment with captopril. We observed no significant change in the pressor response between conditions in spite of the fact that in 3 of 5 cats tested, baseline blood pressure was reduced after captopril injection. Therefore, we believe the effect of captopril on the contraction-induced cardiovascular response was not due to reduced baseline blood pressure.

It is important to note that there may be a distinct difference in the manner that prostaglandins influence the cardiovascular response to both dynamic and static exercise. In humans performing dynamic treadmill exercise, oral administration of indomethacin augmented the pressor response during running. Although Stassen et al found no increase in systemic vascular resistance after treatment with indomethacin, Cowley et al found that calf blood flow measured immediately postexercise was attenuated by about 40%. However, oral administration of indomethacin may have minimized the drug’s effectiveness, since intravenous injection of indomethacin has been shown to augment vascular resistance in dynamically contracting dog skeletal muscle. Consequently, it appears that vascular resistance and, in turn, blood flow in exercising muscle can be reduced after indomethacin, a situation that would favor an enhanced build-up of substances capable of inducing the exercise reflex. This would suggest that the vasodilator action of prostaglandins is important during dynamic exercise. Conversely, during static contraction we found no differences in muscle blood flow comparing pre- and postindomethacin conditions. Therefore, the lack of change in skeletal muscle blood flow during static muscle contraction may have allowed us to observe the reflex cardiovascular response to reduced prostaglandin levels without the influence of confounding local hemodynamic alterations. Thus, it is possible that prostaglandins play a more important role in reflex excitation of the cardiovascular system during static than dynamic exercise. Further research will be necessary to answer this question thoroughly.

It also should be recognized that prostaglandins may share with other chemical stimuli, e.g., potassium, the

Figure 5. Original record of cardiovascular responses to electrically stimulated hind limb contraction (A) before indomethacin, (B) after indomethacin, and (C) after indomethacin and captopril.
Prostaglandins Contribute to the Exercise Pressor Reflex

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Changes in LV dP/dt

Changes in Mean Arterial Blood Pressure

Changes in Heart Rate

Changes in Triceps Surae Tension

Figure 6. Changes (mean ± SE) in mean arterial blood pressure, left ventricular dP/dt, heart rate, and average developed triceps surae muscle tension in response to electrically stimulated hind limb contraction before and after indomethacin (Indo) and after indomethacin + captopril (n = 6). Numbers below histograms represent control values. *p < 0.05 initial response vs. post-Indo. †p < 0.05 post-Indo vs. post-Indo + captopril.

Table 1. Blood Flow at Rest and During Contraction Before and After Indomethacin Administration

<table>
<thead>
<tr>
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<th>Blood flow (ml/min/g)</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
</tr>
<tr>
<td>Left triceps surae muscles</td>
<td></td>
</tr>
<tr>
<td>Preindomethacin</td>
<td>0.07 ± 0.02</td>
</tr>
<tr>
<td>Postindomethacin</td>
<td>0.09 ± 0.02</td>
</tr>
<tr>
<td>Left kidney</td>
<td></td>
</tr>
<tr>
<td>Preindomethacin</td>
<td>1.47 ± 0.2</td>
</tr>
<tr>
<td>Postindomethacin</td>
<td>0.91 ± 0.6*</td>
</tr>
<tr>
<td>Right kidney</td>
<td></td>
</tr>
<tr>
<td>Preindomethacin</td>
<td>1.48 ± 0.2</td>
</tr>
<tr>
<td>Postindomethacin</td>
<td>0.91 ± 0.2*</td>
</tr>
</tbody>
</table>

Values are means ± SE. *p < 0.05, comparing initial and postindomethacin responses during both rest and contraction. There were no significant differences in blood flow between the right and left kidney before or after indomethacin either at rest or during contraction. Average developed muscle tension also was not significantly different, comparing pre- and postindomethacin conditions.

capability of enhancing sensory nerve activity in skeletal muscle afferents and inducing local vasodilation. Thus, the same stimulus could initiate both reflex vasoconstriction and direct local vasodilation. The magnitude of any resulting pressor response would be determined by the balance of these two opposing effects on systemic flow. Variables that contribute to the hemodynamic response probably include the type and intensity of contraction as well as the active muscle mass.

An additional factor that may be associated with the effect of prostaglandins on the exercise reflex is muscle pain. It has been shown that both prostacyclin and PGE₂, while not capable of producing overt pain, can induce hyperalgesia that becomes overt pain in the presence of such substances as bradykinin and histamine. This observation implies that the sensation of pain associated with intense muscular activity may be attributed, in part, to the presence of prostaglandins. In the same sense, the hyperalgesia caused by prostaglandins may be the result of an enhanced sensitivity of nociceptors, as well as ergoreceptors, to algic substances such as bradykinin and potassium that may accumulate during contraction. The end result could be an additional contribution to the exercise reflex from increased sensitivity of nociceptors associated with cardiovascular reflexes.

In conclusion, our study has provided data demonstrating that prostaglandins contribute to the reflex cardiovascular response to static contraction in the cat. We observed that inhibition of prostaglandin synthesis attenuates the magnitude of the contraction-induced cardiovascular response, while treatment with exogenous PGE₂ partially restored the response. Finally, we...
determined that both bradykinin and prostaglandins are capable of contributing independently to the exercise reflex.

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References


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