Morphine Effects on Cardiac Output and Regional Blood Flow Distribution in Conscious Dogs

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This study documents the changes in selected regional hemodynamics occurring in response to large doses of intravenous morphine. It was performed in normal conscious dogs. Their cardiovascular systems was unaltered by the presence of other drugs or recent surgery. The animals had been surgically prepared previously by implantation of chronic indwelling electromagnetic and Doppler ultrasonic flow probes on the aorta and the cranial mesenteric, renal and iliac arteries and placement of aortic catheters. Morphine, 1 mg/kg, produced mesenteric vascular dilation (30 per cent maximum decrease in resistance), renal vascular dilation (11 per cent maximum decrease in resistance) and nonsignificant changes in iliac vascular resistance. Morphine, 3 mg/kg, resulted in a similar amount of renal dilation (maximum 12 per cent decrease in resistance) but constricted the mesenteric vasculature (maximum 120 per cent increase in resistance) and the iliac vasculature (68 per cent maximum increase in resistance). These changes were observed despite the lack of sustained major changes in cardiac output, blood pressure, total peripheral resistance, or heart rate. It is therefore concluded that morphine has only minimal effects on systemic hemodynamics, but has significant effects when the alterations it produces in regional hemodynamics are considered. Such alterations may be physiologically significant when perfusion to these individual organs is a concern. The minimal systemic effects of high dose morphine is a phenomenon, for the most part, common to both dogs and humans. Whether similar regional hemodynamic changes as these occur in humans cannot be determined at this time since continuous flow monitoring techniques have, as yet, not been applied to humans. (Key words: Analgesics: morphine. Arteries: mesenteric; renal; iliac. Heart: cardiac output. Kidney: blood flow. Measurement techniques: regional blood flow, conscious dogs.)

Traditionally the mainstay of surgical anesthesia has been primarily potent inhalational agents. In the 1940s the use of parenterally administered narcotic agents, whose principle action was that of providing analgesia, was instituted to supplement anesthesia.1-4 Morphine in high doses is currently used extensively as the analgesic component of a balanced anesthetic. Its popularity is attributed to a lack of systemic toxicity and to a lesser degree of cardiovascular depression compared to inhalational agents. Because of the latter fact, morphine is often considered to be indicated for critically ill patients.5-9 The generalized cardiovascular responses for high-dose morphine have been characterized.5,10-12 With the exception of several studies that looked at the coronary circulation,13-15 little data is available concerning what alterations, if any, occur in organ blood flow and cardiac output distribution when morphine is administered in the absence of other pharmacologic agents.

The objectives of the present study were threefold: 1) to examine the alterations in cardiac output and some regional blood flows and vascular resistances that occur in response to large doses of intravenous morphine; 2) to do so utilizing techniques designed to yield instantaneous and continuous measurements of these variables; and 3) to perform the study in healthy, conscious animals in which the effects of recent surgery and anesthesia, which can modify these circulatory responses, were absent.

Methods

This study was performed on 24 conscious, unmedicated mongrel dogs. These animals were of either sex and ranged in weight from 20–30 kg. They were free of heart worms, intestinal parasites and pneumonia and were healthy in appearance.

Surgery for implanting instrumentation was performed under intravenous sodium pentobarbital anesthesia, 30 mg/kg. Two groups of animals were initially instrumented; one for evaluation of systemic and one for evaluation of regional hemodynamics. In the regional hemodynamics group, ten animals received a midline laparotomy. Electromagnetic flow probes, (Zepeda Instruments, Seattle, Washington) 5–6 mm in diameter, were implanted around the
cranial mesenteric and right iliac arteries. A hydraulic cuff occluder was placed around each of these arteries distal to the flow probe for flow zeroing purposes. A 6-mm Doppler ultrasonic flow probe was placed around the left renal artery. A small heparin-filled Tygon® catheter was positioned in the aorta via a lumbar artery. In the systemic hemodynamics group, seven animals received a thoracotomy through the left fifth intercostal space. Electromagnetic flow probes, 20–26 mm in diameter, were positioned around the ascending aorta. A small heparin-filled Tygon® catheter was placed in the thoracic aorta. In both groups of animals, the instrumentation wires and catheters were run subcutaneously and exteriorized at an interscapular site. The animals were then allowed to recover.

Aortic pressure was measured via the previously implanted Tygon® catheters with a Statham® P23 Db strain gauge manometer (Statham Instruments, Inc., Oxnard, California). Arterial blood gases were measured with a PHM-71 MK-2 acid-base analyzer (Radiometer, Copenhagen, Denmark). Cardiac output, mesenteric arterial blood flow, and iliac arterial flow flow were measured with electromagnetic flowmeters (Benton Instruments, Cupertino, California). Zero flow was determined in the mesenteric and iliac beds by inflation of the hydraulic occluders. Zero flow in the aorta was assumed during the diastolic phase of the cardiac cycle. Renal arterial blood flow was measured with a Doppler ultrasonic flowmeter. This system had an accurate electronic zero and its calibration for volume flow has been previously described.

Experiments were performed after the animals had regained their presurgical vigor and sufficient time had elapsed for adequate tissue growth around the flow probes, usually 14–21 days. Aortic pressure, cardiac output, and heart rate in the systemic group, or aortic pressure, mesenteric, renal and iliac blood flows and heart rate in the regional group, were recorded continuously on an eight-channel direct-writing oscillograph (Gould-Brush®, Cleveland, Ohio). Electronic resistance-capacitance filters with 2- to 8-s time constants were used to obtain mean values for aortic pressure, cardiac output, and mesenteric, renal, and iliac blood flows. In the systemic group, total peripheral resistance was calculated in resistance units by dividing mean arterial pressure by cardiac output, i.e., torr/l·min⁻¹. In the regional group, mesenteric vascular resistance, iliac vascular resistance and renal vascular resistance were calculated in resistance units by dividing mean arterial pressure by the respective mean blood flow, i.e., torr/ml·min⁻¹.

With the animals resting quietly on their right side, a peripheral iv was established. Control or baseline measurements of all cardiovascular data were then recorded for a sufficient period of time to assure a steady state had been reached. Morphine sulfate (Knoll Pharmaceutical Co., Whippany, New Jersey), diluted with normal saline to a total volume of 10 ml, was then infused intravenously over a 5-min period. All variables were continuously recorded for an additional 25 min for a total recording period of 30 min from the beginning of the drug infusion. Changes from the control values were noted at 2.5 and 5 min (midpoint and end of drug infusion, respectively) as well as at 10, 15, 20, and 30 min. The changes at each of these time points were compared statistically with the baseline values by use of a Student's paired t test. Thus, each animal served as its own control. Statistically significant changes were indicated by a p value of < 0.05. Two morphine dosages were administered: 1 mg/kg and 3 mg/kg. Both dosages were administered randomly to each animal in the systemic and regional hemodynamics groups. Twenty-four hour intervals were allowed after an animal received 1 mg/kg and 48-h intervals after receiving 3 mg/kg of morphine before the other dose was studied. For various technical reasons, it was very difficult to keep all of the instrumentation working perfectly in all animals during the course of the study. Thus, while the systemic and regional hemodynamic groups initially had ten and seven animals, respectively, the data points in the figures may represent a lesser number of animals. This will be pointed out in the Results section, where applicable.

Because arterial blood gases changed during the high-dose morphine infusion it was felt necessary to instrument a third group of animals. These experiments were designed to see if the noted regional hemodynamic alterations were perhaps due to changes in PaCO₂ and/or PaO₂ rather than morphine itself. Since the observed changes had been smaller in the renal circulation than in the mesenteric and iliac areas, and since this vascular bed was considered to be the most vital of the three studied, we elected to examine this phenomenon only in the renal bed. Seven additional animals were instrumented with a Doppler ultrasonic flow probe on the renal artery and an aortic catheter. These animals, while lying on their right side awake and breathing room air spontaneously through a standard canine anesthesia mask, had baseline cardiovascular and arterial blood gas data recorded. The anesthesia mask was then connected to an Ayres ' T' piece with a Jackson-Reese modification into which was flowing a mixture of nitrogen 12 l/min, carbon dioxide 1 l/min (6.6 per cent) and oxygen 2 l/min
Table 1. Effects of 1 mg/kg (n = 6) and 3 mg/kg (n = 7) of Morphine on Systemic Hemodynamics in Conscious Dogs

<table>
<thead>
<tr>
<th></th>
<th>1 mg/kg Morphine</th>
<th>3 mg/kg Morphine</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>2.5 Min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>83 ± 7</td>
<td>36 ± 13†</td>
</tr>
<tr>
<td>MBP</td>
<td>96 ± 6†</td>
<td>18 ± 5†</td>
</tr>
<tr>
<td>CO</td>
<td>2.96 ± 0.2†</td>
<td>20 ± 6†</td>
</tr>
<tr>
<td>TPR</td>
<td>38 ± 2</td>
<td>−1 ± 1</td>
</tr>
</tbody>
</table>

Infusion

HR = heart rate (beats/min), MBP = mean arterial blood pressure (torr), CO = cardiac output (l/min), and TPR = total peripheral resistance (torr·min⁻¹).
* Actual mean control values ± SEM for these variables are indicated under the control column. The mean per cent change ± SEM from those controls are noted for 30 min.
† Statistically significant changes (P < 0.05) from the control values.

(13 per cent). They continued to breathe this mixture for 15 min during which time serial arterial blood gases were taken and continuous renal hemodynamics recorded. The animals were then returned to room air and data were again recorded 5 min later. This regime reproduced PACO₂ and PaO₂ changes in a spontaneously breathing conscious animal, similar to those noted in animals receiving the higher dose of morphine. Again, changes were compared to the baseline values with Student’s t test for paired data.

Results

In table 1 and figures 1 and 2, changes discussed will be referred to as early (2.5–5 min), middle (5–15 min) and late (15–30 min) with reference to the observation period.

Systemic Hemodynamics (Table 1)

Morphine, 1 mg/kg (n = 6). Morphine produced an early 36 ± 15 per cent increase (P < 0.05) in heart rate (HR). HR then decreased to values not significantly different from the control value of 83 ± 7 beats/min. Mean aortic pressure (MBP) was increased 18 ± 5 per cent early (P < 0.02), and was decreased 8 ± 3 per cent late (P < 0.05), from a control level of 96 ± 4 torr. Cardiac output (CO) increased 20 ± 6 per cent early (P < 0.05) and was decreased by 13 ± 3 per cent late (P < 0.01), from a control value of 2960 ± 210 ml/min. Total peripheral resistance (TPR) decreased slightly 7 ± 2 per cent midperiod (P < 0.05) from a control value of 33 ± 2 torr·min⁻¹ but was otherwise unchanged. There was one less animal in this dosage group than in the high dose systemic group because of the development of an electronic problem with the aortic flow probe.

Morphine, 3 mg/kg, (n = 7). This dose of morphine increased HR 31–34 per cent early (P < 0.01) from a control value of 72 ± 5 beats/min. HR then returned to near control levels and was unchanged thereafter. MBP did not change significantly. CO increased 21 ± 4 per cent (P < 0.001) but then returned to levels not significantly different from the control value of 2750 ± 290 ml/min. TPR was not significantly altered.

Regional Hemodynamics

Morphine, 1 mg/kg (n = 9), (fig. 1). In the mesenteric bed (n = 7), this dose of morphine increased mesenteric arterial blood flow (MA) 26–55 per cent (P < 0.05) from a control value of 548 ± 97 ml/min and decreased mesenteric vascular resistance (MR) 22–30 per cent (P < 0.01) from a control of 0.46 ± 0.13 torr/ml·min⁻¹, most of the observation period.

In the kidney (n = 9), morphine increased renal artery blood flow (KA) 13 ± 5 per cent early (P < 0.05), from a control value of 155 ± 17 ml/min. Renal vascular resistance (KR) decreased 11 ± 5 per cent (P < 0.05) from a control of 0.74 ± 0.10 torr/ml·min⁻¹ middle-late period.

Morphine increased iliac artery blood flow (IA) (n = 7) 59 ± 15 per cent early (P < 0.01) from a control value of 223 ± 17 ml/min, but thereafter this flow returned to near control levels and was not significantly altered. Iliac resistance (IR) was unchanged.

Morphine, 3 mg/kg (n = 10), (fig. 2). In the mesenteric bed (n = 9), this dose of morphine decreased MA 29–44 per cent (P < 0.01), for most of the period of
Fig. 1. Depicted are the changes in mesenteric artery (MA), renal artery (KA), and iliac artery (IA) blood flows and the corresponding mesenteric (MR), renal (KR) and iliac (IR) vascular resistances noted during a 30-min observation period in conscious dogs in response to a 5-min iv infusion of 1 mg/kg of morphine. Variations are depicted on the ordinate as mean per cent change from the conscious control value. The actual control flow and resistance values ± SEM are shown in the inset. Asterisks indicate statistically significant changes from control at the $P < 0.05$ level.

observation, from a control value of $352 \pm 40$ ml/min. MR was correspondingly increased throughout, the highest value being $120 \pm 31$ per cent ($P < 0.01$) above the control level of $0.32 \pm 0.04$ torr/ml·min$^{-1}$.

In the kidney ($n = 10$), KA increased 21–34 per cent ($P < 0.05$) throughout the recording period, from a control level of $163 \pm 15$ ml/min. However, KR was significantly decreased only late in the period, by $12 \pm 4$ per cent ($P < 0.02$), from a control value of $0.67 \pm 0.08$ torr/ml·min$^{-1}$.

Morphine produced a $25 \pm 6$ per cent decrease ($P < 0.01$) in IA ($n = 10$) and a 57–68 per cent increase ($P < 0.05$) in IR from their respective control values of $231 \pm 27$ ml/min and $0.50 \pm 0.06$ torr/ml·min$^{-1}$.

Arterial blood-gas changes were studied during the 30-min observation period only in the two systemic hemodynamic groups. They showed that 1 mg/kg of morphine caused no significant changes in $P_{a_{O_2}}$ or $P_{a_{CO_2}}$. Morphine, in the 3 mg/kg dose, produced a 5–7 torr increase ($P < 0.02$) in $P_{a_{CO_2}}$ from a control level of $32 \pm 2$ torr and a $12 \pm 16$ torr decrease ($P < 0.05$) in $P_{a_{O_2}}$ from a control value of $86 \pm 3$ torr. These changes generally occurred early by the end of the morphine infusion and lasted the duration of the observation period.
MORPHINE 3mg/kg

Fig. 2. Depicted are the changes in mesenteric artery (MA), renal artery (KA), and iliac artery (IA) blood flows and the corresponding mesenteric (MR), renal (KR), and iliac (IR) vascular resistances noted during a 30-min observation period in conscious dogs in response to a 5-min iv infusion of 3 mg/kg of morphine. Variations are depicted on the ordinate as mean per cent change from the conscious control value. The actual control flow and resistance values ± SEM are shown in the inset. Asterisks indicate statistically significant changes from control at the P < 0.05 level.

Hypercarbia/Hypoxia-renal Hemodynamics

(Table 2)

Administration of a gas mixture containing elevated carbon dioxide (6.6 per cent) and lowered oxygen (13 per cent) concentrations (n = 7) resulted in P_{aCO_2} and P_{aO_2} levels comparable to those seen upon administration of high-dose morphine. Both KA and KR increased slightly but these changes were not statistically significantly different from their control values. In the case of KA they do not approximate to the 21–34 per cent increase that occurred with 3 mg/kg of morphine and in the case of KR the changes actually are in the opposite direction of those seen with morphine.

Discussion

These studies have confirmed that large intravenous doses of morphine have only small or transient systemic effects on the normal canine cardiovascular
### Table 2. Effects of Hypercarbia/Hypoxia on Renal Hemodynamics in Conscious Dogs (n = 7)

<table>
<thead>
<tr>
<th></th>
<th>Control*</th>
<th>2.5 Min</th>
<th>5 Min</th>
<th>10 Min</th>
<th>15 Min</th>
<th>20 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>(P_{\text{a}CO_2})</td>
<td>33 ± 1</td>
<td>42 ± 2†</td>
<td>44 ± 2†</td>
<td>42 ± 1†</td>
<td>44 ± 2†</td>
<td>34 ± 1</td>
</tr>
<tr>
<td>(P_{\text{a}O_2})</td>
<td>98 ± 1</td>
<td>71 ± 2†</td>
<td>71 ± 2†</td>
<td>72 ± 4†</td>
<td>73 ± 1†</td>
<td>95 ± 2</td>
</tr>
<tr>
<td>MBP</td>
<td>101 ± 4</td>
<td>9 ± 4†</td>
<td>10 ± 2†</td>
<td>9 ± 3†</td>
<td>6 ± 3</td>
<td>0 ± 2</td>
</tr>
<tr>
<td>KA</td>
<td>105 ± 11</td>
<td>4 ± 6</td>
<td>9 ± 8</td>
<td>6 ± 7</td>
<td>5 ± 5</td>
<td>-3 ± 3</td>
</tr>
<tr>
<td>KR</td>
<td>1.0 ± 0.07</td>
<td>7 ± 7</td>
<td>4 ± 7</td>
<td>5 ± 6</td>
<td>2 ± 5</td>
<td>3 ± 3</td>
</tr>
</tbody>
</table>

Hypercarbia/Hypoxia

\(P_{\text{a}CO_2}\) and \(P_{\text{a}O_2}\) and the mean per cent change ± SEM from control
for MBP, KA, and KR are noted during a 15-min period of breathing a high-\(CO_2\) low-O\(_2\) mixture and also 5 min after returning to breathing room air (20 min).

† Statistically significant changes \((P < 0.05)\) from the control value.

\(P_{\text{a}CO_2}\) = arterial partial pressure carbon dioxide (torr), \(P_{\text{a}O_2}\) = arterial partial pressure oxygen (torr), MBP = mean arterial blood pressure (torr), KA = renal artery blood flow (ml/min), and KR = renal vascular resistance (torr/ml.min\(^{-1}\)).

* Actual mean control values ± SEM for these variables are indicated under the control column and were taken with the animals breathing room air. The mean actual values ± SEM for system. This would agree, with a few exceptions, with data reported in conscious humans.\(^5,10,11\) These exceptions are the transient elevations in HR and MBP seen at the 2.5- to 5-min periods. These changes may be contrary to traditional thinking about systemic morphine changes in humans,\(^10\) namely, bradycardia and hypotension. This was probably related to a brief central nervous system excitation as the drug was initially being administrated to these unseparated animals. Also, it was administered at a somewhat faster rate than is employed clinically. However, during the mid-late portion of the observation period, HR, CO, and MBP were changed minimally from their respective control values; systemic effects were similar to those in normal humans.\(^9\) Our animals were normovolemic, conscious and in a recumbent lateral position. With similar conditions in humans, it is unusual to see significant hypotension with morphine.

This study has also documented important regional circulatory changes. Morphine, 1 mg/kg, dilates the mesenteric bed while a 3 mg/kg dose constricts this bed. Likewise, small intravenous doses of morphine in humans seem to dilate the splanchnic vasculature.\(^20\) A constricting effect of high-dose morphine, occurring on the venous outflow side, has been noted in the splanchnic circulation in anesthetized dogs.\(^21,22\) Similarly, in the iliac bed there is a variable effect with dose. The smaller dose does not change IA significantly but the large dose reduces IA and increases IR considerably. These dual effects of morphine are interesting. Smaller doses of morphine may produce a central sympathetic withdrawal action as has been proposed in human studies involving forearm blood flow\(^23,24\) as well as in helical strip preparations with canine cutaneous arteries.\(^25\) It also may be that direct local dilatory actions contribute. This latter effect has been shown in anesthetized dogs with an acutely denervated skeletal muscle preparation.\(^26\) A mixed local and centrally mediated action for morphine has recently been proposed for human peripheral vasculature.\(^28\) With the larger dose of morphine, central nervous system actions of the drug may predominate in terms of regional vascular effects. Morphine has been shown to increase catecholamine levels in dogs via an adrenal medullary release mechanism,\(^29,30\) as well as by a lesser important mechanism of catecholamine release from sympathetic nerve endings.\(^32,33\) The fact that the increase in perfusion pressure of an isolated rabbit artery preparation perfused with plasma from a conscious dog given high-dose morphine is attenuated by phentolamine,\(^30\) confirms this. Our results also agree with Lowenstein’s results in dogs anesthetized with chloralose-urethane.\(^27\) In his study, flows were controlled with a perfusion device and intravenous morphine increased limb resistance, indicating vasoconstriction. A decrease in skeletal muscle flow with high-dose morphine has likewise been noted utilizing radioactive microsphere techniques on conscious monkeys.\(^15\)

The present study demonstrated increased blood flow and decreased vascular resistance in the renal bed with both dosages of morphine. The flow changes appeared to be dose-related. These results can be contrasted with existing data for morphine and other anesthetics. It is generally held that inhalational anesthetics reduce renal blood flow.\(^34,35\) Studies on halothane, utilizing similar techniques to those utilized in this investigation, showed it reduced renal resistance but either did not change or slightly decreased renal blood flow.\(^36\) One other study on the effects of morphine on renal blood flow demonstrated a slight decrease in flow utilizing a radioactive microsphere technique in conscious monkeys.\(^15\) The discrepancy between this latter study and our results with morphine may be explained by the fact that the microsphere technique only measures flow at a single point.
in time. Thus, important changes may have been missed. Also to be considered is a species difference between monkeys and dogs. It is interesting in the present study that the renal bed dilated while the other beds constricted. This may be related to differences in either the density or sensitivity of adrenergic receptors in the kidney. Previous work in conscious dogs examined regional vascular responses to acute blood loss, a situation that produces reflex adrenergic activation. Under such conditions, the iliac and mesenteric beds constricted early whereas the renal bed dilated slightly and did not constrict until the blood loss has progressed to a severe level.\textsuperscript{37}

A major question in the present study that required answering, was whether the observed regional hemodynamic alterations could have been due to changes in blood gases induced by 3 mg/kg of morphine rather than to the morphine itself. It is very difficult to control ventilation in a conscious animal. To do so, it is necessary to introduce additional surgery and/or pharmacologic agents. Both of these violate one of the basic objectives of this study: to examine changes in an intact, conscious animal preparation. By simply allowing the animals to breathe a controlled gas mixture that would simulate blood-gas changes seen with morphine, the surgical and pharmacological purity of the preparation was maintained. The results clearly demonstrated that changes in \(P_{aCO_2}\) and \(P_{aO_2}\) did not affect renal hemodynamics in the manner that high-dose morphine did. This is strong evidence that the observed changes with morphine were due to the drug \textit{per se} and not blood-gas alterations. This is not totally surprising. The kidney is an organ whose blood flow is not thought to be metabolically dependent as is the case with \(CO_2\) and \(O_2\) in the brain and heart. While it cannot be ruled out that our regional flows with morphine were influenced indirectly by altered ventilatory patterns, this also is unlikely. Ventilatory patterns were definitely changed upon administration of the elevated \(CO_2\) and lowered \(O_2\) mixture. However, renal parameters only changed minimally. A separation of direct morphine effects and indirect blood-gas effects is also supported by systemic data from conscious dogs breathing carbon dioxide.\textsuperscript{28} There, HR and MBP changes were not similar to those seen in the present study with morphine. The fact that renal parameters did not change with altered blood gases in this study does not definitely prove that changes seen in the mesenteric and iliac beds could not have been so influenced. But in view of the convincing renal data, we feel this is an unlikely possibility.

In conclusion, implantation of chronically indwelling flow probes in humans is not feasible. Thus, this study utilized a well-established conscious animal model.\textsuperscript{14,36,37,38} Such a model offered several advantages: 1) hemodynamic changes can be continuously monitored; 2) the specific effects of an intervention, in this case, effects of high-dose intravenous morphine on regional circulations, can be examined; and 3) these can be accomplished without the confounding interactions of other drugs and acute surgical manipulations, both of which have been present in previous human and animal studies.\textsuperscript{31,22,27,20–43} It has been found that systemic hemodynamics in the dog remain reasonably stable with high-dose intravenous morphine, as they do in clinical situations. However, significant changes occur in regional hemodynamics. These are manifested as mesenteric and renal dilation with minimal effects in the iliac bed with 1 mg/kg of morphine. Three mg/kg of morphine results in mesenteric and iliac constriction and again renal dilation. Mechanisms of these changes can only be speculated upon at this time. Both direct end organ effects as well as indirectly mediated changes via reflex neural control mechanisms are probably involved. Good data in this area are lacking and work is currently underway to elucidate the mechanism of these individual organ hemodynamic changes.

The authors thank Pat Quinn, Tina Marron, and Lisa Monaco for their help with the technical preparation and care of the animals and Arnold Sherman, Marc Beckerman and Rich Thomas for their help with the electronics and instrumentation portion of this study.

References