12-1979

Patterns of Fetal Lamb Regional Cerebral Blood Flow during and after Prolonged Hypoxia

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Running Head: REGIONAL CEREBRAL BLOOD FLOW IN HYPOXIC FETAL LAMB

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Presented in part at the Society for Pediatric Research Meeting, Atlanta, Georgia, April 4, 1979.

LOMA LINDA UNIVERSITY

Graduate School

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by

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*A Thesis in Partial Fulfillment

Of the Requirements for the Degree

Master of Science in Physiology

December 1979

Each person whose signature appears below certifies that this thesis in his opinion is adequate, in scope and quality, as a thesis for the degree Master of Science.

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SPECULATION

In the fetal lamb during prolonged intrauterine hypoxia, total and regional cerebral blood flows increase to the same extent without evidence of preferential shunting to critical brainstem or subcortical areas. Neuropathologic studies have indicated relative sparing of these areas during similar animal experimental or human neonatal conditions. This suggests that the pattern of hypoxic ischemic insult to the neonatal central nervous system associated with asphyxia may differ from that produced by hypoxia alone. In addition, during asphyxia these pathologic changes may result primarily from hypotension and decreased regional cerebral blood flow, or from regional metabolic derangements in the cerebral tissue.

INTRODUCTION

Prolonged intrauterine hypoxia associated with fetal distress constitutes one of the most common causes of neurologic insult occurring in the neonatal period. Perinatal asphyxia causes a variety of neuropathologic changes, including severe neuronal necrosis, status marmaratus of the basal ganglia and thalamus, parasagittal cerebral neuronal necrosis, periventricular leukomalacia and periventricular-intraventricular hemorrhage.[26] Not only is the pathogenesis of such lesions poorly understood, but the underlying control mechanisms and distributions of regional cerebral blood flow during both normal conditions and perinatal asphyxia

are unknown. In previous experiments in newborn monkeys, Windle[28] demonstrated that total asphyxia resulted primarily in subcortical and brainstem lesions. In contrast, Brann and Myers[3] showed in newborn monkeys that "prolonged partial asphyxia" produced by maternal hypoxia or carbon monoxide hypoxia, maternal hypotension, or umbilical cord compression, primarily affected the cerebral cortex while sparing critical brainstem structures.[3] These later findings are considered more applicable to human neonatal asphyxia because of the similarities observed in the distribution of neuropathologic lesions as well as in the occurrence of cerebral edema.[20]

Numerous investigators have measured cerebral blood flow in the fetus and newborn animal, using a variety of techniques, including measurement of cerebral venous outflow of ^{131}I[1], electromagnetic flow probes on the carotid arteries,[16,18,22] ^{133}xenon clearance for gray and white matter blood flow,[12,21] and radioisotope labeled microspheres.[6,13,17,24]

Hypoxia has been noted to cause an increase in total blood flow to the fetal brain,[16,21] and arterial oxygen content has been considered a more important contributing factor than the partial pressure of oxygen in affecting total cerebral blood flow.[12] In the hypoxic acidotic infant or fetal lamb, autoregulation appears disturbed and hypotension has been associated with decreased cerebral blood flow.[14,15]

Regional cerebral blood flow has been studied to a

limited extent during hypoxia. In acutely anesthetized monkeys, with the use of the ^{14}C-antipyrine technique, a 20 to 80% decrease in cerebral blood flow was noted during periods of prolonged hypoxia accompanied by marked hypercarbia and acidosis.[23] Recently Lou et al.[15] used radioactive labeled microspheres to quantitate flow to four regions of the fetal lamb during variation of cerebral perfusion pressure by partial umbilical cord occlusion or by phlebotomy.[15] During asphyxia, flows to all regions of the brain increased 4-to-6 fold except with the added insult of hypotension, when flows to all regions decreased uniformly.

The purpose of this study was to understand further the control mechanisms of fetal regional cerebral blood flow under both normal conditions as well as during periods of hypoxic stress. The major questions which we wished to explore were: 1) whether differences in regional cerebral blood flow to the brainstem, subcortex, and cortex occur in the fetal lamb; 2) the extent to which these flows change during and after prolonged intrauterine hypoxia; and 3) whether preferential shunting to critical areas occurs during fetal hypoxia.

MATERIALS AND METHODS

The principle of our method was to study near-term pregnant sheep and their fetuses during three different periods: control, hypoxia and recovery. We used five

separate sets of radioactive labeled microspheres to measure the blood flow to 34 separate regions of the central nervous system. In addition, we measured cardiac output and flow to other major organs before, during and after hypoxia.

Twelve ewes of 120 to 140 days gestation and their fetuses were chronically catheterized. The ewe was anesthetized with 2 ml of 0.2% tetracaine HCl given intraspinally, in addition to 400 mg of sodium pentobarbital intravenously. We placed Tygon catheters (2.3 mm od) in branches of the maternal popliteal artery and uterine vein. Through a small hysterotomy incision, we extracted a fetal hindlimb, and following the injection of local anesthesia (0.5% lidocaine), we placed catheters (1.8 mm od) into both a dorsal pedal artery and vein and advanced them into the descending aorta and inferior vena cava below the ductus venosus, respectively. Through a separate small incision, we also extracted a fetal forelimb and after anesthetizing the skin placed two catheters, one from a radial artery into the brachiocephalic artery of the ascending aorta, and one from the cephalic vein into the superior vena cava. In addition, we positioned an amniotic fluid catheter over the left chest wall. Following closure in layers, the fetal and maternal catheters were exteriorized on the ewe's flank and the ewe left to recover.

Four to six days after surgery, we carried out the experiments. We recorded control fetal and maternal blood pressure and heart rates. In addition, we obtained anaerobic

heparinized blood samples from the fetal ascending and descending aorta, superior and inferior vena cava, maternal artery and uterine vein, measured the O_2 and CO_2 tensions and pH, using appropriate microelectrodes (Radiometer BMS 3A, London Company, Westlake, OH) and measured the hematocrit.

In order to determine fetal organ blood flows, we used microspheres 15 (±1) microns in diameter labeled with ^{57}Co, ^{51}Cr, ^{113}Sn, ^{85}Sr, or ^{46}Sc (Minnesota Mining and Manufacturing Co., St. Paul, MN). These were suspended in a solution of 10% dextran and 0.05% polyoxyethylene sorbitan monooleate (Tween 80) to minimize aggregation and provide for even distribution. Prior to the experiment, we placed vials containing microspheres into the ultrasonic bath for 10 to 30 minutes for dispersion. To measure control regional cerebral flow and distribution of organ blood flow, we injected the microspheres over a 15-second period into the inferior (2/3) and superior (1/3) vena cava. During the period of injection and for 75 seconds thereafter, we withdrew blood reference samples at the rate of 4.8 $ml \cdot min^{-1}$ simultaneously from both the ascending and the descending aorta, using an infusion-withdrawal pump (Model 972, Harvard Apparatus Company, Inc., Millis, MA).

After placing the ewe's head in a plastic hood, we induced hypoxia by having the ewe inspire 9 to 10% O_2, and 5% CO_2 to offset the respiratory alkalosis induced by hyperventilation, at a gas flow rate of $15 l \cdot min^{-1}$. We sampled

blood from the fetal ascending aorta every five minutes until the O_2 tension equaled 12 to 15 torr. This was considered our zero time reference for institution of hypoxia. At 15, 30 and 90 minutes after the onset of hypoxia, we injected microspheres labeled with different radionuclides. We obtained blood for complete blood gas determinations prior to each microsphere injection and restored fetal blood volume with equal amounts of maternal blood. Occasionally we administered 3 to 5 cc of sodium bicarbonate in order to correct the metabolic acidosis induced by hypoxia. At the end of the 90-minute hypoxic period, we removed the ewe from the hood and allowed her to breathe room air. After another 60 minutes we injected the fifth set of microspheres.

The ewe and fetus were sacrificed with 30 ml of T61 (National Laboratories Corp., Summerville, NJ). The fetus was removed, towel dried, and weighed and the major fetal organs (heart, lungs, liver, gastrointestional tract, kidneys, adrenals and spleen) as well as the placental cotyledons and amniotic membranes were removed, weighed, ashed and reweighed. We dissected the fetal brain into 34 discrete regions, including the following: cortical structures--the gray and white matter of the frontal, parietal, temporal and occipital lobes; subcortical structures--thalamus, hypothalamus, caudate nucleus, hippocampus and cerebellum; brainstem structures--midbrain, pons and medulla; as well as the cervical spinal cord. These were weighed separately and

placed into plastic-covered vials. All samples were counted for radioactivity (Auto-Gamma Scintillation Spectrometer, Model 5912, Packard Instrument Company, Inc., Downers Grove, IL). Specimens from the brain weighed approximately 5 gms and contained 400 to 800 microspheres. Using a digial computer, we calculated the quantity of microspheres per organ, and then converted the counts to absolute blood flows expressed as $ml \cdot min^{-1} \cdot 100gm^{-1}$ organ weight, $ml \cdot min^{-1} \cdot kg$ fetus, relative flow, and percent of cardiac output.

For each variable under consideration we performed statistical calculations on the control measurements, the experimental measurements and the paired differences between experimental and control values. We computed mean values, standard deviations, and standard errors of the means, and used the paried t-test to determine the significance of changes from control.

RESULTS

Control Total and Regional Fetal Cerebral Blood Flow

Total fetal cerebral blood flow equaled 155 (±16 SEM) $ml \cdot min^{-1} \cdot 100g$ brain $tissue^{-1}$ (Fig 1, Table 1). Flow was not uniform to all parts of the brain, however, and Figure 1 shows the hierarchy of cerebral blood flow with an increase in flow from a cephalad to a caudad direction. Thus, the mean cortical blood flow equaled 134 (±15) $ml \cdot min^{-1} \cdot 100gm^{-1}$, the mean subcortical flow was 186 (±19) $ml \cdot min^{-1} \cdot 100gm^{-1}$,

and the mean brainstem flow was 254 (±23) $ml \cdot min^{-1} \cdot 100gm^{-1}$ (Fig 1). There was a surprising consistency of similar blood flows to various structures within the major regions, except for a slight but insignificant elevation of mean cortical gray matter flow of 139 (±17) $ml \cdot min^{-1} \cdot 100gm^{-1}$ as compared to a mean white matter blood flow of 120 (±12) $ml \cdot min^{-1} \cdot 100gm^{-1}$ (Fig 1).

Fetal Blood Gases and Cardiovascular Response During Hypoxia

Figure 2 depicts the changes in fetal ascending aortic O_2 and CO_2 tensions and pH during and after the 90-minute hypoxic period. During the entire hypoxic period, the ascending aortic O_2 tension was maintained at 12 to 15 torr (O_2 content about 5 $ml \cdot dl^{-1}$) while the CO_2 tension remained relatively constant. Fetal pH decreased from a control value of 7.34 (±0.01) to 7.31 (±0.01) units at 15 minutes, and to 7.24 (±0.02) at 90 minutes of hypoxia.

Figure 3 shows the slight elevation in fetal mean arterial blood pressure during hypoxia to 54 (±2) from 46 (±2) mm Hg, and an initial bradycardia (15%) to 145 (±8) from 170 (±9) $beats \cdot min^{-1}$. The cardiac output remained relatively constant at 551 (±38) $ml \cdot min^{-1} \cdot kg$ fetal $weight^{-1}$; however, the fraction of cardiac output to the brain doubled to 9.2 (±0.6) from 4.2 (±0.5) percent.

Changes in Regional Cerebral Blood Flow During Hypoxia

As shown in Figure 4, after 15 minutes of hypoxia,

blood flow to the brainstem increased to 541 (±63) from 254 (±23) $ml \cdot min^{-1} \cdot 100gm^{-1}$, flow to subcortical regions increased to 348 (±33) from 186 (±19) $ml \cdot min^{-1} \cdot 100gm^{-1}$, and flow to the cortex increased to 257 (±24) from 134 (±15) $ml \cdot min^{-1} \cdot 100gm^{-1}$. Table 1 shows the mean changes (± SEM) in absolute flow at 15, 30 and 90 minutes of hypoxia. Cerebral flow remained elevated at these levels during the entire hypoxic period. Even after the ewe had been returned to room air for one hour, blood flow persisted at elevated levels (Table 1, Fig 4).

At first glance it would appear that fetal hypoxia results in preferential shunting of flow to the brainstem and subcortical regions from the cortex (Fig 4). However, as shown in Figure 5, the percent increase in blood flow to the major brain regions remained relatively uniform. For instance, at 15 and 30 minutes, flow increased 92% to all regions, and at 90 minutes increased 102%. One hour after normal oxygen levels had been restored, cerebral flow remained 50% above control values. Thus, there is no evidence of preferential shunting of blood flow to certain brain regions during hypoxia.

Figures 6 to 9 depict the changes in blood flow to discrete brain regions during and after hypoxia. The patterns of change in flow in the different areas within the three major areas (i.e., cortex, subcortex, brainstem) were quite similar. For instance, in the cortex (Fig 6), flow changes

to the frontal, parietal, temporal and occipital areas varied only slightly. Although the gray matter tended to have higher flows than did white matter, this difference was not statistically significant. Neither were there significant differences between the blood flow to the right [154 (±15)] and left [156 (±17)] sides of the brain or brainstem. We observed similar patterns of response in the subcortical (Fig 7) and brainstem (Fig 8) regions, and in the cervical cord (Fig 9).

Relations Between O_2 Tension, O_2 Content, pH, and Cerebral Blood Flow

Total brain blood flow increased following decreases in O_2 tension ($R = 0.6412$) and O_2 content ($R = 0.7111$) (Fig 10A, 10B), and the R values were not significantly different. Cerebral flow similarly increased following decreased pH ($R = 0.5938$) (Fig 11).

To examine the combined effects of O_2, CO_2 and pH on total cerebral blood flow we performed a multiple linear regression analysis. Cerebral flow was somewhat more highly correlated with the three variables P_{O_2}, P_{CO_2} and pH than with (O_2), P_{CO_2} and pH, but the difference between the two regressions was not statistically significant. In both instances the regression coefficient of CO_2 tension was not significantly different from zero (possibly reflecting the degree to which P_{CO_2} was controlled during these experiments). CO_2 tension was subsequently eliminated from the

analysis without significant effect. The resulting empirical equation was:

$Q(ml \cdot min^{-1} \cdot 100g^{-1}) = 4530 - 9.5(+1.5) \times P_{O_2}(torr) - 560\ (\pm 110) \times pH.$

Both regression coefficients were significant with $p<10^{-5}$ and the overall regression was significant with $p<10^{-10}$. The multiple correlation coefficient was 0.773.

Changes in Organ Blood Flow During Hypoxia

During hypoxia, blood flow to the heart and adrenals also increased and persisted one hour after recovery. Blood flows to the lungs, kidneys and placenta decreased during this period but returned to control values. Table 2 gives the mean changes in flow during and after the hypoxic period in both absolute value and as percent change.

Control Regional Cerebral Blood Flow

The control value of total cerebral flow of 155 (±16) $ml \cdot min^{-1} \cdot 100gm^{-1}$ found in this study agrees with results of previous investigations using the microsphere technique.[6,13,17,24] Dissection of the brain into 34 specific areas allowed us to examine regional flow distribution with reasonable discrimination (Fig 1, Table 1). Perhaps the most striking observation was the hierarchy of flows with progressive increase in flow from a cephalad to a caudad direction, the mean brainstem flow equaling almost twice that of a cortex. There was a surprising uniformity of blood flows to various structures

within these three major regions. Blood flow to the cortical gray matter was slightly higher than flow to the white matter [139 (±17) vs 120 (±12) $ml \cdot min^{-1} \cdot 100gm^{-1}$], but the difference was not statistically significant.

Our results in the fetal lamb differ considerably from those of previous studies in the newborn puppy, in which regional cerebral flow was determined by use of ^{14}C antipyrine.[10] In neonatal pups, cortical flow averaged 35 $ml \cdot min^{-1} \cdot 100gm^{-1}$ with no significant differences observed in 35 separate regions. However, in longitudinal studies, total flow increased significantly to 75 $ml \cdot min^{-1} \cdot 100gm^{-1}$ at three weeks of life and to adult values at thirteen weeks. Significant regional flow differences then appeared within the first few weeks of life. This lack of difference in regional flows at birth was explained[10] by the relative paucity of morphologic and functional maturation in the newborn pup, as the majority of brain growth occurs during the first thirteen weeks of life postnatally.

In contrast, we observed significant differences in regional cerebral flow in the fetal lamb, a fact which may reflect morphologic and functional maturation associated with the increase in brain growth near term. Although the ratio of brain to body weight of the fetal lamb is only 2% in contrast to 10% in the human fetus,[8] the patterns of intrauterine brain growth in both these species are similar and suggest that the fetal lamb may serve as a reasonably

good model of cerebral blood flow.[19] Our studies in the fetal lamb, as well as previous studies in the newborn puppy, suggest that changes observed in regional flow relate to patterns of regional intrauterine brain growth, a circumstance which is probably a reflection of changes in local metabolism and neurophysiological function, as well as of the development of the cerebral microcirculation.[10]

Changes in Total Cerebral Blood Flow During Prolonged Intrauterine Hypoxia

Our finding that total brain blood flow increased 80 to 100% during the 90-minute period of intrauterine hypoxia has been noted by previous investigators using several techniques, including an electromagnetic flowmeter on the carotid artery,[16] ^{133}xenon clearance (primarily measuring gray matter blood flow)[12,21] and radioactive labeled microspheres.[17] Total brain flow doubled by fifteen minutes after the onset of hypoxia and persisted at this level throughout the hypoxic period. The fraction of cardiac output to the brain also doubled [to 9.2 (±0.6) from 4.2 (±0.5) percent] while the cardiac output remained constant. This suggests that the increase in cerebral blood flow resulted primarily from a change in cerebrovascular resistance, because the mean arterial blood pressure increased only slightly. Although the arterial pH decreased to 7.24 (±0.02) at 90 minutes the linear multiple regression analysis suggests that this change in pH would account for about only 10% of the observed

flow changes.

In contrast to these results in the fetal lamb subjected to moderate degrees of prolonged hypoxia, previous studies in the fetal monkey, lamb and newborn puppy subjected to either "prolonged partial" asphyxia or "total" asphyxia associated with marked hypercapnea, acidosis and hypotension found marked decreases in total and regional cerebral blood flow, as well as significant neuropathological changes.[3,12,15] Thus, changes in cerebral flow appears to be one of the mechanisms by which the fetus withstands prolonged intrauterine hypoxia. Apparently it is only when additional metabolic or cardiovascular adaptive mechanisms fail that cerebral blood flow decreases, an effect perhaps associated with fetal hypotension. However, pathologic studies demonstrate cerebral edema and neuronal necrosis in the presence of significant hypotension.[23] This suggests that after the hypoxic insult, cerebral edema develops and could further impair recovery by affecting the microcirculation and decreasing total cerebral flow. We currently are evaluating this possibility.

Changes in Regional Cerebral Blood Flow During Hypoxia

As previously discussed, we noted a hierarchy of blood flows during the control period, with flow greatest in the brainstem, less in the subcortical regions, and least in the cortex (Fig 1). During hypoxia, flow increased significantly

to all regions (Fig 4), but as noted in Figure 5, the percent increase to the three major regions was quite similar at 15, 30 and 90 minutes, as well as 60 minutes after recovery. Thus, no preferential shunting of cerebral flow to critical brainstem or subcortical structures occurred during hypoxia, despite the greater flow to these areas under control conditions. This is somewhat surprising when one takes into account previous neuropathologic studies in the fetal brain subjected to "prolonged partial intrauterine asphyxia," which showed involvement of the cortex and subcortex[3] with sparing of the brainstem. This suggests that during hypoxia, blood flow within the brain might be redistributed, but this was not observed in our studies.

An additional aspect of regional flow distribution during hypoxia concerns fetal brain growth and energy metabolism. Previous studies in several species have shown that the brainstem and cerebellum are the areas of greatest brain growth during the fetal and neonatal period.[2] Measurements of DNA, RNA, protein, lipid and carbohydrate metabolism suggest that the energy requirements for these metabolically active regions are greater than for other brain areas and these regions would be the most susceptible to an insult such as hypoxia.[5] Yet this does not appear to occur. In adult cats subjected to both ischemic and hypoxic insults, changes in energy metabolism measured by NADH fluorescence demonstrated no correlation between metabolically active

regions (e.g. gray matter) and the resulting metabolic changes associated with the ischemic insult.[27] Likewise, during hypoxia in the newborn animal, cerebral energy requirements have been shown to be lower than adult animals and this may be another factor accounting for the ability of the fetus to tolerate longer periods of hypoxia.[25] The importance of aerobic glucose metabolism has already been demonstrated in the fetal lamb brain[9] but at the present time, no in vivo studies have examined whether regional metabolic differences occur, and whether the brainstem responds differently to a metabolic insult or has potential alternative adaptive mechanisms.

Cerebral Blood Flow After Hypoxia

Cerebral flow determined following a 60-minute recovery period when fetal heart rate, blood pressure, and blood gas values were normal remained about 50 percent above control values. This phenomenon was unexpected. Many metabolic disturbances have been reported in association with hypoxia, including changes in ATP, phosphocreatine, lactate, pyruvate, cyclic AMP, and extracellular potassium concentrations.[11,25] The persistence of elevated cerebral blood flow is most likely related to some metabolic perturbation which affects the extracellular and intracellular compartments, causing cerebrovascular dilation and decreased vascular resistance. There was no significant change in blood pressure or cardiac

output in these experiments to indicate any other form of compensatory cardiovascular adjustment.

Determinant Factors in Fetal Cerebral Blood Flow During Hypoxia

The multiple linear regression analysis as well as Figures 10A, 10B and 11 illustrate the relation between decreases in fetal blood O_2 levels and pH and elevation of cerebral flow. Although several previous investigators have reported that O_2 content is more important than O_2 tension in affecting cerebral flow,[12] in this study the correlation coefficient obtained when O_2 tension was compared to cerebral flow ($R = 0.6412$) was not significantly different from that for O_2 content ($R = 0.7111$).

Acidosis also is associated with increased cerebral flow ($R = 0.5938$). This is known to be an important factor in controlling cerebral flow in adult as well as in newborn goats subjected to post hypoxic, lactic acid, or respiratory acidosis.[4] A correlation between cerebral flow during hypoxia and acidosis in fetal lambs also has been observed in previous investigations,[4] but this point is disputed.[12]

In summary, many previous investigations of the response of the fetus to hypoxic stress have shown dramatic and self-protective cardiovascular, metabolic and neuroendocrine adaptive responses. Our studies of fetal cerebral blood flow during prolonged hypoxia have noted the following:

1) Significant differences in fetal regional cerebral blood flow occur in utero. Brainstem and subcortical flows are substantially greater than flows in other regions of the brain. 2) During prolonged intrauterine hypoxia, total and regional cerebral flow increases between 80 and 120% and is maintained at these levels during the hypoxic period. 3) One hour after fetal oxygenation is restored, cerebral flow remains elevated 50% above control values. 4) No significant preferential shunting of regional cerebral blood flow occurs during prolonged hypoxia in utero.

ACKNOWLEDGEMENTS

This study was supported by USPHS Grant 03807. We thank Ms. Diane McClure and Mr. Charles W. Hewitt for technical assistance.

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APPENDIX

OF

FIGURES

LEGENDS TO FIGURES

Fig 1 Control total and regional fetal cerebral blood flow ($ml \cdot min^{-1} \cdot 100gm^{-1}$) to discrete regions of the brain. Regional values are based on combined data for both right and left sides of brain. The values are means (±SEM) from 12 lambs.

Fig 2 Fetal ascending aortic P_{O_2}, O_2 content, P_{CO_2}, and pH before, during and after the 90-minute hypoxic period. Mean values ±SEM.

Fig 3 Mean arterial blood pressure, heart rate, cardiac output and percent cardiac output to brain before, during and after the 90-minute hypoxic period. Mean values ±SEM.

Fig 4 Changes in total and regional fetal cerebral blood flow ($ml \cdot min^{-1} \cdot 100gm^{-1}$) to the cortex, subcortex and brainstem during and after the 90-minute hypoxic period. Values are mean ±SEM.

Fig 5 Percent increase above control values in total and regional cerebral blood flow during and after the hypoxic period. Values are mean ±SEM.

Fig 6 Changes in gray and white matter cerebral flow ($ml \cdot min^{-1} \cdot 100gm^{-1}$) to the frontal, perietal, temporal, and occipital cortex during and after the 90-minute hypoxic period.

Fig 7 Changes in subcortical regional cerebral blood flow ($ml \cdot min^{-1} \cdot 100gm^{-1}$) during and after the 90-minute hypoxic period. Values are mean ±SEM.

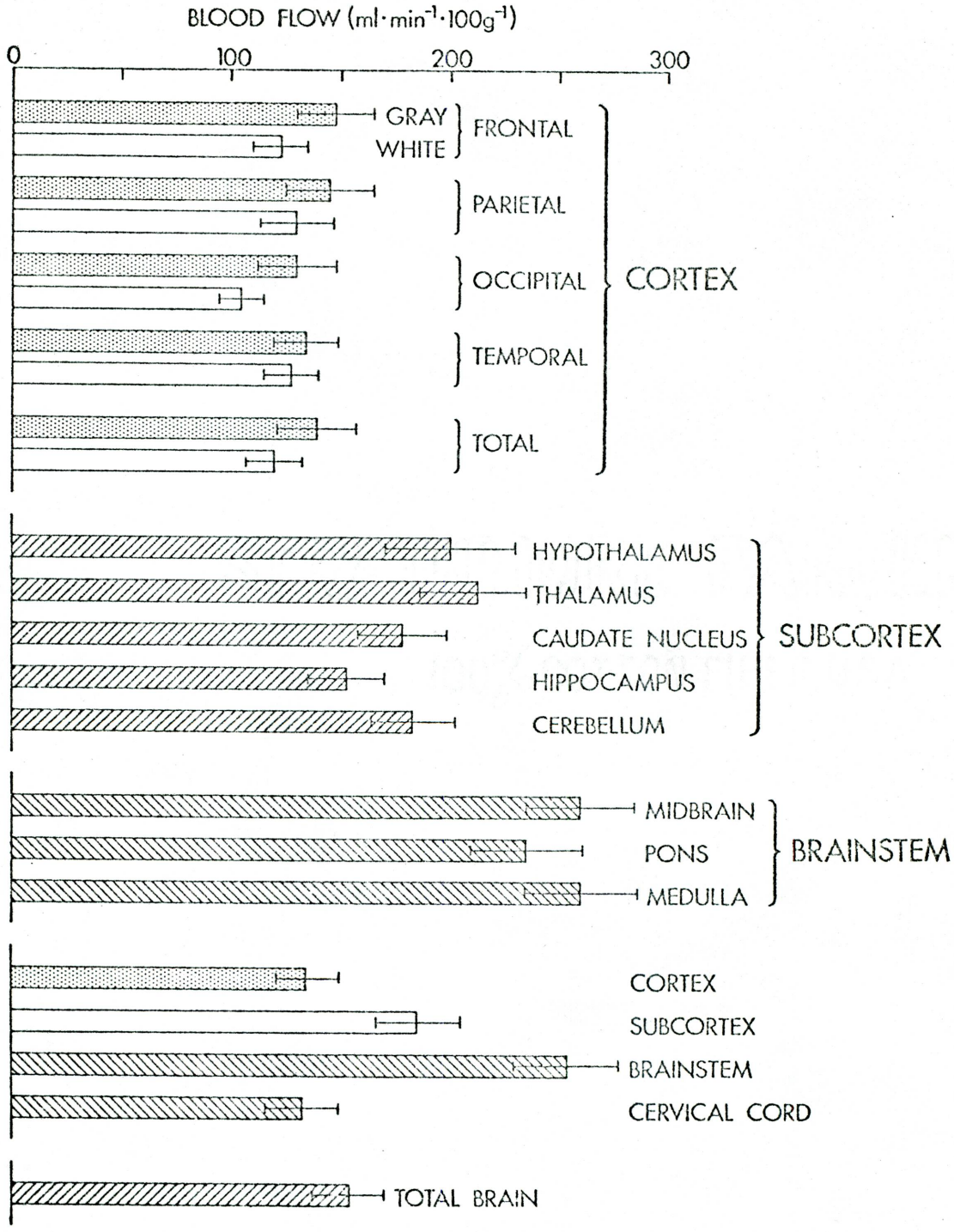
Fig 8 Changes in brainstem regional cerebral blood flow ($ml \cdot min^{-1} \cdot 100gm^{-1}$) during and after the 90-minute hypoxic period. Values are mean ±SEM.

Fig 9 Changes in cervical cord blood flow ($ml \cdot min^{-1} \cdot 100gm^{-1}$) during and after the 90-minute hypoxic period. Values are mean ±SEM.

Fig 10 A. Relation of total cerebral flow to ascending aortic oxygen tension (R = 0.6412).

B. Relation of fetal cerebral flow to ascending aortic O_2 content (R - 0.7111).

Fig 11 Relation of total fetal cerebral flow to ascending aortic blood pH (R - 0.5938).


BLOOD FLOW (ml·min⁻¹·100g⁻¹)
0
100
200
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GRAY
WHITE
FRONTAL
PARIETAL
OCCIPITAL
TEMPORAL
TOTAL
CORTEX
HYPOTHALAMUS
THALAMUS
CAUDATE NUCLEUS
HIPPOCAMPUS
CEREBELLUM
SUBCORTEX
MIDBRAIN
PONS
MEDULLA
BRAINSTEM
CORTEX
SUBCORTEX
BRAINSTEM
CERVICAL CORD
TOTAL BRAIN

Figure 1

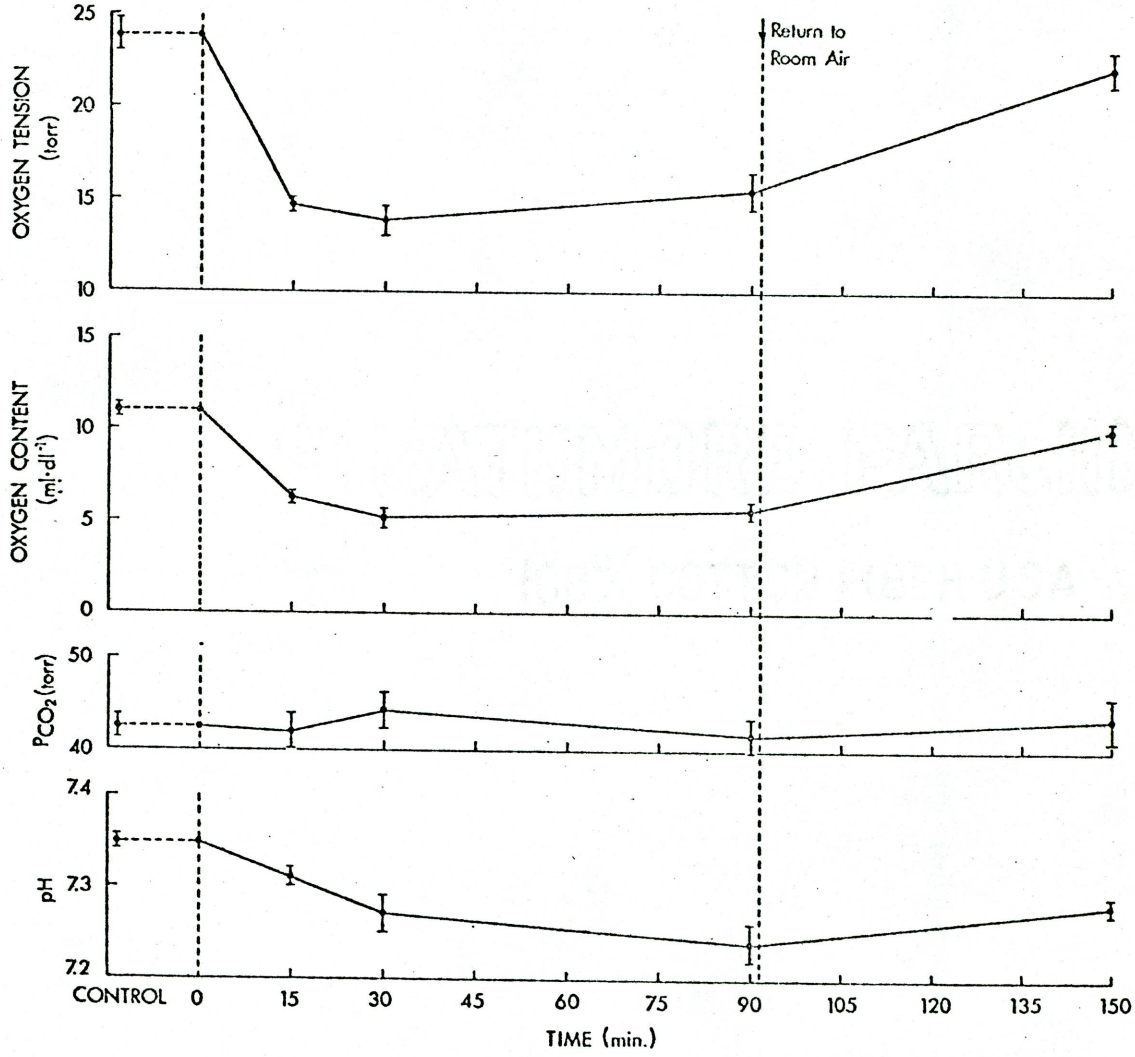
OXYGEN TENSION (torr)
25
20
15
10
Return to Room Air
OXYGEN CONTENT (ml·dl⁻¹)
15
10
5
0
PCO2 (torr)
50
40
pH
7.4
7.3
7.2
CONTROL
0
15
30
45
60
75
90
105
120
135
150
TIME (min.)

Figure 2

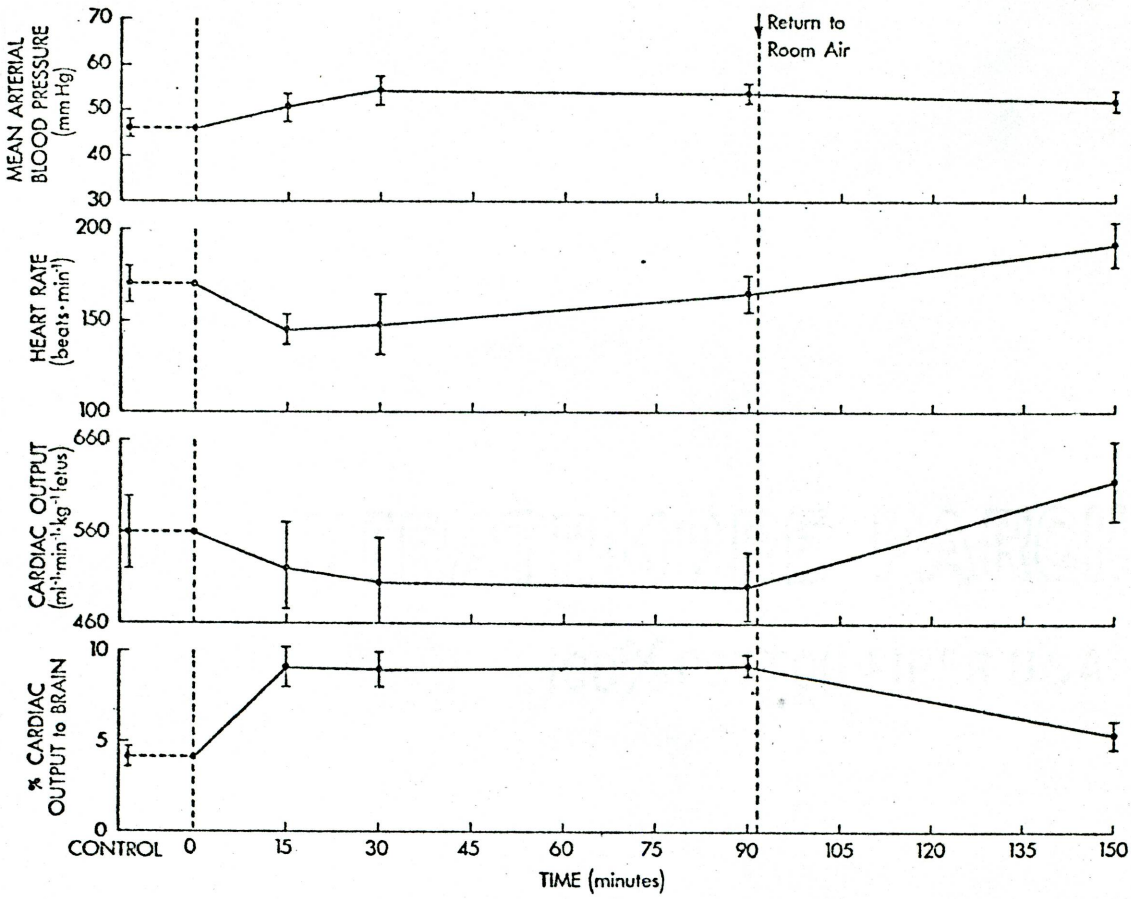
MEAN ARTERIAL BLOOD PRESSURE (mm Hg)
70
60
50
40
30
Return to Room Air
HEART RATE (beats·min⁻¹)
200
150
100
CARDIAC OUTPUT (ml·l·min⁻¹·kg⁻¹ fetus)
660
560
460
% CARDIAC OUTPUT to BRAIN
10
5
0
CONTROL
0
15
30
45
60
75
90
105
120
135
150
TIME (minutes)

Figure 3

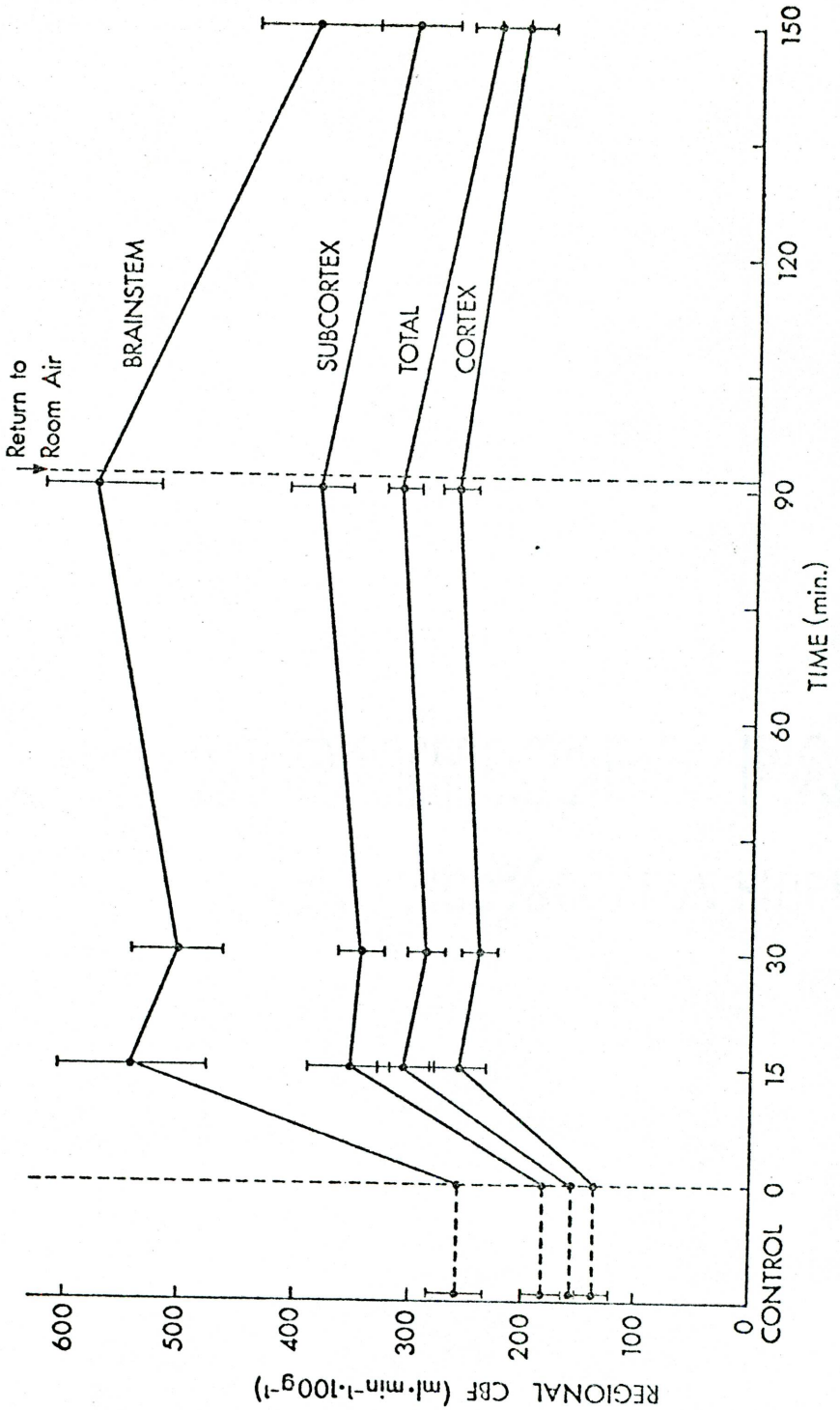
REGIONAL CBF (ml·min⁻¹·100g⁻¹)
600
500
400
300
200
100
0
CONTROL
0
15
30
60
90
120
150
TIME (min.)
Return to Room Air
BRAINSTEM
SUBCORTEX
TOTAL
CORTEX

Figure 4

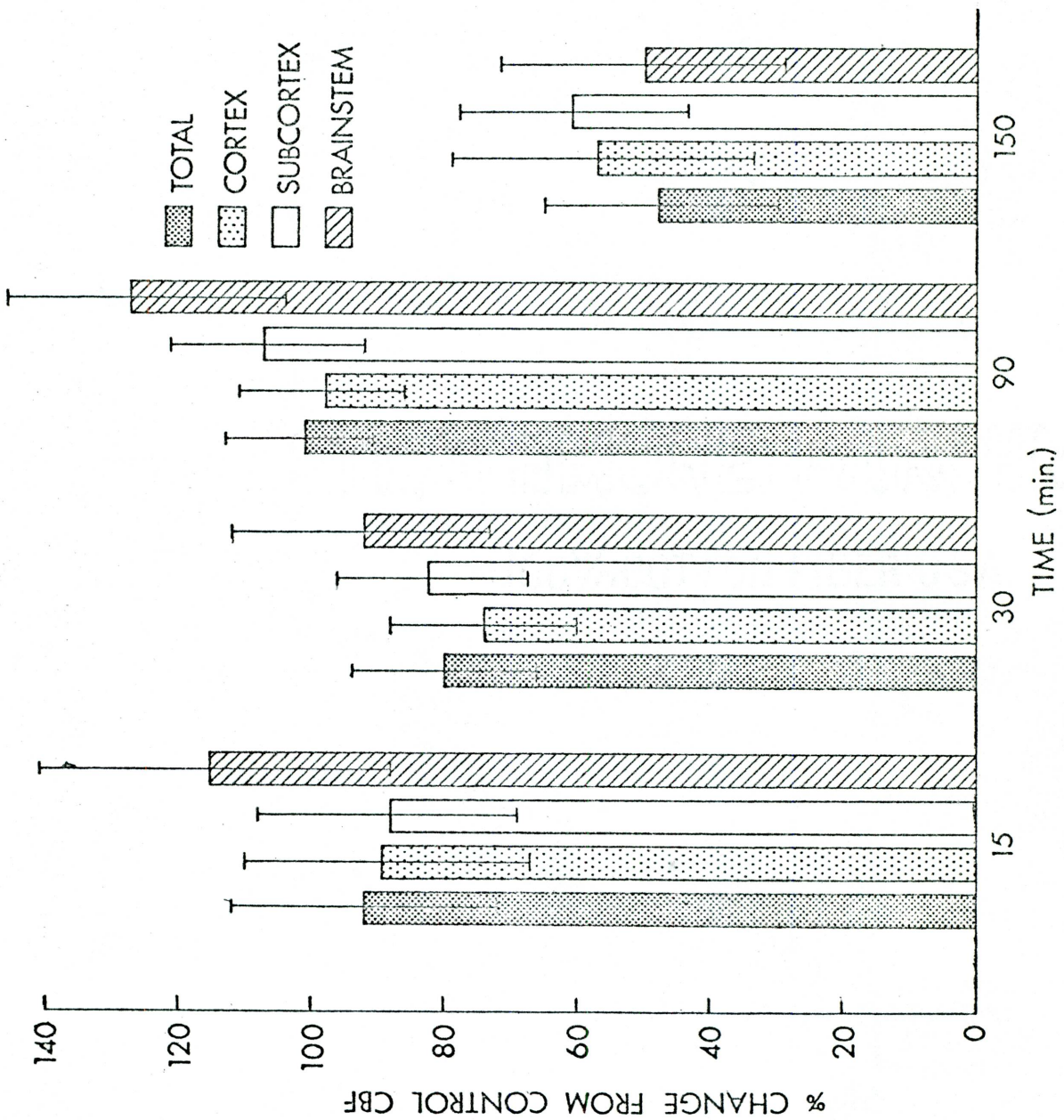
TOTAL
CORTEX
SUBCORTEX
BRAINSTEM
140
120
100
80
60
40
20
0
% CHANGE FROM CONTROL CBF
15
30
90
150
TIME (min.)

Figure 5

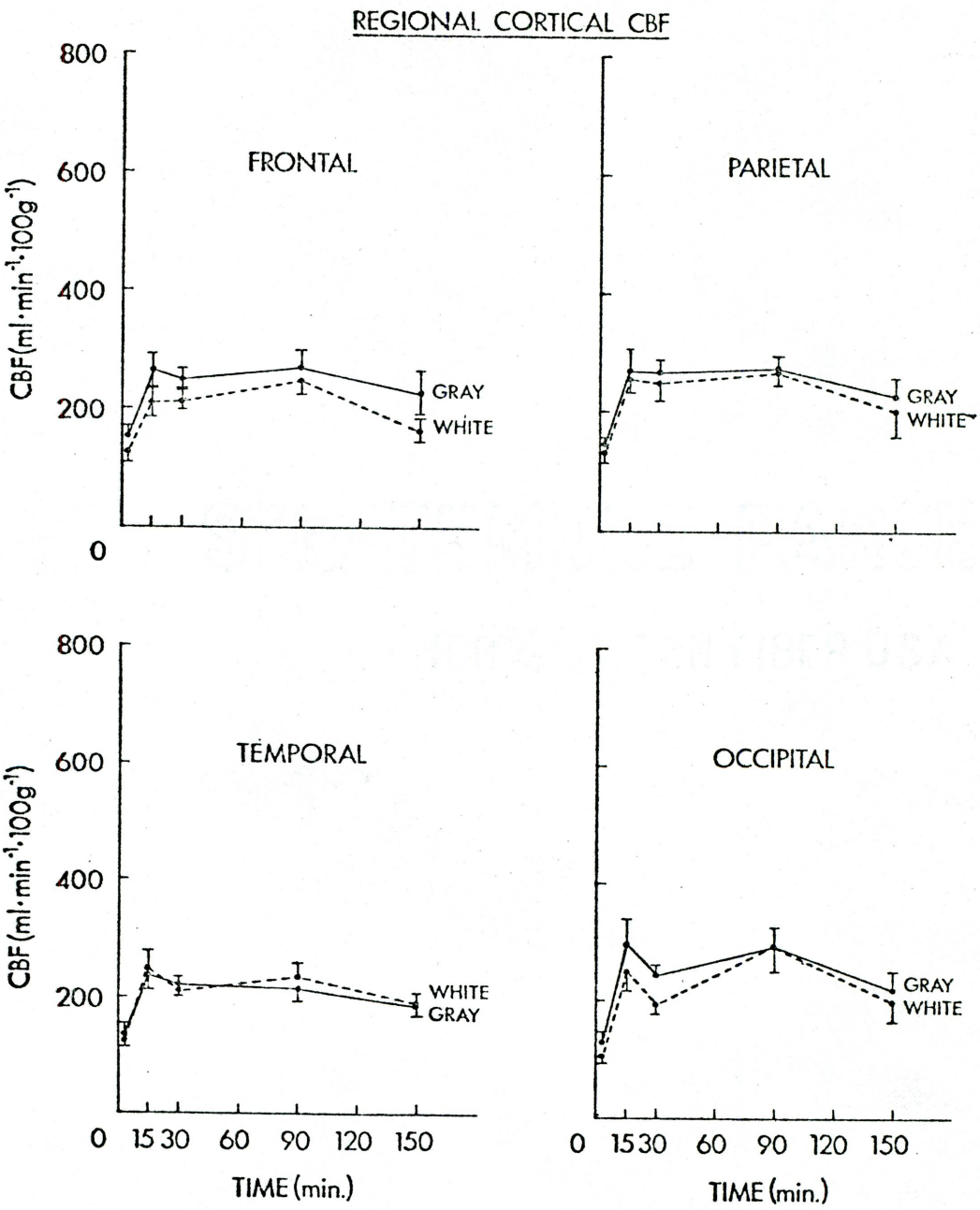
REGIONAL CORTICAL CBF
800
600
400
200
0
CBF(ml·min⁻¹·100g⁻¹)
FRONTAL
GRAY
WHITE
PARIETAL
GRAY
WHITE
TEMPORAL
WHITE
GRAY
OCCIPITAL
GRAY
WHITE
0 15 30 60 90 120 150
TIME (min.)

Figure 6

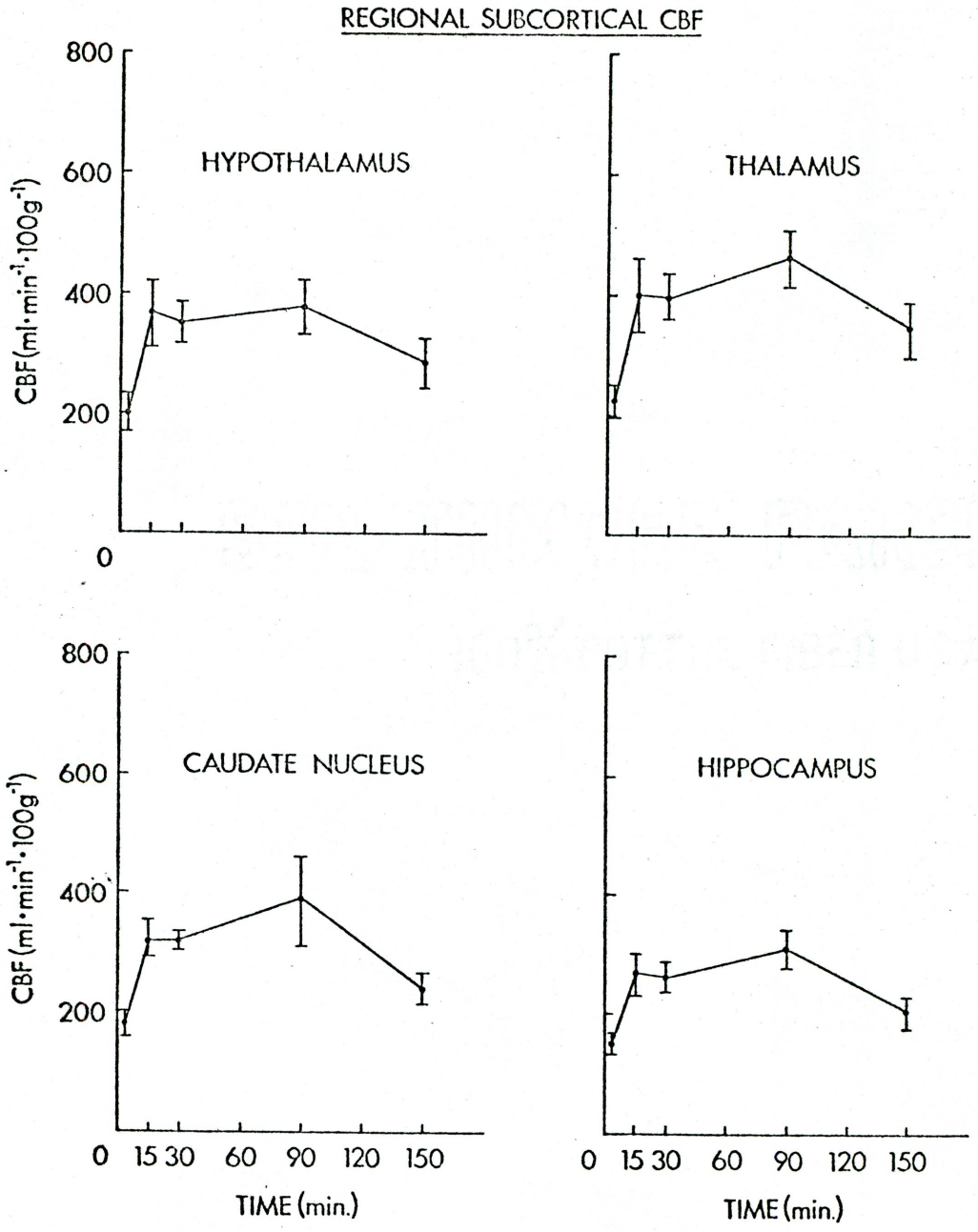
REGIONAL SUBCORTICAL CBF
HYPOTHALAMUS
THALAMUS
CAUDATE NUCLEUS
HIPPOCAMPUS
CBF(ml·min⁻¹·100g⁻¹)
800
600
400
200
0
0 15 30 60 90 120 150
TIME (min.)

Figure 7

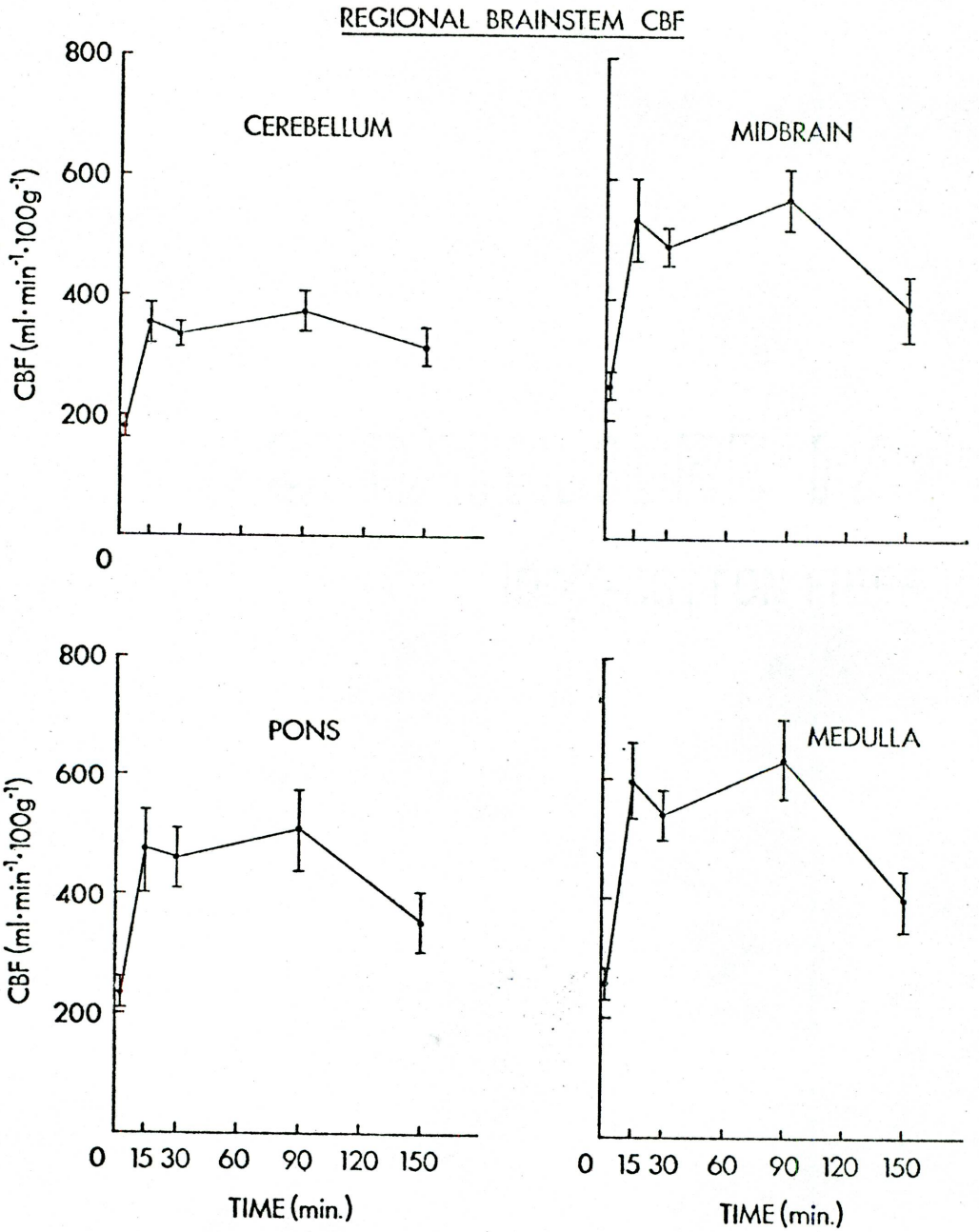
REGIONAL BRAINSTEM CBF
CEREBELLUM
MIDBRAIN
PONS
MEDULLA
CBF (ml·min⁻¹·100g⁻¹)
800
600
400
200
0
0 15 30 60 90 120 150
TIME (min.)

Figure 8

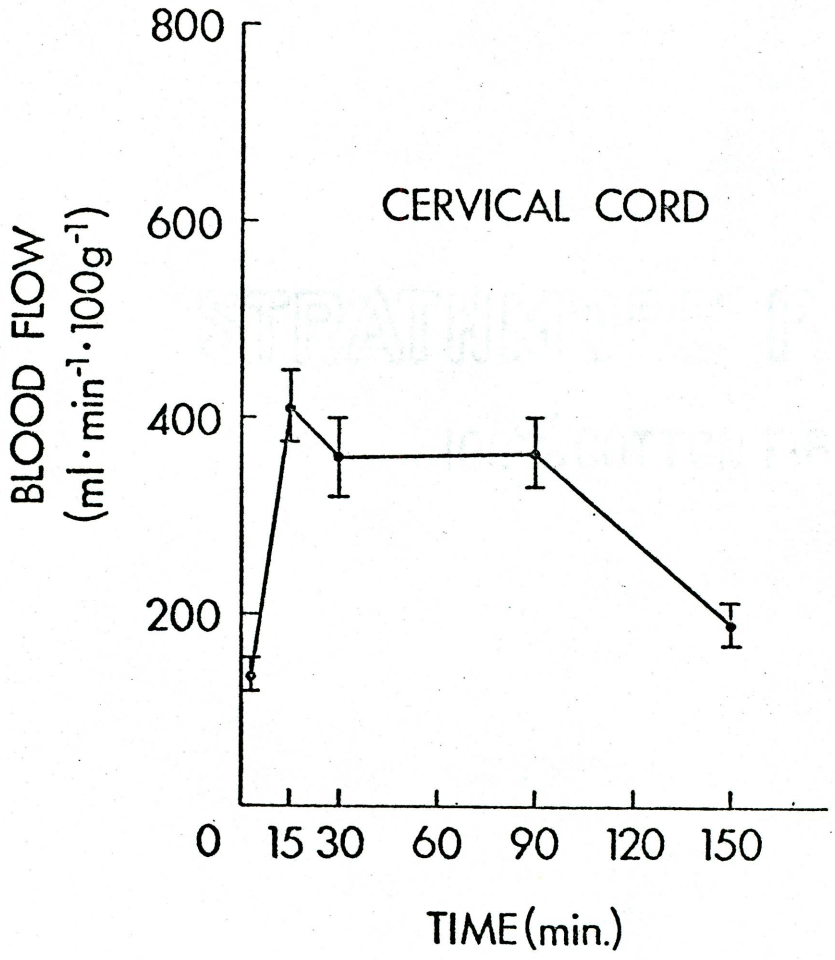
800
600
400
200
0
15 30
60
90
120
150
CERVICAL CORD
BLOOD FLOW
(ml·min-1·100g-1)
TIME (min.)

Figure 9

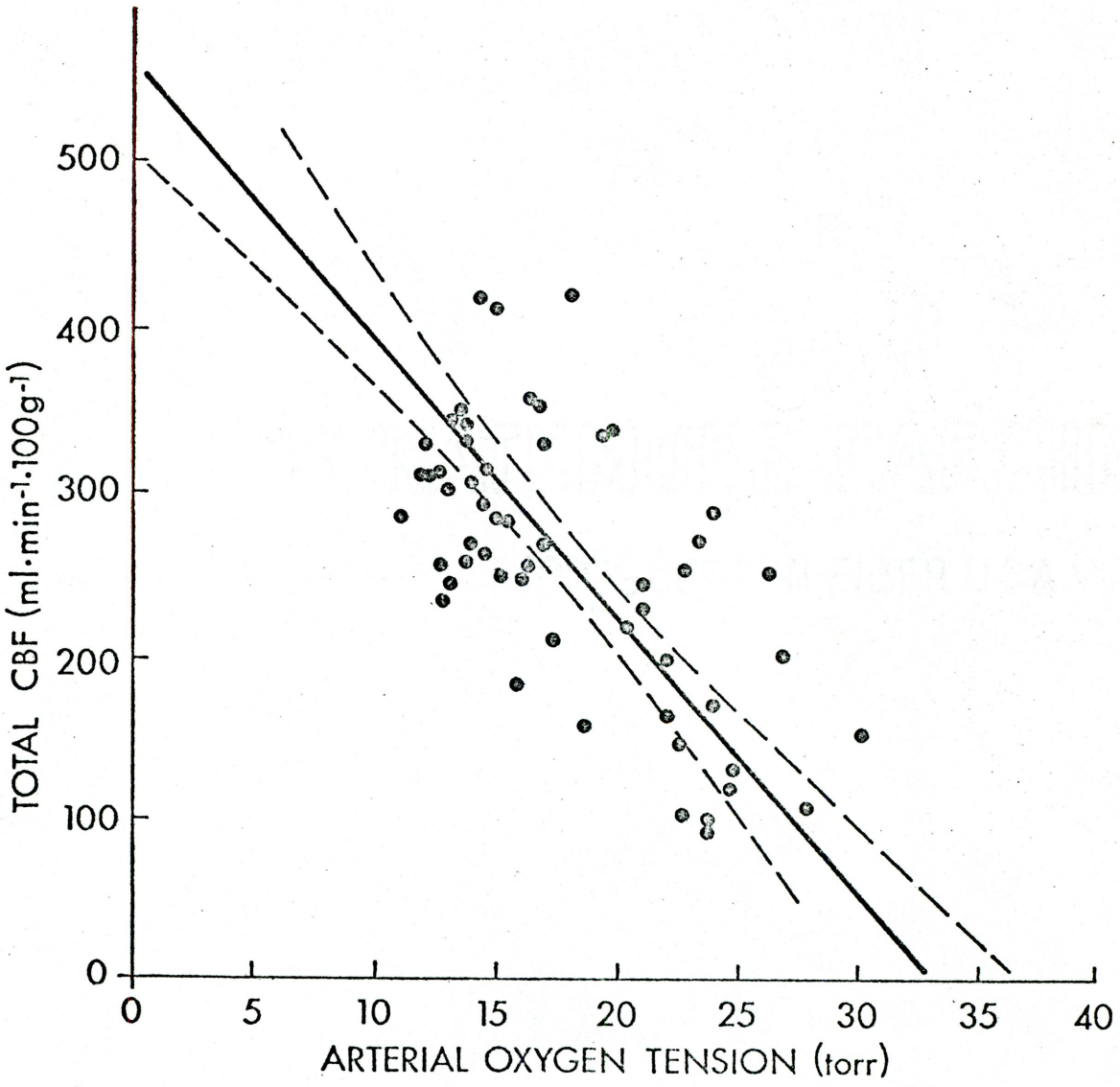
TOTAL CBF (ml·min⁻¹·100g⁻¹)
500
400
300
200
100
0
0
5
10
15
20
25
30
35
40
ARTERIAL OXYGEN TENSION (torr)

Figure 10 A

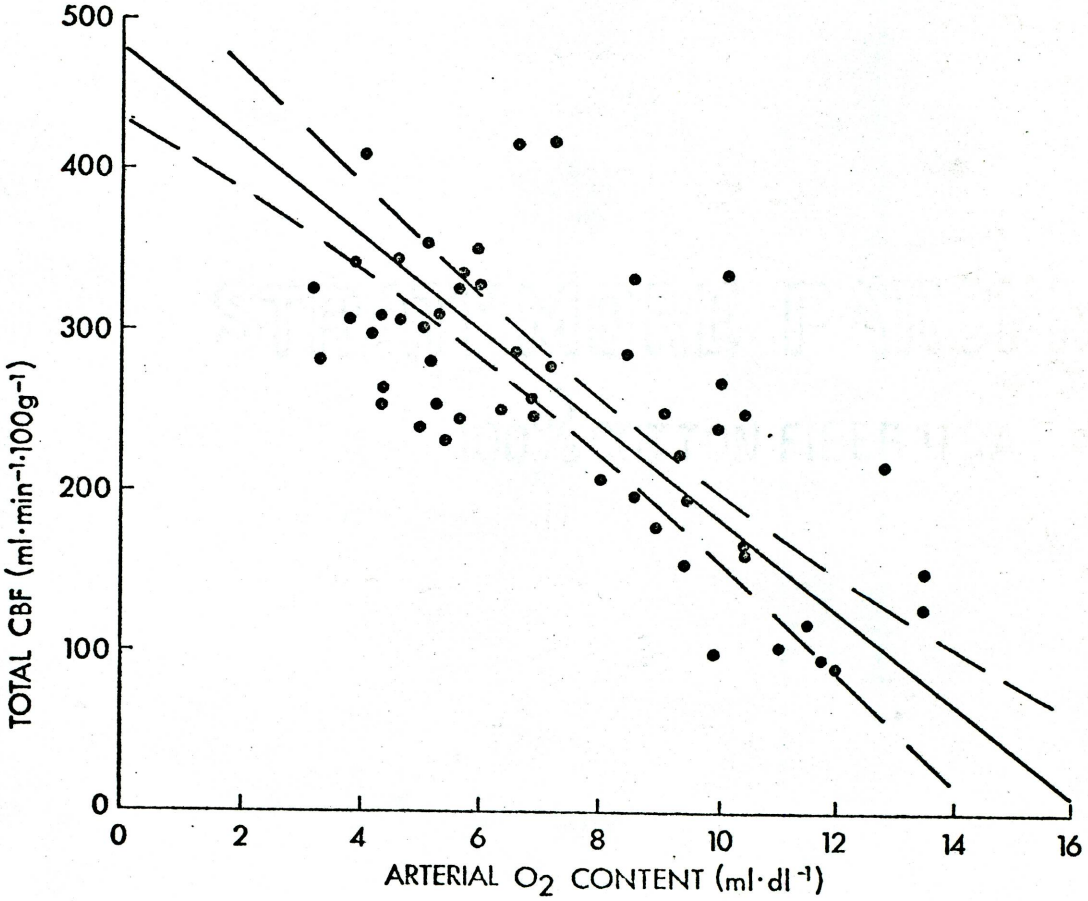
500
400
300
200
100
0
TOTAL CBF (ml·min⁻¹·100g⁻¹)
0
2
4
6
8
10
12
14
16
ARTERIAL O2 CONTENT (ml·dl⁻¹)

Figure 10 B

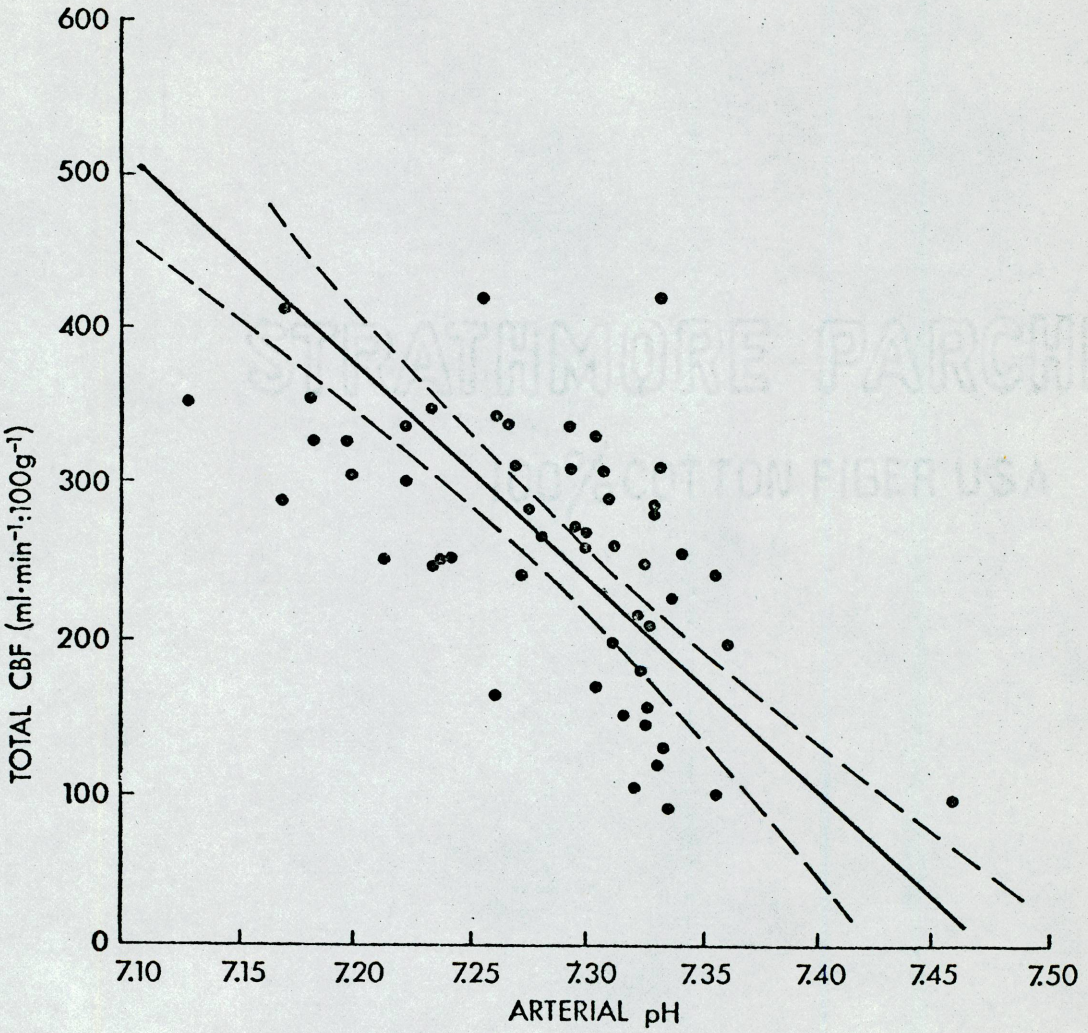
600
500
400
300
200
100
0
TOTAL CBF (ml·min⁻¹:100g⁻¹)
7.10
7.15
7.20
7.25
7.30
7.35
7.40
7.45
7.50
ARTERIAL pH

Figure 11

	CONTROL	15-MIN HYPOXIA Mean Change		30-MIN HYPOXIA Mean Change		90-MIN HYPOXIA Mean Change		60-MIN POST HYPOXIA Mean Change	
	($ml \cdot min^{-1} \cdot 100g^{-1}$)	($ml \cdot min^{-1} \cdot 100g^{-1}$)	(%)	($ml \cdot min^{-1} \cdot 100g^{-1}$)	(%)	($ml \cdot min^{-1} \cdot 100g^{-1}$)	(%)	($ml \cdot min^{-1} \cdot 100g^{-1}$)	(%)
TOTAL BRAIN	154.9 (± 16.3)*	+142.9 (± 31.1)	+ 92.2Ψ	+124.0 (± 22.4)	+80.0Ψ	+157.6 (± 17.4)	+101.7Ψ	+ 73.9 (± 27.6)	+47.7†
CORTEX	133.5 (± 14.9)	+118.6 (± 28.6)	+ 88.8Ψ	+ 98.5 (± 18.7)	+73.8Ψ	+131.4 (± 16,2)	+ 98.5Ψ	+ 76.3 (± 29.7)	+57.2†
GRAY MATTER	139.4 (± 16.7)	+119.4 (± 30.1)	+ 85.7Ψ	+101.4 (± 20.5)	+72.7Ψ	+126.0 (± 18.2)	+ 90.3Ψ	+ 77.8 (± 31.7)	+55.8†
WHITE MATTER	119.9 (± 12.3)	+119.3 (± 26.9)	+ 99.5Ψ	+ 92.5 (± 15.6)	+77.2Ψ	+146.2 (± 19.3)	+121.9Ψ	+ 72.4 (± 25.7)	+60.4†
SUBCORTEX	186.0 (± 19.0)	+165.2 (± 36.6)	+ 88.8)Ψ	+151.6 (± 27.3)	+81.5Ψ	+198.2 (± 26.3)	+106.5Ψ	+114.1 (± 31.6)	+61.3Ψ
BRAINSTEM	254.4 (± 22.8)	+292.4 (± 67.7)	+114.9Ψ	+253.3 (± 50.0)	+92.5Ψ	+332.7 (± 56.8)	+126.8Ψ	+127.8 (± 54.5)	+50.3†

* ± SEM

Ψ $p<0.01$

† $p<0.05$

TABLE 1 FETAL LAMB CEREBRAL BLOOD FLOW DURING AND AFTER PROLONGED INTRAUTERINE HYPOXIA

	CONTROL Mean Change ($ml \cdot min^{-1} \cdot 100g^{-1}$)	15-MIN HYPOXIA Mean Change ($ml \cdot min^{-1} \cdot 100g^{-1}$)	(%)	30-MIN HYPOXIA Mean Change ($ml \cdot min^{-1} \cdot 100g^{-1}$)	(%)	90-MIN HYPOXIA Mean Change ($ml \cdot min^{-1} \cdot 100g^{-1}$)	(%)	60-MIN POST HYPOXIA Mean Change ($ml \cdot min^{-1} \cdot 100g^{-1}$)	(%)
BRAIN	154.9 (± 16.3)*	+142.9 (± 31.1)	+ 92.2Ψ	+124.0 (± 22.4)	+ 80.0Ψ	+157.6 (± 17.4)	+101.7 Ψ	+ 73.9 (± 27.6)	+47.7 Ψ
HEART	217.8 (± 18.5)	+386.2 (± 59.7)	+177.3Ψ	+403.5 (± 79.2)	+185.2Ψ	+460.3 (± 58.7)	+211.3 Ψ	+181.2 (± 27.5)	+83.2 Ψ
LUNGS	213.6 (± 48.5)	-113.4 (± 68.8)	- 53.1	+ 10.7 (± 97.9)	+ 5.0	-115.4 (± 63.6)	- 54.1	+ 44.7 (±117.1)	+20.9
KIDNEYS	138.8 (± 13.2)	- 38.3 (± 13.5)	- 27.6†	- 46.6 (± 12.4)	- 33.6†	+ 1.8 (± 19.1)	+ 1.3	+ 53.6 (± 24.6)	+38.6
ADRENALS	497.2 (± 54.7)	+716.8 (±170.7)	+144.2Ψ	+617.7 (±170.6)	+124.2Ψ	+862.5 (±287.6)	+173.5 †	+387.7 (± 95.5)	+78.0 Ψ
PLACENTA	83.9 (± 5.5)	+ 5.7 (± 5.7)	+ 6.8	- 1.1 (± 5.7)	- 1.3	- 9.2 (± 5.5)	- 11.0	- 11.7 (± 5.5)	-14.0

* ± SEM

Ψ p 0.01

† p 0.05

TABLE 2 ORGAN BLOOD FLOWS