CEREBRAL HEMODYNAMIC AND METABOLIC ALTERATIONS DURING ENDOTOXIN SHOCK IN THE DOG

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ABSTRACT

CEREBRAL HEMODYNAMIC AND METABOLIC ALTERATIONS DURING ENDOTOXIN SHOCK IN THE DOG

By

Janet Lea Parker

Cerebral hemodynamics, vascular reactivity, and metabolic alterations were studied in spontaneously respiring dogs following intravenous administration of 1 mg/kg (n=5), 2 mg/kg (n=16), and 5 mg/kg (n=6) E. coli endotoxin. Cerebral venous outflow was measured directly from the cannulated confluence of the sagittal, straight, and transverse (lateral) sinuses, with the transverse sinuses occluded. This method eliminates the major sources of extracranial vascular contamination of the cerebral venous outflow. All preparations were required to meet criteria of vascular separation and reactivity before considered acceptable for use.

Cerebral blood flow and cerebral perfusion pressure decreased immediately upon administration of 1, 2 or 5 mg/kg endotoxin, and remained below control values for the entire four hour experimental period. By the fourth hour of shock cerebral blood flow had decreased 37, 48, and 45% of control

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in the 1, 2 and 5 mg/kg doses, respectively, and cerebral perfusion pressure had increased to levels approaching (but not equaling) control values.

Upon administration of endotoxin, cerebral vascular resistance transiently decreased, returned to levels not significantly different from control, and gradually increased to levels which were significantly above control by at least the fourth hour of shock. At 240 minutes post-endotoxin cerebral vascular resistance was 25, 55 and 37% above control in the 1, 2 and 5 mg/kg doses of endotoxin, respectively. Thus, cerebral blood flow decreased following endotoxin administration, due initially to the decreased perfusion pressure and subsequently, to the increased cerebral vascular resistance and, to a minor extent, to the decreased perfusion pressure.

Vascular reactivity studies indicated that the cerebral autoregulatory and "venous-arteriolar" responses were well maintained after four hours of endotoxin shock. The cerebral vascular responsiveness to inhalation of 7.5% carbon dioxide, however, was depressed after shock. Prior to endotoxin administration, cerebral vascular resistance decreased to 37% of control in response to the CO_2 challenge. After 1, 2, 3 and 4 hours post-endotoxin, resistance decreased to only 81, 80, 80 and 75% of control, respectively.

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Endotoxin administration generally caused an increased respiratory activity, resulting in increased P_{O_2} and decreased P_{CO_2} in the systemic arterial blood. Initially, the hyperventilation did not produce an adequate compensation, as indicated by the early acidosis in the 2 mg/kg and 5 mg/kg doses. Cerebral venous blood pH decreased, and blood gas changes included decreased P_{O_2} and increased arterial-venous differences of percent oxygen saturation, total CO_2, and HCO_3^- concentrations. Thus, brain tissue and acid-base balance, reflected in cerebral venous (sagittal sinus) pH and bicarbonate concentrations, demonstrated increased acidosis during endotoxin shock.

Saline control experiments (n=8) yielded no significant alterations in cerebral blood flow, vascular reactivity, or arterial and venous blood gases.

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CEREBRAL HEMODYNAMIC AND METABOLIC ALTERATIONS DURING ENDOTOXIN SHOCK IN THE DOG

By

Janet Lea Parker

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Physiology

1975

To

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DEDICATION

To my husband, Paul E. Parker, for his unfailing support and encouragement, and to my father, F. Glenn Smith, Jr., and the loving memory of my mother, Helen.

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ACKNOWLEDGEMENTS

The author gratefully acknowledges the academic and research guidance from her major professor, Dr. Thomas E. Emerson, Jr., and the assistance from the other members of her doctoral committee: Drs. Jerry B. Scott, Donald K. Anderson, Rudy A. Bernard and W. Doyne Collings. The skillful surgical and technical assistance of Mr. Robert J. Young is also appreciated.

The author wishes to extend special recognition to the late Mr. Tom Talley, former teacher, Thomas Jefferson High School, and to Dr. David R. Redden, Professor, North Texas State University, for their early encouragement of her career.

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CHAPTER I

INTRODUCTION

The central nervous system has been implicated by many investigators in the pathogenesis of irreversible gram-negative endotoxin shock. As early as 1890, Charrin and Gley (17) administered crude pyrocyaneus endotoxin to produce shock in rabbits. They reported that shocked animals displayed depressed responses to neural stimulation and suggested that this was due to central "paralysis". More recently, the introduction of small doses of endotoxin into the carotid artery or into the ventricular or cerebrospinal fluid systems of dogs (24,90,91,114,115) was shown to elicit a shock syndrome which bears many resemblances to clinical septic shock. In addition, cross-circulation studies completed in isolated head-trunk preparations (24) have shown that endotoxin is capable of eliciting a marked centrally-mediated hypotensive response.

Shock is often described as "inadequate tissue perfusion" and the central nervous system is most sensitive to such deprivation (85). In this regard, few studies have concentrated on possible cerebral vascular involvement in

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the response of the central nervous system to endotoxin. Moss et al. (85) demonstrated that cerebral hypoxemia can induce the "shock lung syndrome", characterized by pulmonary interstitial and intra-alveolar edema and hemorrhage. These authors believed that these symptoms of shock were caused by autonomically mediated venous spasm, mediated by hypothalamic hypoxia. In addition, cerebral hypotension has been reported (14) to produce hemodynamic alterations characteristic of shock. Thus, cerebral ischemia subsequent to inadequate blood flow during shock may be a contributory factor in the pathogenesis of the shock state, and the measurement of cerebral blood flow and vascular resistance is of value in evaluating this theory.

The hypothesis tested in this study was: Do alterations in cerebral hemodynamics, vascular reactivity and cerebral metabolism (arterial and cerebral venous blood gases) indicative of cerebral ischemia occur during endotoxin shock in the dog?

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CHAPTER II

SURVEY OF THE LITERATURE

Clinical Background of Septic Shock

Clinically, the pathogenesis and treatment of shock secondary to sepsis remains a difficult problem, and despite intensive research and improved treatments based on this research, the mortality rates reported are usually in the range of 50 to 90% (27,53,109,120). The most frequent causative agents of septic shock are gram-positive and gram-negative bacteria, although due to antibiotic control of most gram-positive agents, most infections initiating shock are caused by gram-negative organisms. In addition, an organism is presented with gram-negative bacteria more often since these are normal inhabitants of the gastrointestinal tract (92).

Altemeir et al. (2) reported that the most frequent source of gram-negative infections is the genitourinary tract. Approximately half of the patients presenting gram-negative sepsis showed a history of recent urinary tract operations or instrumentation. Irritations and infections in the respiratory tract (following tracheostomy), reproductive tract (due to septic abortion) and gastrointestinal

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tract (peritonitis) have also been indicated as primary foci of gram-negative infections, and predisposing conditions (diabetes mellitis, cirrhosis, patient age) may also increase susceptibility (109).

Bacteremia or septicemia usually begins with clinical manifestations of chills, fever, vomiting, diarrhea and prostation. When the septicemia proceeds to shock, additional symptoms occur: (1) hypotension, (2) tachycardia, (3) tachypnea, (4) cool, pale extremeties, often associated with peripheral cyanosis, (5) mental obtundation, and (6) oliguria (92,111). Several authors of clinical reports have used the term "cold shock", typified by the symptoms listed above, as the more advanced stage of shock associated with catecholamine release (16,110), and the term "warm shock" to describe an earlier stage of shock associated with hypotension and a hyperdynamic circulation (16,80, 110). At this time the skin is dry and pink, extremities warm and urine output usually adequate (16,40,80,110). Although metabolic acidosis is generally considered to be the classic acid-base alteration in shock (80,124), it is usually a late development, and the typical early response of patients in septic shock is respiratory alkalosis (80,92, 124). Progressive pulmonary insufficiency is often reported (5,8,109,113), resulting in deterioration of pulmonary function and severe hypoxia. A myriad of other clinical abnormalities have been described, including coagulation

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defects, decreased platelet counts and elevated blood urea nitrogen, creatinine, and lactate (92), although the laboratory data varies greatly.

Shoemaker (111) reported that the natural history of shock is a progression from compensatory responses to decompensation, the shock syndrome thus resulting from failure of compensatory mechanisms to "provide adequate circulatory drive to meet physiologic needs, be they normal or increased".

Research Models of Septic Shock

As previously indicated, common organisms causing sepsis are similar to those found in the human gastrointestinal tract and include: (1) Escherichia coli, (2) Klebsiella aerobactor, and (3) Proteus, Pseudomonas, and Bacteriodes species, in decreasing frequency. The abnormalities of the shock state are incompletely understood, but appear to be initiated by endotoxins from the cell walls of the gram-negative bacteria listed above (109). An intravenous injection or infusion of the purified endotoxin of any one of these bacteria into otherwise healthy animals produces signs and symptoms similar to those seen in human septic shock. The purified endotoxin is a lipopolysaccharide protein complex, which is obtained by extracting bacteria, commonly E. coli, by various procedures (23). The Boivin trichloracetic acid procedure is a commonly used

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technique and yields endotoxin of high potency (23). To achieve a degree of shock corresponding to that reported in the clinical conditions mentioned in the previous section, an endotoxin dosage in the research model yielding an LD_{50} to LD_{90} is commonly used.

Many animal species have been used by various laboratories in the experimental shock model, including dogs (18-20,28-34,54-57,93,122), cats (50,71), rabbits (86,102), sheep (7), calves (99), mice (127), and primates (59,61,66, 96,107,118). However, clear-cut differences may exist in the responses of the human species of septic shock and those of the animals used in the experimental model (84,106). A notable example is the dog. In this animal, one of the manifestations of what is termed by some authors as irreversible shock is mesenteric congestion, perhaps precipitated by constriction of hepatic sphincters (18-20,42,106). Such congestion, however, is not seen in the primate intestine in shock (66,74,96,106). Although direct extrapolation of particular findings to human septic shock may be difficult, as in the area mentioned above, the use of the experimental animal model has contributed greatly to an overall understanding of the shock state (109).

Systemic Circulatory Effects of Endotoxin Shock

Administration of intravenous *E. coli* endotoxin in anesthetized dogs is immediately followed by a period of

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rapid systemic hypotension within 5 minutes, succeeded by a temporary partial recovery during the next 20-60 minutes, and a later progressive decline in blood pressure (18,19,42, 50,67,122). In baboons (59,66,96) endotoxin administration causes a decrease in blood pressure over the first 30 minutes followed by a gradual progressive decline. The initial decrease in arterial pressure must be due either to a fall in total peripheral resistance or to a decline in cardiac output (48). Most authors have reported that the decrease in arterial pressure is accompanied by a decrease in cardiac output and either no change or an increase in total peripheral resistance (18,63,122). Similar results were obtained following endotoxin administration in unanesthetized dogs (93). These animals demonstrated the classic decrease in mean arterial pressure, accompanied by diminished cardiac output, greatly elevated total peripheral resistance, increased heart rate and decreased stroke volume.

Several authors have attributed the initial decrease in cardiac output in the dog to a decrease in venous return (10,11,42,122). Cardiac output and venous return are also diminished in the baboon (59,66) although the time sequence varies in comparison to the dog. A primary decrease in venous return is also supported by recent studies by Hinshaw et al. (55,56) which indicate the absence of a direct toxic action of endotoxin upon the myocardium, at least in the

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early hypotensive stage of shock. Thus, initially, the decrease in arterial pressure is due to a decrease in cardiac output subsequent to decreased venous return to the heart.

The direct causes for the decreased venous return apparently vary according to the species being considered. In the monkey (59,66), the decrease in venous return occurs slowly, and the sites of venous pooling have not been specifically identified (27,59,66). However, in the dog, Gilbert (42) reported that hepatic venoconstriction with consequent portal hypertension and hepatic venous pooling of blood was the cause of the decreased venous return. On the other hand, Blattberg and Levy (10,11) studied endotoxin shock in dogs in which the portal venous pressure was prevented from rising via a Servo-pump, or the liver was actually bypassed, and found that significant pooling of blood still occurred. This group also performed ligations of the aorta at various levels and correlated the resulting fall in blood pressure after endotoxin administration with the amount of blood pooled at the various ligations. They concluded that in the early post-endotoxin period, approximately equal volumes of pooled blood are found in and out of the hepatosplanchnic area (11). In summary, the systemic circulatory response to endotoxin in the dog is typified by pooling of blood in the hepatosplanchnic (and other) regions, thus decreasing cardiac output, and decreasing

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arterial pressure. Thus, peripheral rather than direct cardiac mechanisms are primarily responsible for the systemic hypotension of shock, at least in the early stages.

Transvascular Fluid Fluxes During Endotoxin Shock

Theoretically, venous return could also decrease due to decreases in blood volume via transcapillary loss of fluid. Endotoxin shock has been shown to be associated with net transvascular fluid flux changes. Initially, decreases in hematocrit, viscosity, and plasma protein, and a slight increase in plasma volume indicate a net fluid influx (18-20). The subsequent direction of the fluid fluxes during shock, however, is controversial. Fluid filtration has been shown to occur in the hepatosplanchnic bed of the dog (20,58). In addition, several authors have reported evidence for fluid filtration in other vascular beds, often based upon measurements of thoracic lymph flow, decreases in plasma volume, and increases in hematocrit (19,20). However, when the effects of splanchnic constriction are abolished via splenectomy, hematocrit remains unaltered and plasma volume increases (18,19). In addition, the validity of the dye dilution techniques for determination of plasma volume in endotoxin shocked animals may be questionable, due to slower, uneven mixing and sequestration of blood during shock (68). In this regard, measurements of blood and plasma volumes in the dog may be of

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limited significance when applied to primates, due to the unique pooling of blood in canine hepatosplanchnic vasculature.

If net fluid filtration in extra-splanchnic vasculature does occur, the specific location of this efflux has not been defined. Indeed, convincing evidence for net fluid reabsorption throughout the entire period of shock has been presented (64,121), based upon organ weight and resistance alterations in several vascular beds, including skin and skeletal muscle. Weidner et al. (121) and Hinshaw and Owens (64) reported that canine forelimb weight decreases were associated with decreasing vascular resistance, suggesting that the weight loss was due to extravascular fluid reabsorption. Limb weight losses in the cat and monkey (58) during endotoxin shock also support this concept. Thus, blood volume decreases subsequent to transcapillary fluid loss cannot explain the decrease in venous return in the dog or primate.

Effect of Endotoxin Shock Upon the Myocardium

In the intermediate and preterminal stages of shock, the question of a direct effect of endotoxin shock upon the myocardium and the involvement of the failing myocardium in the development of irreversibility is controversial. Most authors agree that the heart will ultimately fail in shock

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(1,12,13,54-57,75-77), although reports vary as to the mechanism of the myocardial dysfunction. Alican et al. (1) reported that heart failure was seen late in shock, and suggested that this was the result of prolonged inadequate coronary perfusion. Hinshaw et al. (55,56) used an isolated, working heart preparation and were unable to demonstrate functional alterations in the myocardium in the first 3-4 hours after endotoxin administration, but found consistent signs of myocardial failure in the 4-6 hour period post-endotoxin. Their results did not demonstrate a direct cardiotoxic action of endotoxin, and suggest that failure occurs only after prolonged hypotension. However, Brand and Lefer (13) reported the discovery of a myocardial depressant factor (MDF) obtained from the blood of shock animals, which was later reported as having cardiodepressant (negative inotropic) action (75,76). This group reported that plasma MDF activity is inversely related to the splanchnic blood flow in shock and that pancreatectomy prior to shock abolishes MDF production (77). In contrast, Hinshaw et al. (60) reported that although heart failure can be clearly demonstrated 4-6 hours following endotoxin administration, the blood of endotoxin shocked animals does not appear to possess a toxic factor which impairs myocardial function. More recently, this group used pancreatectomized animals and found that the presence or absence of the

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pancreas bore no relationship to the degree of myocardial failure following endotoxin (54), thus weakening the hypothesis of a pancreatic myocardial depressant factor as a primary factor causing the heart failure of endotoxin shock. They suggested that inadequate coronary perfusion and abnormal diastolic filling were the potent factors in the precipitation of myocardial failure (57). Elkins et al. (26) used selective coronary artery perfusion during endotoxin shock and demonstrated that high coronary artery perfusion improved cardiac performance during shock, supporting the importance of adequate coronary artery perfusion, and the absence of a circulating MDF.

Effects of Endotoxin on Peripheral Vascular Hemodynamics

As previously indicated, the hepatosplanchnic vascular bed in dogs is greatly affected by systemic endotoxin administration, manifested primarily by intravascular sequestration of blood within the capacitance vessels (10,11,18,42, 106). In addition, Blattberg and Levy (10,11) presented evidence for considerable blood pooling in extra-hepatosplanchnic vascular beds of the body.

Emerson et al. (34) demonstrated that following intravenous administration of a lethal dose of endotoxin, renal resistance in natural flow kidneys increased transiently, and then began to decline toward control levels by 30

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minutes post-endotoxin. Renal blood flow was markedly decreased for the two hour experimental period, apparently in proportion to the decreased perfusion pressure. Similar results were reported in the baboon (96) following systemic administration of coliform endotoxin. Renal arterial blood flow decreased 79% at three minutes post-endotoxin and remained significantly depressed for the next two hours. Renal vascular resistance peaked at three minutes and returned to near control values at 60 minutes post-endotoxin.

Intravenous endotoxin administration (2 mg/kg) has been shown to decrease blood flow and increase resistance in skin and skeletal muscle vasculature (89,121). In the isolated gracilis muscle, blood flow remained depressed for four hours following endotoxin; vascular resistance increased transiently and then began to wane toward control levels. In the isolated canine forelimb (121), E. coli endotoxin (2 or 5 mg/kg, intravenous) decreased forelimb blood flow and increased segmental vascular resistances, especially in the skin vascular bed.

Local (intra-arterial) administration of endotoxin elicits varying responses, depending on the vascular bed being studied. Isolated intestinal loops and hepatic vasculature demonstrate increased resistance when perfused with endotoxin (63). The splenic artery, however, dilates in response to intra-arterial injections of E. coli endotoxin (47). Arterial and venous resistances increase in

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the isolated pulmonary circulation, although this does not occur when whole blood is not the perfusate, indicating the lack of a direct effect of endotoxin upon pulmonary vasculature (62). Administration of endotoxin directly into coronary arteries of dogs decreases coronary vascular resistance (38). However, in the renal, hindlimb, and forelimb vasculature, local administration of endotoxin causes minimal transient effects (43,67).

Involvement of the Central Nervous System and Cerebral Vascular Bed in Endotoxin Shock

Several studies have reported possible involvement of the central nervous system in endotoxin shock. As early as 1890, Charrin and Gley (17) administered intravenous crude pyocyaneus endotoxin to produce shock in rabbits, and reported that the shocked animals displayed depressed responses to vasopressor and vasodepressor nerve stimulation. They suggested that this was due to central (medullary) "paralysis". Penner and Klein (91) employed a cross circulation technique in which the cephalic blood flow of one animal was derived from the systemic circulation of another animal, and vice versa. Shigella toxin was injected into the latter animal, and visceral lesions, hemoconcentration, hyperglycemia and other symptoms of shock appeared in the former dog whose head received blood containing the toxin. They suggested that the Shigella toxin acts directly on the

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hypothalamus of the brain to cause diffuse sympathomimetic changes resulting in the pathologic alterations. This study was critized by other workers (25) on the grounds that considerable leakage of tagged materials from the isolated head preparation to the systemic circulation occurs. In addition, Weill et al. (122) repeated the work of Penner and Klein and reported that the pathologic changes were not limited to the animal whose brain was perfused with endotoxin. However, they did not rule out the possibility that the central nervous system may have an important influence on the subsequent course and lethality of shock once it had been initiated.

Penner and Bernheim (90) reported that the administration of very small doses of endotoxin into the third ventricle resulted in ulcerative lesions of the gastrointestinal tract and other symptoms suggestive of shock. The doses which they used were ineffective systemically. They suggested that a prime site of systemic endotoxin action may be central nervous centers and that these centers might mediate autonomic activity leading to pathologic changes. These studies were confirmed by the experiments of Simmons et al. (114,115), in which relatively small doses of E. coli endotoxin were injected into the lateral ventricles in dogs. They found that hyperventilation occurred immediately, and cardiac output, heart rate, and arterial pressure decreased

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Recently, Dobbins (24) used a neurally intact, vascularly isolated head-trunk preparation, in which a donor dog supplied constant-flow perfused arterial blood to the head of the recipient animal. Endotoxin administration to the donor animal or into the perfusion circuit to the head resulted in marked hypotension in the recipient trunk. In addition, although histamine, acetylcholine, epinephrine and other vasoactive drugs elicited blood pressure changes in the recipient trunk when administered into the perfusion circuit, these responses were abolished following bilateral denervation of the recipient dogs carotid sinus-body complexes. In contrast, when endotoxin was infused into a similar debuffered preparation, recipient systemic pressure again fell markedly. These studies support the concept that endotoxin is capable of eliciting centrally mediated hypotensive responses.

However, in order for endotoxin to exert a direct effect upon the central nervous system, the molecule itself must contact the elements of the central nervous system. Trippodo *et al.* (117), using the Limulus *in vitro* endotoxin assay, determined that up to 2 hours after endotoxin administration, and even during the period of highest plasma concentration of endotoxin (5-30 min) no endotoxin was

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detected in cerebrospinal fluid. They theorized that because of its high molecular weight (10^5 to 10^6) endotoxin does not cross the blood brain barrier. This suggests that during the early stage of endotoxemia, the endotoxin does not exert its effects by acting directly on the central nervous system. This, however, is controversial, and certainly does not exclude the possibilities that endotoxin causes the release of a substance or reacts with a substance to exert its effect upon the central nervous system, or that the time course of the reactions (or transport) of endotoxin is not in concert with the plasma endotoxin levels.

Shock is often described as "inadequate tissue perfusion" and the central nervous system is most sensitive to such deprivation (85). In this regard, few studies have concentrated on possible cerebral vascular involvement in the response of the central nervous system to endotoxin. Moss et al. (85) demonstrated that cerebral hypoxia can induce the "shock lung syndrome", characterized by pulmonary interstitial and intraalveolar edema and hemorrhage. These authors believe that these symptoms of shock were caused by autonomically mediated pulmonary venous spasms, initiated by hypothalamic hypoxia. In addition, Brown et al. (14) reported that cerebral hypotension produced hemodynamic changes characteristic of shock. Thus, cerebral ischemia subsequent to inadequate flow during shock may be a contributory factor in the pathogenesis of the shock state, and the

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measurement of cerebral blood flow and vascular resistance is of value in testing this hypothesis.

The cerebral vascular bed is a difficult one to isolate and study, due to the extensive arterial and venous communications with extracerebral circuits. Indirect methods of measuring and calculating cerebral blood flow have been reported, and most involve applications of the Fick principle. Popular techniques use modifications of the Kety-Schmidt nitrous oxide method (69), but the limitations of this technique are especially vulnerable when applied to the cerebral vasculature, due to the extensive communications and collaterals with extra-cerebral circuits. For example, the venous blood sample should be representative of all parts of the brain and be uncontaminated by extracerebral blood. In man, this criterion is more easily met than in other animals, as the internal jugular venous bulb is situated so that only cerebral venous blood enters it. This, of course, is not the situation in the dog. In addition, it is difficult to be certain of even mixing of the indicator in the arterial blood, due to the number of arterial supplies entering the brain. Other authors have used radioactive indicators or dyes injected into one or both internal carotid arteries, but again, the limitations described above render the quantitative measurement of cerebral blood flow difficult, complicated, and uncertain (44). Thus, although the nontraumatic nature of most of

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these techniques is certainly of value in the clinical situation, they present certain limitations when applied to the canine cerebral vascular bed, and when accuracy is demanded in the experimental situation.

Some authors have reported techniques of measuring cerebral blood flow in which all of the extracranial structures (skin, muscle, etc.) were removed from the skull and upper neck region, a very traumatic procedure. Others (73) have simply tied the vertebral arteries and reported carotid artery blood flow as representing cerebral blood flow without taking into consideration the extensive arterial communications. In consideration of these factors, and the limitations of the other direct and indirect methods reported above, the method used in this study (direct collection of the cerebral venous outflow) appears to yield the best data with the least amount of trauma to the experimental animal. This technique has been previously described by Rapela and Green (94), and involves collection of the outflow of the dorsal saggital and straight sinuses. Details of this technique will be discussed further in this thesis.

Gallo and Schenk (39) reported marked decreases in carotid and vertebral artery flows during endotoxin shock. However, these arterial flows are not truly representative of cerebral blood flow as they widely communicate with extracerebral vascular beds. Also these workers reported a decreased "cerebral" vascular resistance whereas in the

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monkey, Weiner (123) reported an increased cerebral vascular resistance during entodoxin shock. Buyniski et al. (15) measured cerebral outflow directly after only one hour following endotoxin administration. They found an increased cerebral vascular conductance but did not follow this for longer than one hour. Recently, Emerson and Parker (30,31) used artificially respired dogs in a similar preparation, and found an initial decrease in cerebral blood to 63% of control, which decreased further to 39% of control by the fourth hour of shock. Cerebral vascular resistance was significantly higher than control values by the fourth hour of shock. Parker and Emerson (88) reported preliminary results of a similar study in spontaneously respiring dogs, which confirmed the increased vascular resistance occurring in the third to fourth hour of shock. Results of this study are presented in this thesis.

Very few studies have reported on changes in cerebral vascular reactivity or cerebral metabolic alterations during endotoxin shock. Buyniski et al. (15) have reported a marked reduction in the cerebral vascular responsiveness to increases in arterial P_{CO_2} levels, although this was studied for only one hour post-endotoxin. Mamo et al. (81) reported reduced reactivity of cerebral vessels to hypercarbia in 21 out of 27 patients with cerebrovascular disease. Clinically, several authors have suggested that an increase in cerebral

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P_{CO_2} following ischemia causes prior maximal dilation, and thus impairs the reactivity of the cerebral vessels to increased arterial P_{CO_2} during the hours immediately following acute experimental ischemia (35,81,82). Cerebral venous levels of P_{CO_2} or other blood gases have not been measured.

The function of the central nervous system during shock depends greatly upon its nutritional supply through its vascular bed. Thus, measurement of cerebral vascular responses during shock is of value in testing the hypothesis that cerebral hemodynamics, vascular reactivity, and cerebral metabolism are altered or impaired during shock, and may therefore play a role in the pathogenesis of experimental gram-negative endotoxin shock.

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CHAPTER III

METHODS

Mongrel dogs of both sexes weighing 20±2 kg were anesthetized with sodium pentobarbital (30 mg/kg). An endotracheal tube was inserted and the animals were allowed to respire spontaneously. Following completion of the required surgery, the animals received intravenous injections of sodium heparin (10,000 units) supplemented during the experiment at a rate of approximately 500 units per hour. The sodium pentobarbital was also supplemented throughout the experiment at a rate of about 50 mg per hour. All pressure recordings were made from appropriate pressure transducers (Statham Laboratories, Model P23Gb) connected to a Sanborn polygraph (Sanborn Co., Model 60-1300). Blood gas determinations were made using a Radiometer blood gas system.

Cannulations

The right femoral artery was cannulated with polyethylene tubing (PE 240) for measurement of systemic arterial pressure. The right femoral vein was cannulated (PE 240) to allow replacement of the cerebral blood flow into the systemic circuit and for introduction of intravenously

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administered drugs throughout the experiment. A closed loop of tubing (PE 320) connected the left femoral artery and vein in the animals in which arterial blood samples were taken and in animals which were bled for the hemorrhage portion of the experiment. This arterial-venous shunt was initially filled with normal saline and was clamped when not in use.

Preparation of cerebral circuit

A midline incision was made in the skin from a point approximately one inch posterior to the cisterna magna extending approximately to the level of the orbit. The skull was exposed and the muscle and connective tissue was cleaned from the dorsal and posterior surfaces. The technique used to isolate the cerebral venous circulation has been previously described by Rapela and Green (44,94). The outflow from the sagittal and straight sinuses, which drain only cerebral structures, was collected by drilling a hole in the skull at the level of the confluence of the sinuses, and fitting a snug cannula into this opening. Communications of the confluence of the sinuses with the extracerebral circulation of the lateral and sigmoid sinuses was abolished by drilling an additional hole on each side of the skull so as to intercept the lateral sinus and occlude it with softened bone wax injected into the sinus cavity. The amount of bone wax injected was approximately 0.1-0.2 ml on each side.

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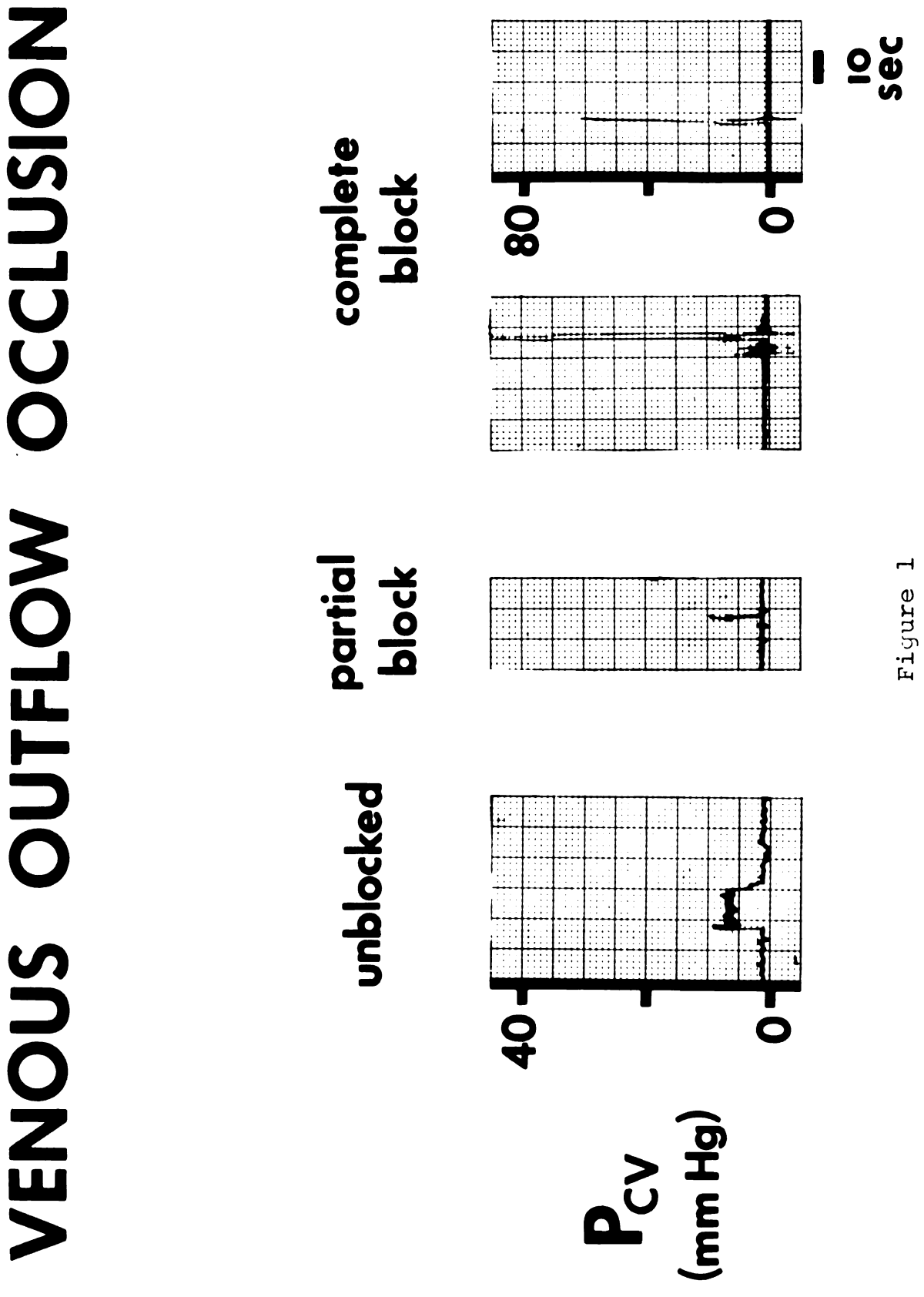
Following blockage of the lateral (transverse) canals, the cerebral and extracerebral vascular circuits of this region are almost completely separate. This was verified in these experiments by observation of the venous outflow pressure response during transient clamping of the outflow tubing. Cerebral venous pressure was measured by a needle inserted into the outflow tubing near the skull and proximal to the area to be clamped. The pressure response in a tight, relatively communication-free circuit is a rapid, high rise; a rapid rise in the venous pressure to 40 mm Hg or greater was considered to represent the cerebral circuit as being free of any major connections with extracerebral vascular compartments (94). An example of this response is illustrated in Figure 1. In a theoretical case of perfect separation of the vascular circuits, venous pressure will approach arterial pressure during transient occlusion of the outflow tubing. Failure to achieve verification of a tight system was usually caused by either incomplete blockage of the transverse canals or abnormal cerebral anastomoses, and these animals were not used in the experiments. The performance of the cerebral vascular bed was observed during graded levels of hemorrhage and during inhalation of carbon dioxide to test the degree of cerebral reactivity during these conditions in the preparations. Graded levels of hemorrhage were used to exhibit characteristic cerebral

Figure 1. Response of cerebral venous pressure (P_{CV}) to transient occlusion of the outflow tubing during unblocked, partially blocked, and completely blocked lateral sinuses.


VENOUS OUTFLOW OCCLUSION
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vascular autoregulation, and inhalation of 7.5-10% CO_2 was used to demonstrate the cerebral reactivity to systemic hypercarbia, as these are considered exceptional characteristics of the cerebral vascular bed (9,35,70,94). Also, Green and Rapela (44) have demonstrated that similar autoregulatory responses are elicited by reducing cerebral perfusion pressure either by hemorrhage or by graded carotid artery occlusion. Thus, with the procedure described, about 60% of the cerebral venous outflow was collected, relatively uncontaminated by extracerebral blood flow (94).

Cerebral outflow from the tubing flowed by gravity into a constant-volume 30cc reservoir and was returned to the dog via the femoral vein. Initially, the constant-volume reservoir was filled with 25cc Dextran (60,000 MW) so that no fluid was lost by the animal in filling the reservoir. A needle was inserted into the cisterna magna to allow measurement of cerebral spinal fluid pressure. A thermal probe extension was attached to the exposed end of the animal's tracheal tube to allow respiratory recordings on the polygraph paper. Blood flows were measured with a graduated cylinder and stopwatch. A rectal thermometer was used to monitor body temperature.

Pufified E. coli endotoxin (Difco) was diluted to the appropriate dosage in normal saline to yield 20cc suspension solution. Following a suitable control period, the endotoxin was administered intravenously over a five minute

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Group I (N=12) consists of animals which received a dose of 2 mg/kg endotoxin and were subsequently followed for four hours without interruption. This group serves as the primary group used for studying the cerebral responses to this dose of endotoxin. Control values of the cerebral blood flow, cerebral perfusion pressure (aortic pressure minus cerebral venous pressure), cerebral vascular resistance (cerebral perfusion pressure/cerebral blood flow), cerebrospinal fluid pressure, respiratory rate, heart rate and body temperature were taken before endotoxin administration, every 5 minutes for the first 15 minutes and at 30 minute intervals for the remainder of the four hour period. In eight of the twelve animals, arterial and cerebral venous blood pH, P_{CO_2}, and P_{O_2} values were taken during the control period and at 30 minute intervals throughout the experimental period. Percent oxygen saturation, total CO_2 (mMol/l plasma), and HCO_3^- content (meq/l plasma) were calculated from these values using the animal's body temperature and the Siggaard-Anderson alignment nomogram. During the four hour observation period, the animal's progress was not interferred with except to add pentobarbital and heparin periodically, as described above. Either one or two tests were performed, before and again after the four hour experimental period. In half the animals (N=6), the cerebral vascular response to graded levels of hemorrhage was

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completed to test the cerebral autoregulatory response before and after four hours of endotoxin shock. Following the test given before administering the endotoxin, the animals were allowed to stabilize before obtaining the base control values for the experiment. In the remaining half (N=6), the cerebral vascular responses to: 1) 7.5 or 10% carbon dioxide inhalation, and 2) graded increases in cerebral venous pressure (venous-arteriolar response) were tested before and after the four hours of shock. The carbon dioxide was administered via respiratory bags attached to a Y cannula on the end of the animal's tracheal tube; on the other side of the Y a flutter valve was attached to prevent inhalation of room air during inspiration. Cerebral venous pressure was increased by raising the tip of the outflow tubing to gradually increasing heights yielding graded increases in pressure.

Six of these animals were followed for an additional hour of shock and four animals of this group were followed for a total of six hours of shock following endotoxin administration. The autoregulatory, venous-arteriolar, and carbon dioxide responses were tested in these animals after six hours of shock. Eight additional animals died prior to the end of the four hour shock period.

Group II (N=4) consists of animals also receiving a dose of 2 mg/kg E. coli endotoxin, and treated similarly to those in Group I except that the experimental period was

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interrupted every hour to test the cerebral vascular response to inhalation of carbon dioxide. The cerebral vascular parameters were monitored as described for Group I.

Group III (N=5) consists of experiments in which the cerebral responses to a lower dose of endotoxin (1 mg/kg) were studied. Cerebral blood flow, cerebral perfusion pressure, cerebral vascular resistance, cerebrospinal fluid pressure, respiratory rate, body temperature, and heart rate were measured as in Group I. Arterial and cerebral venous blood gases were obtained during the control period and at 30 minute intervals in five of the animals. In three, the response to carbon dioxide inhalation was tested hourly, in three the autoregulatory response was tested before and after four hours of shock, and in two animals the venous-arteriolar response was tested before and after four hours of shock.

Group IV (N=6) consists of experiments in which the cerebral response to a greater dose of E. coli endotoxin (5 mg/kg) was studied. Cerebral blood flow, cerebral perfusion pressure, cerebral vascular resistance, cerebrospinal fluid pressure, respiratory rate, heart rate, and body temperature were followed as in Group I. Arterial and cerebral blood gases were measured in all six animals during the control period and at 30 minute intervals during the shock period. All animals were followed without interruption

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during the four hours of shock. The response to carbon dioxide before and after four hours of shock was completed in all animals except two, in which the response after four hours of shock was not completed due to death of the animal. An additional animal, not included in the study, died after 1½ hours of shock.

Group V (N=8) is the control series of animals, in which 20 cc of normal saline was administered over a 5 minute period and the animals followed for four hours. Cerebral blood flow, cerebral perfusion pressure, cerebral vascular resistance, cerebrospinal fluid pressure, respiratory rate, heart rate and body temperature were followed as in the experimental animals. Arterial and cerebral venous blood gases (pH, P_{CO_2}, P_{O_2}) were obtained during the control period and at 30 minute intervals in all animals. Two of the animals were followed for a total of six hours following after administration of saline. The cerebral vascular response to inhalation of carbon dioxide before and after four hours of the control period was tested in seven animals, and after six hours in two animals. Autoregulation and the venous arteriolar response was tested before and after the control period in seven animals. Control animals received heparin and pentobarbital as needed.

Statistical analysis was completed using the standard Student's "t" test for paired replicates (78), and is

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described in Appendix A of this thesis. Two-way analysis of variance was also used for between-group comparisons. F and t values were considered significant in these analyses when yielding a "P" value less than 0.05.

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CHAPTER IV

RESULTS

Hemodynamic Alterations

The average responses of the cerebral perfusion pressure (systemic pressure minus venous pressure), cerebral blood flow, cerebral vascular resistance and cerebrospinal fluid pressure following administration of 2 mg/kg endotoxin are shown in Figure 2. Cerebral perfusion pressure decreased significantly during the first five minutes and remained below control during the entire 4 hour experimental period. The general pattern of most experiments was that of an initial rapid decrease followed by a partial (but statistically significant) recovery, and another smaller decrease followed by a gradual rise toward control levels. Cerebral blood flow rapidly decreased from 34.1 to 17.0 ml/min (-50%, $P < 0.005$) during the first five minutes after endotoxin administration. A small increase to 20.9 ml/min (36% below control) occurred at min 30, followed by a gradual decline over the remainder of the experiment to 16.9 (48% below control, $P < 0.005$). Cerebral vascular resistance decreased significantly (-35%, $P < 0.05$) during the first five minutes, rose to levels not different than control

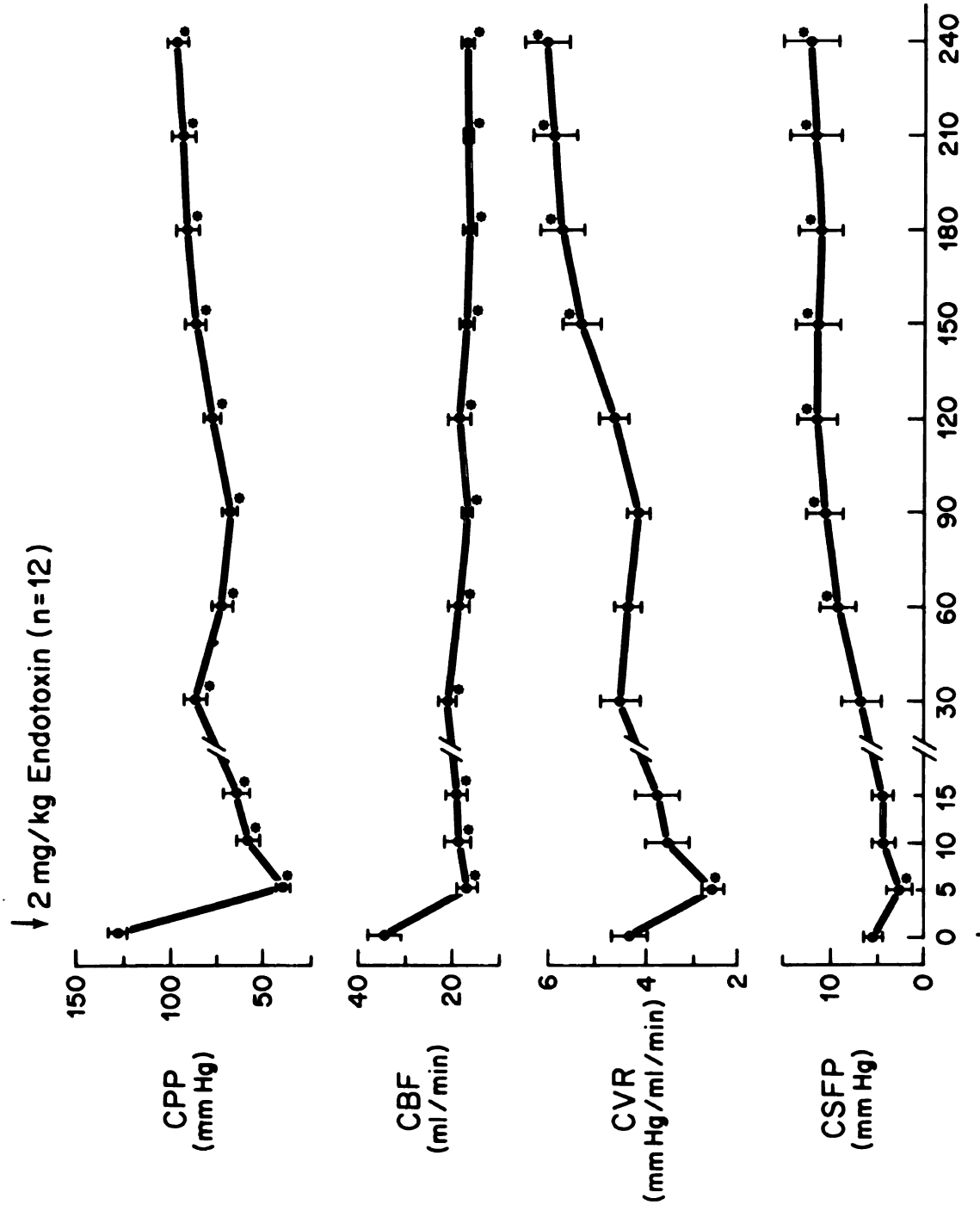
Figure 2. Average hemodynamic responses of the cerebral vascular bed following intravenous administration of 2 mg/kg E. coli endotoxin.

CPP = cerebral perfusion pressure

CBF = cerebral blood flow

CVR = cerebral vascular resistance

CSFP = cerebrospinal fluid pressure


2 mg/kg Endotoxin (n=12)
CPP (mm Hg)
150
100
50
CBF (ml/min)
40
20
CVR (mm Hg/ml/min)
6
4
2
CSFP (mm Hg)
10
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0 5 10 15 30 60 90 120 150 180 210 240
Time (min)
Means ± SE
•p<0.05

Figure 2

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($P > 0.05$), and continued rising over the remainder of the experiment, the increase becoming significant ($P < 0.05$) at 150 min post-endotoxin. Cerebral vascular resistance at 4 hours post-endotoxin was 6.00, a value that averaged 55% above control ($P < 0.05$). Cerebrospinal fluid pressure decreased transiently at min 5 ($P < 0.05$), then began rising, and leveled off at a level significantly above control ($P < 0.05$) for the last three hours of the experiment.

A representative tracing from one of these experiments is shown in Figure 3. Systemic pressure rapidly decreased, cerebrospinal fluid pressure decreased, and respiratory activity increased during the first five minutes following endotoxin administration. During this period, cerebral blood flow and cerebral vascular resistance (calculated) decreased. Systemic pressure partially recovered before decreasing again, and then rose to levels near control over the last two hours. Cerebrospinal pressure and respiratory activity were usually increased. Cerebral blood flow was depressed during the entire 4 hours, and cerebral vascular resistance had increased to 8.34 mm Hg/ml/min by the fourth hour.

Average cerebral hemodynamic responses following administration of 5 mg/kg endotoxin are shown in Figure 4. The pattern of the responses is similar to that of the lower dose of endotoxin. Cerebral perfusion pressure and cerebral

Figure 3. Representative tracing from an experiment following intravenous administration of 2 mg/kg E. coli endotoxin.

P_{SYST} = systemic arterial pressure

P_{CSF} = cerebrospinal fluid pressure

CBF = cerebral blood flow

CVR = cerebral vascular resistance

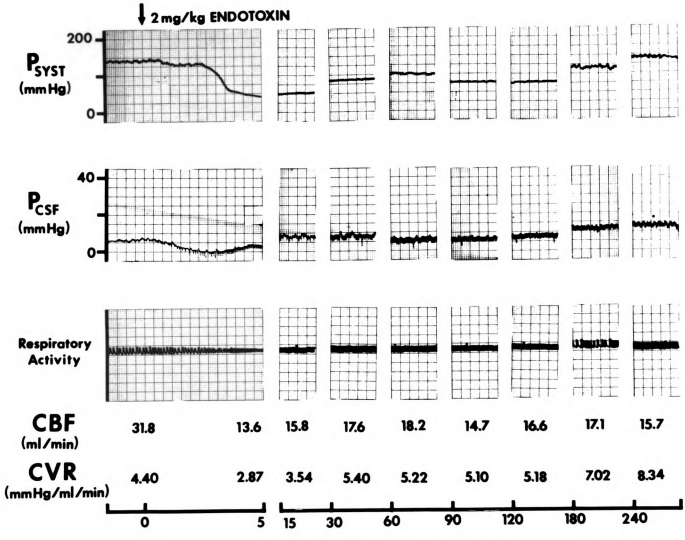

2 mg/kg ENDOTOXIN
200
P_{SYST}
(mmHg)
0
40
P_{CSF}
(mmHg)
0
Respiratory
Activity
CBF
(ml/min)
31.8
13.6
15.8
17.6
18.2
14.7
16.6
17.1
15.7
CVR
(mmHg/ml/min)
4.40
2.87
3.54
5.40
5.22
5.10
5.18
7.02
8.34
0
5
15
30
60
90
120
180
240
Time (min)

Figure 3

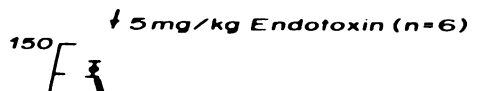
Figure 4. Average hemodynamic responses of the cerebral vascular bed following intravenous administration of 5 mg/kg E. coli endotoxin.

CPP = cerebral perfusion pressure

CBF = cerebral blood flow

CVR = cerebral vascular resistance

CSFP = cerebrospinal fluid pressure



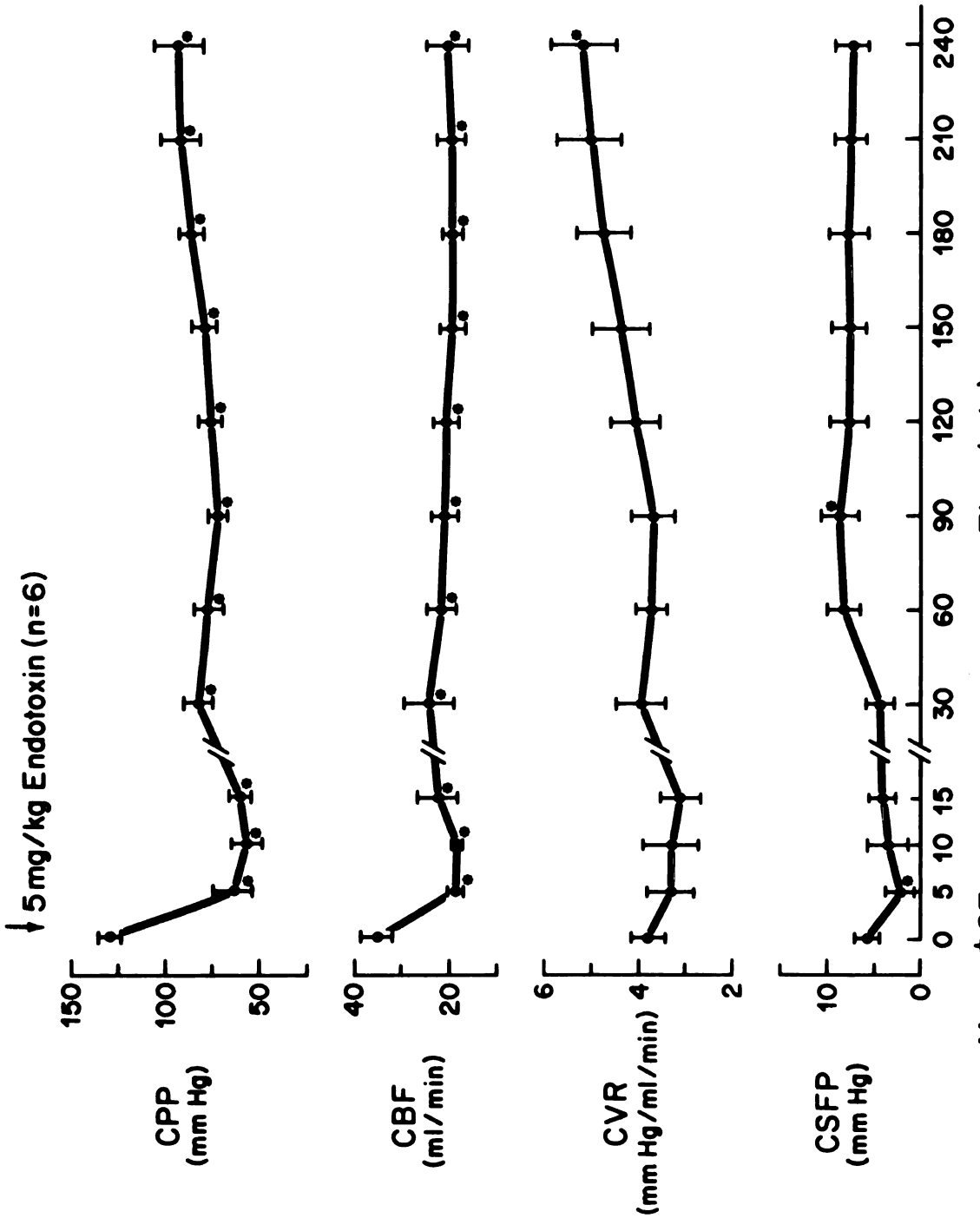

5mg/kg Endotoxin (n=6)
CPP (mm Hg)
150
100
50
CBF (ml/min)
40
20
CVR (mm Hg/ml/min)
6
4
2
CSFP (mm Hg)
10
0
0 5 10 15 30 60 90 120 150 180 210 240
Time (min)
Means ± SE
*p<0.05

Figure 4

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blood flow decreased rapidly and significantly during the first ten minutes (56% and 47%, respectively) and remained below control during the entire 4 hour experimental period ($P < 0.05$). Initially, cerebral vascular resistance tended to decrease, although due to the variation of the response this decrease was not significant ($P > 0.05$). Resistance then gradually rose, and reached levels significantly above control by the fourth hour of shock (37% above control, $P < 0.05$). Cerebrospinal fluid pressure initially decreased ($P < 0.05$), then increased to a level above control at min 90 ($P < 0.05$) and decreased to levels not different from control from min 120-240 ($P > 0.05$). In general, the individual responses of these animals were similar to that illustrated in Figure 3 for the 2 mg/kg dose of endotoxin.

Endotoxin administration resulted in death either during or immediately following the 4 hour experimental period in 8 and 3 animals in the 2 and 5 mg/kg doses, respectively. A tracing obtained during one of these experiments is illustrated in Figure 5. Systemic pressure decreased dramatically during the first 5 minutes from 105 to 27 mm Hg, gradually increased to 63 mm Hg, and then declined during the last hours of the experiment. Cerebral blood flow rapidly fell during the first 5 minutes, and remained depressed during the experimental period. The transient increase in cerebral blood flow which occurred at 15 min post-endotoxin may be due to cerebral dilation caused by increased levels of P_{CO_2}

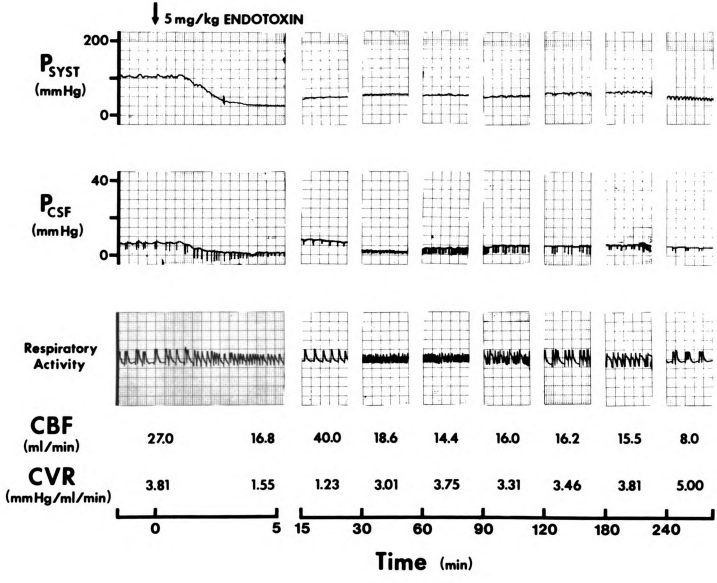
Figure 5. Representative tracing from an experiment terminating in death of the animal due to intravenous administration of 5 mg/kg E. coli endotoxin.

P_{SYST} = systemic arterial pressure

P_{CSF} = cerebrospinal fluid pressure

CBF = cerebral blood flow

CVR = cerebral vascular resistance


5 mg/kg ENDOTOXIN
200
P_{SYST} (mmHg)
0
40
P_{CSF} (mmHg)
0
Respiratory Activity
CBF (ml/min)
27.0
16.8
40.0
18.6
14.4
16.0
16.2
15.5
8.0
CVR (mmHg/ml/min)
3.81
1.55
1.23
3.01
3.75
3.31
3.46
3.81
5.00
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30
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Time (min)

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subsequent to the decreased respiratory activity which occurred during this period. Cerebral vascular resistance decreased initially, and rose to levels above control by min 240 ($P < 0.05$).

Changes in cerebral hemodynamics and cerebrospinal fluid pressure following administration of 1 mg/kg endotoxin are illustrated in Figure 6. Cerebral perfusion pressure fell from an average of 139 to 69 mm Hg ($P < 0.05$) during the first 10 minutes, partially recovered to 97 mm Hg at min 30, decreased again and then gradually rose toward control levels. However, perfusion pressure remained below control for the entire 4 hour period ($P < 0.05$). Cerebral blood flow decreased from 29.5 to 20.2 (-32%, $P < 0.05$) during the first ten minutes, and by four hours post-endotoxin was 38% below control ($P < 0.01$). Cerebral vascular resistance initially decreased 31% ($P < 0.05$), increased to near control levels ($P > 0.05$) and became significantly above control by the fourth hour of shock (25% above control, $P < 0.05$). The only significant change which occurred in the cerebrospinal fluid pressure was a transient decrease ($P < 0.05$) which occurred at min 5.

The control series of animals demonstrated little effect of the surgical maneuvers upon the course of the experiment over the four hour period. Figure 7 shows that the only changes in the cerebral hemodynamics occurring following administration of 20 cc of normal saline into the

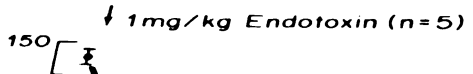
Figure 6. Average hemodynamic responses of the cerebral vascular bed following intravenous administration of 1 mg/kg *E. coli* endotoxin.

CPP = cerebral perfusion pressure

CBF = cerebral blood flow

CVR = cerebral vascular resistance

CSFP = cerebrospinal fluid pressure



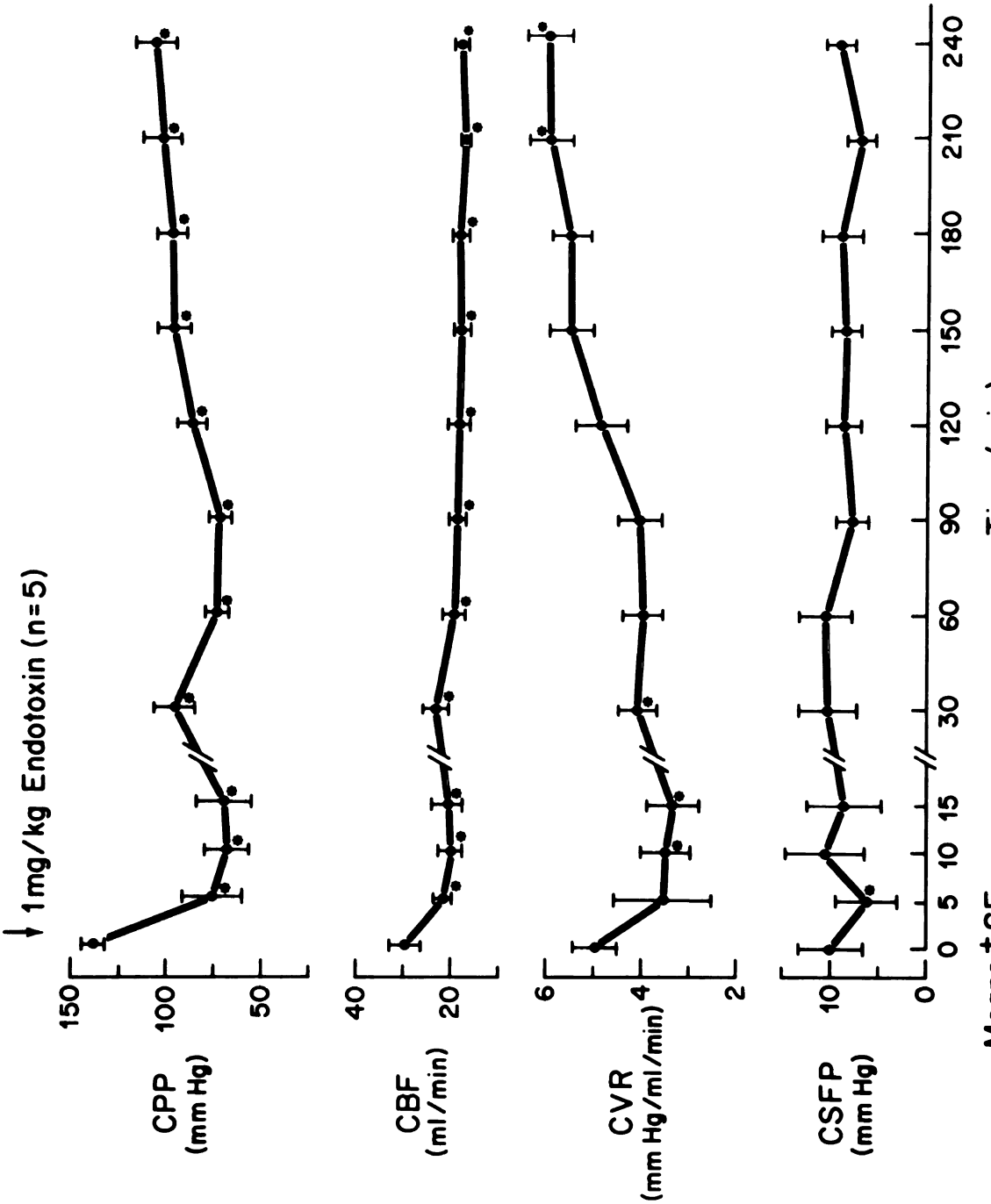

↓ 1mg/kg Endotoxin (n=5)
CPP (mm Hg)
150
100
50
CBF (ml/min)
40
20
CVR (mm Hg/ml/min)
6
4
2
CSFP (mm Hg)
10
0
0 5 10 15 30 60 90 120 150 180 210 240
Time (min)
Means ± SE
•p<0.05

Figure 6

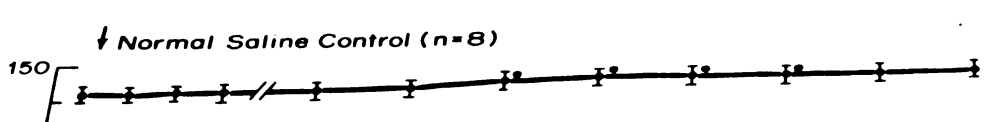
Figure 7. Average hemodynamic responses of the cerebral vascular bed during control experiments.

CPP = cerebral perfusion pressure

CBF = cerebral blood flow

CVR = cerebral vascular resistance

CSFP = cerebrospinal fluid pressure



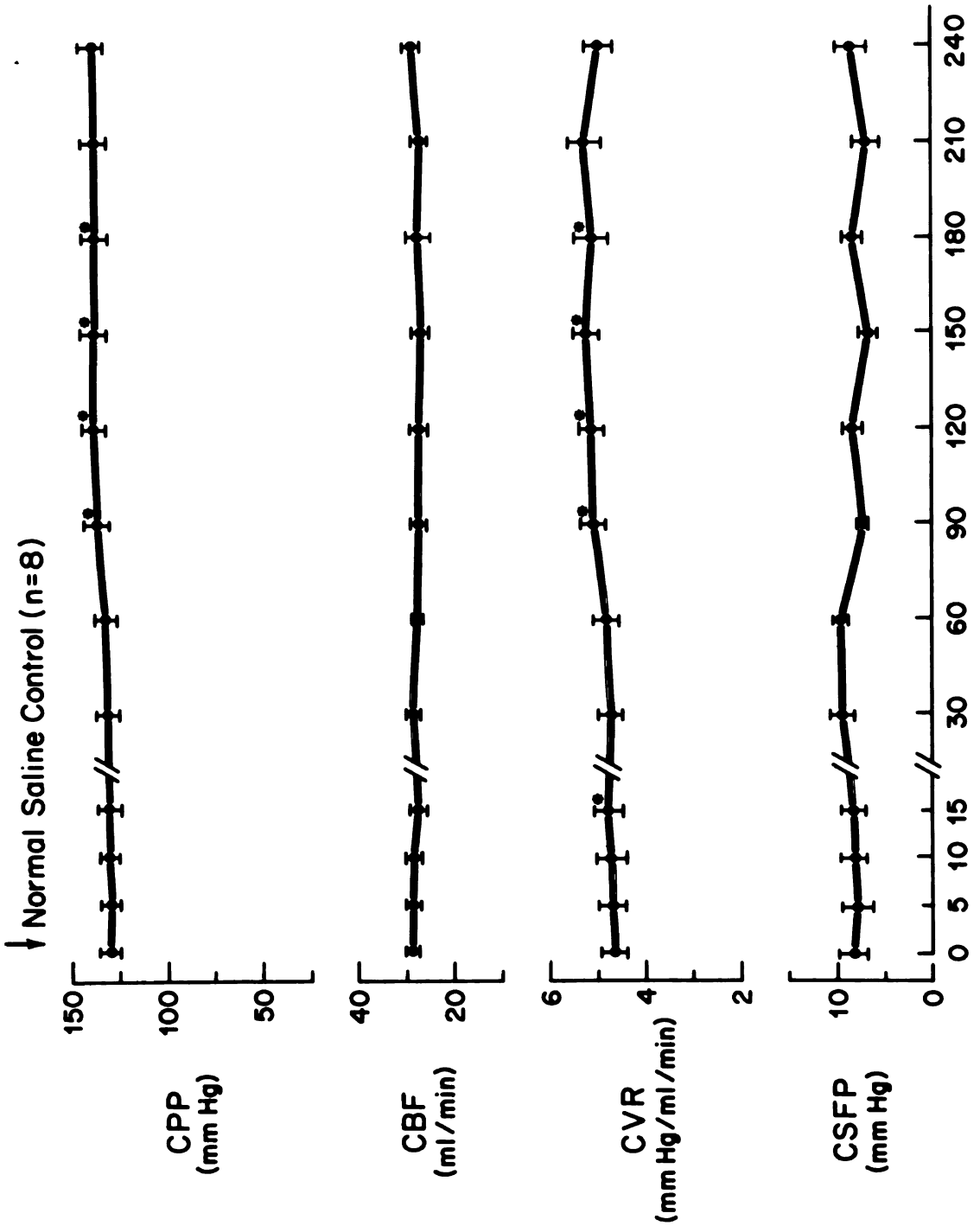

Normal Saline Control (n=8)
CPP (mm Hg)
150
100
50
CBF (ml/min)
40
20
CVR (mm Hg/ml/min)
6
4
2
CSFP (mm Hg)
10
0
0 5 10 15 30 60 90 120 150 180 210 240
Time (min)
Means ± SE
*p<0.05

Figure 7

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preparation were a small increase in cerebral perfusion pressure and cerebral vascular resistance from min 90-180, and a very slight increase in resistance at min 15. The increased perfusion pressure was due to a small rise in systemic pressure during this time period, and as a result, the concomitant period of increased cerebral vascular resistance may be due to autoregulation of the cerebral vasculature, as cerebral blood flow did not change during the entire 4 hours. Cerebrospinal fluid pressure also remained unchanged.

A composite of the percent change of the cerebral blood flow responses of each of the four groups mentioned above is shown in Figure 8. The percent change of cerebral blood flow was significant at least at the $P < 0.05$ level at every point for each dose of endotoxin. At four hours post-endotoxin cerebral blood flow in the 1, 2, and 5 mg/kg doses was reduced by 37, 48, and 45%, respectively. In contrast, at none of these points did the cerebral blood flow in the control series change significantly. At four hours post-endotoxin the percent change of cerebral blood flow was significant at the $P < 0.001$ levels for the animals receiving 2 mg/kg endotoxin, and at the $P < 0.01$ levels for the 1 mg/kg dose. Of course, the n value for the two groups was different, but the general trend of the graphs shown indicates a greater effect of 2 mg/kg and 5 mg/kg endotoxin in reducing blood flow than the 1 mg/kg dose.

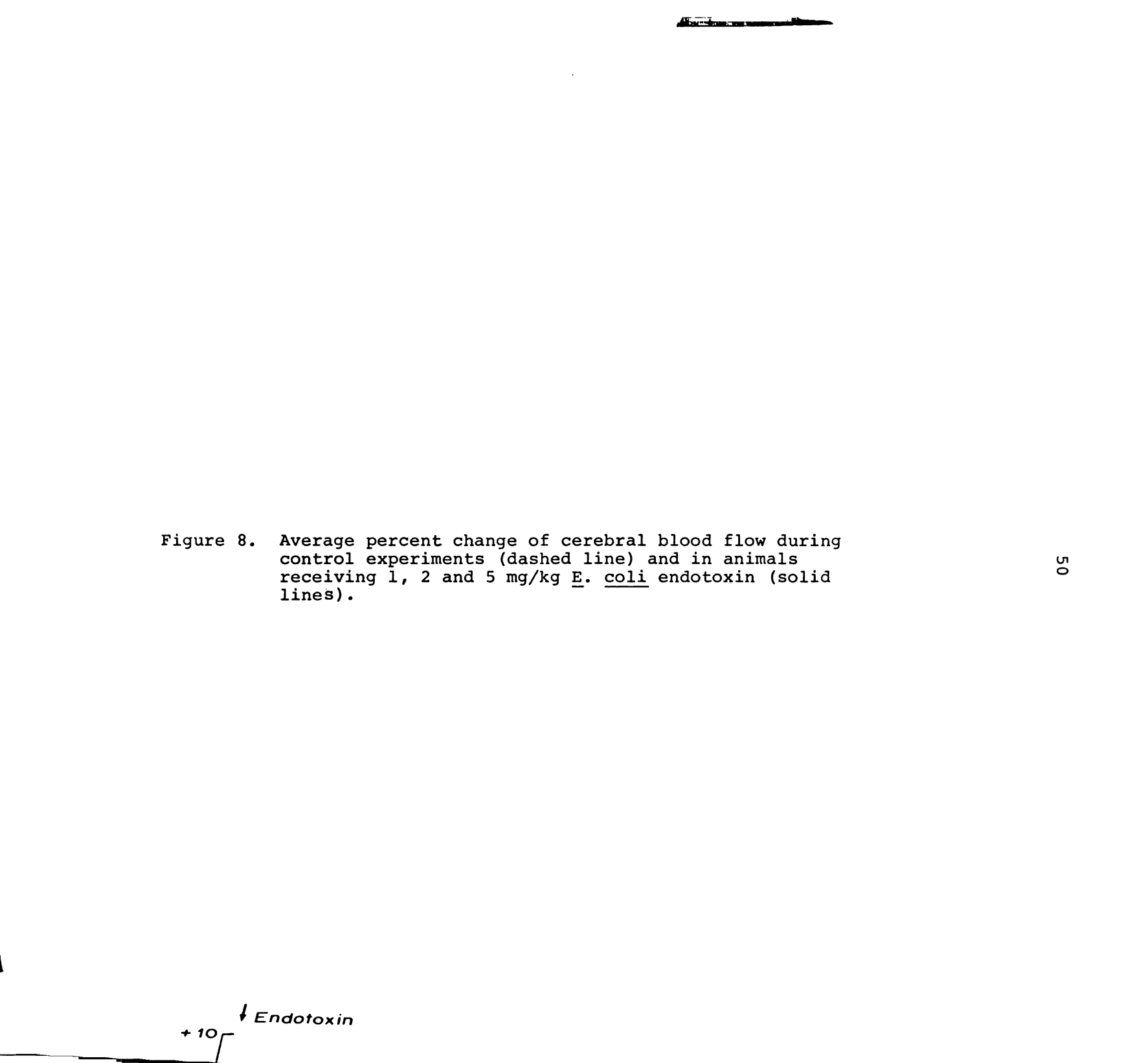

Figure 8. Average percent change of cerebral blood flow during control experiments (dashed line) and in animals receiving 1, 2 and 5 mg/kg E. coli endotoxin (solid lines).

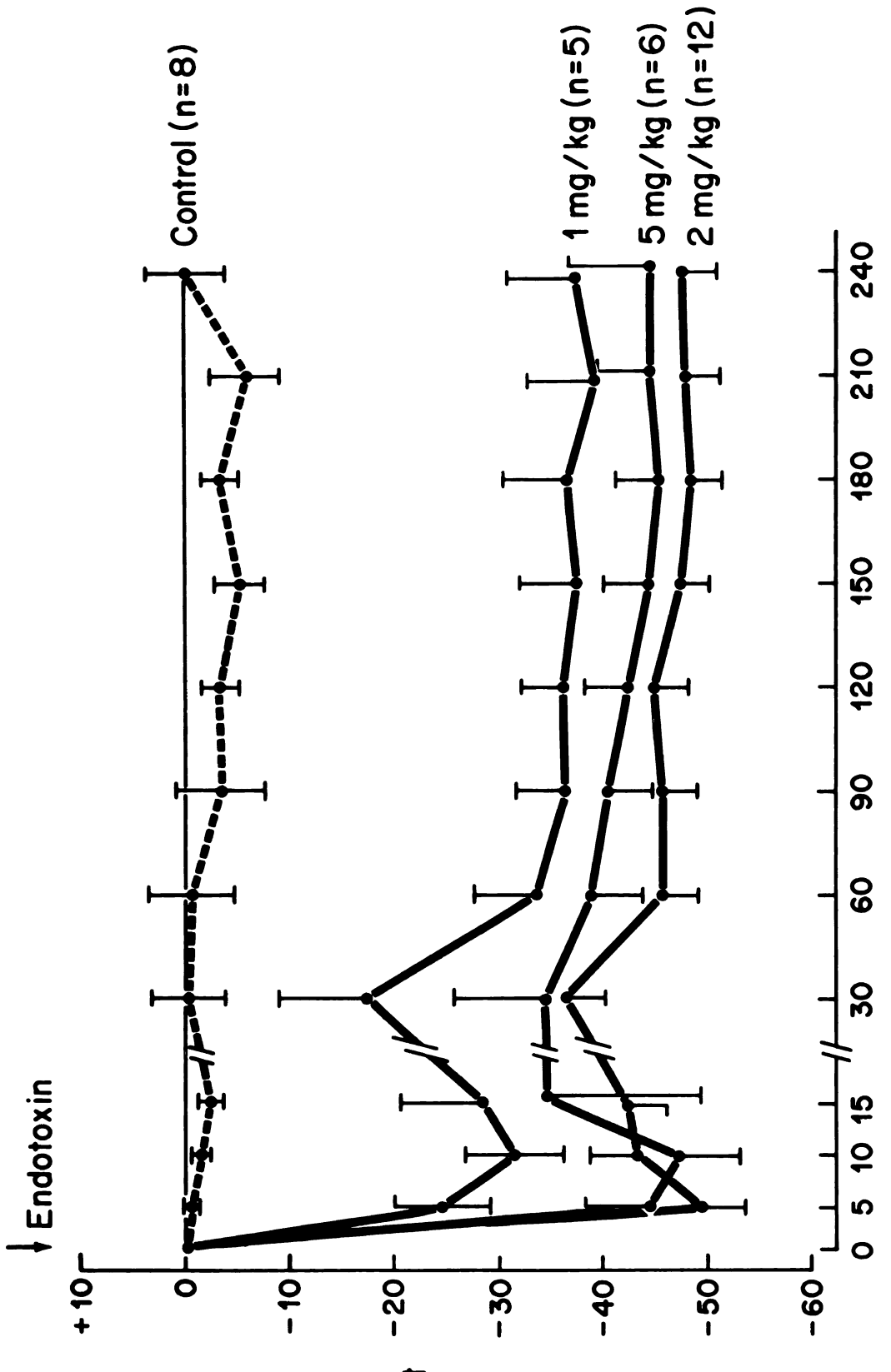
Endotoxin
Control (n=8)
1 mg/kg (n=5)
5 mg/kg (n=6)
2 mg/kg (n=12)
+10
0
-10
-20
-30
-40
-50
-60
Percent Change (%)
0 5 10 15 30 60 90 120 150 180 210 240
Time (min)
Means ± SE

Figure 8

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The percent change of cerebral vascular resistance in these groups is shown in Figure 9. Again, it appears that the percent increase in resistance is greatest in the 2 mg/kg dose and least in the 1 mg/kg dose of endotoxin. At four hours post-endotoxin, the 1, 2, and 5 mg/kg doses of endotoxin had increased cerebral vascular resistance by 25, 55, and 37%, respectively ($P < 0.05$). Cerebral vascular resistance in the control experiments had increased 6.6%, a value not significantly different from control ($P > 0.05$). As indicated on the graph, the general response of all doses of endotoxin was that of an initial transitory decrease in cerebral vascular resistance, a leveling off at near control levels, and a gradual increase over the remainder of the experiment. Interestingly, however, in the lowest dose of endotoxin (1 mg/kg), the percent change of cerebral vascular resistance remained significantly below control for the entire first hour, whereas the 2 mg/kg dose returned to control levels by min 10, although the initial decrease for the two doses was nearly identical. Thus, it appears that the initial dilation period was extended in the lower dose of endotoxin; indeed the subsequent increase in resistance was also delayed and became significant only during the final 30 minutes of the fourth hour. Although individual points of the 2 and 5 mg/kg doses were not significantly different using the Student's t test, two-way analysis of variance was performed on the data comprising these two

Figure 9. Average percent change of cerebral vascular resistance during control experiments (dashed line) and in animals receiving 1, 2 and 5 mg/kg endotoxin (solid lines).

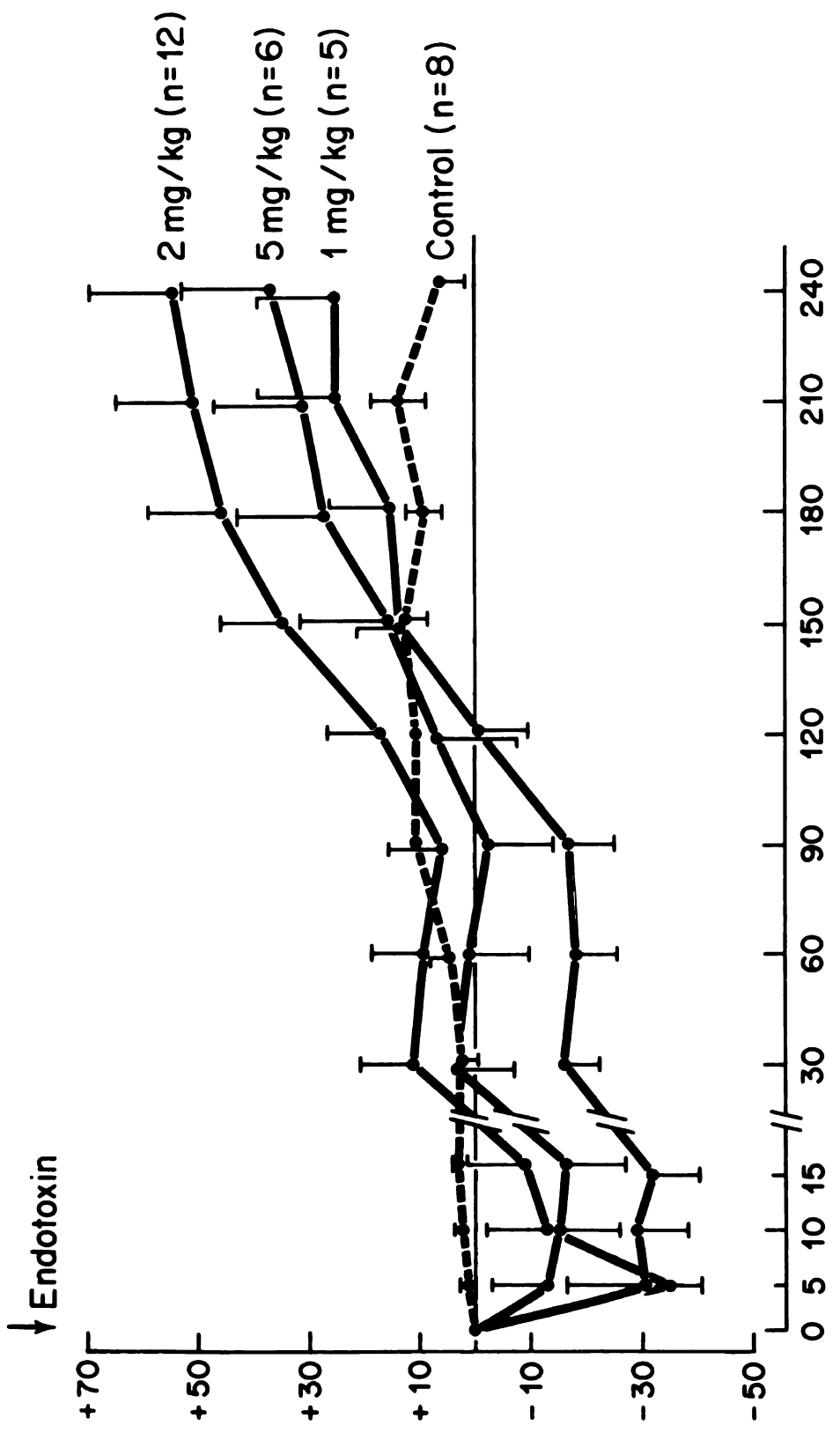

2 mg/kg (n=12)
5 mg/kg (n=6)
1 mg/kg (n=5)
Control (n=8)
Endotoxin
+70
+50
+30
+10
-10
-30
-50
Percent Change (%)
0 5 10 15 30 60 90 120 150 180 210 240
Time (min)
Means (T=1SE)

Figure 9

curves. The "F" value demonstrated that these curves were significantly different from each other at the 0.01 level of confidence. Thus, indeed, the 2 mg/kg dose appeared to be most effective in increasing cerebral vascular resistance. The 1 and 5 mg/kg dose curves were not significantly different utilizing this method of analysis.

Results of the experiments which were given a dose of 2 mg/kg endotoxin and were followed for a total of 6 hours are illustrated in Figure 10. This graph demonstrates that the increase in resistance described previously as occurring from hours 2 to 4 began leveling off from hours 4 to 6. In turn, cerebral blood flow decreased only slightly from hours 4 to 6, and no further increase in perfusion pressure was noted during these hours.

Alterations in Cerebral Vascular Reactivity

Responses of the cerebral vascular bed to progressive decreases in cerebral perfusion pressure (autoregulation), increases in cerebral venous pressure (venous-arteriolar response), and increases in arterial P_{CO_2} levels (response to CO_2 challenge) are illustrated in Figures 11-14. Figure 11 exhibits the plots of the autoregulatory curves before and after 4 hours of shock due to 2 mg/kg endotoxin. In the upper graph A, the mean cerebral vascular resistance prior to endotoxin administration (solid line) decreased as the perfusion pressure decreased over the range from control

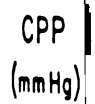
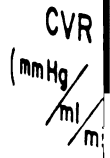


Figure 10. Average hemodynamic responses of animals receiving 2 mg/kg E. coli endotoxin and followed for six hours.

CPP = cerebral perfusion pressure

CBF = cerebral blood flow

CVR = cerebral vascular resistance



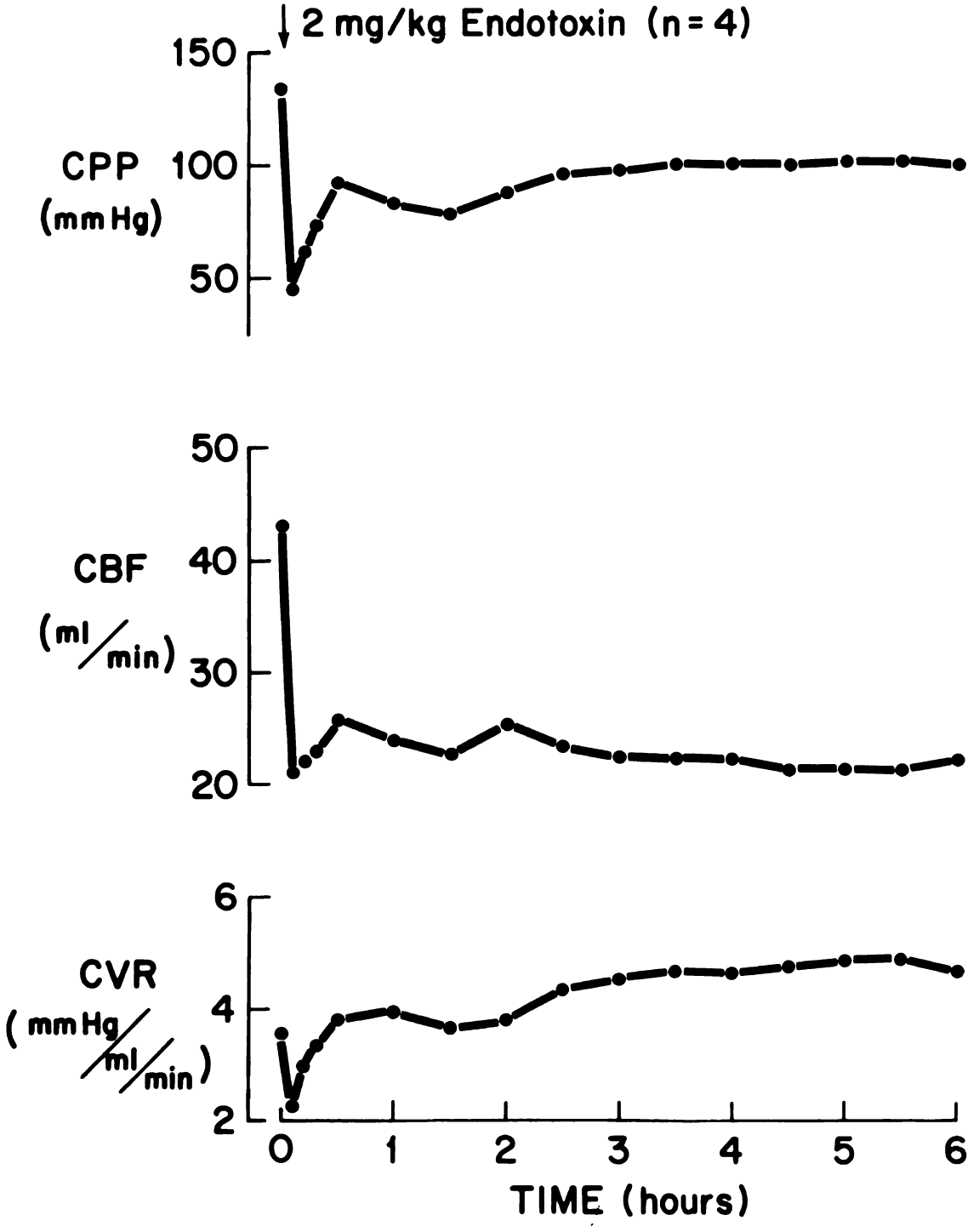

2 mg/kg Endotoxin (n = 4)
150
CPP
100
(mm Hg)
50
50
CBF
40
(ml/min)
30
20
6
CVR
4
(mm Hg/ml/min)
2
0
1
2
3
4
5
6
TIME (hours)

Figure 10

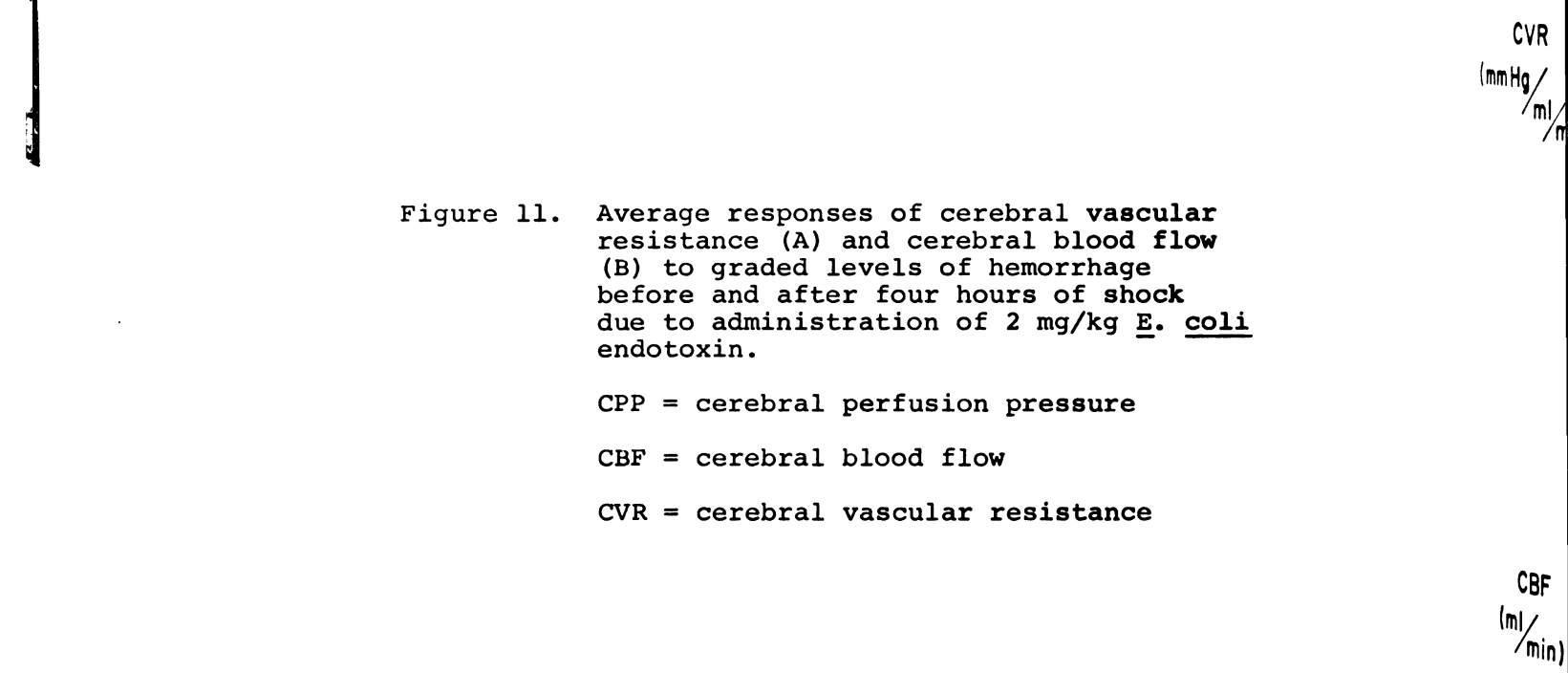


Figure 11. Average responses of cerebral vascular resistance (A) and cerebral blood flow (B) to graded levels of hemorrhage before and after four hours of shock due to administration of 2 mg/kg E. coli endotoxin.

CPP = cerebral perfusion pressure

CBF = cerebral blood flow

CVR = cerebral vascular resistance

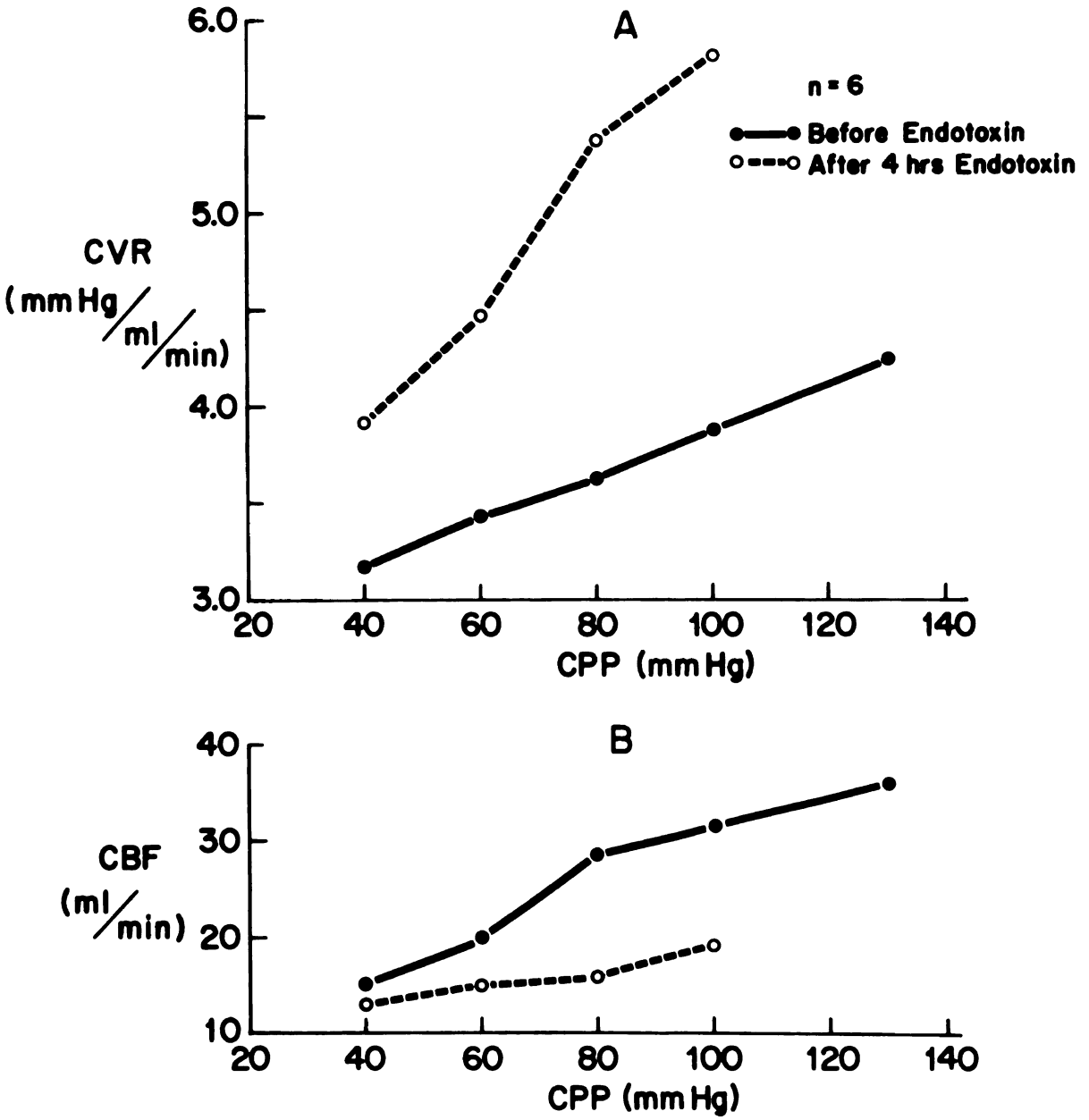

A
n = 6
Before Endotoxin
After 4 hrs Endotoxin
CVR
(mm Hg / ml / min)
6.0
5.0
4.0
3.0
20
40
60
80
100
120
140
CPP (mm Hg)
B
CBF
(ml / min)
40
30
20
10
20
40
60
80
100
120
140
CPP (mm Hg)

Figure 11

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(130 mm Hg) to 40 mm Hg. The decrease in resistance was significant ($P < 0.05$) at 80, 60, and 40 mm Hg and occurred in all but one animal at 100 mm Hg. Following four hours of endotoxin shock (dashed line) cerebral vascular resistance decreased in every animal with each decrease in perfusion pressure over the range from 100 mm Hg to 40 mm Hg. The lower graph, B, shows the changes occurring in the cerebral blood flow during the same decreases in cerebral perfusion pressure. Before endotoxin, cerebral blood flow decreased from 31.8 to 28.4 ml/min as cerebral perfusion pressure was dropped from 100 to 80 mm Hg, the average decrease being 19%. After 4 hours of shock, as cerebral perfusion pressure was again dropped from 100 to 80 mm Hg, cerebral blood flow decreased from 19.3 to 16.0 ml/min, the average decrease being only 9%. In addition, the slope of the line after endotoxin (dashed line) is not as great, i.e., the line is more horizontal to the pressure axis, than that before endotoxin (solid line). Thus, the autoregulatory response is unimpaired following shock.

Figure 12 illustrates the cerebral "venous-arteriolar" response to increases in venous pressure before and after 4 hours of shock due to administration of 2 mg/kg endotoxin. This graph indicates the cerebral vascular resistance changes, in absolute value and in percent change, as the cerebral venous pressure was increased to 6 and 11 mm Hg and then decreased back to control levels. Prior to

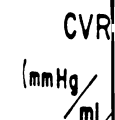
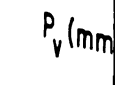


Figure 12. Average response of cerebral vascular resistance to increases in cerebral venous pressure before and after four hours of shock due to administration of 2 mg/kg E. coli endotoxin.

CVR = cerebral vascular resistance

P_V = cerebral venous pressure



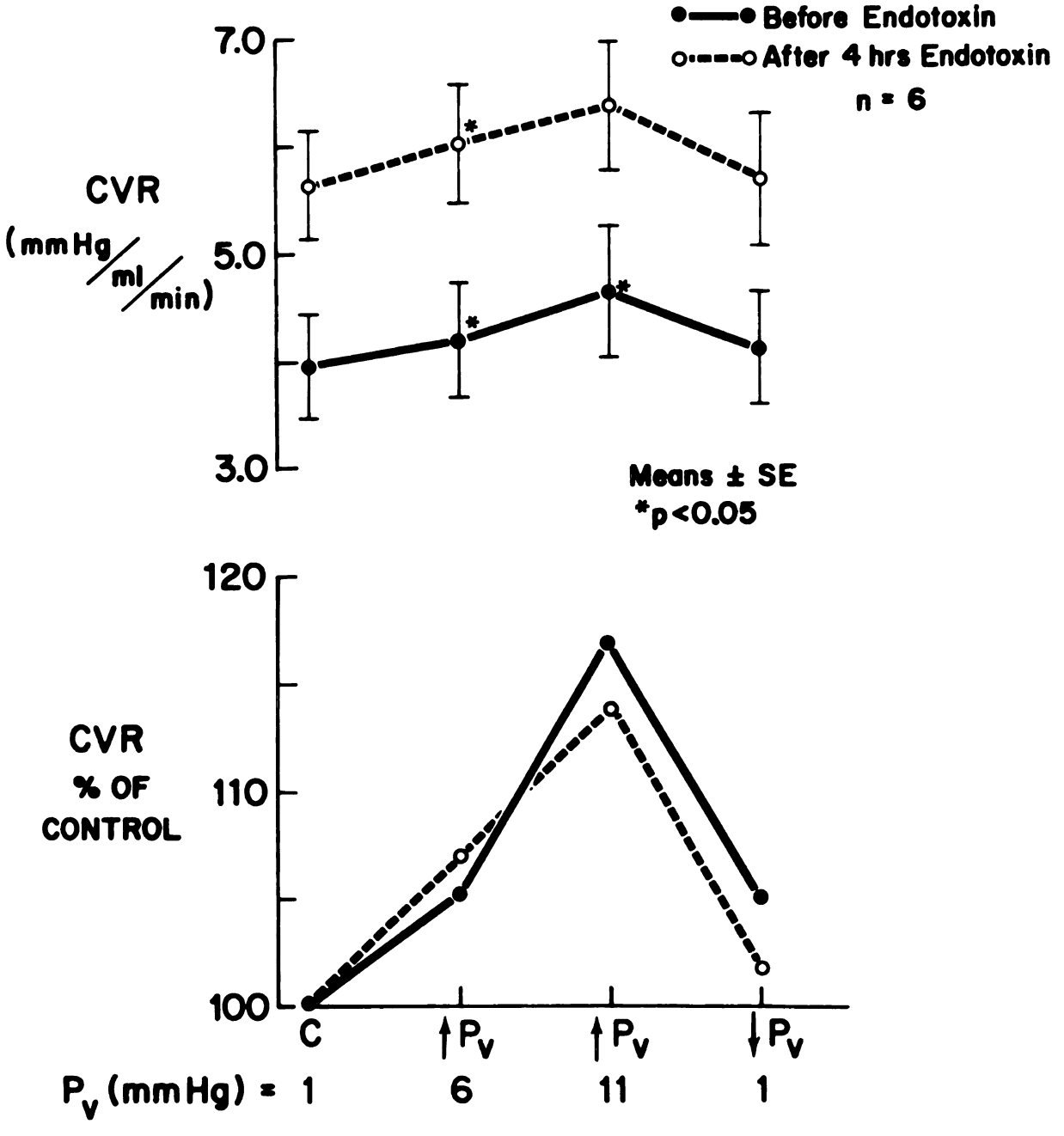

Before Endotoxin
After 4 hrs Endotoxin
n = 6
7.0
5.0
3.0
CVR
(mmHg/ml/min)
Means ± SE
*p<0.05
120
110
100
CVR
% OF
CONTROL
C
Pv
Pv
Pv
Pv (mmHg) = 1
6
11
1

Figure 12

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endotoxin administration, cerebral resistance increased each time the venous pressure was increased (5.2 and 16.8%, respectively) and then decreased as the venous pressure was reduced. After 4 hours of shock, the mean cerebral vascular resistance again increased at each increase in venous pressure (7.1 and 13.8%, respectively), and then decreased to near control as the venous pressure was reduced. Although the second increase in resistance prior to shock was not significant, only one of these animals showed a decrease. Thus, the cerebral vascular response to increases in venous pressure was maintained following the four hours of endotoxin shock.

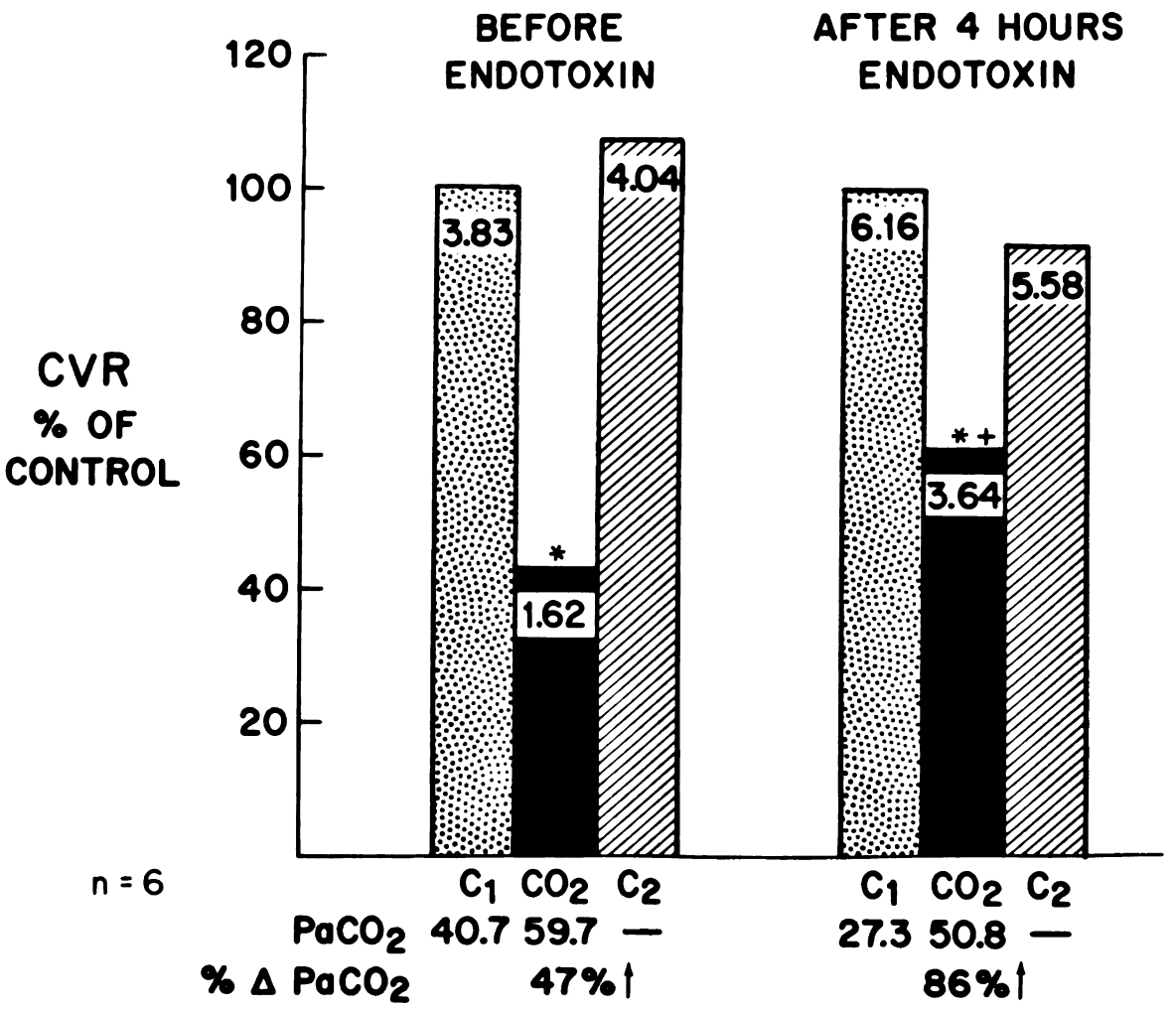
The reactivity of the cerebral vascular bed to an increase in arterial P_{CO_2} before and after 4 hours of shock due to administration of 2 mg/kg is shown in Figure 13. The absolute levels of the cerebral vascular resistance are written at the top of each bar. Prior to endotoxin, the cerebral vascular bed responded to the CO_2 challenge with a large decrease in cerebral vascular resistance to a level of 42.9% of control ($P < 0.001$). After 4 hours of shock, the cerebral vascular resistance during the increase in arterial P_{CO_2} decreased to a level of only 60.2% of control ($P < 0.001$). In addition, the percent change in resistance during shock was significantly less than that prior to shock, indicating a lessened ability of the cerebral vascular bed to dilate in response to the CO_2 challenge after endotoxin

Figure 13. Average percent change of cerebral vascular resistance due to inhalation of 7.5% carbon dioxide prior to and four hours after administration of 2 mg/kg E. coli endotoxin.

CVR = cerebral vascular resistance

C_1 = initial control state, room air ventilation

C_2 = control state after CO_2 challenge, room air ventilation



*p<0.05, compared with control, C_1

+p<0.05, compared with CO_2 before Endo

Figure 13

administration. This occurred in spite of increased vascular resistance (6.16 compared to 3.83) and a greater percent change in the P_{CO_2} (86% increase post endotoxin compared to only 47% increase prior to endotoxin). Although the absolute level of arterial P_{CO_2} during CO_2 inhalation is lower after 4 hours of shock, this decrease is not significant, and in fact, the animal which demonstrated the greatest loss of CO_2 responsiveness also showed a greater arterial P_{CO_2} during CO_2 inhalation after 4 hours of shock than before shock.

Figure 14 illustrates the hourly responses of the cerebral vascular bed to the CO_2 challenge before and during endotoxin shock. These animals are not the same as those illustrated in Figure 13, but also received 2 mg/kg endotoxin, and were interrupted every hour to test this response. Prior to endotoxin, these animals demonstrated a marked decrease in cerebral vascular resistance in response to the increased arterial P_{CO_2}, to an average of 37% of control. At only one hour post-endotoxin, this dilatory response was markedly diminished, as resistance only decreased to a value averaging 81% of control, in response to the increased P_{CO_2}. Average values of percent of control at 2, 3, and 4 hours post-endotoxin were 80, 79, and 75%, respectively. In every animal, the cerebral vascular resistance decreased with each CO_2 challenge, but the decrease was always considerably smaller than that observed in the control state.

Figure 14. Average percent change of cerebral vascular resistance due to inhalation of 7.5% carbon dioxide prior to and at hourly intervals after administration of 2 mg/kg *E. coli* endotoxin.

CPP = cerebral perfusion pressure

CVR = cerebral vascular resistance

C = control state, room air ventilation

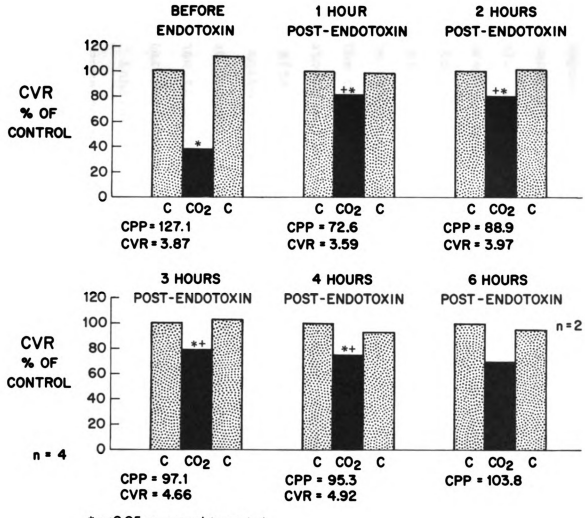

BEFORE ENDOTOXIN
1 HOUR POST-ENDOTOXIN
2 HOURS POST-ENDOTOXIN
CVR % OF CONTROL
120
100
80
60
40
20
0
C CO2 C
CPP = 127.1
CVR = 3.87
CPP = 72.6
CVR = 3.59
CPP = 88.9
CVR = 3.97
3 HOURS POST-ENDOTOXIN
4 HOURS POST-ENDOTOXIN
6 HOURS POST-ENDOTOXIN
n = 2
n = 4
CPP = 97.1
CVR = 4.66
CPP = 95.3
CVR = 4.92
CPP = 103.8
*p<0.05 compared to control
+p<0.05 compared to CO2 before Endo

Figure 14

Two additional animals from another group were studied at 6 hours post-endotoxin, and their data is also presented here for comparison. As indicated, even at 6 hours, the CO_2 response was still depressed. The cerebral vascular resistance at this time only decreased at a level of 69% of control. Cerebral vascular resistance and cerebral perfusion pressure at each hour prior to CO_2 inhalation is also given to point out that the resistance pattern of this group of animals was similar to that previously reported for the other experimental groups.

The control series of experiments clearly maintained the autoregulatory and venous-arteriolar responses four hours after initiation of the control period. In addition, these animals, in contrast to those which received endotoxin, did not demonstrate a decrease in the cerebral vascular response to increased arterial P_{CO_2}. Initially, cerebral bascular resistance decreased to 33% of control in response to CO_2 inhalation, and four hours later, cerebral vascular resistance decreased to 35% of control during CO_2 inhalation. In two control experiments which were followed for a total of 6 hours, cerebral vascular resistance decreased to 32% of control in response to the CO_2 challenge both before and after 4 hours of shock.

Cerebral Metabolic Changes

Systemic arterial and cerebral venous blood gas changes during endotoxin shock are shown in Figures 15-18. As shown in Figure 15, immediately following the administration of 2 mg/kg endotoxin, the respiratory rate increased dramatically and remained significantly above control during the entire four hours. Arterial P_{O_2} remained increased over nearly all of the experimental period, while cerebral venous P_{O_2} decreased by 60 min and remained depressed. Arterial P_{CO_2} decreased below normal, and except for a slight decrease at 30 min, the cerebral venous P_{CO_2} remained unchanged following endotoxin administration. Blood pH decreased considerably in the cerebral venous blood except at the fourth hour, and except for an initial transient decrease during the first hour, the arterial pH was unchanged following endotoxin administration. Thus, the major changes which occurred in the cerebral venous blood during endotoxin shock due to 2 mg/kg endotoxin were a decrease in P_{O_2} and pH.

As seen in Figures 16 and 17, the blood gas and respiratory alterations which occurred following administration of the 5 mg/kg and 1 mg/kg doses of endotoxin were comparable to those described above. The respiratory responses of these doses were variable, but often significantly increased. The venous blood gases of both doses indicate a decreased P_{O_2} and a significantly unchanged but tending to increase P_{CO_2} over the four hours. The cerebral venous pH decreased

Figure 15. Average responses of respiratory rate, and systemic arterial and venous blood gases following administration of 2 mg/kg E. coli endotoxin.

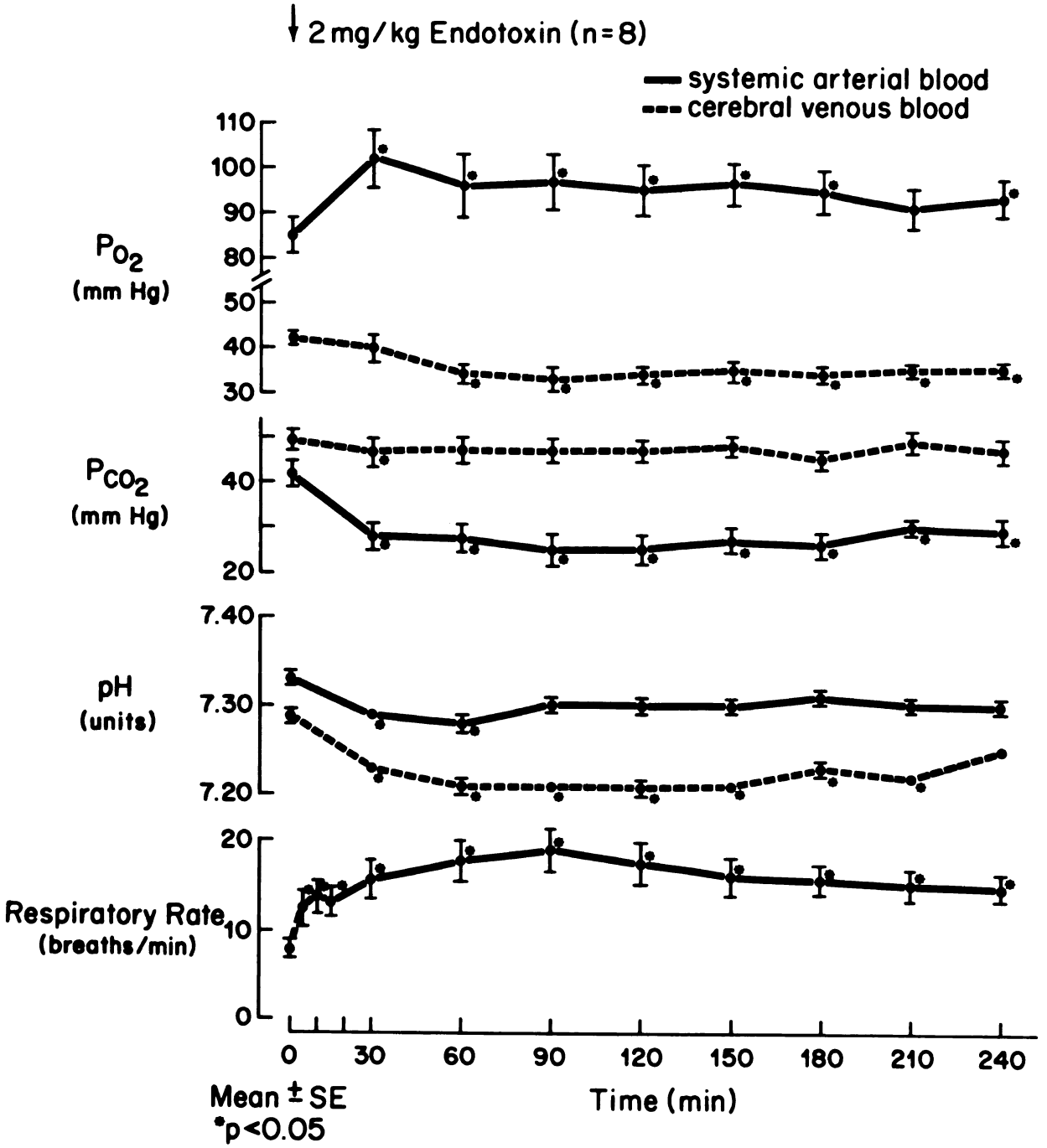

2 mg/kg Endotoxin (n=8)
systemic arterial blood
cerebral venous blood
P_{O_2} (mm Hg)
110
100
90
80
50
40
30
P_{CO_2} (mm Hg)
40
20
pH (units)
7.40
7.30
7.20
Respiratory Rate (breaths/min)
20
10
0
0
30
60
90
120
150
180
210
240
Time (min)
Mean ± SE
*p<0.05

Figure 15

Figure 16. Average responses of respiratory rate, and systemic arterial and venous blood gases following administration of 5 mg/kg E. coli endotoxin.

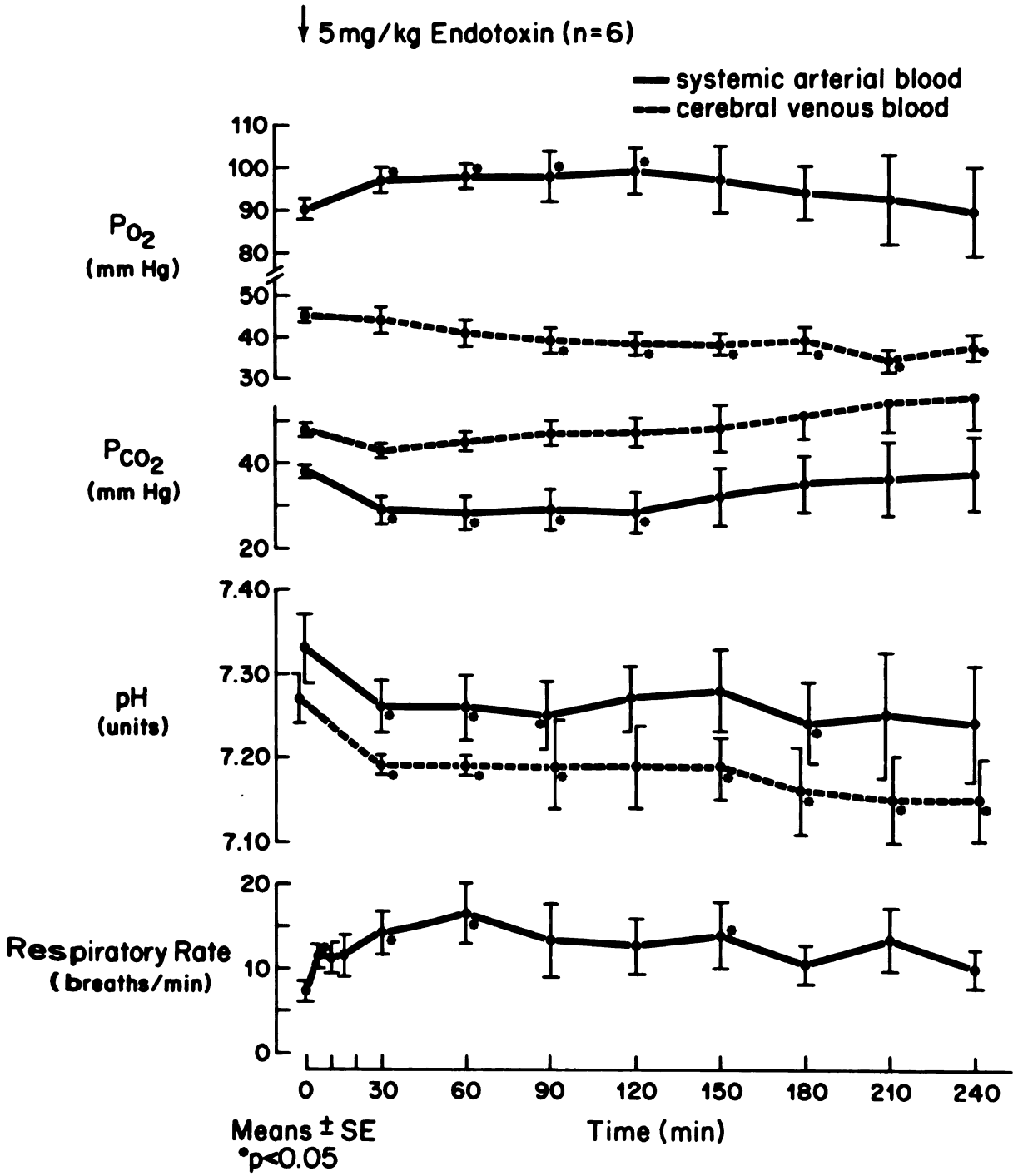

5mg/kg Endotoxin (n=6)
systemic arterial blood
cerebral venous blood
P_{O_2} (mm Hg)
110
100
90
80
50
40
30
P_{CO_2} (mm Hg)
40
20
pH (units)
7.40
7.30
7.20
7.10
Respiratory Rate (breaths/min)
20
10
0
0
30
60
90
120
150
180
210
240
Means ± SE
*p<0.05
Time (min)

Figure 16

Figure 17. Average responses of respiratory rate, and systemic arterial and venous blood gases following administration of 1 mg/kg *E. coli* endotoxin.

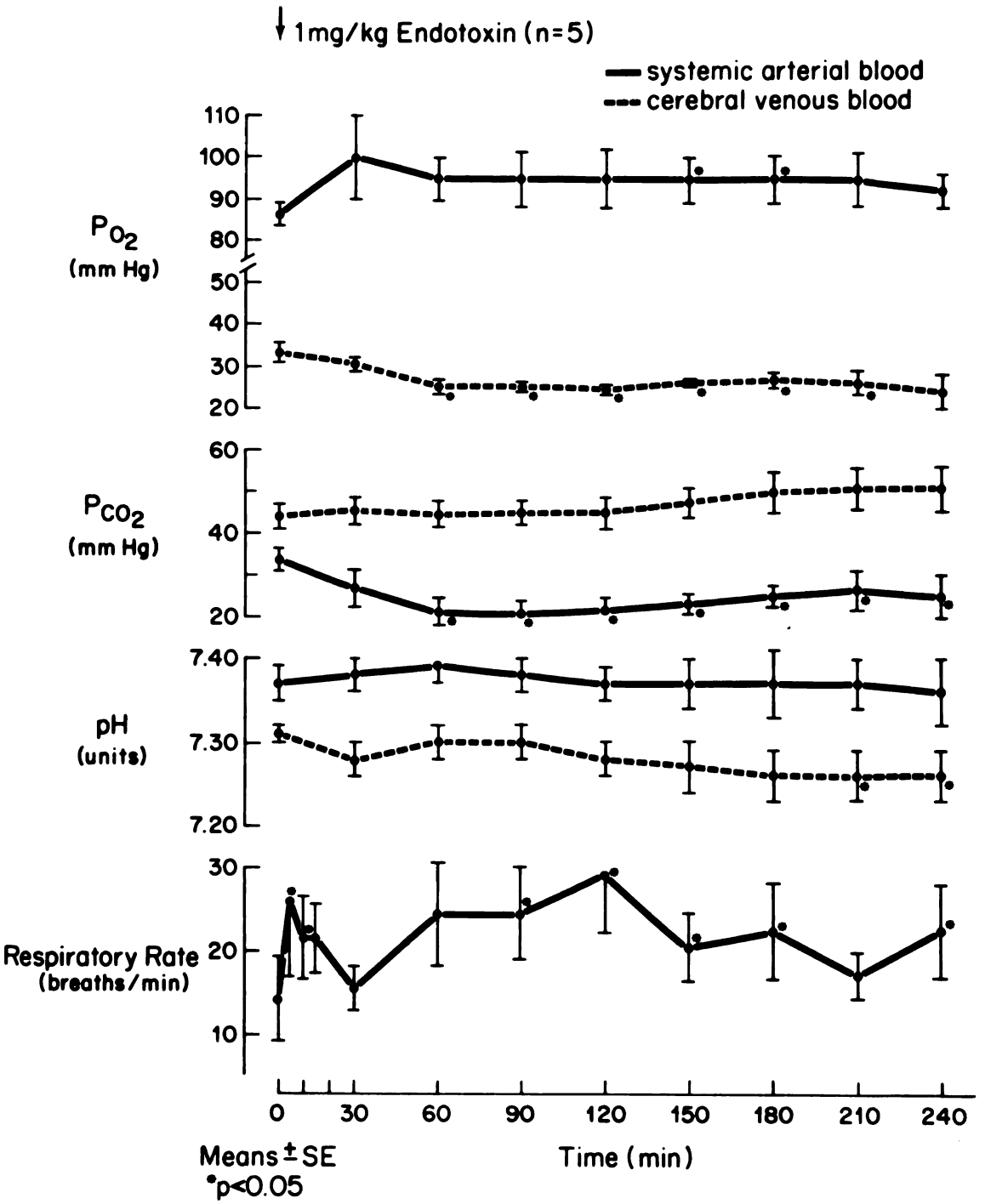

1mg/kg Endotoxin (n=5)
systemic arterial blood
cerebral venous blood
P_{O_2} (mm Hg)
110
100
90
80
50
40
30
20
P_{CO_2} (mm Hg)
60
40
20
pH (units)
7.40
7.30
7.20
Respiratory Rate (breaths/min)
30
20
10
0
30
60
90
120
150
180
210
240
Means ± SE
*p<0.05
Time (min)

Figure 17

further and more quickly following administration of the 5 mg/kg dose than either the 1 mg/kg or 2 mg/kg doses of endotoxin.

The animal's body temperature and the P_{CO_2}, P_{O_2}, and pH values shown above for the 2 mg/kg dose were used to calculate the arterial and cerebral venous oxygen saturation, total CO_2 (mMol/l plasma) and bicarbonate (HCO_3^-, mEq/l plasma) from the Siggaard-Anderson alignment nomogram. The changes occurring in these parameters during endotoxin shock are shown in Figure 18. As illustrated, the arterial-venous differences of all three parameters increased during endotoxin shock. The increase in the arterial-venous difference of the oxygen saturation was due to decreased oxygen saturation of the cerebral venous blood. Although hemoglobin content was not measured, one can tell intuitively from this graph that the arterial-venous difference for oxygen content increased dramatically, also. In turn, the increases in arterial-venous differences of total CO_2 and HCO_3^- were due to disproportionate decreases in arterial levels of these values rather than to increases in the venous values; indeed, the venous levels of total CO_2 and HCO_3^- actually tended to decrease.

None of these alterations in systemic arterial or cerebral venous blood gases occurred in the saline control experiments, as seen in Figure 19. Respiratory rate also

Figure 18. Average responses of systemic arterial and cerebral venous oxygen saturation, total CO_2 and HCO_3^- content following administration of 2 mg/kg E. coli endotoxin.

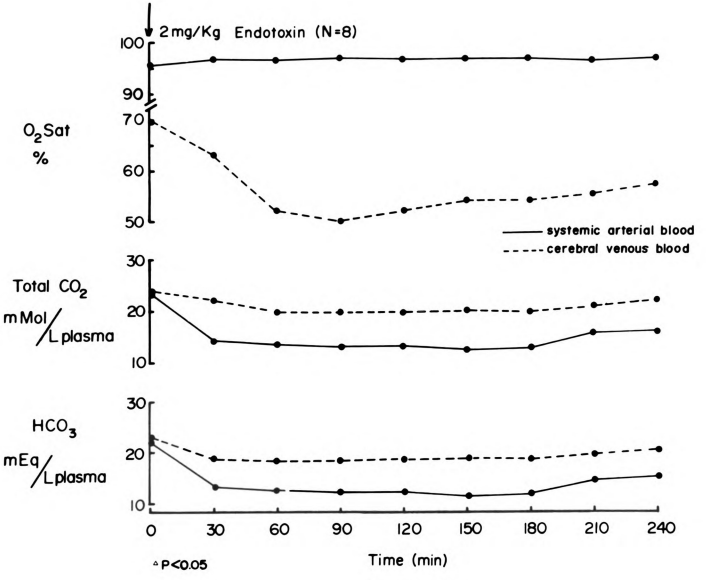

2 mg/Kg Endotoxin (N=8)
100
90
70
60
50
O_2Sat
%
systemic arterial blood
cerebral venous blood
30
20
10
Total CO_2
mMol/L plasma
30
20
10
HCO_3
mEq/L plasma
0
30
60
90
120
150
180
210
240
Time (min)
▵ P<0.05

Figure 18

Figure 19. Average responses of respiratory rate, and systemic arterial and venous blood gases during control experiments.

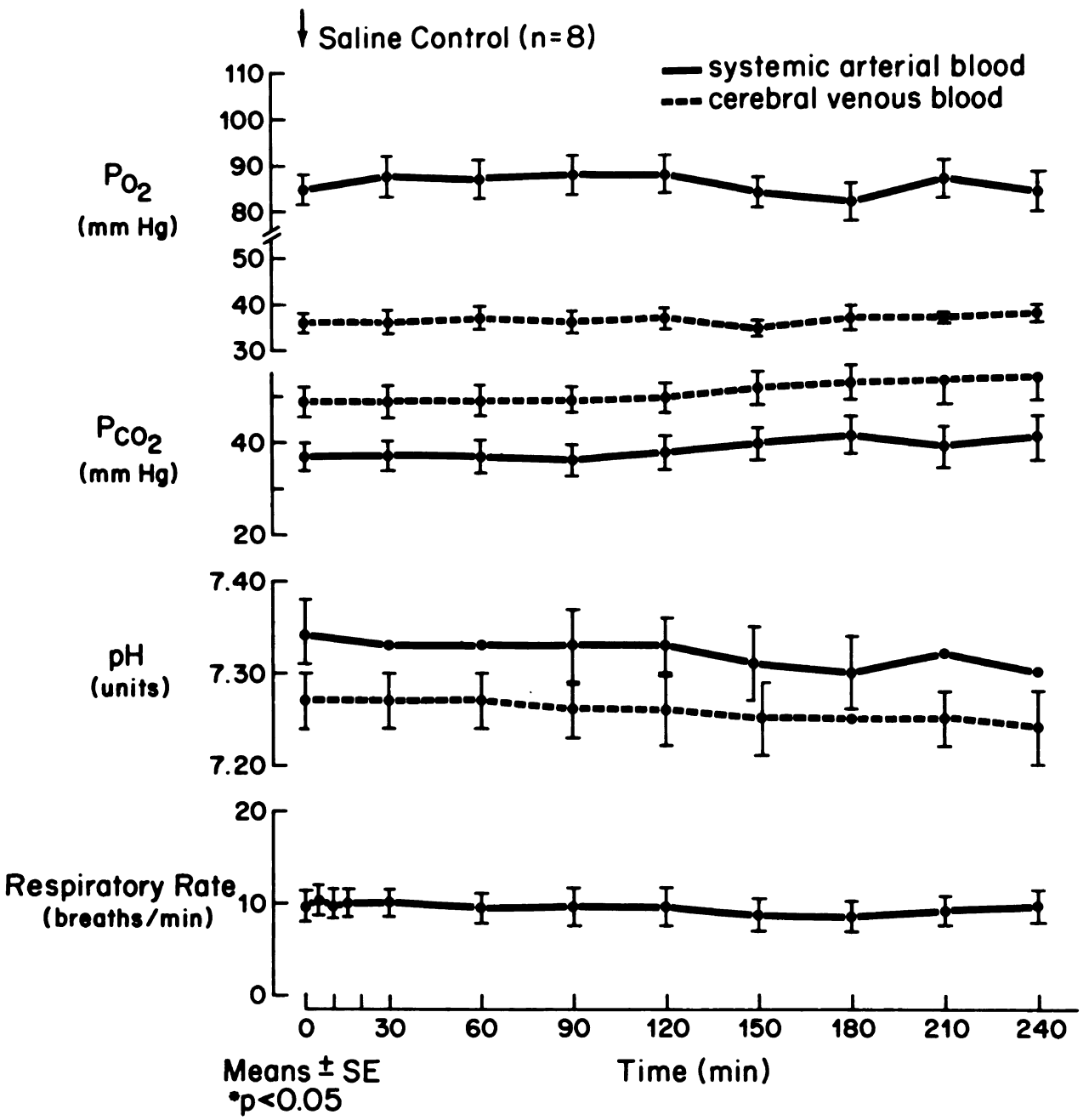

Saline Control (n=8)
systemic arterial blood
cerebral venous blood
P_{O_2} (mm Hg)
110
100
90
80
50
40
30
P_{CO_2} (mm Hg)
40
20
pH (units)
7.40
7.30
7.20
Respiratory Rate (breaths/min)
20
10
0
0
30
60
90
120
150
180
210
240
Means ± SE
*p<0.05
Time (min)

Figure 19

remained statistically unchanged throughout the four hour observation period of the control experiments.

CHAPTER V

DISCUSSION

The intravenous administration of purified E. coli endotoxin into dogs produced significant changes in each of the three areas studied: 1) cerebral hemodynamics, 2) cerebral vascular reactivity, and 3) arterial and cerebral venous blood gases. Cerebral blood flow was considerably decreased during the entire four to six hour experimental period. Cerebral vascular resistance transiently decreased, returned to control levels, and gradually increased to levels above control by three hours post-endotoxin. The reactivity of the cerebral vascular bed to increased levels of P_{CO_2} was diminished, although the venous-arteriolar response and cerebral autoregulation were maintained. Finally, blood gas alterations in the cerebral vascular bed include increased arterial-venous differences of P_{O_2}, P_{CO_2}, and pH and calculated differences of percent O_2 saturation, total CO_2, and bicarbonate content increased also. The three doses of endotoxin used in this study (1, 2, and 5 mg/kg) produced responses similar in magnitude and direction, although the lowest dose tended to produce the least hemodynamic alterations.

The technique used in this study to isolate and directly measure the cerebral outflow was that described by Rapela and Green (44,94). The measurement of the cerebral venous outflow is considerably more practical and less traumatic than measuring arterial inflow. The measurement of arterial inflow requires more extensive dissection and metering of blood flow in at least four arteries simultaneously because of the numerous arterial anastomoses between intra and extracranial circulations (44). With the current technique, a portion of the cerebral venous outflow is collected directly without contamination from extra-cerebral vascular beds. The surgery involved is a relatively simple dissection which eliminates communications of the cranial and extracranial veins and sinuses of the skull. This separation is supported by latex injection studies which demonstrate that no significant amount of the blood escapes from this portion of the brain via communications with collateral venous channels (44). It is important to remember that all experimental preparations were required to meet the following criteria before considered acceptable for use: 1) a rapid increase in cerebral venous pressure to at least 40 mm Hg during transient occlusion of the outflow tubing, and 2) good cerebral reactivity as demonstrated by autoregulation and good vasodilation in response to CO_2 inhalation. The first criterion insures a tight, relatively communication-free system for collection of the cerebral venous outflow, and

autoregulation and cerebral vasodilation during systemic hypercapnia are considered outstanding characteristics of a reactive cerebral vascular bed (9,35,70,94).

Administration of endotoxin caused a rapid and severe depression of cerebral blood flow over the entire observation period of 4 to 6 hours. By the fourth hour of shock, the 1, 2, and 5 mg/kg doses of endotoxin had reduced cerebral blood flow by 37, 48, and 45%, respectively. These results are in agreement with those previously reported in similar experiments (30,31) performed in artificially respired dogs. In these animals, a 2 mg/kg dose of endotoxin initially decreased cerebral blood flow to 63% of control, and by the fourth hour of shock, cerebral blood flow had decreased to 40% of control. In contrast, Buyniski et al. (15) similarly measured cerebral blood flow and reported that cerebral vascular conductance was increased following administration of S. typhosa endotoxin, and that cerebral blood flow decreased only slightly. However, blood flow was measured for only one hour after endotoxin administration.

Other investigators, utilizing different techniques to measure cerebral blood flow, have reported evidence for a decrease in cerebral blood flow during endotoxin shock. Gallo and Schenk (39) reported a decrease in carotid and vertebral blood flows following administration of 5 mg/kg endotoxin to dogs. Weiner (123) administered 10 mg/kg

E. coli endotoxin (LD_{88}) into rhesus monkeys and reported that cerebral blood flow had decreased from 35.2 to 7.0 ml/min at 120 minutes post-endotoxin. This decrease in blood flow is greater than that observed in the present study. Blood flow in these experiments was only followed for two hours, and was not measured directly, but was accomplished by cephalic counting of injected ^{131}Cs activity. Thus, radioactivity of the animal's entire head was counted introducing the skin and muscle vascular responses as additional considerations. Miller (83) reported the cardiovascular effects of endotoxin in unanesthetized monkeys using the distribution of radioactive microspheres to measure regional fractions of cardiac output and blood flow. This group found that the fraction of the cardiac output to the brain and brain blood flow was decreased 80 minutes after endotoxin administration.

Thus, the evidence presented in the present study for decreased cerebral blood flow following endotoxin administration is supported by most of the studies cited above, although most of these studies employed indirect methods of measuring cerebral blood flow and were not studied for longer than two hours.

It is of interest to compare these results with cerebral blood flow alterations during shock induced by hemorrhagic hypotension. Rittman and Smith (101) measured blood flow in the carotid and vertebral arteries and reported

that a 24% reduction of the blood volume was associated with a 40% reduction in "cerebral" blood flow. However, Green and Rapela (44) measured cerebral outflow directly and found that as systemic pressure was lowered stepwise, cerebral vascular resistance declined and cerebral blood flow remained at near control levels for nearly two hours of hypovolemic hypotension. The difference thus observed in the response of the cerebral vasculature in hemorrhagic hypotension and shock and in endotoxin shock may consequently indicate a difference in the significance of the cerebral vasculature and central nervous system in the pathogenesis of the two types of shock.

As with the other vascular beds of the body, the blood flow to the cerebral vascular bed is dependent upon changes in perfusion pressure (arterial pressure minus venous pressure) and the resistance to blood flow through the cerebral vasculature. In the present study, the initial decrease in cerebral blood flow occurred concomitantly with decreased systemic arterial pressure, and thus decreased cerebral perfusion pressure. Therefore, the early decrease in cerebral blood flow was due to a decreased pressure gradient across the bed rather than an increase in resistance. In fact, the immediate decrease in blood flow was associated with a decrease in cerebral vascular resistance. Subsequently, the decreased blood flow was due partially to an increasing resistance and partially to a decreased perfusion pressure,

and in the last hours studied, cerebral perfusion pressure was nearing (but not equaling) control values and as a result a greater amount of the decrease in cerebral blood flow was due to the increased vascular resistance. Thus, although the decreased cerebral perfusion pressure played a role in decreasing cerebral blood flow throughout the entire experimental period, it was primarily responsible for the decrease seen in the early hours of shock.

The pattern of cerebral vascular resistance alterations during endotoxin shock are very interesting. Following endotoxin administration, resistance transiently decreased, rose to control levels, and gradually increased to levels significantly above control by minutes 150-240, depending on the dose given. By the fourth hour of endotoxin shock, cerebrovascular resistance had increased by 25, 55, and 37% in the 1, 2, and 5 mg/kg doses, respectively. Thus, there appear to be two phases in the resistance response of the cerebral vascular bed to endotoxin: 1) an initial decrease, and 2) a long term increase.

The initial decrease in cerebral vascular resistance occurred concomitantly with the decreased cerebral perfusion pressure. Thus, it resulted from an active increase in vessel calibre, as the decreased arterial pressure would lower transmural pressure and produce a passive decrease in vessel calibre. This early decrease in resistance is probably an exhibition of the cerebral autoregulatory

phenomenon, as most authors have reported that endotoxin has no direct effect upon cerebral vasculature, as shown by local injections (15,118,123). In turn, this phenomenon may be theoretically due to: 1) increased concentration of vasodilator metabolites, 2) a myogenic response of the cerebral vascular smooth muscle, or 3) a neurogenic response mediated through decreased pressure in the carotid sinus.

The involvement of a neurogenic mechanism appears unlikely. Although it has been suggested that decreased pressure in the carotid sinus may cause cerebral dilation (100), most authors report that neither the carotid sinus or aortic pressure receptor reflexes play a necessary role in cerebral vascular autoregulation (95). Thus, the probable causes of the initial decreased vascular resistance are increased concentration of vasodilator metabolites and/or an intrinsic myogenic response. Theoretically, increased concentrations of vasodilator metabolites would occur as a result of the decreased cerebral blood flow (subsequent to decreased perfusion pressure). Possible metabolic chemicals which have been postulated as participating in local blood flow regulation in many vascular beds include oxygen, carbon dioxide, potassium, hydrogen, adenosine, adenine nucleotides, and intermediary metabolites (49,72,104) and most of these chemicals have been shown to be vasodilator in the cerebral vascular bed (72,116). The myogenic response is based on the theory that the vascular smooth muscle is inherently

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responsive to stretch or changes in tension (6,37). In this manner, a decrease in transmural pressure within the vessel causes a decreased wall tension and hence relaxation of vascular smooth muscle, resulting in vasodilation (and vice versa). Thus either or both of these two general mechanisms, metabolic and myogenic, may be important in producing the initial decreased cerebral vascular resistance concomitant with the decreased cerebral perfusion pressure.

These studies show that the long-term resistance response of the cerebral vascular bed is an increase. Resistance increased with all three doses of endotoxin by at least the fourth hour of shock, and was maintained through the sixth hour post-endotoxin in the extended experiments. Resistance increased in the face of a rising arterial (and thus transmural) pressure, indicating an active decrease in cerebral vessel calibre, although passive factors could be involved, as will be discussed later. This response was not simply a loss of the cerebral autoregulatory response, as the cerebral vascular bed was at least as capable of autoregulation after 4 hours of shock as during the control state prior to endotoxin administration (Figure 11). However, a theoretical possibility of an altered but intact cerebral autoregulatory response around a lowered cerebral blood flow cannot be excluded.

The mechanism involved in the resistance rise is unknown. This effect, however, is probably due to some

biological response of the animal to the endotoxin rather than a direct effect of the endotoxin upon the vasculature. It is known that endotoxin administration causes the release of vasoactive substances (27,31,83,123). In this regard, the release of histamine (61,119), kinins (123), and catecholamines (50,109) have been reported to occur during endotoxin shock. In general, however, the cerebral vascular bed has been shown to be poorly responsive to most of these chemicals, including catecholamines (97), although this is highly controversial. Vasoconstrictor prostaglandins are another possibility, as they have been suggested as being involved in the local regulation of cerebral blood flow under certain conditions (126) and have been shown to be released during endotoxin shock (3). However, Emerson et al. (32,33) recently demonstrated little or no vasoconstrictor effects of $PGF_{2\alpha}$ or PGE_1 in the cerebral vasculature. Serotonin has also been reported to significantly decrease carotid artery blood flow (46) and produce vasoconstriction of pial vessels when applied topically to the surface of the brain (98). However, Davis et al. (22) have shown that the amounts of serotonin released during endotoxin shock are small and occur only within the first 5 minutes. The time course in the present experiments for the development of the increased cerebral vascular resistance was 3 to 4 hours, and so serotonin does not appear to be a likely candidate for causing the increased resistance. Thus, although

certainly a possibility, it is difficult to define a specific vasoactive agent responsible for the long term increase in resistance observed during endotoxin shock, and, in addition, if such a substance is responsible, it does not decrease or abolish the cerebral autoregulatory or venous-arteriolar responses.

Changes in plasma osmolality have been shown to affect vascular resistance and blood flow (41,105). Also marked hypoglycemia has been reported to occur late in shock (36, 65), and theoretically, lowered plasma osmolality due to decreases in plasma glucose levels might increase cerebral vascular resistance. However, measurements of osmolality changes in dogs (121) demonstrate a slight hyperosmolality during the third and fourth hours of endotoxin shock, and cannot explain the long-term increase in cerebral vascular resistance.

The cerebral vascular bed has been shown to be highly responsive to changes in arterial P_{CO_2} levels. Thus, in theory, lowered P_{CO_2} levels might cause the cerebral vasoconstriction. Indeed, arterial P_{CO_2} was decreased following administration of 1 and 2 mg/kg, and in particular, during the period of increased resistance. However, 3 and 4 hours following administration of the 5 mg/kg dose, cerebrovascular resistance was increased in spite of the normocapnia occurring over the same period. In addition, even in the 1 and 2 mg/kg doses (Figures 15 and 17), the

arterial P_{CO_2} levels were constant or tending to increase over the period in which the resistance was increasing. Thus, although the arterial levels of P_{CO_2} may play a role in increasing the cerebral vascular resistance, it is not a necessary one.

Although the absolute values of P_{CO_2} were not decreasing in concert with the period of increasing vascular resistance, an alteration of the vascular responsiveness to any given level of P_{CO_2} could have theoretically caused an increase in the cerebral vascular resistance. Indeed, the cerebral vascular response to a CO_2 challenge was clearly depressed from 1 to 6 hours after administration of endotoxin. The initial response lowered resistance to 37% of control. After 1, 2, 3, and 4 hours of shock cerebral vascular resistance only decreased to 80, 79, and 75% of control, respectively, during increased arterial P_{CO_2} levels. P_{CO_2} arterial levels were measured during the pre-endotoxin and 4-hour CO_2 challenge, and although the absolute value of the P_{CO_2} during CO_2 inhalation was lower after 4 hours of shock (Figure 13), this difference was not significant. In fact, the experiment which demonstrated the greatest decrease in the CO_2 response after endotoxin also demonstrated a higher arterial P_{CO_2} during CO_2 inhalation after 4 hours of shock. Thus, the diminished cerebral reactivity to CO_2 does not appear to be due simply to a difference in the arterial P_{CO_2} levels at these times. Buyniski *et al.*

(15) also reported a reduction in the cerebral vascular response to CO_2, although the response was only studied for one hour post-endotoxin, and occurred when cerebral resistance was well below control. Clinical reports have also indicated reduced reactivity of cerebral vessels to hypercarbia in patients with occlusive cerebrovascular disease (35,81,82). However, these authors suggested that this observation is based on the theory that vasodilation is limited due to existing partial or maximal vasodilation in the ischemic areas. This explanation is not applicable to the loss of response to hypercarbia during endotoxin shock, as in the current study, the dilatory response to the CO_2 challenge is depressed in spite of normal or increased resistance.

Although these studies demonstrate a depressed cerebrovascular response to CO_2 during endotoxin shock, the critical question, of the importance of this effect in determining the long term increase in resistance, is uncertain and subject to several considerations. For example, the diminished responsiveness to CO_2 was well-established by the first and second hours of shock, times at which the resistance was not increased above control. In addition, certain levels of hypotension have been shown to abolish or decrease the cerebral vascular responsiveness to CO_2 (52). This may play a role in the present experiments, as systemic pressure, and thus cerebral perfusion, was decreased during the entire

experimental period, especially during the early hours. However, again, the explanation generally given for this effect is prior dilation, and in the 3rd and 4th hours post-endotoxin the CO_2 response was diminished despite an elevated vascular resistance. The possibility that another mechanism, other than prior dilation, is involved in the CO_2 response alterations during systemic hypotension cannot be excluded. At any rate, hypotension does not explain the continued depression of the response during the period of increasing systemic pressure.

A passive decrease in cerebral vessel calibre could theoretically occur if alterations in the capillary membrane caused an increase in the capillary permeability to protein. In turn, increased protein concentrations in the interstitial fluid would promote fluid filtration and an increase in tissue pressure, resulting in a decreased transmural pressure gradient across the cerebral vascular wall. Increased tissue pressure in the brain would probably be reflected by an increased cerebrospinal fluid pressure. Indeed, cerebrospinal fluid pressure increased and cerebral vascular resistance increased in the 2 mg/kg dose. It seems, though, that an increase in cerebral tissue pressure would also impair the cerebral autoregulatory response, when, in fact, this did not occur. In addition, resistance increased in the 5 mg/kg dose in spite of a normal cerebrospinal fluid pressure. Also, cerebral blood flow has been

shown to be little affected by large increases(40 mm Hg) in cerebrospinal fluid pressure (4,112). However, one cannot exclude the possibility that an increase in brain tissue pressure did occur, and was not accurately represented by the cerebrospinal fluid pressure. Perhaps measurements of intracranial pressure, such as those described (79) using sagittal sinus wedge pressures or intracranial balloons would be of value in testing this hypothesis.

The development of microemboli in the cerebral vascular bed must also be considered as a possible means of increasing cerebral vascular resistance during shock. Indeed, these emboli have been shown to develop in other vascular beds due to endotoxin shock (21,51). Anticoagulants have also been suggested as reducing the lethality of shock (51, 123), and may thus be an indirect indication of the basis of the results obtained in this study. To test this hypothesis, further studies might be completed in this preparation, using the increased levels of anticoagulants reported in these studies.

In summary, the mechanism of the increased cerebral vascular resistance observed during endotoxin shock is uncertain, and may involve any one or a combination of the considerations listed in the preceding paragraphs. Despite the mechanism involved in this response, the elevated resistance combines with the lowered perfusion pressure to produce cerebral ischemia.

Systemic arterial blood gas changes during endotoxin shock included an increased P_{O_2}, decreased P_{CO_2}, and an early decrease in pH, except in the 1 mg/kg dose, in which no alteration in pH was noted. The increases in arterial P_{O_2} and decreases in P_{CO_2} were usually associated with an increased respiratory rate (Figure 15). Apparently, the hyperventilation and hypocapnia did not compose an adequate compensation initially, indicated by the early acidosis in the 2 mg/kg and 5 mg/kg doses. Previous investigators have noted the development of a metabolic acidosis during endotoxin shock (28,29). However, reports in unanesthetized dogs (93) indicate that an adequate respiratory compensation results in normal or elevated arterial pH during endotoxin shock. Cerebral venous blood gases have not been previously reported. These included decreased P_{O_2}, decreased pH, and no significant change (but a tendency to increase) in the P_{CO_2}. The sagittal venous system, as it accounts for most of the venous drainage of the cerebral hemispheres in the dog (108), rapidly reflects cerebral tissue respiratory or metabolic acidosis, and in turn, the increased arterial-venous differences accompanying reductions in blood flow. In this manner, brain tissue acid-base balance, reflected in cerebral venous (sagittal sinus) pH and bicarbonate concentrations, demonstrated increased acidosis following administration of 2 mg/kg endotoxin, as venous pH decreased significantly and bicarbonate concentrations tended to

decrease. In addition, calculated arterial-venous differences of oxygen saturation increased greatly (Figure 18) following endotoxin administration. If hemoglobin concentration is assumed not to decrease (in fact it probably increased due to increased hematocrit (18) observed by other authors), one can also infer from this graph that the arterial-venous difference of oxygen content increased dramatically, also.

The alterations of cerebral hemodynamics, cerebral vascular reactivity, and arterial and cerebral venous blood gases described in this study are possible indications of the degree of cerebral ischemia occurring during endotoxin shock in the dog. Shock has been described as "inadequate tissue perfusion", and the central nervous system has been shown to be most sensitive to such deprivation (14,85). The function of the central nervous system during shock, therefore, is highly dependent upon the state of the vascular nutritional supply, and vascular changes in hemodynamics or reactivity may subsequently play a role in the function and response of the nervous system following administration of endotoxin, and in turn, the pathogenesis of the shock state.

CHAPTER VI

SUMMARY AND CONCLUSIONS

The purpose of this study was to determine the cerebral hemodynamics, vascular reactivity, and cerebral metabolic alterations following intravenous endotoxin administration in the dog. Cerebral venous outflow was measured directly from the cannulated confluence of the sagittal, straight, and transverse (lateral) sinuses with the transverse sinuses occluded (94), thus eliminating the primary communications of the cerebral venous outflow with the extracranial circulation. Purified E. coli endotoxin was administered in three doses, 1, 2, and 5 mg/kg, to determine if the effects were dose dependent over these doses.

Cerebral blood flow and cerebral perfusion pressure decreased immediately following administration of all three doses of endotoxin, and remained significantly below control during the entire experimental period. By the fourth hour of shock, cerebral blood flow was decreased 37, 48, and 45% in the 1, 2, and 5 mg/kg doses, respectively. Cerebral vascular resistance transiently decreased, returned to control levels, and progressively rose to levels significantly

above control by minutes 150 to 240, depending on the dose administered. By four hours post-endotoxin, cerebral vascular resistance was 25, 55, and 37% above control in the 1, 2, and 5 mg/kg doses, respectively. Thus, the cerebral vascular resistance response to endotoxin was biphasic: 1) an initial decrease, and 2) a long-term increase. The mechanism causing the increase in resistence is unknown, but various possibilities discussed were: 1) circulating vasoactive agents, 2) alterations in vascular responsiveness to carbon dioxide, 3) passive changes via increases in tissue pressure, and 4) development of microemboli in the cerebral vasculature. In summary, cerebral blood flows decreased following endotoxin administration, due initially to the decreased perfusion pressure and subsequently, primarily to increased cerebral vascular resistance.

Vascular reactivity studies indicated that the autoregulatory and "venous-arteriolar" responses were well maintained after four hours of endotoxin shock. The cerebral vascular responsiveness to carbon dioxide, however, was depressed during shock.

Endotoxin administration generally caused an increased respiratory activity, resulting in increased P_{O_2} and decreased P_{CO_2} in the systemic arterial blood. Initially, the hyperventilation did not compose an adequate compensation, indicated by the early acidosis in the 2 mg/kg and 5 mg/kg doses. Cerebral venous blood gas changes include

decreased P_{O_2} and pH, and increased arterial-venous differences of percent oxygen saturation, total CO_2 and HCO_3^- concentrations. Thus, brain tissue and acid-base balance, reflected in cerebral venous (sagittal sinus) pH and bicarbonate concentrations, became more acidotic during endotoxin shock.

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APPENDICES

APPENDIX A

STATISTICAL METHODS

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STATISTICAL METHODS

The Student's t test for paired observations (75) was used for statistical analysis in these experiments. The experimental condition was preceded by a suitable control period, and therefore, each animal served as its own control. Since the experimental design thus permitted pairing of the data, the application of the null hypothesis implied that the mean of the differences of the paired measurements (universe mean) should be zero. The alternative to the null hypothesis, therefore, would be that the mean difference is not zero, i.e., the populations are different. This is stated as follows:

$$H_0 : \mu_d = 0, \qquad H_A : \mu_d \neq 0$$

The probability of obtaining such a difference was calculated, utilizing the Student's t test and tables, and confidence levels (usually 95%) were used to accept or reject the null hypothesis.

To use the Student's t test, the control values were designated X and the experimental values designated X'. The sum of the differences, ΣD, was calculated, where $D = (X - X')$. The mean of this sample of differences, $\bar{D}$, and

its standard deviation (S) were used to calculate t as follows:

$$\bar{D} = \frac{\Sigma D}{n} \qquad S = \sqrt{\frac{n\Sigma D^2 - (\Sigma D)^2}{n(n-1)}}$$

$$t = \frac{\pm \bar{D}}{S/\sqrt{n}}$$

The probability of obtaining this mean difference was then found in the Student's t-table of values. If the significance level was not within the confidence limits (P 0.05) the null hypothesis was rejected and the alternative accepted.

A computer program (in FOCAL language) was written incorporating these formulas, and calculations were then run on a PDP 8/E (Digital Equipment Corporation) high speed magnetic core memory unit.

APPENDIX B

RAW DATA

CEREBRAL PERFUSION PRESSURE

2 mg/kg endotoxin

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	122.8	43.0	107.8	106.2	121.1	93.1	76.8	82.0	92.0	93.0	93.0	92.9
2	103.5	59.0	58.2	62.5	84.9	80.5	53.2	60.5	66.0	72.0	72.1	72.7
3	114.2	28.3	40.1	37.0	56.0	60.1	51.0	50.0	57.1	63.4	67.9	71.0
4	136.0	41.0	88.0	93.0	89.8	50.0	68.5	89.5	101.0	110.0	110.8	117.3
5	118.0	58.0	78.0	71.0	78.0	84.0	74.0	84.0	87.0	82.0	87.0	87.0
6	135.0	27.0	40.0	54.0	97.0	84.0	90.0	98.0	106.0	107.0	111.0	115.0
7	140.0	39.0	38.0	56.0	95.0	95.0	75.0	86.0	112.0	120.0	134.0	134.0
8	131.0	26.5	39.5	41.5	74.5	51.0	71.0	85.0	76.0	87.0	95.0	101.0
9	155.0	55.0	61.0	95.0	110.0	95.0	73.0	78.0	87.5	93.5	94.5	96.0
10	127.8	37.0	63.0	69.0	89.0	74.0	78.0	93.0	105.0	113.0	110.0	106.0
11	132.0	35.0	46.0	43.0	77.0	48.0	52.0	69.0	76.0	69.0	74.0	86.0
12	114.0	30.0	47.0	50.0	70.5	61.0	61.0	62.0	71.0	75.0	80.0	75.0
Mean	127.4	40.0	59.0	65.0	87.0	73.0	69.0	78.0	86.4	90.4	94.1	96.2
SEM	4.0	3.4	6.4	6.6	5.1	5.2	3.5	4.4	5.1	5.4	5.7	5.6

CEREBRAL BLOOD FLOW

2 mg/kg endotoxin

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	30.7	12.0	13.8	14.8	17.0	16.7	14.4	13.4	14.0	13.3	14.3	16.5
2	52.4	32.0	33.6	32.0	29.6	22.0	14.8	15.3	15.4	14.6	13.3	13.0
3	21.5	7.8	13.2	11.6	13.6	12.4	14.4	11.6	11.2	10.6	10.0	10.0
4	20.0	10.8	15.0	14.6	14.4	9.0	12.2	13.4	12.2	11.6	12.3	12.2
5	55.8	30.4	37.6	33.7	32.8	38.1	31.0	37.8	30.9	26.4	26.5	25.2
6	40.8	12.6	11.6	16.6	19.4	20.8	21.8	24.9	24.0	24.0	24.0	25.1
7	31.8	13.6	12.4	15.8	17.6	18.2	14.7	16.6	16.8	17.1	17.7	15.7
8	30.0	11.4	12.8	14.4	16.0	13.6	17.4	15.6	14.5	15.2	15.7	15.9
9	26.5	18.2	18.2	19.8	23.5	15.8	16.2	16.0	16.5	18.0	18.1	19.4
10	48.0	19.8	20.4	20.5	27.4	20.0	21.8	22.3	21.4	20.7	20.5	19.5
11	24.0	17.2	18.2	17.2	19.3	12.0	13.1	15.4	15.4	15.0	15.9	15.4
12	27.2	18.4	19.2	18.2	20.6	20.9	19.5	17.0	14.9	14.2	14.3	14.5
Mean	34.1	17.0	18.8	19.1	20.9	18.3	17.6	18.3	17.3	16.7	16.9	16.9
SEM	3.5	2.2	2.4	2.0	1.8	2.2	1.5	2.1	1.6	1.4	1.4	1.4

CEREBRAL VASCULAR RESISTANCE

2 mg/kg endotoxin

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	4.00	3.58	7.81	7.18	7.12	5.57	5.33	6.12	6.57	6.99	6.50	5.63
2	1.98	1.84	1.73	1.95	2.86	3.66	3.59	3.95	4.29	4.93	5.42	5.59
3	5.31	3.63	3.04	3.19	4.12	4.85	3.54	4.31	5.10	5.98	6.79	7.10
4	6.80	3.79	5.87	6.36	6.24	5.55	5.61	6.68	8.27	9.48	9.01	9.61
5	2.11	1.91	2.02	2.11	2.38	2.20	2.39	2.22	2.82	3.11	3.28	3.45
6	3.31	2.14	3.45	3.25	5.00	4.04	4.13	3.94	4.42	4.46	4.63	4.58
7	4.40	2.87	3.06	3.54	5.40	5.22	5.10	5.18	6.67	7.02	7.57	8.54
8	4.37	2.32	3.09	2.88	4.66	3.75	4.08	5.45	5.24	5.72	6.05	6.35
9	5.85	3.02	3.35	4.80	4.68	6.01	4.51	4.88	5.30	5.19	5.22	4.95
10	2.66	1.87	3.09	3.37	3.25	3.70	3.58	4.17	4.91	5.46	5.37	5.44
11	5.50	2.03	2.53	2.50	3.99	4.00	3.97	4.55	4.94	4.60	4.65	5.58
12	4.19	1.63	2.45	2.75	3.42	2.92	3.13	3.65	4.77	5.28	5.59	5.17
Mean	4.21	2.55	3.46	3.66	4.43	4.29	4.08	4.59	5.28	5.69	5.84	6.00
SEM	0.43	0.23	0.49	0.47	0.40	0.33	0.27	0.34	0.40	0.46	0.43	0.49

CEREBROSPINAL FLUID PRESSURE

2 mg/kg endotoxin

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	3.5	0.0	6.0	6.0	8.5	12.0	11.0	10.0	11.0	10.5	9.5	9.0
2	4.5	0.0	2.0	2.0	0.0	2.0	7.5	8.5	7.5	7.5	6.0	5.0
3	--	--	--	--	--	--	--	--	--	--	--	--
4	14.5	14.5	16.0	12.8	26.0	19.0	24.0	18.0	18.0	15.8	22.0	22.0
5	6.5	6.0	7.0	5.0	4.0	5.5	6.5	9.0	5.0	4.0	3.5	2.5
6	5.5	-1.5	-1.5	-0.5	1.0	10.0	10.0	10.0	8.5	6.0	5.5	5.5
7	5.0	3.5	4.0	5.5	7.0	15.0	12.0	14.0	17.0	21.0	22.0	25.0
8	3.5	1.5	1.5	2.0	2.5	5.5	9.0	9.0	8.5	10.0	11.0	12.5
9	5.5	6.0	6.0	7.0	9.0	8.0	6.0	5.0	5.0	5.5	6.0	6.5
10	9.5	1.5	5.5	7.5	15.0	19.0	22.0	29.0	30.0	28.0	32.0	32.0
11	5.5	0.5	2.0	1.5	4.0	5.0	4.0	3.5	1.5	1.5	1.5	2.0
12	-1.0	-2.0	-1.0	-1.0	-1.0	-0.5	5.0	8.5	10.0	11.0	11.0	11.5
Mean	5.7	2.7	4.3	4.4	6.9	9.1	10.6	11.3	11.1	11.0	11.8	12.1
SEM	1.2	1.4	1.5	1.2	2.4	2.0	2.0	2.1	2.4	2.4	2.9	3.0

RESPIRATORY RATE

2 mg/kg endotoxin

	Time (min)											
Dog #	0	5	10	15	30	60	90	120	150	180	210	240
1	4	8	7	6	6	10	10	11	10	10	10	8
2	4	4	4	4	4	5	6	5	5	5	8	15
3	8	2	9	11	17	15	18	10	16	16	16	17
4	7	11	12	11	17	19	17	19	18	17	22	24
5	10	11	13	18	26	18	22	19	19	17	22	14
6	6	26	21	15	16	21	21	18	19	21	22	21
7	9	18	22	18	14	18	21	21	9	10	9	12
8	6	13	10	11	10	24	22	18	22	15	12	9
9	15	24	24	16	19	28	32	24	25	20	16	15
10	4	3	7	5	5	6	5	5	6	8	5	5
11	6	9	15	17	24	14	20	21	21	21	18	15
12	14	18	24	24	28	34	33	36	24	26	20	21
Mean	8	12	14	13	15	18	19	17	16	15	15	15
SEM	1	2	2	2	2	2	3	3	2	2	2	2

ARTERIAL P_{O_2}

2 mg/kg endotoxin

Dog #	Time (min) 0	30	60	90	120	150	180	210	240
5	60	60	60	61	61	60	61	66	69
6	86	110	88	103	93	101	90	82	95
7	100	111	120	118	108	100	101	98	106
8	92	94	98	103	100	106	102	80	99
9	85	119	120	101	86	100	104	99	94
10	80	106	80	97	102	97	99	103	87
11	92	118	117	109	118	114	113	108	104
12	80	94	87	83	91	92	85	88	86
Mean	84	102	96	97	95	96	94	91	93
SEM	4.2	6.8	7.7	6.2	6.0	5.7	5.6	5.0	4.2

VENOUS P_{O_2}

2 mg/kg endotoxin

Dog #	Time (min) 0	30	60	90	120	150	180	210	240
5	43	37	38	34	34	37	36	32	36
6	48	40	40	46	45	43	42	43	40
7	40	39	31	27	31	40	37	38	32
8	43	34	27	28	28	24	29	32	34
9	34	49	42	27	32	35	37	37	38
10	48	51	35	37	37	37	32	34	34
11	43	43	28	34	37	34	34	34	33
12	39	30	33	28	28	27	28	32	33
Mean	42	40	34	33	34	35	34	35	35
SEM	1.6	2.5	1.9	2.3	2.0	2.2	1.6	1.4	1.0

ARTERIAL P_{CO_2}

2 mg/kg endotoxin

Dog #	Time (min) 0	30	60	90	120	150	180	210	240
5	48.0	38.0	43.0	42.5	38.5	36.0	41.0	36.0	44.5
6	45.5	29.0	29.0	28.0	32.5	28.0	27.5	32.5	28.0
7	40.5	32.0	23.0	17.0	20.0	27.0	28.5	33.0	24.0
8	44.0	28.0	17.0	14.0	17.0	15.0	16.0	25.5	17.0
9	30.0	20.0	16.0	18.0	19.5	27.0	23.0	28.0	25.5
10	59.0	40.0	43.0	40.0	36.0	37.0	28.0	31.0	38.0
11	31.0	18.0	20.5	20.0	18.0	21.0	17.0	22.0	26.0
12	36.0	22.0	27.0	20.0	19.0	21.0	23.0	30.0	28.5
Mean	42.0	28.4	27.3	25.0	25.1	27.0	26.0	30.0	29.0
SEM	3.4	2.9	3.8	3.8	3.2	2.7	2.8	1.6	3.0

VENOUS P_{CO_2}

2 mg/kg endotoxin

Dog #	Time (min) 0	30	60	90	120	150	180	210	240
5	51.0	53.0	55.5	57.0	53.0	53.5	50.5	57.5	56.0
6	51.5	47.5	50.5	42.0	48.0	47.0	46.0	43.5	40.5
7	50.0	49.0	41.0	44.0	43.0	46.0	49.5	50.0	44.0
8	54.0	47.0	45.0	41.0	39.0	37.0	34.0	41.0	37.0
9	41.0	33.0	38.0	41.5	41.5	46.0	44.5	44.0	44.0
10	60.0	60.0	62.0	60.0	62.0	58.0	51.0	57.0	56.0
11	40.0	36.0	38.0	45.0	45.0	48.0	41.0	44.0	50.0
12	48.0	45.0	44.0	42.0	42.0	46.0	44.0	54.0	49.0
Mean	49.4	46.3	47.0	47.0	47.0	48.0	45.1	49.0	47.1
SEM	2.3	3.1	3.1	2.7	2.7	2.2	2.0	2.3	2.5

ARTERIAL pH

2 mg/kg endotoxin

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
5	7.34	7.30	7.24	7.25	7.25	7.25	7.24	7.26	7.21
6	7.32	7.32	7.30	7.32	7.31	7.38	7.39	7.35	7.39
7	7.36	7.29	7.34	7.36	7.34	7.31	7.29	7.27	7.34
8	7.34	7.24	7.30	7.30	7.34	7.37	7.33	7.30	7.30
9	7.43	7.38	7.34	7.34	7.30	7.30	7.33	7.31	7.32
10	7.21	7.21	7.19	7.23	7.25	7.24	7.34	7.33	7.27
11	7.35	7.31	7.26	7.25	7.27	7.28	7.28	7.29	7.31
12	7.28	7.27	7.29	7.34	7.36	7.30	7.31	7.27	7.28
Mean	7.33	7.29	7.28	7.30	7.30	7.30	7.31	7.30	7.30
SEM	0.04	0.00	0.03	0.03	0.03	0.03	0.03	0.03	0.03

VENOUS pH

2 mg/kg endotoxin

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
5	7.30	7.25	7.21	7.20	7.20	7.20	7.20	7.19	7.16
6	7.29	7.27	7.24	7.26	7.25	7.28	7.29	7.31	7.32
7	7.31	7.22	7.28	7.25	7.25	7.19	7.20	7.21	7.29
8	7.27	7.17	7.22	7.19	7.23	7.24	7.24	7.22	7.25
9	7.40	7.30	7.26	7.26	7.23	7.21	7.24	7.24	7.26
10	7.20	7.14	7.15	7.15	7.15	7.18	7.24	7.20	7.24
11	7.30	7.30	7.11	7.12	7.16	7.18	7.20	7.21	7.22
12	7.24	7.20	7.20	7.25	7.23	7.20	7.22	7.19	7.22
Meam	7.29	7.23	7.21	7.21	7.21	7.21	7.23	7.22	7.25
SEM	0.04	0.00	0.03	0.00	0.03	0.00	0.03	0.00	0.00

CEREBRAL PERFUSION PRESSURE

5 mg/kg endotoxin

	Time (min)											
Dog #	0	5	10	15	30	60	90	120	150	180	210	240
1	129	85	54	55	78	71	67	74	67	74	77	83
2	133	68	50	40	69	72	63	69	77	84	85	89
3	139	39	43	72	101	95	89	95	94	101	102	113
4	135	110	95	69	90	70	82	90	94	101	120	125
5	103	26	31	49	56	54	53	56	58	59	51	40
6	138	56	70	80	112	108	82	76	87	97	115	110
Mean	130	64	57	61	84	78	73	77	80	86	92	93
SEM	5.5	12.5	9.2	6.2	8.5	8.0	5.7	5.8	6.1	7.0	10.6	12.4

CEREBRAL BLOOD FLOW

5 mg/kg endotoxin

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	36.6	21.8	17.8	16.8	19.7	22.2	24.0	22.4	20.4	20.1	19.7	18.9
2	31.5	17.0	14.0	11.6	16.1	23.0	18.7	18.8	19.1	20.7	20.5	21.6
3	45.0	16.0	16.6	23.0	23.4	19.6	18.0	17.1	15.8	16.0	15.7	16.4
4	25.8	20.0	15.2	14.3	14.9	15.3	15.9	15.5	14.4	14.4	15.1	16.1
5	27.0	16.8	21.0	40.0	18.6	14.4	16.0	16.2	16.2	15.5	13.7	8.0
6	48.0	21.2	24.4	27.0	52.0	36.8	34.2	32.0	31.6	27.8	33.5	40.0
Mean	35.7	18.8	18.2	22.1	24.1	21.9	21.1	20.3	19.6	19.1	19.7	20.2
SEM	3.8	1.0	1.6	4.3	5.7	3.3	2.9	2.5	2.6	2.0	3.0	4.4

CEREBRAL VASCULAR RESISTANCE

5 mg/kg endotoxin

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	3.52	3.90	3.03	3.27	3.95	3.19	2.79	3.30	3.28	3.68	3.91	4.39
2	4.22	4.00	3.57	3.44	4.29	3.13	3.34	3.67	4.03	4.06	4.15	4.12
3	3.09	2.44	2.59	3.13	4.32	4.85	4.94	5.56	5.95	6.36	6.50	6.89
4	5.23	5.50	6.25	4.83	6.04	4.58	5.16	5.81	6.53	7.01	7.95	7.76
5	3.81	1.55	1.48	1.23	3.01	3.75	3.31	3.46	3.58	3.81	3.72	5.00
6	2.88	2.64	2.87	2.96	2.12	2.93	2.40	2.38	2.75	3.48	3.43	2.75
Mean	3.79	3.34	3.29	3.14	3.96	3.74	3.66	4.03	4.35	4.73	4.94	5.15
SEM	0.35	0.58	0.65	0.47	0.54	0.33	0.46	0.55	0.63	0.63	0.75	0.76

CEREBROSPINAL FLUID PRESSURE

5 mg/kg endotoxin

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	6.0	8.0	7.0	4.0	6.0	10.0	7.5	6.5	6.5	6.5	6.0	6.0
2	8.0	5.0	5.0	4.0	5.0	10.0	12.0	10.5	11.0	11.5	10.5	10.5
3	5.5	-4.0	-3.0	1.0	3.0	11.5	12.0	10.5	10.0	10.0	12.0	13.0
4	8.0	5.0	12.0	10.0	10.0	13.0	15.0	14.0	13.5	13.5	11.0	10.5
5	6.0	0.0	1.0	5.0	1.5	3.0	5.0	5.0	4.0	5.5	5.0	4.0
6	0.0	-1.0	-1.0	0.0	0.0	1.0	1.0	0.0	0.0	-1.0	0.0	0.0
Mean	5.6	2.2	3.5	4.0	4.3	8.1	8.8	7.8	7.5	7.7	7.4	7.3
SEM	1.2	1.9	2.3	1.4	1.5	2.0	2.1	2.0	2.0	2.1	1.9	2.0

RESPIRATORY RATE

5 mg/kg endotoxin

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	8	14	15	17	19	17	17	19	21	18	19	17
2	12	13	9	10	11	12	6	14	11	8	10	12
3	4	9	11	8	9	9	9	8	9	8	10	6
4	7	12	16	21	21	30	33	24	30	15	30	15
5	6	7	4	4	19	25	9	6	6	7	5	5
6	6	14	11	8	8	6	6	5	7	6	6	4
Mean	7	11	11	11	14	17	13	13	14	10	13	10
SEM	1	1	2	3	2	4	4	3	4	2	4	2

ARTERIAL P_{O_2}

5 mg/kg endotoxin

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
1	95	99	101	98	101	107	102	104	107
2	96	105	97	109	107	110	93	115	114
3	90	92	100	109	108	106	106	103	95
4	95	109	111	111	113	115	109	114	109
5	83	94	94	82	79	74	78	53	53
6	82	85	85	76	83	68	73	60	53
Mean	90	97	98	98	99	97	94	92	89
SEM	2.6	3.6	3.5	6.2	5.8	8.3	6.1	11.3	11.5

VENOUS P_{O_2}

5 mg/kg endotoxin

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
1	46	38	36	40	36	35	33	34	35
2	47	45	44	36	37	38	43	43	39
3	49	49	42	43	39	39	38	38	41
4	40	37	35	31	35	33	36	34	37
5	39	37	33	31	32	34	32	20	20
6	47	57	55	50	50	49	53	35	47
Mean	45	44	41	39	38	38	39	34	37
SEM	1.7	3.3	3.3	3.0	2.6	2.4	3.2	3.1	3.7

ARTERIAL P_{CO_2}

5 mg/kg endotoxin

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
1	34	24	24	30	20	20	24	22	20
2	40	31	32	24	21	24	32	23	24
3	39	33	29	26	25	27	26	28	29
4	34	20	17	25	33	36	34	44	44
5	37	23	21	18	20	18	24	19	23
6	44	43	44	51	47	65	67	77	80
Mean	38	29	28	29	28	32	35	36	37
SEM	1.6	3.5	3.9	4.6	4.4	7.2	6.7	9.1	9.3

VENOUS P_{CO_2}

5 mg/kg endotoxin

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
1	49	46	42	43	44	42	44	43	42
2	42	47	44	50	41	41	43	43	41
3	53	43	47	43	44	45	49	45	46
4	43	39	41	48	52	57	56	70	70
5	49	38	40	36	39	35	42	39	41
6	49	48	54	62	60	70	75	82	87
Mean	48	43	45	47	47	48	51	54	55
SEM	1.7	1.7	2.1	3.6	3.2	5.3	5.2	7.3	7.9

ARTERIAL pH

5 mg/kg endotoxin

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
1	7.34	7.29	7.30	7.28	7.34	7.37	7.33	7.35	7.37
2	7.37	7.23	7.24	7.28	7.34	7.33	7.23	7.32	7.34
3	7.31	7.28	7.32	7.35	7.37	7.35	7.35	7.33	7.33
4	7.35	7.34	7.33	7.36	7.34	7.40	7.31	7.39	7.35
5	7.36	7.21	7.20	7.15	7.15	7.15	7.18	7.10	7.10
6	7.26	7.20	7.15	7.10	7.08	7.05	7.03	6.99	6.95
Mean	7.33	7.26	7.26	7.25	7.27	7.28	7.24	7.25	7.24
SEM	0.04	0.03	0.04	0.04	0.04	0.05	0.05	0.08	0.07

VENOUS pH

5 mg/kg endotoxin

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
1	7.27	7.21	7.23	7.22	7.23	7.24	7.23	7.24	7.24
2	7.32	7.18	7.17	7.19	7.22	7.23	7.19	7.21	7.26
3	7.24	7.21	7.25	7.29	7.28	7.28	7.25	7.29	7.26
4	7.27	7.26	7.24	7.30	7.27	7.32	7.24	7.28	7.26
5	7.29	7.13	7.10	7.09	7.08	7.07	7.07	6.95	6.95
6	7.22	7.15	7.12	7.06	7.04	7.00	6.99	6.93	6.91
Mean	7.27	7.19	7.19	7.19	7.19	7.19	7.16	7.15	7.15
SEM	0.03	0.00	0.00	0.05	0.05	0.04	0.05	0.06	0.08

CEREBRAL BLOOD FLOW

1 mg/kg endotoxin

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	28.2	20.0	18.0	15.0	17.6	16.2	17.4	17.0	14.0	14.1	14.4	13.4
2	27.2	24.0	17.0	17.4	24.0	17.6	16.4	16.9	18.0	18.6	17.6	18.0
3	28.0	18.0	16.2	17.2	21.0	15.0	15.0	14.8	15.6	16.0	14.4	16.2
4	22.6	19.0	18.4	22.8	25.6	19.8	18.0	18.0	18.4	19.2	19.2	19.6
5	41.4	28.6	31.6	32.0	31.2	28.3	26.2	26.6	24.5	23.0	21.5	22.8
Mean	29.5	21.9	20.2	20.9	23.9	19.4	18.6	18.7	18.1	18.2	17.4	18.0
SEM	3.2	2.0	2.9	3.1	2.3	2.4	2.0	2.1	1.8	1.5	1.4	1.6

CEREBRAL PERFUSION PRESSURE

1 mg/kg endotoxin

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	131	51	41	31	60	81	76	80	78	81	72	64
2	143	135	71	68	106	69	90	114	120	127	135	134
3	154	35	43	50	89	58	49	64	77	81	85	105
4	142	120	100	120	132	90	80	90	113	100	115	112
5	125	40	90	82	97	73	71	90	97	103	111	120
Mean	139	76	69	70	97	74	73	87	97	98	104	107
SEM	5.1	21.3	12.0	15.1	11.8	5.4	6.8	8.2	8.8	8.5	11.2	11.8

CEREBRAL VASCULAR RESISTANCE

1 mg/kg endotoxin

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	4.63	2.54	2.27	2.07	3.39	4.98	4.34	4.68	5.57	5.74	5.00	4.78
2	5.26	5.63	4.18	3.90	4.43	3.91	5.49	6.76	6.79	6.83	7.68	7.44
3	5.50	1.94	2.65	2.91	4.24	3.87	3.25	4.29	4.95	5.08	5.91	6.48
4	6.31	6.33	5.43	5.26	5.16	4.54	4.42	5.00	6.14	5.21	5.99	5.71
5	3.02	1.40	2.85	2.56	3.11	2.58	2.71	3.38	3.96	4.48	5.16	5.26
Mean	4.94	3.57	3.48	3.34	4.07	3.97	4.04	4.82	5.48	5.47	5.95	5.93
SEM	0.55	1.01	0.58	0.57	0.37	0.41	0.49	0.56	0.48	0.40	0.48	0.47

CEREBROSPINAL FLUID PRESSURE

1 mg/kg endotoxin

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	6.0	1.5	10.0	6.0	9.0	9.0	5.5	6.0	5.0	5.0	3.5	5.5
2	15.0	9.0	8.0	7.0	11.0	7.5	7.0	8.5	7.7	7.0	7.0	9.0
3	2.5	0.0	1.0	1.2	4.0	6.5	5.5	6.0	8.0	9.0	6.5	9.2
4	16.5	14.0	24.0	20.0	17.0	19.0	13.0	15.0	13.0	15.0	11.0	13.5
Mean	10.0	6.1	10.8	8.6	10.3	10.5	7.8	8.9	8.4	9.0	7.0	9.3
SEM	3.4	3.3	4.8	4.0	2.8	2.9	1.8	2.1	1.7	2.2	1.5	1.6

RESPIRATORY RATE

1 mg/kg endotoxin

	Time (min)											
Dog #	0	5	10	15	30	60	90	120	150	180	210	240
1	5	9	8	8	8	12	11	11	10	9	7	6
2	35	64	39	28	24	24	48	44	34	44	20	46
3	6	13	13	20	14	16	20	20	16	20	22	27
4	12	20	22	20	13	20	20	20	19	18	16	16
5	12	24	27	32	20	50	24	50	24	20	20	17
Mean	14	26	22	22	16	24	25	29	21	22	17	22
SEM	5	10	5	4	3	7	6	8	4	6	3	7

ARTERIAL P_{O_2}

1 mg/kg endotoxin

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
1	89	146	99	101	96	93	91	91	93
2	81	87	93	97	97	92	87	77	79
3	93	90	112	117	117	114	117	117	102
4	93	89	84	89	89	94	96	97	96
5	75	90	87	73	75	81	83	93	90
Mean	86	100	95	95	95	95	95	95	92
SEM	3.5	11.4	4.9	7.1	6.8	5.4	5.9	6.4	3.8

VENOUS P_{O_2}

1 mg/kg endotoxin

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
1	35	30	26	26	28	26	24	22	15
2	34	35	23	23	23	27	31	23	22
3	37	32	21	27	21	27	26	25	26
4	26	27	28	22	23	23	22	23	20
5	37	29	27	29	26	29	32	36	38
Mean	34	30	25	25	24	26	27	26	24
SEM	2.0	1.3	1.4	1.3	1.2	1.0	1.9	2.6	4.0

ARTERIAL P_{CO_2}

1 mg/kg endotoxin

Dog #	Time (min) 0	30	60	90	120	150	180	210	240
1	33.5	28.2	22.0	21.0	22.0	27.0	32.0	30.5	27.5
2	33.2	12.0	19.0	18.5	17.5	20.0	22.5	19.5	16.0
3	31.0	26.5	13.0	13.5	16.5	19.5	21.5	19.5	20.0
4	27.5	27.0	23.0	17.0	20.0	18.5	17.5	20.0	19.5
5	44.5	39.5	31.0	34.0	33.0	32.5	32.0	43.5	44.5
Mean	33.9	26.6	21.6	20.8	21.8	23.4	25.1	26.6	25.5
SEM	2.8	4.4	2.9	3.5	3.0	2.7	2.9	4.7	5.1

VENOUS P_{CO_2}

1 mg/kg endotoxin

Dog #	Time (min) 0	30	60	90	120	150	180	210	240
1	47.9	46.1	45.4	45.4	46.4	48.6	51.0	54.5	47.5
2	38.8	47.0	44.0	44.0	46.4	53.0	60.0	57.0	56.5
3	40.0	39.0	36.7	42.0	37.0	41.0	41.5	40.5	41.0
4	41.5	40.5	40.5	38.0	36.0	38.0	36.5	38.5	37.5
5	52.0	56.0	54.5	57.0	56.5	58.0	60.0	63.0	69.0
Mean	44.0	45.7	44.2	45.3	44.5	47.7	49.8	50.7	50.3
SEM	2.5	3.0	3.0	3.2	3.7	3.7	4.8	4.8	5.7

ARTERIAL pH

1 mg/kg endotoxin

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
1	7.37	7.36	7.36	7.37	7.37	7.36	7.36	7.35	7.38
2	7.38	7.35	7.35	7.35	7.34	7.30	7.27	7.30	7.27
3	7.29	7.32	7.35	7.33	7.36	7.38	7.37	7.34	7.31
4	7.41	7.43	7.43	7.47	7.43	7.47	7.49	7.46	7.48
5	7.39	7.34	7.44	7.38	7.35	7.33	7.34	7.38	7.37
Mean	7.37	7.38	7.39	7.38	7.37	7.37	7.37	7.37	7.36
SEM	0.02	0.02	0.02	0.02	0.02	0.03	0.04	0.03	0.04

VENOUS pH

1 mg/kg endotoxin

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
1	7.30	7.28	7.28	7.25	7.26	7.24	7.23	7.25	7.26
2	7.31	7.22	7.31	7.31	7.25	7.21	7.18	7.18	7.20
3	7.27	7.27	7.26	7.26	7.28	7.26	7.28	7.26	7.21
4	7.35	7.32	7.36	7.34	7.34	7.38	7.35	7.34	7.36
5	7.31	7.29	7.31	7.33	7.26	7.24	7.25	7.26	7.27
Mean	7.31	7.28	7.30	7.30	7.28	7.27	7.26	7.26	7.26
SEM	0.01	0.02	0.02	0.02	0.02	0.03	0.03	0.03	0.03

CEREBRAL PERFUSION PRESSURE

control experiments

	Time (min)											
Dog #	0	5	10	15	30	60	90	120	150	180	210	240
1	132.0	135.0	139.0	139.0	145.0	145.0	155.0	154.0	155.0	155.0	160.0	167.0
2	142.0	143.5	139.2	142.2	141.2	142.0	144.5	146.0	142.9	145.2	141.0	148.0
3	123.0	126.0	126.0	126.0	125.0	126.5	140.5	144.5	139.0	132.5	138.0	136.5
4	128.0	125.0	129.0	126.0	127.0	123.5	125.0	128.0	130.5	127.5	132.5	123.0
5	104.0	106.0	106.0	103.0	108.5	106.0	106.0	107.0	99.0	101.0	95.0	97.5
6	121.0	123.0	120.0	121.0	120.0	125.0	129.0	135.0	135.0	135.0	130.0	130.0
7	130.0	131.0	132.0	130.0	128.0	135.0	139.0	138.0	142.0	140.0	142.0	140.0
8	159.0	158.0	158.0	161.0	163.0	163.0	161.0	161.0	163.0	162.0	160.0	158.0
Mean	130.0	131.0	131.0	131.0	132.0	133.0	138.0	139.0	138.0	137.0	137.0	138.0
SEM	5.7	5.4	5.4	6.0	6.0	6.1	6.2	5.9	6.7	6.6	7.2	7.7

CEREBRAL BLOOD FLOW

control experiments

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	23.0	22.8	22.4	23.2	26.6	25.4	23.4	23.6	23.0	22.7	24.1	27.5
2	27.8	26.6	26.2	25.5	25.5	26.0	26.2	25.4	27.0	27.1	29.4	29.3
3	25.8	25.4	24.4	24.4	29.4	31.4	29.5	26.8	25.5	25.3	22.7	23.3
4	37.2	37.6	37.4	37.0	36.3	31.3	26.4	34.3	30.4	39.0	28.5	35.0
5	23.2	23.6	23.4	22.0	22.2	22.0	22.0	22.9	23.0	21.7	22.4	25.7
6	30.0	30.0	30.1	30.8	26.6	30.2	27.8	27.6	27.6	27.0	29.2	27.0
7	27.7	27.8	28.0	27.4	27.9	26.9	26.4	26.0	24.1	25.3	22.8	24.6
8	33.2	32.6	32.8	32.4	32.0	30.0	35.5	32.6	33.2	33.2	32.4	33.5
Mean	28.5	28.3	28.1	27.8	28.3	27.9	27.2	27.4	26.7	27.7	26.4	28.2
SEM	1.7	1.8	1.8	1.8	1.5	1.2	1.5	1.4	1.3	2.0	1.4	1.5

CEREBRAL VASCULAR RESISTANCE

control experiments

	Time (min)											
Dog #	0	5	10	15	30	60	90	120	150	180	210	240
1	5.74	5.92	6.21	5.99	5.45	5.71	6.62	6.53	6.74	6.83	6.64	6.07
2	5.11	5.39	5.31	5.58	5.54	5.46	5.52	5.75	5.29	5.36	4.80	5.05
3	4.77	4.96	5.16	5.16	4.25	4.03	4.76	5.39	5.45	5.24	6.08	5.84
4	3.44	3.32	3.45	3.41	3.50	3.95	4.73	3.73	4.29	3.27	4.65	3.51
5	4.48	4.49	4.53	4.68	4.89	4.82	4.82	4.67	4.31	4.65	4.24	3.79
6	4.03	4.10	3.99	3.93	4.51	4.14	4.64	4.89	4.89	5.00	4.45	4.81
7	4.69	4.71	4.67	4.74	4.59	5.02	5.26	5.31	5.89	5.53	6.22	5.69
8	4.79	4.85	4.82	4.97	5.09	5.43	4.54	4.94	4.91	4.88	4.94	4.72
Mean	4.63	4.72	4.77	4.81	4.73	4.82	5.11	5.15	5.22	5.10	5.25	4.94
SEM	0.24	0.28	0.30	0.29	0.24	0.25	0.24	0.29	0.29	0.35	0.32	0.33

CEREBROSPINAL FLUID PRESSURE

control experiments

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	6.0	6.0	6.0	6.0	7.0	9.0	7.0	7.0	8.0	9.0	7.0	7.5
2	13.2	13.0	14.0	12.5	12.5	11.5	7.5	10.0	6.5	9.0	3.0	6.5
3	3.0	3.5	4.5	5.0	8.5	8.5	5.0	4.5	3.0	3.0	2.0	4.0
4	15.0	14.0	13.0	13.0	13.0	9.5	8.0	11.5	8.5	13.0	8.5	16.1
5	4.0	4.0	5.0	5.5	5.0	5.0	4.0	5.0	4.0	7.0	3.0	2.5
6	10.0	8.0	9.0	8.0	8.0	13.0	8.0	9.0	10.0	10.0	14.0	11.0
7	11.0	11.0	10.0	11.0	15.0	11.0	7.5	11.0	7.5	9.0	8.5	14.0
8	3.0	3.5	3.0	5.0	7.0	10.0	10.0	8.5	7.5	9.0	8.0	8.5
Mean	8.2	7.9	8.1	8.3	9.5	9.7	7.1	8.3	6.9	8.6	6.8	8.8
SEM	1.7	1.5	1.4	1.2	1.3	0.9	0.7	0.9	0.8	1.0	1.4	1.7

RESPIRATORY RATE

control experiments

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	11	11	11	11	12	11	10	10	10	10	12	11
2	16	16	12	10	16	16	16	16	17	17	17	16
3	14	16	14	12	16	16	20	20	12	10	12	18
4	6	8	8	10	6	5	6	6	6	6	8	8
5	4	4	4	4	4	4	5	4	4	4	4	4
6	12	12	12	18	12	9	11	11	11	11	9	9
7	5	5	5	4	4	3	3	3	3	3	3	3
8	11	11	12	12	11	11	7	8	7	8	7	7
Mean	10	10	10	10	10	9	10	10	9	8	9	10
SEM	2	2	1	2	2	2	2	2	2	2	2	2

ARTERIAL P_{O_2}

control experiments

Dog #	Time (min) 0	30	60	90	120	150	180	210	240
1	87	75	83	75	87	75	84	82	73
2	87	83	88	95	95	90	87	97	97
3	89	85	81	89	94	88	93	100	88
4	70	82	79	89	75	70	64	67	63
5	68	75	75	70	77	75	70	77	80
6	86	87	75	86	74	83	70	80	84
7	99	105	103	107	100	99	95	98	94
8	94	110	109	97	103	93	90	95	93
Mean	85	88	87	88	88	84	82	87	84
SEM	3.8	4.6	4.5	4.2	4.1	3.6	4.2	4.3	4.1

VENOUS P_{O_2}

control experiments

Dog #	Time (min) 0	30	60	90	120	150	180	210	240
1	32	31	33	32	31	30	28	32	34
2	31	28	28	28	30	30	30	33	29
3	32	33	39	34	32	35	33	34	37
4	39	45	39	39	41	38	42	36	36
5	29	29	28	26	29	30	31	35	39
6	43	41	43	42	43	42	43	43	42
7	38	41	43	40	40	36	40	38	41
8	42	42	43	45	46	41	46	43	44
Mean	36	36	37	36	37	35	37	37	38
SEM	1.9	2.4	2.3	2.4	2.4	1.7	2.5	1.5	1.7

ARTERIAL P_{CO_2}

control experiments

Dog #	Time (min) 0	30	60	90	120	150	180	210	240
1	49.0	52.0	41.0	45.0	41.0	42.5	42.0	37.5	44.5
2	34.0	28.0	26.0	25.0	26.5	29.5	29.0	27.0	27.0
3	35.0	39.0	45.0	43.0	47.0	49.0	48.0	52.0	48.0
4	44.0	38.0	41.5	38.0	49.0	45.0	50.0	50.0	50.0
5	23.5	23.5	21.0	20.0	19.0	20.0	21.0	21.0	21.0
6	37.0	40.5	48.0	40.0	46.0	51.5	56.0	52.0	55.0
7	37.0	37.5	36.0	39.0	40.0	42.0	48.0	37.0	45.0
8	39.0	36.0	34.0	39.0	38.0	41.0	43.0	38.5	40.5
Mean	37.0	37.0	37.0	36.0	38.0	40.0	42.0	39.4	41.4
SEM	2.6	3.0	3.3	3.1	3.7	3.7	4.1	4.1	4.1

VENOUS P_{CO_2}

control experiments

Dog #	Time (min) 0	30	60	90	120	150	180	210	240
1	56.0	58.0	53.0	53.0	53.0	54.0	53.0	50.0	56.0
2	45.0	41.0	40.0	40.5	39.0	40.0	41.0	39.0	38.0
3	53.0	51.0	56.0	55.0	56.0	58.0	63.0	65.0	68.0
4	49.0	50.0	50.0	48.0	51.0	54.0	58.0	57.0	57.0
5	34.0	32.5	32.0	33.5	32.5	33.0	33.0	31.0	33.0
6	53.0	57.0	62.0	58.0	61.0	68.0	67.0	69.0	70.0
7	49.0	52.0	50.5	53.0	58.0	56.0	54.0	56.0	57.0
8	54.0	48.0	46.0	51.0	49.5	49.0	54.0	53.0	54.5
Mean	49.0	49.0	49.0	49.0	50.0	52.0	53.0	53.0	54.2
SEM	2.5	3.0	3.3	2.9	3.4	3.9	3.9	4.5	4.6

ARTERIAL pH

control experiments

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
1	7.28	7.23	7.26	7.24	7.30	7.28	7.28	7.32	7.26
2	7.35	7.41	7.42	7.43	7.43	7.40	7.39	7.41	7.44
3	7.31	7.28	7.23	7.25	7.31	7.24	7.24	7.26	7.23
4	7.30	7.31	7.31	7.31	7.26	7.26	7.20	7.26	7.20
5	7.42	7.40	7.43	7.40	7.42	7.40	7.39	7.35	7.38
6	7.30	7.28	7.23	7.30	7.23	7.24	7.21	7.24	7.21
7	7.39	7.38	7.39	7.38	7.36	7.37	7.33	7.35	7.32
8	7.33	7.35	7.37	7.32	7.34	7.32	7.31	7.33	7.32
Mean	7.34	7.33	7.33	7.33	7.33	7.31	7.29	7.32	7.30
SEM	0.00	0.00	0.00	0.04	0.03	0.04	0.04	0.00	0.00

VENOUS pH

control experiments

	Time (min)								
Dog #	0	30	60	90	120	150	180	210	240
1	7.21	7.18	7.20	7.19	7.21	7.22	7.23	7.25	7.21
2	7.29	7.36	7.35	7.36	7.35	7.35	7.33	7.35	7.37
3	7.26	7.23	7.19	7.19	7.22	7.18	7.19	7.19	7.17
4	7.25	7.26	7.26	7.26	7.23	7.22	7.20	7.20	7.20
5	7.33	7.34	7.33	7.30	7.33	7.32	7.31	7.29	7.27
6	7.22	7.21	7.19	7.19	7.17	7.18	7.19	7.18	7.15
7	7.32	7.31	7.34	7.32	7.28	7.28	7.28	7.29	7.27
8	7.27	7.29	7.28	7.28	7.28	7.28	7.27	7.27	7.27
Mean	7.27	7.27	7.27	7.26	7.26	7.25	7.25	7.25	7.24
SEM	0.03	0.03	0.03	0.03	0.04	0.04	0.00	0.03	0.04

PERCENT CHANGE

CEREBRAL BLOOD FLOW

2 mg/kg endotoxin

Dog #	Time (min) 5	10	15	30	60	90	120	150	180	210	240
1	-60.9	-55.0	-51.8	-44.6	-45.6	-53.1	-56.4	-54.4	-56.7	-53.4	-46.3
2	-38.9	-35.9	-38.9	-43.5	-58.0	-71.8	-70.8	-70.6	-72.1	-74.6	-75.2
3	-63.7	-38.6	-46.0	-36.7	-42.3	-33.0	-46.0	-47.9	-50.7	-53.5	-53.5
4	-46.0	-25.0	-27.0	-28.0	-55.0	-39.0	-33.0	-39.0	-42.0	-38.5	-39.0
5	-45.5	-32.6	-39.6	-41.2	-31.7	-44.4	-32.3	-44.6	-52.7	-52.5	-54.8
6	-69.1	-71.6	-59.3	-52.5	-49.0	-46.6	-39.0	-41.2	-41.2	-41.2	-38.5
7	-57.2	-61.0	-50.3	-44.7	-42.8	-53.8	-47.8	-47.2	-46.2	-44.3	-50.6
8	-62.0	-57.3	-52.0	-46.7	-54.7	-42.0	-48.0	-51.7	-49.3	-47.7	-47.0
9	-31.3	-31.3	-25.3	-11.3	-40.4	-38.9	-39.6	-37.7	-32.1	-31.7	-26.8
10	-58.8	-57.5	-57.3	-42.9	-58.3	-54.6	-53.5	-55.4	-56.9	-57.3	-59.4
11	-28.3	-24.2	-28.3	-19.6	-50.0	-45.4	-35.8	-35.8	-37.5	-33.8	-35.8
12	-32.4	-29.4	-33.1	-24.3	-23.2	-28.3	-37.5	-45.2	-47.8	-47.4	-46.7
Mean	-49.5	-43.3	-42.4	-36.3	-45.9	-45.9	-45.0	-47.6	-48.8	-48.0	-47.8
SEM	4.1	4.7	3.5	3.6	3.1	3.3	3.3	2.8	3.0	3.4	3.6

PERCENT CHANGE

CEREBRAL BLOOD FLOW

5 mg/kg endotoxin

Dog #	Time (min) 5	10	15	30	60	90	120	150	180	210	240
1	-40.4	-51.4	-54.1	-46.2	-39.3	-34.4	-38.8	-44.3	-45.1	-46.2	-48.4
2	-46.0	-55.6	-63.2	-48.9	-27.0	-40.6	-40.3	-39.4	-34.3	-34.9	-31.4
3	-64.4	-63.1	-48.9	-48.0	-56.4	-60.0	-62.0	-64.9	-64.4	-65.1	-63.6
4	-22.5	-41.1	-44.6	-42.2	-40.7	-38.4	-39.9	-44.2	-44.2	-41.5	-37.6
5	-37.8	-22.2	-48.1	-31.1	-46.7	-40.7	-40.0	-40.0	-42.6	-49.3	-70.4
6	-55.8	-49.2	-43.8	8.3	-23.3	-28.8	-33.3	-34.2	-42.1	-30.2	-16.7
Mean	-44.5	-47.1	-34.4	-34.7	-38.9	-40.5	-42.4	-44.5	-45.4	-44.5	-44.7
SEM	6.0	5.8	16.8	9.0	5.0	4.3	4.1	4.4	4.1	5.0	8.3

PERCENT CHANGE
CEREBRAL BLOOD FLOW

1 mg/kg endotoxin

Dog #	Time (min) 5	10	15	30	60	90	120	150	180	210	240
1	-29.1	-36.2	-46.8	-37.6	-42.6	-38.3	-39.7	-50.4	-50.0	-48.9	-52.5
2	-11.8	-37.5	-36.0	-11.8	-35.3	-39.7	-37.9	-33.8	-31.6	-35.3	-33.8
3	-35.7	-42.1	-38.6	-25.0	-46.4	-46.4	-47.1	-44.3	-42.9	-48.6	-42.1
4	-15.9	-18.6	0.9	13.3	-12.4	-20.4	-20.4	-18.6	-15.0	-15.0	-13.3
5	-30.9	-23.7	-22.7	-24.6	-31.6	-36.7	-35.7	-40.8	-44.4	-48.1	-44.9
Mean	-24.7	-31.6	-28.6	-17.1	-33.7	-36.3	-36.2	-37.6	-36.8	-39.2	-37.3
SEM	4.6	4.5	8.0	8.6	5.9	4.3	4.4	5.5	6.2	6.6	6.7

PERCENT CHANGE

CEREBRAL BLOOD FLOW

control experiments

Dog #	Time (min) 5	10	15	30	60	90	120	150	180	210	240
1	- 0.9	- 2.6	0.9	15.7	10.4	1.7	2.6	0.0	- 1.3	4.8	19.6
2	- 4.3	- 5.8	- 8.3	- 8.3	- 6.5	- 5.8	- 8.6	- 2.9	- 2.5	5.8	5.4
3	- 1.6	- 5.4	- 5.4	14.0	21.7	14.4	3.9	- 1.2	- 1.9	-12.0	- 9.7
4	1.1	0.5	- 0.5	- 2.4	-15.9	-29.0	- 7.8	-18.3	4.8	-23.4	- 5.9
5	1.7	0.9	- 5.2	- 4.3	- 5.2	- 5.2	- 1.3	- 0.8	- 6.5	- 3.4	10.8
6	0.0	0.3	2.7	-11.3	0.7	- 7.3	- 8.0	- 8.0	-10.0	- 2.7	-10.0
7	0.4	1.1	- 1.1	0.7	- 2.9	- 4.7	- 6.1	-13.0	- 8.7	-17.7	-11.2
8	- 1.8	- 1.2	- 2.4	- 3.6	- 9.6	6.9	- 1.8	0.0	0.0	- 2.4	0.9
Mean	- 0.7	- 1.5	- 2.4	0.0	- 0.9	- 3.6	- 3.4	- 5.5	- 3.3	- 6.4	0.0
SEM	0.7	0.9	1.3	3.5	4.2	4.5	1.7	2.4	1.7	3.7	3.9

PERCENT CHANGE

CEREBRAL VASCULAR RESISTANCE

2 mg/kg endotoxin

Dog #	Time (min) 5	10	15	30	60	90	120	150	180	210	240
1	-10.5	95.3	79.5	78.0	39.3	33.3	53.0	64.3	78.4	62.5	40.8
2	-7.1	-12.6	-1.5	44.4	84.8	81.3	99.5	116.7	149.0	173.8	182.3
3	-31.6	-42.7	-39.9	-22.4	-8.7	-33.3	-18.8	-3.9	12.6	27.9	33.7
4	-44.3	-13.7	-6.5	-8.2	-18.4	-17.5	-1.8	21.6	39.4	32.5	41.3
5	-9.5	-4.3	0.0	12.8	4.3	13.3	5.2	33.6	47.4	55.5	63.5
6	-35.3	4.2	-1.8	51.1	22.1	24.8	19.0	33.5	34.7	39.9	38.4
7	-34.8	-30.5	-19.5	22.7	18.6	15.9	17.7	51.6	59.5	72.1	94.1
8	-46.9	-29.3	-34.1	6.6	-14.2	-6.6	24.7	19.9	30.9	38.4	45.3
9	-48.4	-42.7	-17.9	-20.0	2.7	-22.9	-16.6	-9.4	-11.3	-10.7	-15.3
10	-29.7	16.2	26.7	22.2	39.1	34.6	56.8	84.6	105.3	101.9	104.5
11	-63.1	-54.0	-54.5	-27.5	-27.3	-27.8	-17.3	-10.2	-16.3	-15.4	1.5
12	-61.1	-41.5	-34.4	-18.4	-30.3	-25.3	-12.9	13.8	26.0	33.4	23.4
Mean	-35.2	-13.0	-8.7	11.8	9.3	5.8	17.4	34.7	46.0	51.0	54.5
SEM	5.5	11.6	10.2	9.6	9.7	9.9	10.6	11.2	13.5	14.6	15.1

PERCENT CHANGE

CEREBRAL VASCULAR RESISTANCE

1 mg/kg endotoxin

Dog #	Time (min) 5	10	15	30	60	90	120	150	180	210	240
1	-45.1	-51.0	-55.3	-26.8	7.6	-6.3	1.1	20.3	24.0	8.0	3.2
2	7.0	-20.5	-25.9	-15.8	-25.7	4.4	28.5	29.1	29.8	46.0	41.4
3	-64.7	-51.8	-47.1	-22.9	-29.6	-40.9	-22.0	-10.0	- 7.6	7.5	17.8
4	0.3	-13.9	-16.6	-18.2	-28.1	-30.0	-20.8	- 2.7	-17.4	- 5.1	- 4.5
5	-53.6	- 5.6	-15.2	3.0	-14.6	-10.3	11.9	31.1	48.3	70.9	74.2
Mean	-31.2	-28.6	-32.0	-16.1	-18.1	-16.6	-0.2	13.6	15.4	25.4	25.4
SEM	14.6	9.6	8.1	5.1	6.9	8.2	9.7	8.4	12.2	14.2	14.8

5 mg/kg endotoxin

Dog #	Time (min) 5	10	15	30	60	90	120	150	180	210	240
1	10.7	-13.9	- 7.1	12.2	- 9.4	-20.7	- 6.3	- 6.8	4.5	11.1	24.7
2	- 5.2	-15.4	-18.5	1.7	-25.8	-20.9	-13.0	- 4.5	- 3.8	- 1.7	- 2.4
3	-21.1	-16.2	1.3	39.8	57.0	59.9	79.9	92.6	105.8	110.4	123.0
4	5.1	19.5	- 7.6	15.5	-12.4	- 1.3	11.1	24.9	34.0	52.0	48.4
5	-59.3	-61.2	-67.7	-21.0	- 1.6	-13.1	- 9.2	- 6.0	0.0	- 2.4	31.3
6	- 8.3	- 0.3	2.8	-26.4	1.7	-16.7	-17.4	- 4.5	20.8	19.1	4.5
Mean	-13.0	-14.6	-16.1	3.6	1.6	- 2.1	7.5	15.9	27.0	31.4	36.8
SEM	10.3	10.9	10.8	10.0	11.8	12.8	15.0	16.1	16.8	17.8	19.1

PERCENT CHANGE

CEREBRAL VASCULAR RESISTANCE

control experiments

Dog #	Time (min) 5	10	15	30	60	90	120	150	180	210	240
1	3.1	8.2	4.3	- 5.1	- 0.5	15.3	13.8	17.4	18.9	15.6	5.7
2	5.5	3.9	9.2	8.4	6.8	8.0	12.5	3.5	4.9	- 6.1	- 1.2
3	3.9	8.1	8.1	-10.9	-15.5	- 0.2	12.9	14.2	9.8	27.4	22.4
4	-3.5	0.3	-0.9	1.7	14.8	37.5	8.4	4.7	-4.9	5.2	2.0
5	0.2	1.1	4.5	9.1	7.6	7.6	4.2	-3.8	3.7	-5.4	-15.4
6	1.7	-1.0	-2.5	11.9	2.7	15.1	21.3	21.3	24.0	10.4	19.4
7	0.4	-0.4	1.0	- 2.1	7.0	12.1	13.2	15.5	17.9	22.6	21.3
8	1.2	0.6	3.8	6.2	13.3	- 5.2	3.1	2.5	1.8	3.1	- 1.5
Mean	1.6	2.6	3.5	2.4	4.5	11.2	11.2	13.2	9.5	14.0	6.6
SEM	0.9	1.3	1.4	2.8	3.4	4.5	2.1	3.9	3.5	5.8	4.7

CEREBRAL BLOOD FLOW

Experiments terminating in death (due to 2 mg/kg endotoxin)

Dog #	Time (min) 0	5	10	15	30	60	90	120	150	180	210	240
1	18.8	14.6	14.0	13.8	15.1	13.9	13.6	13.7	14.5	--	--	---
2	21.6	13.8	12.4	12.2	11.6	10.4	8.2	6.2	6.0	4.2	--	--
3	21.6	16.0	17.6	17.2	17.2	9.6	---	--	--	--	--	--
4	16.8	8.4	8.0	6.4	8.6	6.0	6.8	--	--	--	--	--
5	20.4	20.0	17.6	16.2	15.0	12.2	10.2	--	--	--	--	--
6	22.4	18.0	15.4	17.8	17.6	11.8	10.6	10.5	--	--	--	--
7	28.6	22.4	9.0	7.2	14.8	18.8	12.5	9.0	6.4	3.0	--	--
8	13.6	9.6	9.6	9.2	9.6	7.0	7.5	6.0	6.0	4.0	--	--
	CEREBRAL PERFUSION PRESSURE											
1	115	34	39	45	52	47	52	53	59	--	--	--
2	119	91	96	96	81	57	55	56	63	64	--	--
3	99	35	40	54	47	34	--	--	--	--	--	--
4	121	37	38	33	41	35	26	--	--	--	--	--
5	126	85	93	88	65	41	45	--	--	--	--	--
6	139	132	101	103	107	62	58	59	--	--	--	--
7	142	70	30	27	43	50	42	38	35	30	--	--
8	108	58	58	57	52	48	48	57	52	45	--	--
	CEREBRAL VASCULAR RESISTANCE											
1	6.10	2.30	2.80	3.30	3.40	3.40	3.80	3.90	4.10	--	--	--
2	5.50	6.60	7.70	7.90	7.00	5.50	6.70	9.00	10.60	15.20	--	--
3	4.60	2.20	2.20	3.10	2.70	3.50	--	--	--	--	--	--
4	7.20	4.40	4.80	5.10	4.70	5.80	3.80	--	--	--	--	--
5	6.17	4.25	5.28	5.43	4.36	3.38	4.36	--	--	--	--	--
6	6.21	7.38	6.58	5.79	6.08	5.27	5.49	5.64	--	--	--	--
7	4.79	2.90	2.72	2.99	2.50	2.39	2.96	3.67	4.69	8.66	--	--
8	7.94	6.06	6.04	6.22	5.42	6.86	6.40	9.50	8.67	11.25	--	--