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# Cerebrovascular Responses To Hypotension And Hypercapnia In The Rabbit: Effect Of Alpha-receptor Blockade And Carotid Artery Occlusion

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# CEREBROVASCULAR RESPONSES TO HYPOTENSION AND HYPERCAPNIA IN THE RABBIT: EFFECT OF ALPHA-RECEPTOR BLOCKADE AND CAROTID ARTERY OCCLUSION

by
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of the requirements for the degree of
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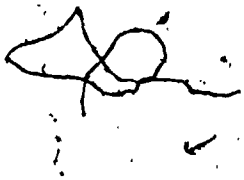

## ABSTRACT

In this study, the responsiveness of the cerebrovasculature to hypercapnia provided an indication of the residual capacity for dilation available (ie. the dilative reserve). The relationship between cerebral blood flow (CBF) and pial vessel caliber responses and the dependence of these responses on the dilative reserve were examined in three groups of rabbits: 31 control animals; 21 phenoxybenzamine treated animals (alpha adrenoreceptor blockade); and 21 animals subjected to carotid artery occlusion. The effects of hemorrhagic hypotension on both CBF($H_2$ clearance) and pial vessel caliber(image splitting technique) and on the cerebrovascular responsiveness to hypercapnia (the $CO_2$ response) were investigated in each group.

Three characteristic autoregulatory regions were identified. (1) During moderate reductions in perfusion pressure (PP) the pial vessels($< 200$ μm) dilated progressively and CBF autoregulation was complete. The dilative reserve was functionally intact as the CBF $CO_2$ response was constant and that of the pial vessels increased. (2) At intermediate PP, autoregulatory pial vessel dilation continued and CBF declined gradually (incomplete autoregulation). Both the pial vessel and CBF $CO_2$ responses decreased, indicating a reduced dilative reserve. (3) The lower limit of autoregulation occurred at a cerebral PP of approx. 35 mm Hg. Both CBF and pial vessel caliber decreased pressure passively and

there was a complete loss of $CO_2$ reactivity - a depletion of the dilative reserve. Phenoxybenzamine infusion resulted in an increase in the dilative reserve and a relative improvement in CBF autoregulation. These changes were related to the decrease in CBF and metabolism caused by phenoxybenzamine. Carotid artery occlusion reduced the pressure in the Circle of Willis. This decreased the dilative reserve and shifted the lower limit of autoregulation to a PP of 45 mm Hg. The dilative reserve and the efficiency of CBF autoregulation were strongly interrelated. Changes in total precapillary resistance closely paralleled alterations in pial vascular resistance whereas the large inflow arteries were unreactive. The pial vessel responses appeared to be qualitatively representative of those occurring in the intraparenchymal vasculature.

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# I CONTROL OF THE CEREBRAL CIRCULATION

## 1. Introduction

The brain is one of the most metabolically active organs of the body but it cannot store appreciable quantities of oxygen or glucose (ie. its primary metabolic substrates). Since the brain must rely almost entirely on a continuous supply of blood to provide these nutrients, there is normally a close coupling between tissue metabolism and cerebral blood flow (CBF). CBF is regulated such that an increase in metabolic activity is accompanied by a corresponding increase in CBF whereas a reduction in brain function is associated with a decline in CBF. The cerebrovascular control mechanisms also maintain CBF constant during moderate alterations in blood pressure (flow would be directly dependent on perfusion pressure in a passive vascular bed). Therefore, flow is carefully regulated to prevent a decrease in the delivery of metabolic substrates.

In all individuals both alterations in regional brain activity and changes in the conditions of cerebral perfusion will occur frequently throughout the day. Thus, in order for the brain to function normally, it is essential that flow be regulated continuously to the needs of tissue metabolism. However, under certain circumstances (eg. severe reductions in blood pressure or interference with the arterial inflow) these mechanisms can fail resulting in

tissue ischemia[1]. Depending on the severity of the flow decrease, brain activity will diminish or cease altogether due to a disruption of normal cell function and cell death may ensue. It is clear that the regulatory capability of the cerebrovasculature has been exceeded or disabled under these conditions, although the reasons for this failure have not been firmly established. Prior to discussing the factors which may contribute to an impairment of the control mechanisms it is necessary to examine the manner in which the regulation of CBF is normally achieved.

## 2. Historical Review

### 2.1 Blood Flow in the Vascular Bed

In 1733, Stephen Hales showed that the rate of tissue perfusion depended both on the driving force provided by the heart (arterial blood pressure) and on the "resistance" of the vessels to flow. He also found that the majority of the vascular resistance was provided by the small arterioles (McDonald, 1974). Poiseulle in 1842, showed empirically that flow of liquid through a rigid tube was proportional to the perfusion pressure (PP) and the fourth power of the radius(Appendix 1). When these two observations were combined,

$$\text{flow} = PP/\text{resistance}$$

$$\text{and} \quad \text{flow} \propto PP.r^4$$

it was apparent that active changes in vascular resistance

[1] Ischemia is a deficient blood flow relative to metabolism.

(and therefore alterations in flow) could be achieved by changes in vessel caliber. Thus the initial studies of the regulation of CBF attempted to determine what factors (if any) were involved in the active control of vessel caliber.

2.2 Active versus Passive Changes in Vessel Caliber and CBF

One of the first methods used to investigate the cerebral circulation involved observing the vessels on the brain surface (pial vessels) through a skull window. In this technique, developed by Donders in 1849 and 1850 (Purves, 1972), a portion of the skull was removed, the membranes covering the brain were excised and a glass window was sealed in place to protect the exposed brain. Using the skull window technique, changes in pial vessel caliber were observed under various conditions (eg. dilation in response to asphyxia and constriction during cervical sympathetic nerve stimulation) (Purves, 1972). These results suggested that the cerebrovasculature was under an active control but unfortunately blood pressure had not been monitored routinely. Hill (1896) argued that since an increase in arterial pressure would cause a passive dilation and a decrease in pressure would result in a passive reduction in vessel diameter, active changes in vessel caliber had not been well established. In his experiments, Hill monitored intracranial pressure as an indicator of changes in vessel caliber and CBF. According to the Monro-Kellie doctrine, the volume of contents within the skull (blood and brain) had to be almost constant. Thus an increase in intracranial

pressure was assumed to be the result of an elevation in blood volume due to an increase in vessel caliber. Using this method, both Roy and Sherington (1890) and Hill (1896) found that alterations in intracranial pressure closely followed changes in arterial pressure. They concluded that CBF varied directly with blood pressure. Although Roy and Sherington had observed an active increase in intracranial pressure in response to the intravenous infusion of strong acids, Hill discounted these findings and stated that there was no active control of CBF under any conditions. His arguments were so convincingly presented, that the concept of a passive cerebrovasculature persisted until the 1930's.

Evidence to the contrary appeared following improvements in the skull window technique by Forbes in 1928. The pial vessels were viewed through a microscope and quantitative measurements of the diameters were made with a micrometer scale. The pial arteries were subsequently shown to respond actively to a variety of stimuli. Wolff and Lennox (1930) found that a rise in $P_aCO_2$[1] (hypercapnia) caused a marked vasodilation and a fall in $P_aCO_2$ (hypocapnia) produced a less pronounced vasoconstriction of the pial arteries. In contrast, an increase in $P_aO_2$ was shown to cause a slight decrease in diameter and severe reductions in $P_aO_2$ (hypoxia) tended to dilate the vessels. Fog (1937,1939) and Forbes et al. (1937) showed conclusively that the pial vessels res-

[1] $P_aCO_2$ is the partial pressure of $CO_2$ in the arterial blood.

ponded actively to changes in blood pressure. The pial arteries constricted in response to an elevation in arterial blood pressure and dilated in response to a decrease in arterial blood pressure. Both indicated a change in cerebrovascular resistance which would oppose the alteration in blood pressure and tend to maintain CBF constant.

Studies in which CBF was measured directly, confirmed that CBF was actively regulated as predicted by the responses of the pial vessels. Lennox and Gibbs (1932) used arteriovenous sampling techniques to show that CBF increased during hypercapnia whereas hypocapnia produced a reduction in CBF. They also found a less pronounced CBF increase following hypoxia. Numerous studies have subsequently supported these findings (Dumke and Schmidt, 1943; Kety and Schmidt, 1948; Sokoloff, 1959), many of which used the quantitative nitrous oxide technique introduced by Kety and Schmidt (1945). Using this technique, CBF was shown to remain relatively constant during either hypotension or hypertension (Kety et al., 1948; 1950; Sokoloff, 1959).

Thus by 1960 it was well established that there was an active regulation of CBF during PP changes. This tendency of the cerebral vessels to maintain a constant blood flow despite moderate changes in arterial blood pressure has been termed autoregulation. It was also clearly demonstrated that the cerebrovasculature responded to $PO_2$ (a metabolic substrate) and $PCO_2$ (a metabolic end product). This suggested a possible means by which CBF could respond to the

needs of metabolism.

## 3. Current Concepts

### 3.1 Control of Vessel Caliber

More recent studies have concentrated on the manner in which active changes in CBF are accomplished. Since changes in cerebrovascular resistance occur as a result of alterations in vessel caliber, it is the mechanisms which are responsible for regulating vessel diameter that have been examined. In general, the cerebral vessels are thought to be influenced by both intrinsic and extrinsic mechanisms.

#### 3.1.1 Local Intrinsic Mechanisms

(i) Myogenic Control.

Smooth muscle responds to an increase or decrease in stretch with a contraction or dilation respectively and this myogenic response indicates that the vessels can respond directly to changes in pressure. A decrease in arterial blood pressure reduces the stretch or tension in the vessel wall which would result in a dilation. Alternatively, an increase in pressure would increase wall tension resulting in a constriction. Both large and small vessels have been shown to respond in this way (Dobrin, 1973; Duling, 1981). Bayliss in 1902, first postulated that the myogenic response was important in the *in vivo* control of vessel caliber following pressure changes. Folkow (1949) proposed that the myogenic mechanism was responsible for autoregulation of

flow in the intestine and hindlimb and other investigations have since suggested that the myogenic response may contribute to the autoregulation of CBF ( Haggendal and Johansson, 1965; Ekstrom-Jodal et al., 1969; Symon et al., 1973).

(ii) Metabolic Regulation.

Vessel caliber is also thought to be controlled by changes in the concentrations of vasoactive metabolites surrounding the vessel. This is supported by the finding that there is a close coupling between brain metabolism and CBF (Sokoloff, 1977). The effects of several vasoactive metabolites on cerebral vessel caliber have been investigated. There is a dose dependent dilation of the pial vessels (maximum of 30-50%) following a perivascular application of either potassium or adenosine. Similarly, vessel caliber has been shown to increase by 40-60% as the hydrogen ion concentration surrounding the vessel increases (Kuschinsky and Wahl, 1978). At present, the hydrogen ion, potassium ion and adenosine are considered the most likely mediators of changes in vessel caliber during alterations in metabolism (Berne, 1981; Kontos, 1981).

Changes in $PO_2$ and $PCO_2$ were also considered as possible mediators of metabolic regulation. However this is now thought to be unlikely since these gases do not appear to have a direct action on the smooth muscle. The vasodilation and increase in CBF measured in hypoxia ($P_aO_2 < 60$ mm Hg) are likely related to the concommitant increases in adenosine, potassium ion and hydrogen ion within the hypoxic

brain (Kuschinsky and Wahl, 1978). The response to carbon dioxide is considered to be controlled primarily by changes in extracellular fluid pH, since the cerebral vessels are insensitive to alterations in $P_aCO_2$ if the extracellular fluid pH is held constant (Kuschinsky and Wahl, 1978; Kontos, 1981).

It has been suggested that metabolic mechanisms play an important role in the autoregulatory control of CBF (metabolic theory). According to this theory, a reduction in pressure is accompanied by a decrease in flow and an accumulation of vasodilator metabolites. This results in arterial dilation and an increase in flow towards normal (Berne, 1964). As discussed above, the most likely mediators of metabolic flow changes are $K^+$, $H^+$ and adenosine. Their concentrations have been measured in the brain during hypotension and it was found that the concentration of hydrogen or potassium ion did not change whereas that of adenosine increased (Wahl and Kuschinsky, 1979, Winn, 1980). Both Berne (1981) and Kontos (1981) have suggested that autoregulation of CBF is governed predominantly by a metabolic mechanism mediated by adenosine. However, the relative contributions of metabolic and/or myogenic mechanisms to the autoregulatory response are as yet not clearly established.

3.1.2 Extrinsic (Neurogenic) Regulation

The cerebral vessels are innervated by adrenergic, cholinergic and peptidergic fibers. Little is known of the

role of peptidergic (vasodilator) fibres in the regulation of the cerebral circulation. The effects of the cholinergic and adrenergic innervation of the cerebral vasculature have been studied more extensively.

Adrenergic fibers originate in the superior cervical ganglion and innervate all cerebral vessels. In comparison to other vascular beds, the cerebral vessels are relatively insensitive to adrenergic nerve stimulation and the associated neurotransmitters (Kontos , 1981; Heistad et al., 1981). Cervical sympathetic stimulation has been shown to cause a 7-13% constriction of the pial vessels [mediated by alpha-receptors] (Wei et al, 1975; Kuschinsky and Wahl, 1975; Auer et al., 1981) and a reduction in CBF of 10-30% in several species (Kuschinsky and Wahl, 1978; Purves, 1978). However, other studies have either been unable to demonstrate any effects of sympathetic stimulation on CBF or they have observed a transient CBF reduction (Heistad and Marcus, 1978; Heistad, 1981).

Cholinergic fibres innervate the pial vessels but do not project to the intraparenchymal vasculature. The facial nerve and greater superficial petrosal nerve (a branch of the facial nerve) provide a part of the cholinergic innervation (Vasquez and Purves , 1979). Electrical stimulation of these fibres has produced a slight pial vessel dilation (Edvinsson and MacKenzie, 1977) and a 10-25% increase in CBF which could be abolished by atropine (D'Alecy and Rose, 1977; Pinard et al., 1979). However, a recent study has

been unable to demonstrate and increase in CBF following stimulation of the greater superficial petrosal nerve (Busija and Heistad, 1981). Many other studies have examined the cerebrovascular effects of cholinomimetic and cholinergic drugs (Edvinsson and MacKenzie, 1977). For example, the direct perivascular application of carbamycholine (a parasympathomimetic agent) produced a dose dependent dilation (maximal of ~15%) which could be blocked with atropine (Kuschinsky et al, 1974).

The majority of available evidence suggests that the effects of the adrenergic and cholinergic nerve fibres on the cerebrovasculature under resting conditions are relatively minor in comparison to metabolic mechanisms. The potential activation of these fibres under physiological conditions (eg. alterations in PP and $P_aCO_2$) and the effects such activity might have on the cerebral circulation are not well understood. However it is clear that neither the sympathetic nor the parasympathetic nervous system are essential in order for the autoregulatory and/or $CO_2$ responses to occur (Edvinsson and MacKenzie, 1977; Kontos, 1981).

### 3.2 Differential Responsiveness of the Vessels

There is considerable evidence that all cerebral vessels do not respond equally to intrinsic or extrinsic control mechanisms. The cerebrovascular responses to hypotension or hypercapnia (ie. intrinsic dilative stimuli) are

much more pronounced in the small pial arterioles than in the large pial arteries (Kontos et al., 1978; Mackenzie et al., 1979; Wei et al., 1980; Gregory et al., 1981). The largest cerebral arteries at the base of the brain may actually decrease in size as blood pressure is reduced (du Boulay et al., 1972) and show very little if any response to hypercapnia (Krueger et al., 1963; Petruk et al., 1974). The cerebral vessel responses to adrenergic activation (ie an extrinsic vasoconstictor stimulus) show a similar but reversed size dependence. Stimulation of the cervical sympathetic nerves results in a modest constriction of the large pial arteries has only a minor effect on the small pial arterioles (Wei et al., 1975; Kuschinsky and Wahl, 1975; Auer et al., 1981). This differential responsiveness of the cerebral vessels to intrinsic and extrinsic stimuli plays a central role in current models of the control of cerebral perfusion.

3.3 Control of CBF

As indicated in the preceeding sections the regulation of CBF is accomplished by changes in total cerebrovascular resistance (CVR). Since the various vascular components (basal arteries, large and small pial vessels, intraparenchymal arterioles, etc.) are effectively connected in series, changes in total CVR will be determined by the sum of the changes in the resistance of the individual components (see Appendix 1). An increase in the resistance of one vascular segment (vasoconstriction) may not cause any

change in total CVR providing there is an equivalent compensatory reduction in the resistance of the remaining components. This compensatory potential would not be possible if all vessels responded similarily to a given stimulus.

Harper and colleagues (1972) have suggested that the cerebral circulation may be considered as two resistances connected in series, each under a different control system (dual effects hypothesis). They postulated that the large extraparenchymal vessels were influenced by the sympathetic nervous system (extrinsic) whereas the intraparenchymal arterioles were regulated by local control mechanisms (intrinsic). They argued that this would explain the relatively minor effects of sympathetic nerve stimulation on CBF since the increase in the resistance of the extraparenchymal vessels would be accompanied by a compensatory decrease in intraparenchymal resistance. Similar models have been proposed by others (Oleson, 1972; Rapela and Martin, 1975). Kontos et al. (1978) have suggested that vessel size rather than location is the primary determinant of vascular responsiveness. However, the basic concept of segmental resistances with differential sensitivity to intrinsic versus extrinsic stimuli is a consistent feature of most models of cerebral circulatory control.

### 3.4 Summary

The cerebral circulation possesses a number of control mechanisms which interact in a complex manner to

regulate CBF. Overall, the sensitivity of the cerebral circulation to intrinsic stimuli is considerably greater than its responses to neurogenic stimulation. The actions of local metabolic mechanisms (affecting primarily small cerebral vessels) normally ensure that the neccessary quantity of nutrients required for cerebral metabolism are supplied to the tissue. Similarily, stresses which tend to reduce CBF (ie. extrinsic vasoconstrictor activation or reductions in PP) are opposed by compensatory dilation of the small cerebral vessels. Clearly, the homeostasis of the CBF/metabolism relationship is dependent on the intrinsic dilative responses of the small vessels. One would postulate that a loss in their capacity to dilate would result in reductions in CBF leading to ischemia.

## II RATIONALE AND OBJECTIVES

### 1. Dilative Reserve of the Cerebrovasculature

Since the ability of CBF to respond appropriately to various intrinsic dilative stimuli is dependent on the responses of the small cerebral vessels, their capacity for dilation will be a primary determinant of CBF reactivity. Cerebrovascular dilation maintains CBF relatively constant during moderate reductions in PP but profound hypotension results in a decrease in flow and a loss of CBF autoregulation. The perfusion pressure at which CBF begins to decrease (approx. 60 mm Hg during hemorrhagic hypotension) is termed the lower limit of autoregulation. It had been assumed that the small cerebral vessels were maximally dilated at this pressure - that is, the vessels were unresponsive to further reductions in pressure as their capacity for dilation (dilative reserve) was completely exhausted (Fitch et al., 1975; 1976).

It has also been proposed that the response to hypercapnia is directly related to the dilative reserve. Harper and Glass (1965) showed that the increase in CBF produced by hypercapnia was reduced during moderate reductions in blood pressure and abolished in severe hypotension. Several studies have subsequently confirmed their findings (Carter et al., 1973; Okuda et al., 1976). Harper and Glass postulated that in severe hypotensive states (ie. below the lower limit of autoregulation), the vessels are

already maximally dilated in response to the blood pressure reduction and thus are unable to dilate further in response to hypercapnia. In general it is assumed that autoregulatory dilation reduces the residual dilative capacity and thus decreases cerebrovascular reactivity to hypercapnia.

2. Effect of Large Arteries on the Dilative Reserve

Although the large arteries are relatively unresponsive to intrinsic dilative stimuli, there is evidence that the large cerebral arteries can modify the autoregulatory and $CO_2$ responses, presumably by altering the dilative reserve. Fitch et al. (1975) demonstrated that the lower limit of autoregulation to hemorrhagic hypotension decreased from 65 mm Hg in control animals to approximately 35 mm Hg in animals pretreated with acute cervical sympathectomy or alpha-adrenoreceptor blockade. They suggested that the sympatho-adrenal discharge accompanying hemorrhage had constricted the large extraparenchymal vessels in control animals. It was argued that the small intraparenchymal vessels dilated to compensate for the increase in large artery resistance and this subsequently decreased their capacity for dilation in response to hypotension. Thus autoregulation failed at a relatively high pressure. They suggested that this extraparenchymal vasoconstriction was prevented by sympathectomy in treated animals. Therefore the dilative reserve was effectively increased and CBF autoregulation continued to a lower pressure. There is additional evidence

to support the fact that the sympathetic nervous system can alter the dilative capacity of the cerebrovasculature. Sympathetic stimulation reduces the CBF response to hypercapnia whereas denervation causes a slight increase in $CO_2$ responsiveness (James et al., 1969; Harper et al., 1972; D'Alecy et al., 1979).

Sengupta et al. (1973,1974) have shown that carotid artery occlusion also affects the cerebrovascular responses to dilative stimuli. Although CBF was unchanged following carotid occlusion at normotension, the CBF response to hypercapnia was reduced and autoregulation was completely abolished (ie. the lower limit of autoregulation was approx. equal to the resting pressure). Their explanation of these results was identical to that given above. They suggested that the small intraparenchymal vessels had dilated to compensate for the increase in inflow artery resistance and were thus unable to respond effectively to hypercapnia or hypotension (ie. their dilative reserve was effectively reduced).

The preceeding discussion suggests that there is a close relationship between CBF autoregulation, the CBF $CO_2$ response and the dilative reserve of the cerebrovasculature. In these studies, the changes in CBF responsiveness were explained using a model of cerebral circulatory control wherein the small cerebral vessels compensated for changes in large artery resistance such that the dilative reserve was altered. At present, fundamental aspects of this model

remain hypothetical since the cerebral vessel responses following changes in large artery resistance (eg. carotid artery occlusion or sympathetic activation/denervation) have not been documented experimentally. Recent investigations of the CBF and pial vessel caliber responses to dilative stimuli have found that there is a discrepancy between the observed changes in CBF and those in pial arteriolar caliber (see next section). Thus, although the above model suggests a rational way in which the cerebrovasculature is affected by alterations in large artery resistance, the basic assumptions of the model have not as yet been confirmed by direct measurement of cerebral vessel calibers.

### 3. Relationship Between CBF, Pial Vessel Caliber and the Dilative Reserve

The pial vessel responses to dilative stimuli have been examined infrequently and even fewer studies have made a comparison of CBF and pial vessel responsiveness obtained from identical preparations. MacKenzie et al. (1979) found that during hemorrhagic hypotension, the pial vessels dilated progressively as pressure was reduced to 35 mm Hg but CBF began to decrease markedly at a blood pressure of approximately 65 mm Hg (ie. the lower limit of autoregulation). This indicated that a loss of CBF autoregulation was not associated with a depletion of the dilative reserve and that there was a discrepancy between changes in total CBF and alterations in pial vascular resistance. A different type

of incongruity was observed between the CBF and pial vessel responses to hypercapnia. Gregory et al. (1981) found that at profound hypotension (approx. 35 mm Hg) CBF responded to hypercapnia but the pial vessels were completely unreactive to $CO_2$. Although the autoregulatory responses suggest that the dilative reserve of the pial vessels was greater than that of the overall cerebrovasculature, the responses to hypercapnia suggest that the reverse may be true - the total dilative reserve exceeds that of the pial vessels.

In either case, the reasons for the reductions in flow at the lower limit of autoregulation are unclear as both studies indicated that there was a residual capacity for vasodilation at low pressures. Other investigations measuring either CBF or vessel caliber have also shown a continued responsiveness of the cerebrovasculature to hypercapnia during severe hypotension. Ekstrom-Jodal et al. (1970) found that there was a residual CBF $CO_2$ response at 50 mm Hg (a pressure below the lower limit of autoregulation). Although this disagrees with the study of Harper and Glass (1965), Wei et al. (1980) have subsequently shown that the pial vessels also continued to respond to hypercapnia at pressures of 40-50 mm Hg. Thus it would appear that there is a reserve capacity for dilation below the lower limit of autoregulation. However the exact manner in which CBF, pial vessel caliber and the dilative reserve are interrelated is poorly defined and our understanding of the control of CBF is far from complete.

## 4. Summary of the Rationale

Various control mechanisms actively regulate CBF to ensure that the delivery of nutrients to the tissue is adequate to supply the metabolic demand. In particular, a decrease in PP is normally balanced by a corresponding change in CVR which maintains CBF constant. However, there are several conditions (eg. hemorrhagic shock or occlusive cerebrovascular disease), in which PP is reduced to such an extent that this regulation fails, CBF decreases to critical levels and ischemic brain damage may occur. In order to prevent or reduce the degree of ischemia, it is necessary to know both the reason for the impairment of flow (ie. why the control mechanisms failed) and the manner in which the regulatory ability can be improved. A determination of both these factors requires a detailed understanding of the manner in which CBF is controlled by the cerebrovasculature.

The regulation of CBF in response to intrinsic stimuli is currently considered to be due to alterations in the resistance of the small cerebral vessels. Since the capacity for dilation of these vessels is limited, their responsiveness to additional dilative stimuli will be dependent on their residual dilative capacity. (I have defined the residual capacity for dilation to be equal to the dilative reserve.) The dilative reserve is thought to be altered by several situations affecting the responses of the small cerebral vessels.

The cerebral arterioles dilate in response to PP

reductions, thereby reducing CVR and maintaining CBF constant. At the lower limit of autoregulation CBF decreases and it has been proposed that the residual dilative capacity is completely exhausted at this limit. A depletion of the reserve would expain why CBF decreases pressure passively with further reductions in PP and why there is a loss of CBF $CO_2$ reactivity at extremely low PP. Conditions which increase large artery resistance (eg. sympathetic activation and carotid artery occlusion) are thought to cause a compensatory dilation of the small cerebral vessels and a reduction in their dilative reserve. This would account for the reduced CBF reactivity to hypercapnia and the increased lower limit of autoregulation seen under these conditions. It is important to note that in these situations alterations in vessel caliber and the dilative reserve have been assumed to occur based on the results of CBF measurements. Recent studies in which both CBF and pial vessel caliber were measured directly suggest that these concepts may require revision.

Although CBF and pial vessel caliber responsiveness within similar preparations are not well documented, there are indications of a poor correlation between their responses. One study has shown that the pial vessels continued to dilate below the lower limit of CBF autoregulation and another found that at profound hypotension CBF reactivity to hypercapnia continued even though the reactiviy of the pial vessels was abolished. These studies suggest that the dila-

tive reserve is not completely depleted at the lower limit of autoregulation and CBF could be increased if this reserve capacity for dilation could be evoked. Alternatively, it is possible that the responses of the pial vessels differ substantially from those of the intraparenchymal arterioles so that changes in pial vascular resistance are not indicative of average changes in total cerebrovascular dilative capacity. If this were true then previous conclusions concerning the control of the cerebrovasculature based on observations of the pial vessels would be of little value. It is clear that a more extensive study of the interrelationship between CBF, pial vessel caliber and the dilative reserve is required in order to define the manner in which CBF is regulated under normal conditions and how this regulation is affected by changes in sympathetic activity or carotid artery occlusion.

## 5. Objectives

The overall objective of this thesis was to investigate systematically the relationship between CBF and pial vessel caliber under a variety of conditions which would alter the dilative reserve. The cerebrovascular reactivity to $CO_2$ provided a measure of the dilative reserve. The first series of experiments examined the responses of the cerebral circulation to hemorrhagic hypotension and the effects of hypotension on the cerebrovascular responses to hypercapnia under control conditions. The effects of sympa-

thetic denervation (expected to increase the dilative reserve) were investigated in a second group of animals and finally, the effects of unilateral carotid artery occlusion (expected to decrease the reserve) were examined in a third group of animals. A detailed study of the interrelationship between changes in CBF, pial vessel responses and the dilative reserve is fundamental to our understanding of the control of the cerebral circulation. Prior to presenting the results from the first series of experiments, the general methods and procedures used will be described.

## III EXPERIMENTAL DESIGN

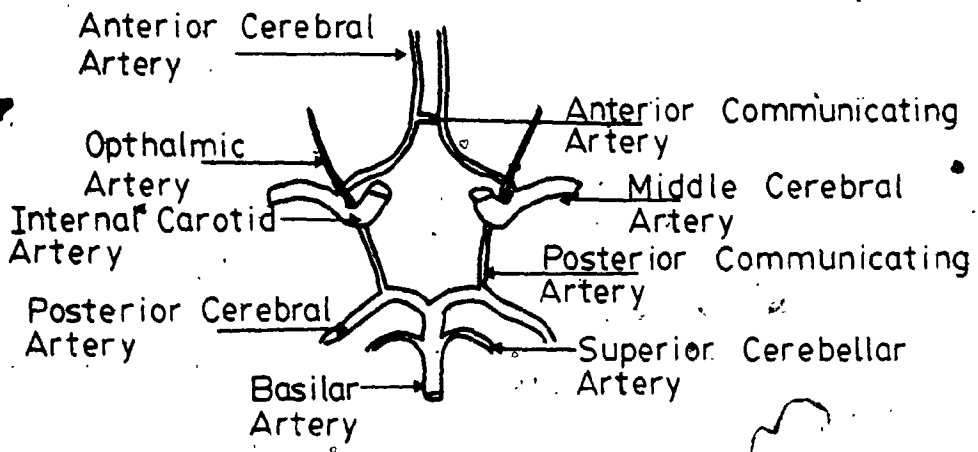
### 1. Animal Model

In these experiments, an animal with a relatively large blood volume (ie. one the size of a rabbit or cat) was required, as the protocol included taking frequent blood samples. The preferred species would have been the cat, since pial vessel and CBF responses could then have been compared directly to several previous studies (Kontos et al., 1978; MacKenzie et al., 1979). However, the species selected also had to be suitable for the study of cerebrovascular responsiveness following carotid artery occlusion (ie. increases in inflow artery resistance). The internal carotid artery in the adult cat is either very small or not patent so that occlusion of this artery would increase inflow artery resistance very little. Although occlusion of the common carotid artery in the cat might produce a larger increase in inflow artery resistance, the anastomosing vessels between the external carotid arteries and the Circle of Willis (the rete mirabile) could subsequently alter the cerebrovascular responses in an inconsistent way (ie. dependent on the vascular responses of the rete). In contrast, the cerebral arterial supply of the rabbit (Figure 1) is very similar to that of both man and primates. This is useful as the effects of carotid artery occlusion have been examined previously in these larger species. Also, there is a branch of the Circle of Willis in the rabbit (the internal

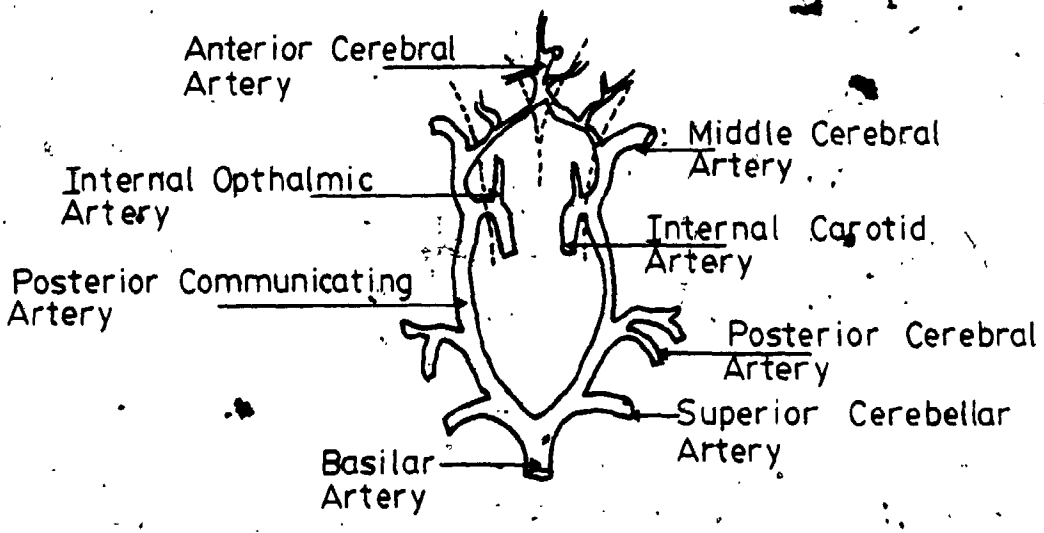
Figure 1

The Circle of Willis in man and that in the rabbit are illustrated in this diagram. In both species the blood is supplied to the brain by two internal carotid arteries and two vertebral arteries. The latter two arteries join together to form the basilar artery.

## MAN


Anterior Cerebral Artery
Anterior Communicating Artery
Opthalmic Artery
Middle Cerebral Artery
Internal Carotid Artery
Posterior Communicating Artery
Posterior Cerebral Artery
Superior Cerebellar Artery
Basilar Artery

## RABBIT


Anterior Cerebral Artery
Middle Cerebral Artery
Internal Opthalmic Artery
Internal Carotid Artery
Posterior Communicating Artery
Posterior Cerebral Artery
Superior Cerebellar Artery
Basilar Artery

opthalmic artery) from which the Circle of Willis pressure can be monitored. This measurement was necessary to determine the increase in inflow artery resistance (ie. pressure decrease) resulting from occlusion. Thus, due to its appropriate size and cerebrovascular anatomy, the rabbit was chosen as the animal model in the present experiments.

## 2. General Animal Preparation

The experiments were performed on rabbits of either sex weighing between 3 and 5 kg. The animals were anesthetized with urethane (ethyl carbamate, 1.5-2.0 gm/kg IV). The initial 7-9 ml of the 20% urethane solution was infused quickly through the ear vein. The remaining urethane was infused at approximately 1ml/min until a stage of surgical anesthesia was reached. Occasionally additional urethane (1-2 ml) was required. No measurements were made at least 30 minutes after supplementary anesthetic was given as urethane was found to increase CBF transiently.

Both femoral arteries and veins were exposed and catheters constructed from PE tubing (90 or 190) were inserted into the vessels. The trachea was exposed and intubated. The rabbit was placed in a stereotaxic headholder and connected to a positive pressure respirator (Harvard, Model 551) supplied with a mixture of oxygen enriched air. Muscle relaxation was maintained using gallamine triethiodide (flaxedil, 3 mg/kg IV) as required. The end-expiratory $CO_2$ of the animal was monitored continuously with an infrared

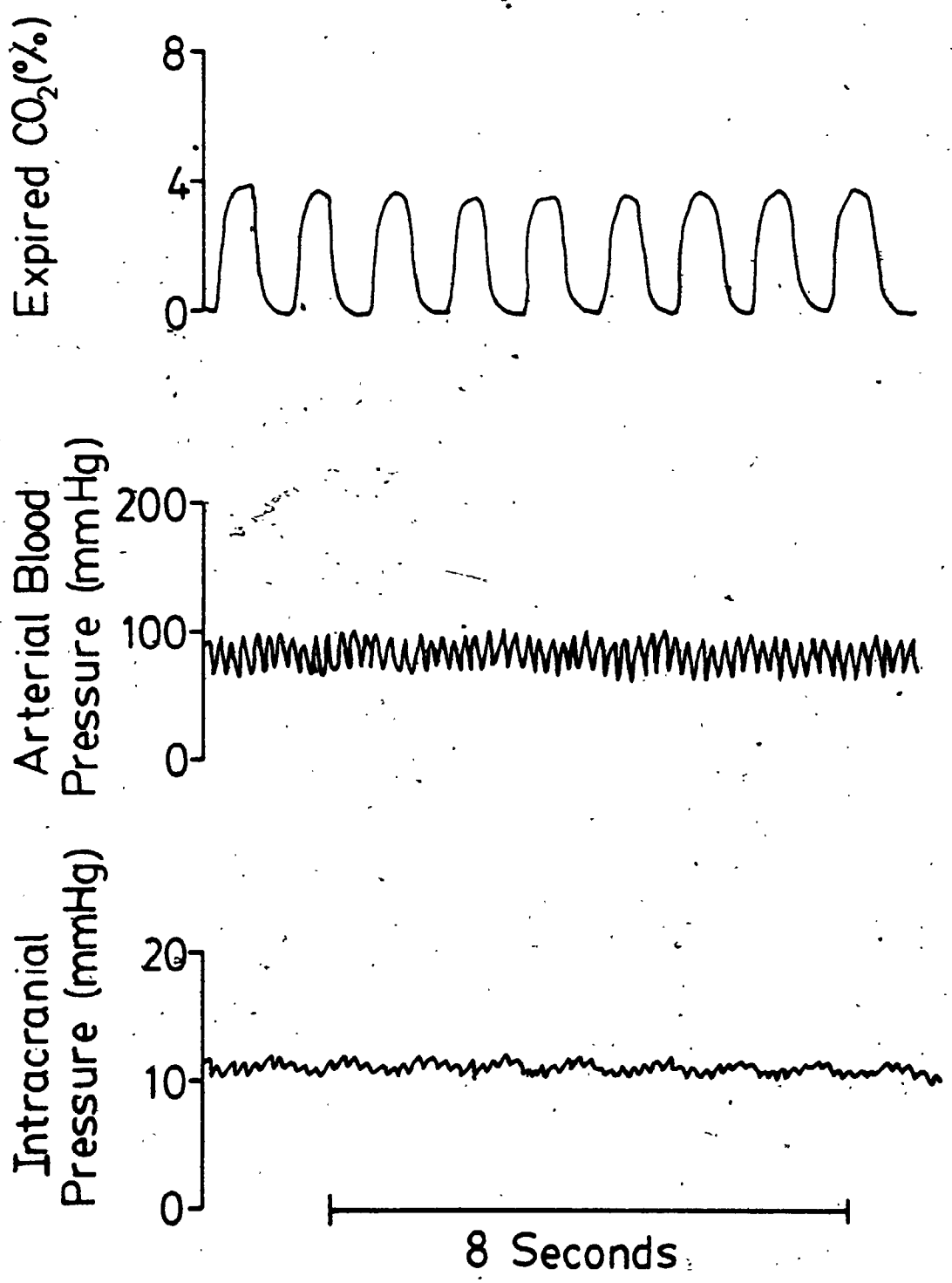
$CO_2$ analyzer (Beckman, Model LB-2) and ventilation was adjusted to achieve normocapnia ($P_aCO_2$=40 mm Hg). This value was chosen as a result of blood gas measurements obtained from ten lightly anesthetized rabbits during spontaneous respiration (mean $P_aCO_2$ of 39±1 mm Hg). Hypercapnia was induced when required, by adding $CO_2$ to the inspired gas mixture such that the arterial $PCO_2$ increased to 60 mm Hg. Immediately prior to each experimental measurement, an arterial blood sample was obtained and analyzed for $PCO_2$, $PO_2$ and pH (Radiometer, Model BMS-3).

All pressure measurements were obtained with strain gauge transducers (Statham Model P23Db) which were calibrated using a mercury manometer. Arterial blood pressure was monitored from the catheter placed in the abdominal aorta via the femoral artery and intracranial pressure was measured through an 18 gauge needle positioned in the cisterna magna. Since cerebral venous outflow pressure is approximately equal to the intracranial pressure, PP was calculated as the difference between the mean arterial blood pressure and intracranial pressure. Sample recordings of the blood pressure and intracranial pressure are shown in Figure 2, which also contains the recording of the end-expiratory $CO_2$ concentration.

A heating blanket was wrapped around the animal to maintain its body temperature between 38 and 39 $^0$C. A slow intravenous infusion of Ringer's lactate was continued throughout the surgical preparation to counteract fluid los-

Figure 2

This figure displays a tracing of the expired $CO_2$ concentration, arterial blood pressure and intracranial pressure recorded from a typical rabbit.


Expired $CO_2$(%)
8
4
0
Arterial Blood Pressure (mmHg)
200
100
0
Intracranial Pressure (mmHg)
20
10
0
8 Seconds

ses. Prior to the induction of hypotension heparin was injected (2000 units IV). PP was then reduced by bleeding from the other arterial catheter into a heparinized pressurized reservoir.

## 3. Methods

### 3.1 Measurement of CBF

#### 3.1.1 Introduction

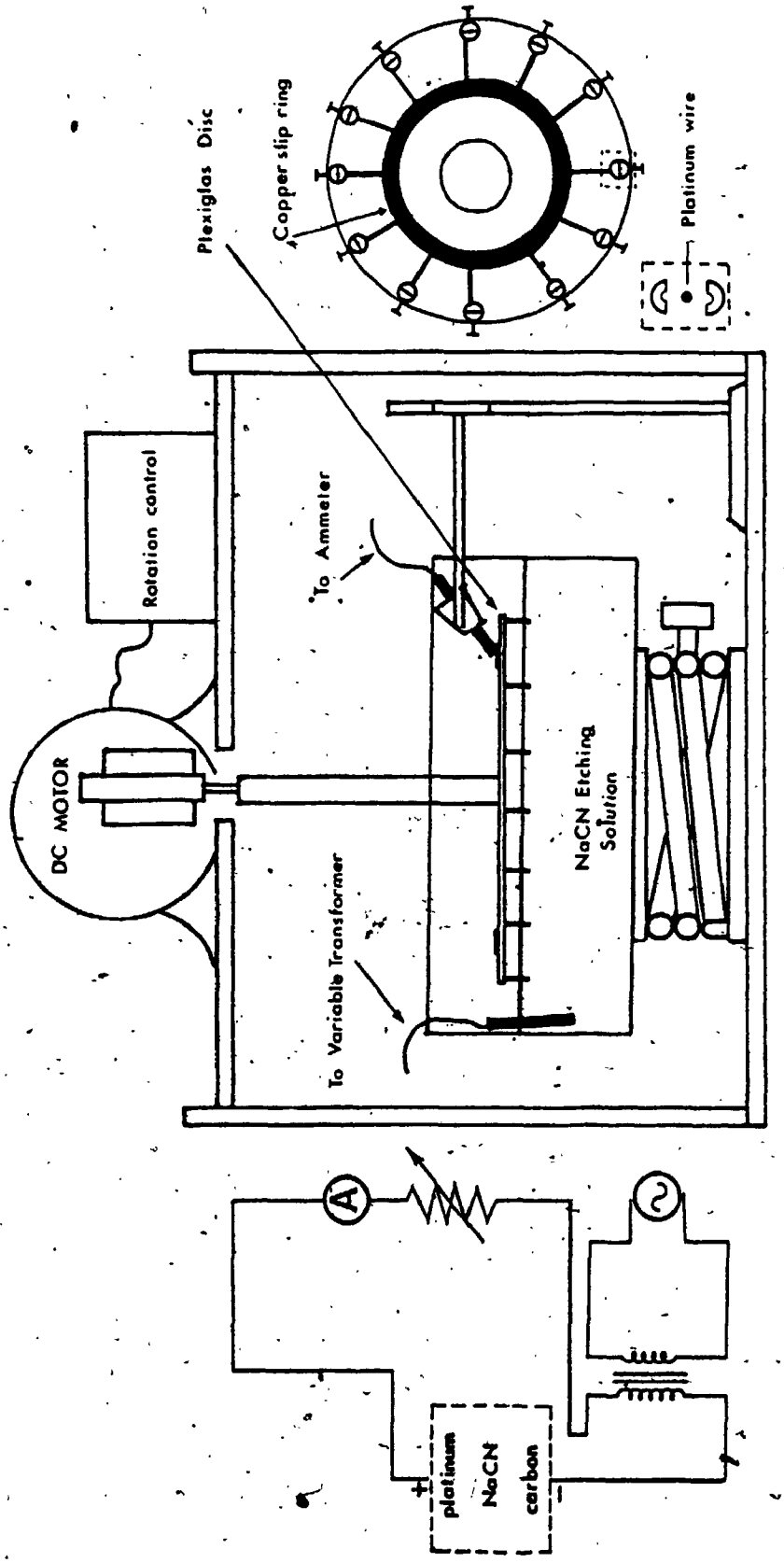
CBF was measured using the hydrogen clearance technique. This method of flow measurement was first employed in 1965 (Aukland) and it was subsequently applied to the study of the cerebral circulation by Fieschi et al. (1965) and Gotoh et al. (1966). The technique uses a polarized electrode to detect the accumulation of hydrogen gas in the tissue and then the washout of the tracer by the blood (for review see Young (1980)).

#### 3.1.2 Construction of the Electrodes

The electrodes were constructed from platinum wire (320 μm in diameter) which was sharpened electrochemically to a tip diameter of 15-25 μm. The etching apparatus used to sharpen the electrodes is shown in Figure 3. A carbon rod (the cathode) and twelve platinum wires (anodes) were positioned in a 15% sodium cyanide:15% sodium hydroxide solution and connected by a DC circuit. All wires were inserted at a uniform depth (approx. 2mm) in order to form a sharp well shaped electrode tip. The initial current pas-

Figure 3

A schematic diagram of the apparatus used to sharpen electrochemically the platinum electrodes (center). Included in the figure are the etching circuit (on the left) and the plexiglass disc which holds the electrodes in the sodium cyanide solution (on the right).


Plexiglas Disc
Copper slip ring
Platinum wire
Rotation control
To Ammeter
DC MOTOR
NaCN Etching Solution
To Variable Transformer
A
platinum
NaCN
carbon
+
-

sing through the electrodes was adjusted to 1400-1600 mA by means of a variable resistor and the disc containing the electrodes was rotated at 2-3 rpm in order to keep fresh electrolyte at the platinum surface. As the amount of metal in the solution decreased so did the current. Etching was terminated once the current fell to 700 mA. The etched electrodes were washed in distilled water and in a solution containing 10% nitric and 30% hydrochloric acid which created active sites on the metal surface. This was followed by a final rinse in distilled water.

The diameter of the sharpened wires was measured using a microscope fitted with a calibrated micrometer eyepiece. The electrodes were considered satisfactory if the tip diameter was $< 25$ μm and the diameter at a distance of 1 mm from the tip was $> 290$ μm (see Figure 4). These electrodes were sharp enough to penetrate the dura and yet had a large enough surface area to provide an adequate signal to noise ratio.

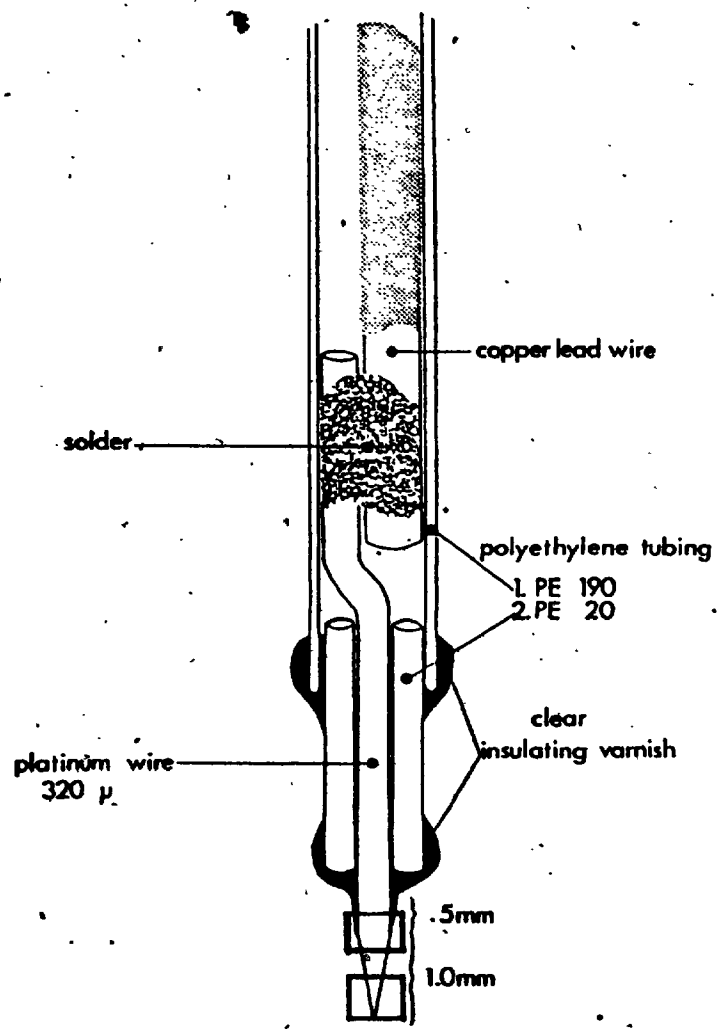
The electrodes were soldered to copper wires and insulated with polyethelene tubing to within 1.5 mm of the bare tip (Figure 4). Initially, the interfaces were sealed with varnish. In later experiments polystyrene Q-dope was substituted as it provided a more durable insulation.

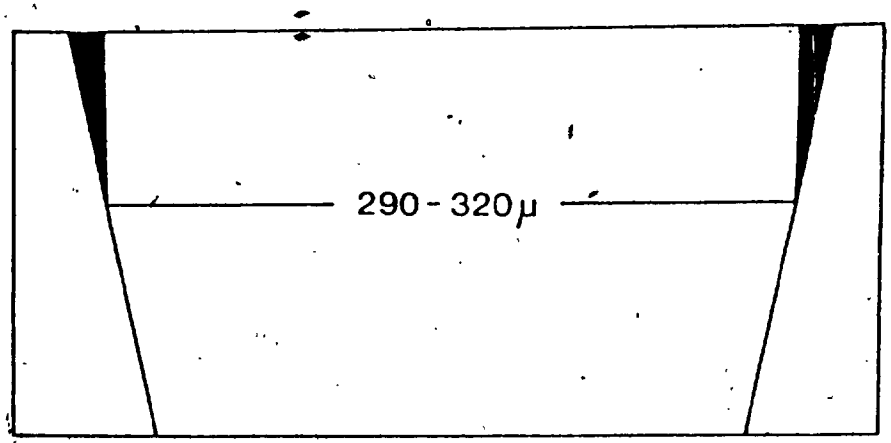
3.1.3 Cranial Preparation

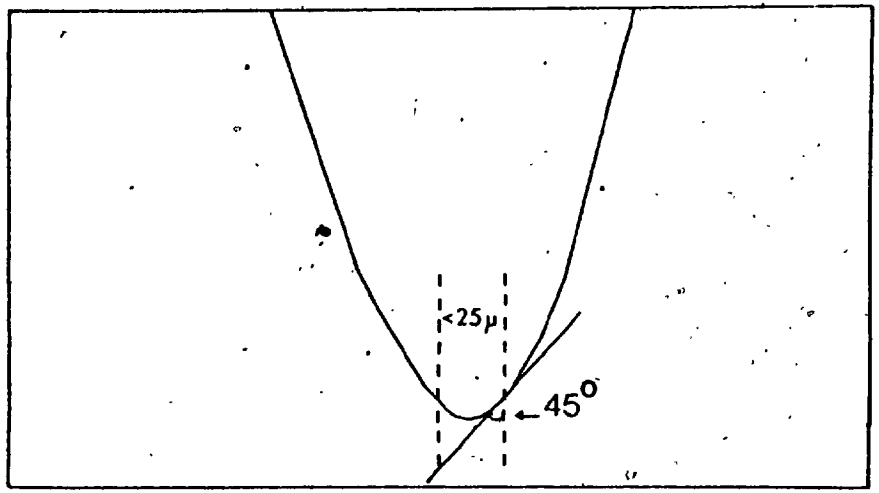
A midline incision was made in the scalp of the rabbit and the skin and muscle were retracted to expose the skull. Six burr holes (3-5 mm in diameter) positioned bila-

Figure 4

This diagram shows the construction of the platinum electrode. The insets indicate the dimensions of the electrode tip.

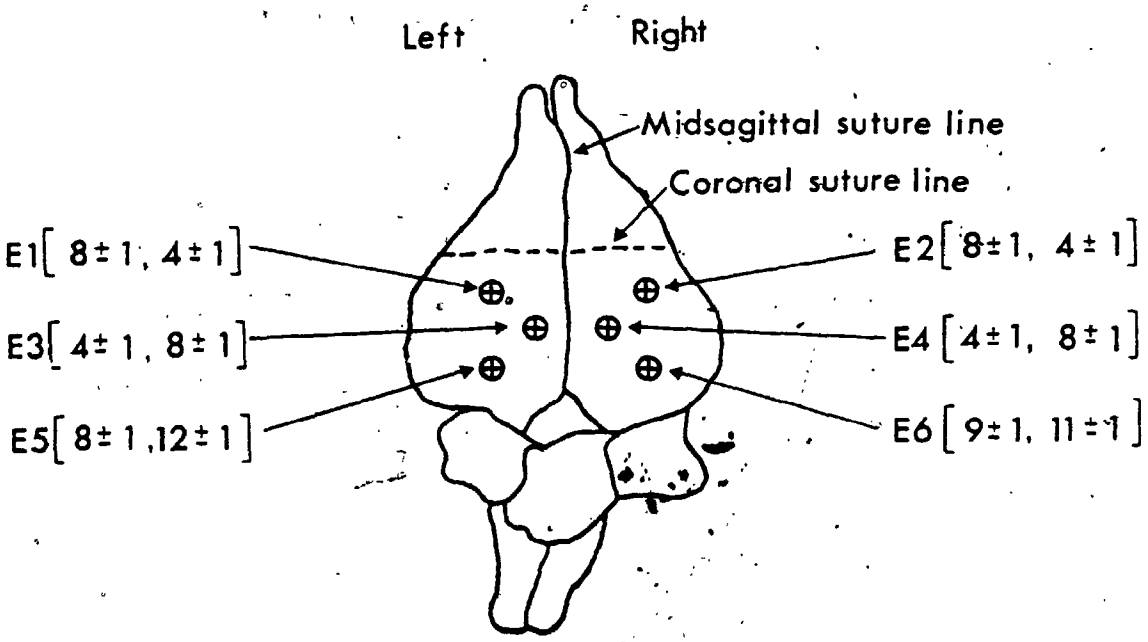

copper lead wire
solder
polyethylene tubing
1. PE 190
2. PE 20
clear
insulating varnish
platinum wire
320 μ
.5mm
1.0mm


290 - 320μ


<25μ
45°

## Figure 5

Figure illustrating the placement of the electrodes in the cerebral cortex of the rabbit. Positions were measured relative to the coronal suture line and the midsagittal suture line.




Electrode Number [Distance from Midsagittal suture line in mm ± S.D., Distance from Coronal suture line in mm ± S.D.]

terally (see Figure 5) were made using a saline cooled dental drill. Bleeding from the bone was terminated using both bone wax and a microfibular coagulant (Avitene). The electrodes were inserted through the meninges and into the cortex to a maximum depth of 1.5 mm. This was done using a microdrive attached to the stereotaxic frame in order to minimize local tissue trauma due to lateral movement or over-insertion during placement. The exposed dura was then covered with absorbable gelatin sponge (gelfoam) and the electrodes were sealed in place using cold curing dental acrylic (Perm Rebase and Repair Acrylic).

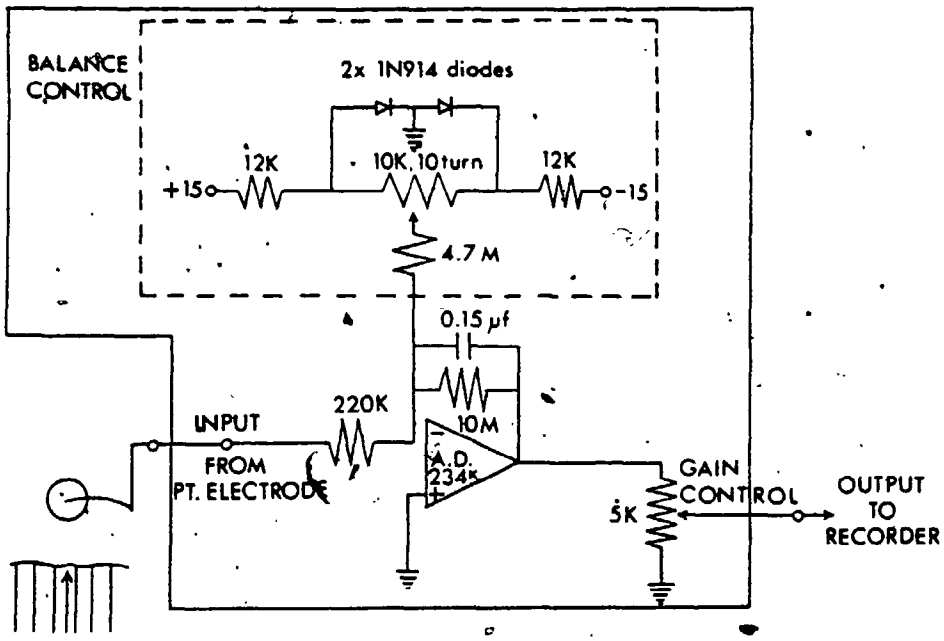
3.1.4 Recording the Hydrogen Partial Pressure

The rabbit was electrically isolated from the operating table with a sheet of plastic. A polarizing voltage of 600 mV was applied to the stainless steel reference electrode placed in the shoulder. The platinum electrode provided an acceptor surface for the oxidation reaction $H_2 \rightarrow 2H^+ + 2e^-$. The current output of the electrode was proportional to the $H_2$ partial pressure in the tissue. Figure 6 shows the system used to amplify and display the electrode output on strip chart recorders (Brinkman 2571). The preparation was allowed to stabilize for at least one hour before flow measurements were made. During this hour, hydrogen was added to the inspired gas in order to establish the electrode sensitivity. In addition, the concentration of inspired $CO_2$ required to increase the $P_aCO_2$ to 60 mm Hg was determined.

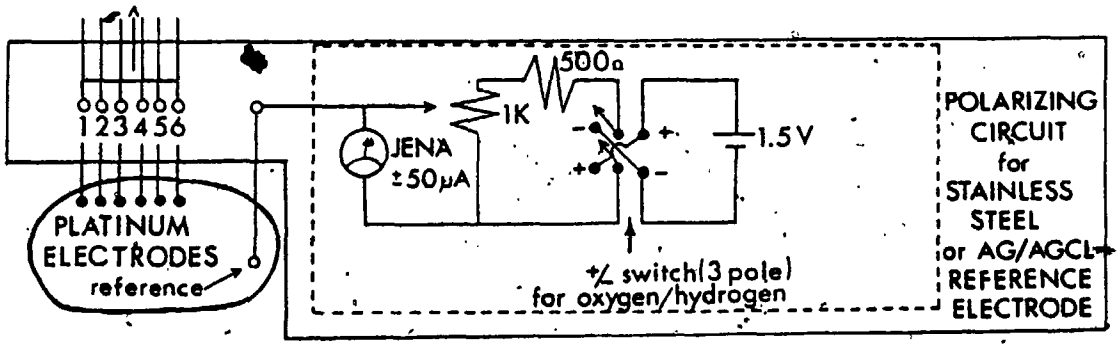
Figure 6

This diagram shows the electronic circuits used to polarize and amplify the signals from the platinum electrodes. The balance control was used to position the baseline recording at a desired zero level.

AMPLIFIER FOR ONE ELECTRODE




TO INDIVIDUAL AMPLIFIERS



3.1.5 Clearance Curves

In order to obtain a flow measurement, hydrogen was added to the inspired gas. Ventilation with this mixture ($\sim$10% $H_2$) was continued until the tissue became saturated (approx. 10 min.). The inhalation of hydrogen was then discontinued abruptly and the clearance of hydrogen (absolute concentration arbitrary) was recorded for 8–10 minutes.

The analysis of the clearance curve (see Appendix 2) was performed using a Hewlett Packard computer (Model 9830). The clearance curve was digitized at 10 and 20 sec intervals (see Figure 7) and the data were stored in the computer. The data analysis program was written such that the operator could select the point at which the analysis began and could also correct for alterations in the zero baseline. In addition to the calculated flow indices, the output from the computer provided a semilog plot of the original data and the fitted curves. This allowed a visual check of the accuracy of the data entry and curve fits.

The initial slope index of the clearance was used as a measure of the mean CBF in the tissue surrounding the electrode tip (Doyle et al, 1975; and Rowan , 1977). During severe blood pressure reductions, the animals could not be maintained at a steady pressure level for more than 2-3 minutes such that the biexponential curve analysis (requiring [redacted]0 minutes of clearance data) was considered unreliable. Therefore only the initial slope index was used in the analysis of the CBF response to hemorrhagic hypo-

## Figure 7

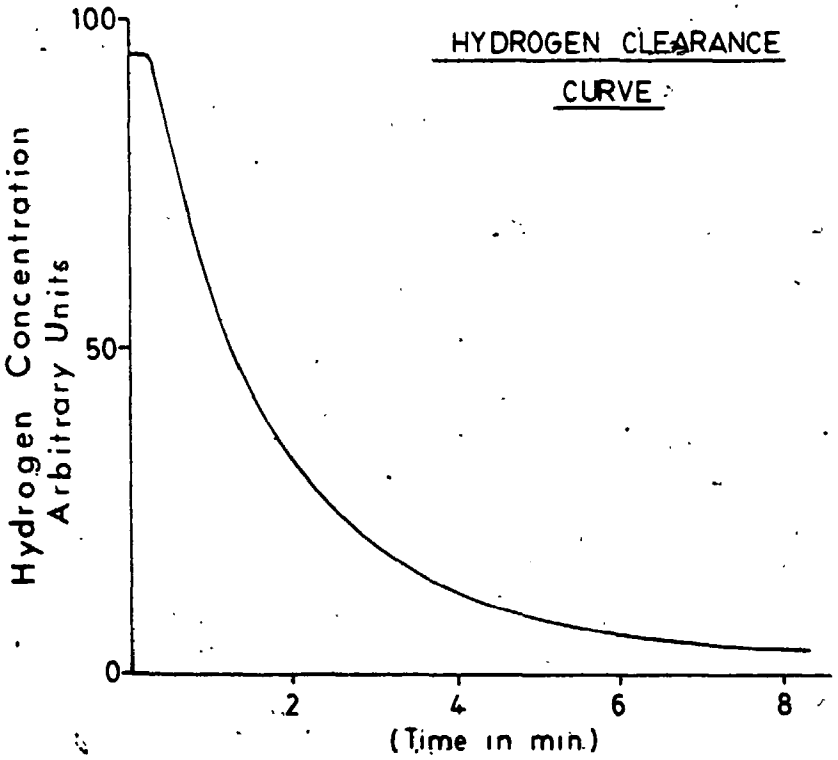
A sample hydrogen clearance curve and the semi-log plot of the curve are presented in the upper and lower sections of this figure, respectively. The fast flow and slow flow values obtained by biexponential curve analysis and the ISI flow calculated from the initial slope of the clearance curve are also shown.

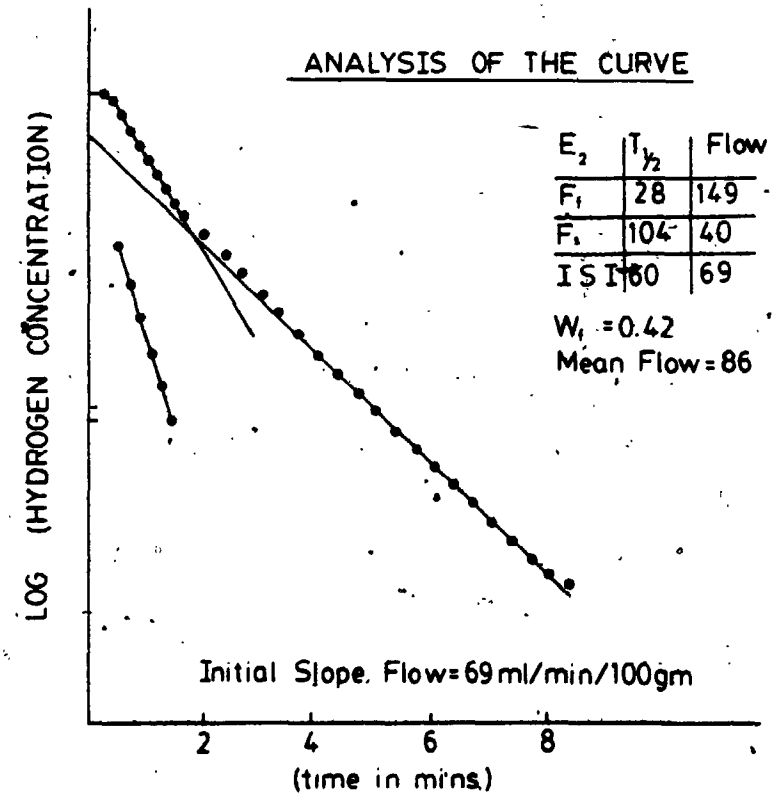
$E_2$- Values for electrode in position #2.

$F_f$- Fast flow component

$F_s$- Slow flow component

ISI- Initial Slope Index of Flow


HYDROGEN CLEARANCE CURVE
Hydrogen Concentration Arbitrary Units
100
50
0
2
4
6
8
(Time in min.)


ANALYSIS OF THE CURVE
LOG (HYDROGEN CONCENTRATION)
E2 | T½ | Flow
F1 | 28 | 149
F2 | 104 | 40
I S I | 60 | 69
W1 = 0.42
Mean Flow = 86
Initial Slope. Flow = 69 ml/min/100gm
2
4
6
8
(time in mins.)

tension.

## 3.2 Measurement of Pial Vessel Caliber

### 3.2.1 Introduction

The pial vessels in the rabbit were viewed using the open skull preparation originally described by Wahl et al. (1972). The vessel diameters were measured with the image technique developed by Baez (1966).

### 3.2.2 Cranial Preparation

A midline incision was made in the scalp of the rabbit. The cut edges were elevated and sutured to a steel ring 6 cm in diameter, thus forming a pool for the paraffin oil (Fischer lightweight). A 2x1 cm craniectomy was made over the parietal cortex using a saline cooled dental drill. Bipolar diathermy was used to halt any bleeding from the scalp or muscle whereas bone bleeding was terminated with avitene and bone wax. The exposed dura was covered with paraffin oil, to a depth of approximately 1-2 cm, infused at a rate such that the temperature of the oil at the brain surface was 37-38 $^{0}$C. The position of the steel ring was adjusted such that the concave suface at the edge of the oil pool was well removed from the area of the craniectomy thus avoiding any refractive distortion in the field of measurement. The dura was incised and the cut dural edges were sealed using bipolar diathermy and reflected. Mannitol (1.0-1.5 mg/kg I.V.) was used in several rabbits to facilitate this procedure by increasing the separation between

the brain surface and the dura. No caliber measurements were made for at least 90 minutes to ensure that the cerebrovascular effects of mannitol infusion had disappeared (Johnston and Harper, 1973).

3.2.3 Image Splitting Technique

In each animal 7-10 pial vessels (arteries and arterioles) of varying sizes were selected for study. Their location on the brain surface and the site of measurement were recorded to ensure that all subsequent measurements would be made at the same location. A schematic diagram of the system used to measure the diameter of the pial vessels is shown in Figure 8. The pial vessels were illuminated with a fibre optic light source (Ealing) and observed through a triocular stereomicroscope (Olympus) at a magnification of 80x.

Pial vessel diameters were measured with an image spitting device (Vickers), viewed by a closed circuit television camera and videomonitor (Panasonic). Two partially reflecting prisms within the image splitting eyepiece doubled and reintegrated the image. The two images were separated by rotating a graduated dial connected to the prisms. The degree of rotation required to juxtapose the two images was proportional to the diameter of the vessel. The image splitter dial was calibrated in microns by measuring monofilament wires of known diameter. Figure 9 demonstrates the linear relationship between the wire diameter and the number of units observed on the dial of the image splitter.

Figure 8

This is a schematic diagram of the instrumentation used to observe and measure the diameter of the pial vessels.

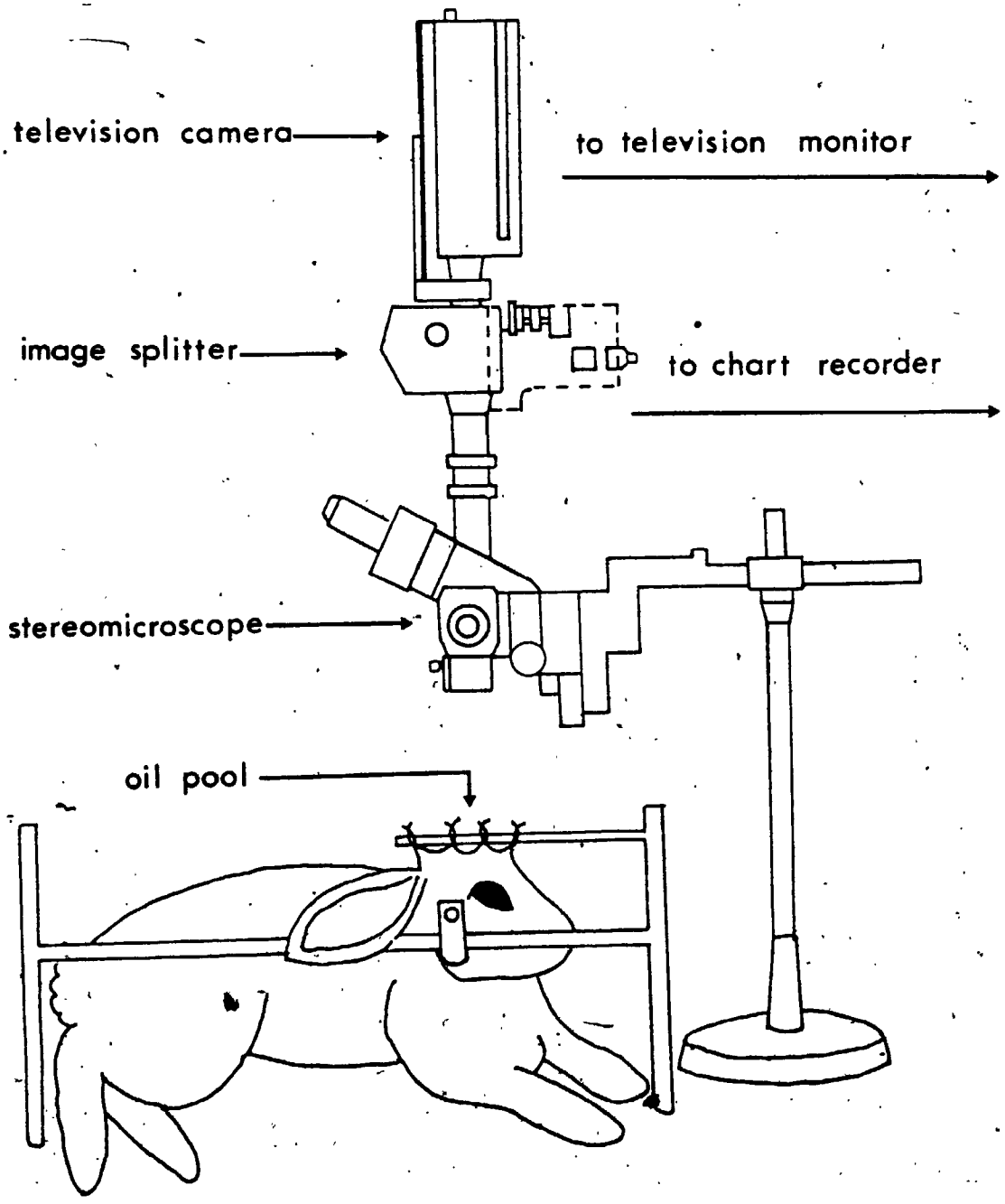
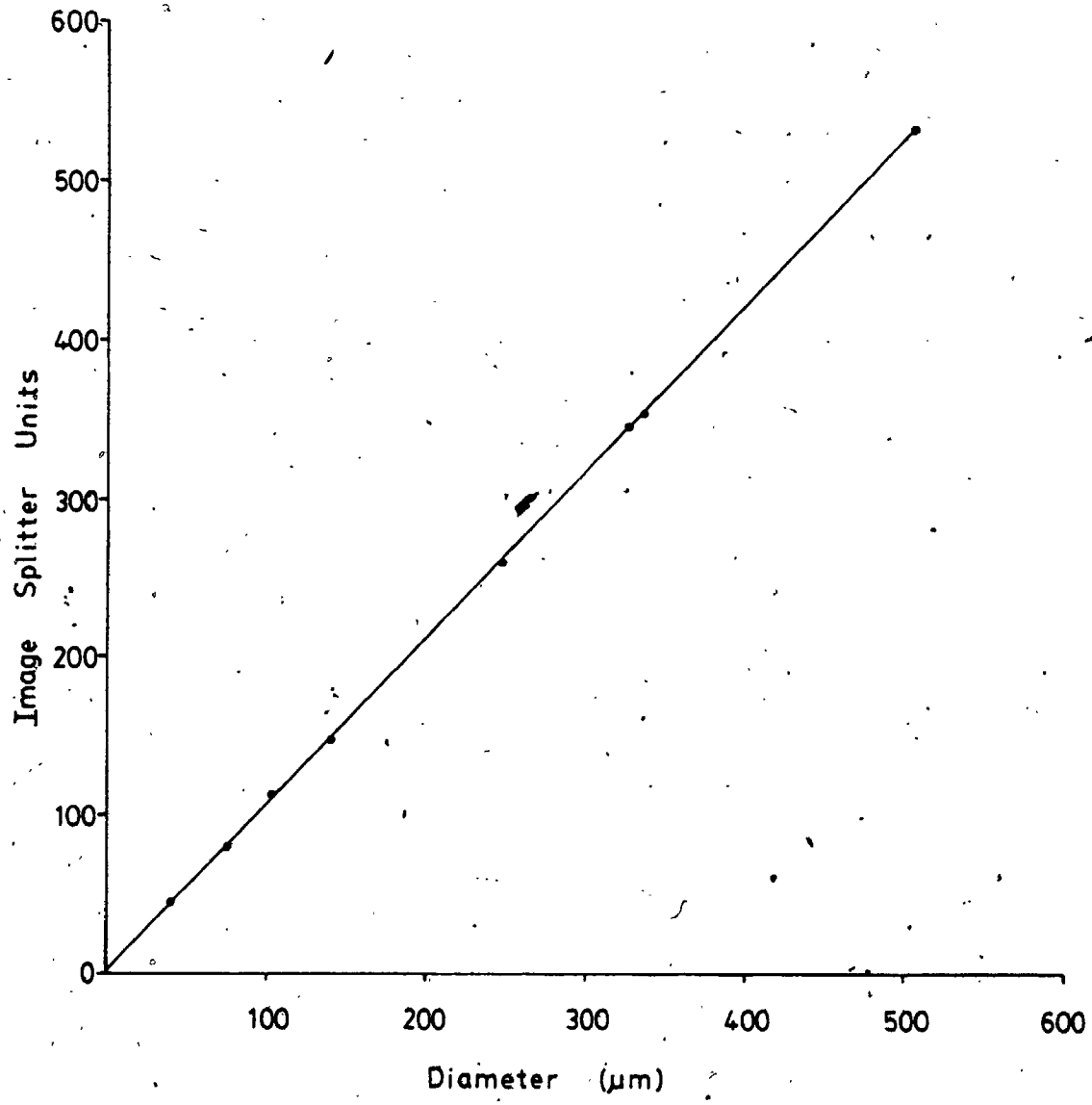

television camera
to television monitor
image splitter
to chart recorder
stereomicroscope
oil pool

Figure 9

This is a graph of the diameter of the monofilament sutures measured in image splitting units (y) versus their size in micrometers (x). A least squares regression analysis of the points determined that $y = 1.056x + 0.033$. The slope of the line was $1.056 \pm .002$.


600
500
400
300
200
100
0
Image Splitter Units
100
200
300
400
500
600
Diameter (µm)

the latter experiments the rotating dial was connected directly to a potentiometer. This allowed permanent recordings of the degree of rotation and therefore vessel diameter to be made. Repeated vessel measurements with either method had a standard deviation of less than 1.5 μm.

## 4. General Protocol

### 4.1 Data Accumulation

(i)Resting PP: Several measurements of CBF or pial vessel caliber were made at normocapnia and normotension and the response to hypercapnia was obtained.

(ii) Hemorrhagic Hypotension: PP was lowered gradually in increments of 10-20 mm Hg and the reduced level of PP was held constant while measurements were made at normocapnia and hypercapnia. This sequence was repeated a number of times until PP had been reduced to 15-25 mm Hg.

### 4.2 Data Analysis

(i) Normalization: Since measurements were not obtained at each pressure level in all animals, the data were converted to a percentage of a control value. Unless specified otherwise, the control value was calculated as the average of all measurements obtained at normocapnia and normotension.

(ii) Organization: The CBF data obtained at normocapnia were grouped in PP intervals of 10 mm Hg (eg. 10-19, 20-29,...) and the mean ± SEM was calculated for each PP range. The data obtained during hypercapnia were treated similarily and the difference between the values obtained at

normocapnia and hypercapnia represented the $CO_2$ response. The pial vessel data were separated into the following three groups according to the control vessel caliber measurement: group I contained vessels <50 μm in diameter; group II contained vessels 50-90 μm in diameter; and group III contained vessels >90 μm in diameter. The grouped data were then analyzed as described above. Student's t-test was used for statistical comparison unless otherwise noted.

4.3 Data Exclusion

In a number of instances, data obtained from individual hydrogen electrodes or pial vessels were excluded from further analysis for the following reasons. (i) Unsatisfactory electrical recordings were obtained from electrodes which had lost their insulating seal during handling. (ii) The clearance curves obtained from all hydrogen electrodes were biexponential. However, the curves from several electrodes were found to have an extremely low $W_f$ (< 15%) when compared to the majority (average $W_f$= 60±2%). The initial slope index of flow in these electrodes was similar to the slow component of the normal clearance curves. These low values most likely occurred as a result of compression of the cortex by the electrode flange and therefore were not considered to be representative of normal cortical CBF. (iii) In several instances, CBF and pial vessel caliber decreased passively as PP was reduced. Although great care was taken when inserting the electrodes and exposing the brain surface, small regions of trauma occasionally occurred

and were thought to be the cause of this pressure-passive behavior. The data from these electrodes and vessels were considered unreliable and were omitted from the analysis.

## 5. Analysis of Resistances

### 5.1 Pial Vascular Resistance

The resistance of each group of pial arterioles was calculated for each PP range using the Poiseuille equation (see Appendix 1). Under this premise, pial vascular resistance was proportonal to the viscosity of blood divided by the fourth power of vessel radius. (Note that for small vessels (diameter $< 300\mu m$), the viscosity of blood decreases significantly with decreasing vessel radius - the Fahraeus-Lindquist effect (Burton, 1965; Charm and Kurland, 1974; McDonald, 1974). The validity and limitations of these calculations are discussed in detail in Appendix 1. Since the absolute values of the above resistances could not be assessed all resistances were converted to a percentage of their respective control values observed at normotension and normocapnia.

### 5.2 Total Precapillary Resistance

The total cerebrovascular resistance (PP/CBF) represents the resistances of all cerebral vessels. However only the arterioles and arteries are likely to participate actively in the control of CBF. In order to compare changes in pial vascular resistance (an active vessel segment) with changes in total precapillary resistance (PCR), the capil-

laries and veins were assumed to be a passive segment of the cerebrovasculature which did not change its resistance to flow substantially under the conditions studied (that is, the capillaries and veins did not contribute to the observed changes in total CVR). Capillary-venous resistance (a constant) was calculated assuming under control conditions a capillary input pressure of 30 mm Hg at normal flow rates (Gore, 1974) and was subtracted from the total CVR to obtain the resistance of the precapillary cerebral vasculature. Implicit in these calculations is the assumption that changes in cortical CBF are representative of those occurring elsewhere in the brain. This has been verified experimentally by Symon et al.(1973) during hemorrhagic hypotension in the baboon.

# IV CONTROL EXPERIMENTS

## 1. Introduction

Many aspects of the cerebral circulation and its control are not well understood (see Chapter II for details). The reason for the decline in CBF at the lower limit of autoregulation is uncertain as is the role of the dilative reserve in determining the autoregulatory and $CO_2$ responses of the cerebrovasculature. In addition, the manner in which changes in pial vessel caliber are related to vessel responses elsewhere in the vascular bed (ie. the relationship between pial vessel caliber and CBF) is not clear. The specific objectives of this group of control experiments was as follows:

(1). to investigate the effects of hemorrhagic hypotension on CBF and pial vessel caliber in the rabbit.

(2). to examine the relationship between the dilative reserve and the autoregulatory responses of the cerebral circulation.

(3). to determine if changes in pial vascular resistance were representative of alterations in total CVR.

## 2. Methods

CBF and pial vessel caliber were measured in 21 and 11 urethane anesthetized rabbits respectively. The techniques, experimental protocol and analysis of the data were identical to that described in Chapter III. Measurements of the parameters were made during stepwise reductions in pressure at normocapnia and hypercapnia. The data were grouped according to PP and the difference between the values obtained under normocapnic and hypercapnic conditions provided the $CO_2$ response. Pial vascular resistance and total precapillary resistance were determined from the data as described previously.

## 3. Results

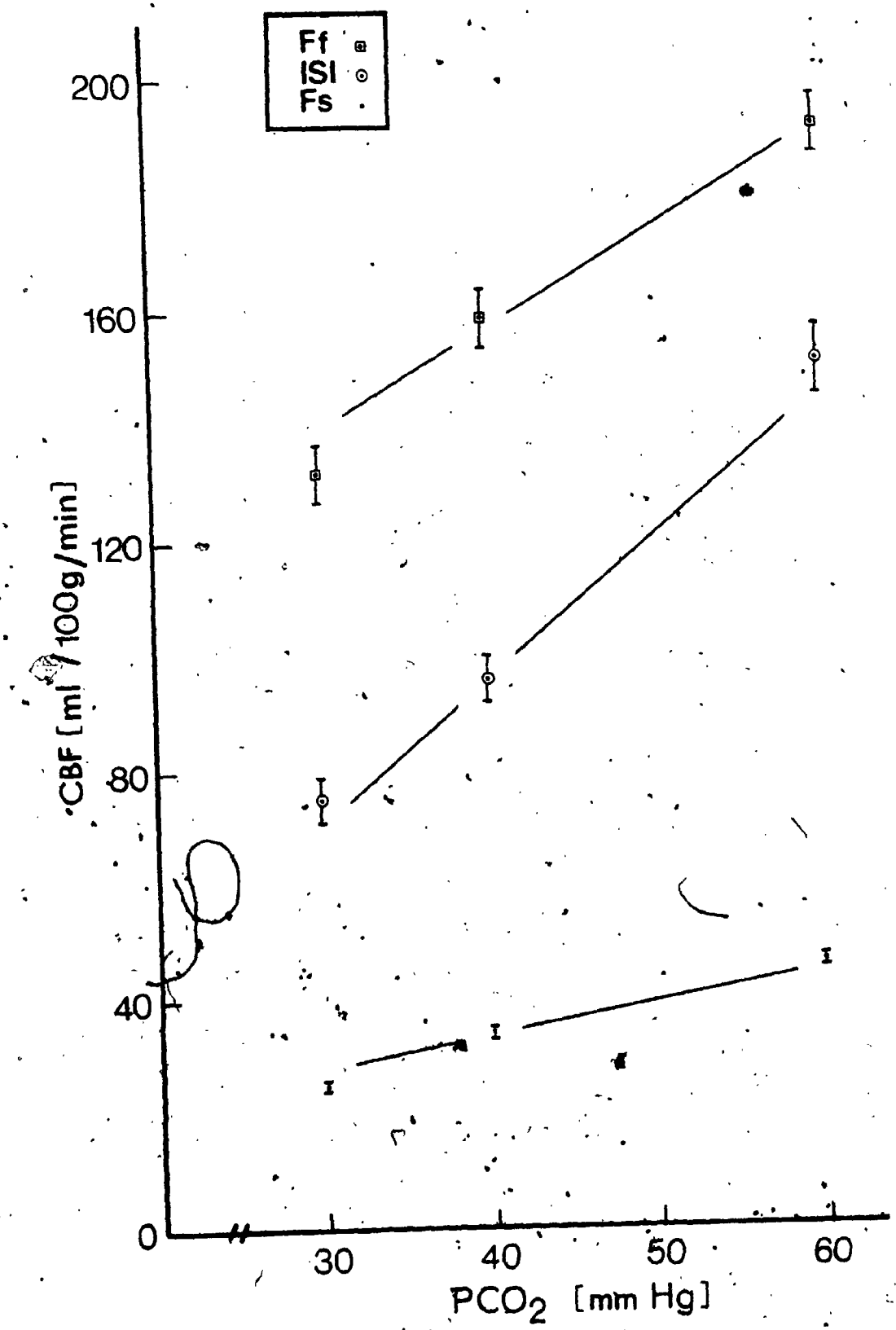
### 3.1 Cerebral Blood Flow

#### 3.1.1 Measurements at Normotension

Satisfactory recordings were obtained from 95 of 105 electrodes. The clearance curves from these electrodes all were biexponential in character. The flow data were initially grouped according to the location of the electrode in the cortex. A comparison of the results obtained from anterior, central and posterior cortical regions showed no significant differences in the control levels of flow or in the responses to hypercapnia or hypotension. Therefore, the data from all locations were combined. The normocapnic and hypercapnic control measurements of the initial slope index (ISI), fast component of flow ($F_f$) and slow flow ($F_s$) are

Figure 10

This graph presents the mean values of the fast flow ($F_f$) component, slow flow ($F_s$) component and the initial slope index (ISI) at hypocapnia (MABP=83±4 mm Hg, ICP=8±1 mm Hg), normocapnia (MABP=94±3 mm Hg, ICP=9±1 mm Hg) and hypercapnia (MABP=102±4 mm Hg, ICP=11±1 mm Hg).


Ff
ISI
Fs
200
160
120
80
40
0
CBF [ml/100g/min]
30
40
50
60
PCO2 [mm Hg]

presented in Figure 10. Included in the graph are the average flow indicies obtained from 5 rabbits at moderate hypocapnia ($P_aCO_2$= 30 mm Hg). The mean flow values at normocapnia ($P_aCO_2$= 40±1 mm Hg) and normotension (PP= 83±3 mm Hg) were as follows: ISI= 96±4: $F_f$= 159±5; and $F_s$= 34±1 ml/100gm/min. The $CO_2$ reactivities (ml/100gm/min/mm Hg $P_aCO_2$) were calculated by linear regression for each flow index (ISI= 2.5 ± 0.2, $F_f$= 1.7 ± 0.2, $F_s$= 0.57 ± 0.04).

3.1.2 Effects of Hemorrhagic Hypotension

The mean values of PP, ICP, and $P_aCO_2$ obtained at normocapnia and hypercapnia during hemorrhagic hypotension are shown in Table 1. The mean pH values are also included and these are somewhat acidotic under resting conditions. The corresponding changes in CBF (ISI) are presented in Figure 11. Under normocapnic conditions, CBF did not differ significantly from control levels until PP was lowered to approximately 65 mm Hg. As PP was reduced from 65 to 35 mm Hg, CBF decreased gradually and at pressures below 35 mm Hg the reductions in flow became pressure passive. Hypercapnia increased CBF substantially to 150-160% control at PP greater than 70 mm Hg. At 65 mm Hg, CBF during hypercapnia decreased markedly. With further PP reductions there was a decline in CBF during hypercapnia. The $CO_2$ response (the additional increase in flow produced by hypercapnia at each PP level) was essentially constant at pressures greater than 65 mm Hg. Between 75-45 mm Hg the $CO_2$ response diminished and it ceased to be significant at a PP of 35 mm Hg.

Table 1

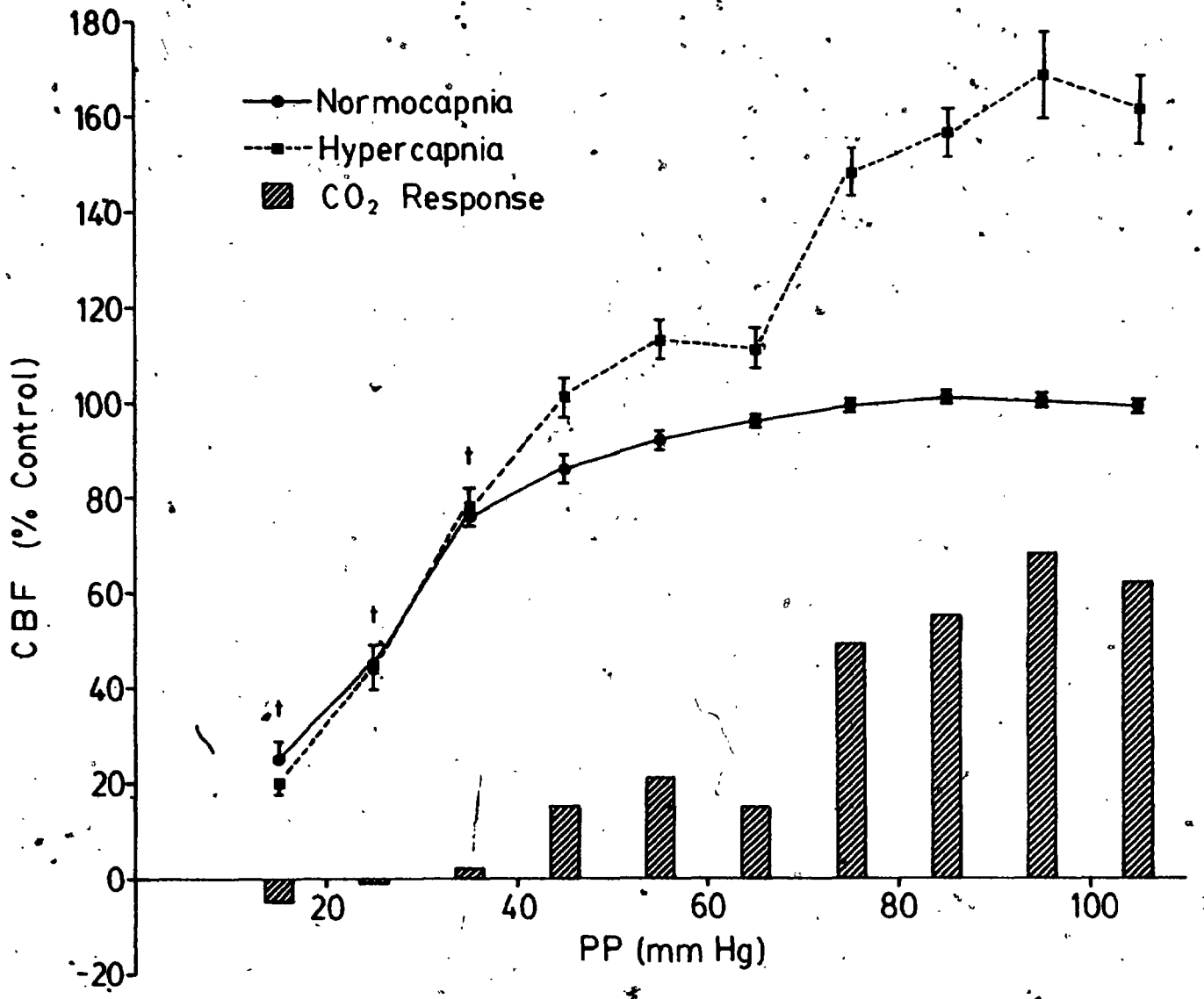
Physiological Variables During Hemorrhagic Hypotension

| State | Variables | | | |
|---|---|---|---|---|
| | PP+ | ICP+ | $P_aCO_2$+ | pH |
| Normocapnia | 17±1* | 6±1 | 37±1 | 7.05±.14 |
| | 24±1 | 5±1 | 39±1 | 7.07±.06 |
| | 35±1 | 7±1 | 40±1 | 7.09±.05 |
| | 45±1 | 6±1 | 41±1 | 7.17±.03 |
| | 55±1 | 8±1 | 40±1 | 7.19±.07 |
| | 66±1 | 10±1 | 41±1 | 7.21±.04 |
| | 75±1 | 9±1 | 40±1 | 7.23±.03 |
| | 84±1 | 9±1 | 40±1 | 7.27±.02 |
| | 94±1 | 8±1 | 39±1 | 7.28±.03 |
| Hypercapnia | 15±1 | 7±1 | 58±2 | 6.96±.03 |
| | 24±1 | 4±1 | 59±1 | 6.92±.03 |
| | 36±1 | 7±1 | 60±1 | 7.07±.01 |
| | 44±1 | 7±1 | 59±1 | 6.99±.05 |
| | 54±1 | 8±1 | 60±1 | 7.02±.05 |
| | 65±1 | 10±1 | 62±1 | 7.10±.04 |
| | 74±1 | 12±2 | 61±1 | 7.16±.02 |
| | 85±1 | 10±1 | 60±1 | 7.13±.02 |
| | 94±1 | 12±3 | 62±1 | 7.15±.03 |
| | 105±2 | 11±1 | 61±1 | 7.18±.03 |

+ mm Hg , * all values are expressed as mean±SEM

Figure 11

The mean CBF responses observed during hemorrhagic hypotension at both normocapnia and hypercapnia are presented in this figure. The additional increases in CBF resulting from hypercapnia (ie. the $CO_2$ responses) are shown in the bar graphs. The symbol $^+$ indicates that the CBF difference between normocapnia and hypercapnia is not statistically significant.


Normocapnia
Hypercapnia
$CO_2$ Response
CBF (% Control)
180
160
140
120
100
80
60
40
20
0
-20
20
40
60
80
100
PP (mm Hg)

## 3.2 Pial Vessel Caliber

### 3.2.1 Measurements at Normotension

The resting diameters of the 77 vessels studied ranged from 20-170 μm at a mean blood pressure of 94±1 mm Hg and $P_aCO_2$ of 39.6±0.6 mm Hg. Since caliber is highly dependent on PP an arbitrary reference pressure of 95 mm Hg was chosen and the calibers were converted to a percentage of the caliber observed when PP was closest to this value. Group I contained 28 vessels with a mean diameter of 38±2 μm, group II contained 30 vessels with a mean diameter of 68±2 μm and group III contained 19 vessels with a mean diameter of 116±4 μm.

In five animals, the induction of hypercapnia at resting perfusion pressures resulted in a compression of the pial vessels at the periphery of the craniotomy due to brain swelling. When this occurred, the animal was returned immediately to normocapnia and no measurements were taken. The response to hypercapnia at normotension was obtained in the remaining five animals. The average response (% change in caliber) of all vessels in a given diameter range was calculated for each animal and used in the determination of the mean $CO_2$ response as shown in Table 2. All vessels dilated during hypercapnia and the response of the smallest vessels (group I) was significantly greater than that of the other two groups (Scheffe's two way analysis of variance).

TABLE 2

Pial Vessel Responses* to Hypercapnia

| MABP (mmHg) | $P_aCO_2$ (mmHg) | Vessel Caliber(um) I | II | III | $CO_2$ Response(%)+ I | II | III |
|---|---|---|---|---|---|---|---|
| 103±3 | 39.2±.4 | 34±2 | 66±2 | 115±5 | - | - | - |
| 104±3 | 60.4±1.0 | 42±2 | 78±3 | 132±10 | 24±4 | 19±4 | 15±4 |
| | | | | | p .05 | ns | |
| | | | | | p .001 | | |

* Mean values ± SEM

\+ Compared statistically with Scheffe's two way analysis of variance

3.2.2 Effects of Hemorrhagic Hypotension

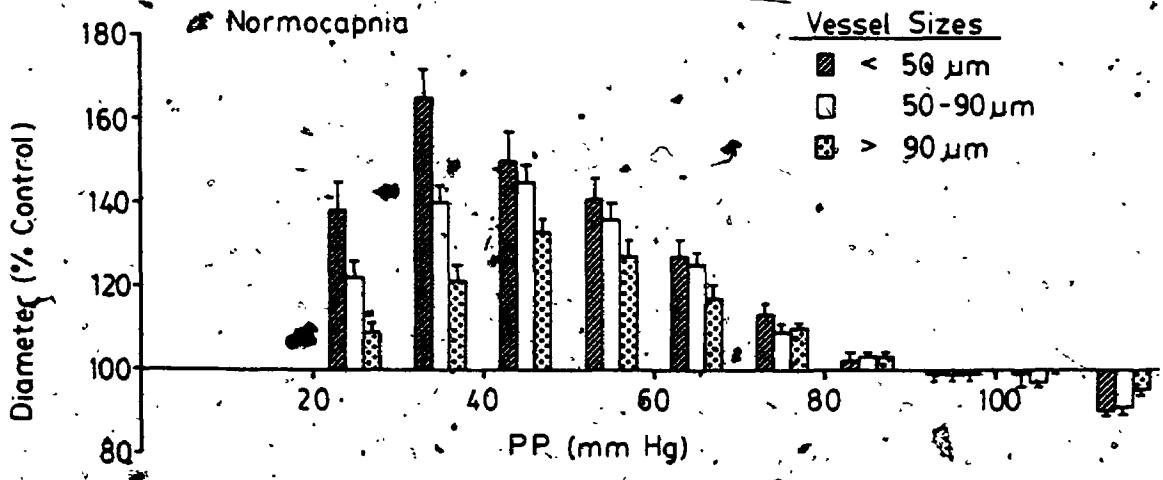
The effects of hemorrhagic hypotension on pial vessel caliber are shown in Figure 12. As PP was decreased under normocapnic conditions, all vessels showed a progressive increase in diameter. The smallest vessels ($< 50$ μm) dilated to 165 ± 6%, the intermediate vessels (50-90 um) to 145 ± 4% and the largest vessels ($> 90$ μm) to 133 ± 3% of their respective control calibers. The maximum dilatation of the smallest vessels occurred at a lower pressure (30-39 mm Hg) than that of the largest vessels (40-49 mm Hg). Once maximal dilatation had been achieved, vessel caliber decreased with further reductions in pressure.

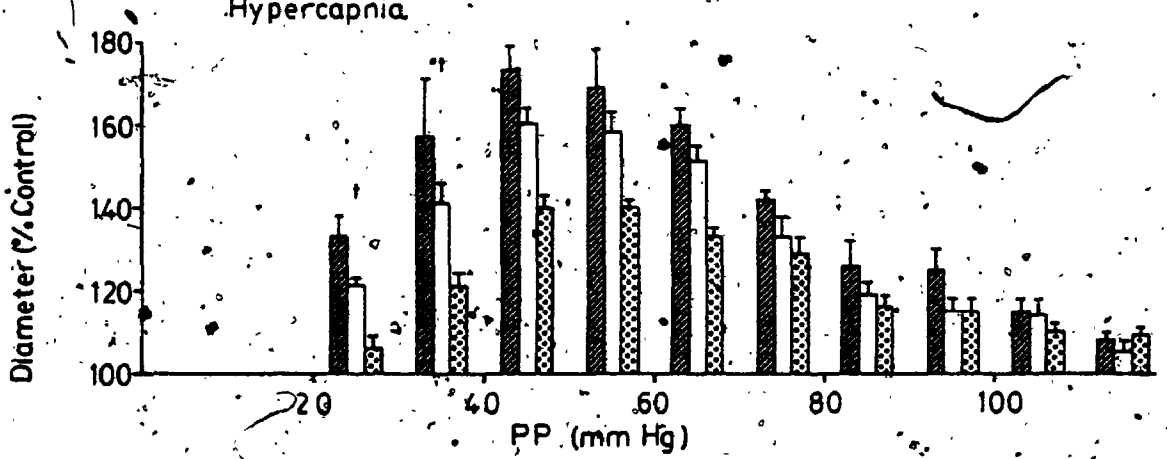
The calibers of the pial vessels during hypercapnia exceeded those during normocapnia at PP levels above 40 mm Hg. A reduction in PP produced a progressive increase in the vessel calibers. The PP at which the vessels attained a maximal dilation was not sharply defined. The small vessels dilated to 173±6%, the intermediate vessels to 160±4% and the largest vessels to 141±3% of their control calibers. Dilation was maximal at a PP of approximately 45 mm Hg for all vessel groups. Below this PP, the vessel calibers decreased.

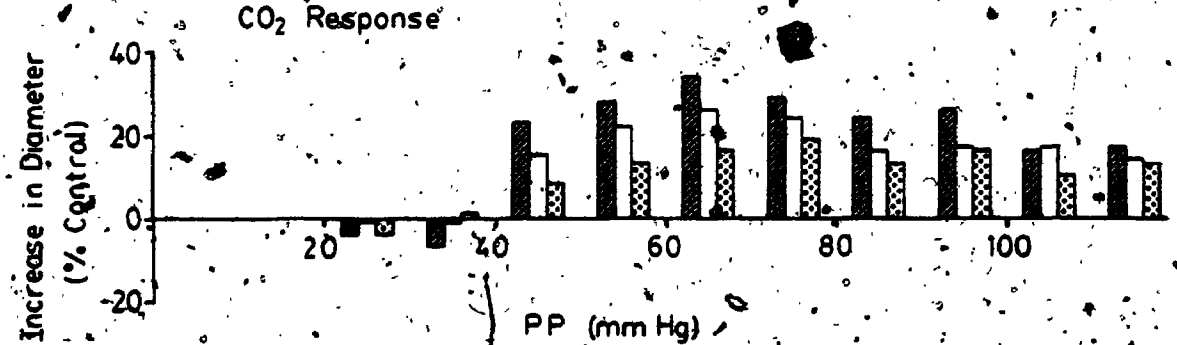
The $CO_2$ response of the pial vessels (ie. the additional increase in caliber produced by hypercapnia) was dependent on the PP. As PP was reduced from normotension to 65 mm Hg, there was an increase in the $CO_2$ response which was most pronounced in the smallest vessels. In the 65-45 mm Hg

Figure 12

This diagram displays the pial vessel diameter responses to hemorrhagic hypotension at both normocapnia and hypercapnia in the upper and mid panels, respectively. The $CO_2$ response at each PP level is shown in the lower panel. The symbol † indicates that the difference between the mean diameter at normocapnia and hypercapnia is not significant.


Normocapnia
Vessel Sizes
< 50 µm
50-90 µm
> 90 µm
Diameter (% Control)
180
160
140
120
100
80
20
40
60
80
100
PP (mm Hg)


Hypercapnia
Diameter (% Control)
180
160
140
120
100
20
40
60
80
100
PP (mm Hg)


$CO_2$ Response
Increase in Diameter (% Control)
40
20
0
-20
20
40
60
80
100
PP (mm Hg)

pressure range, the $CO_2$ response decreased and it was abolished at a PP of 35 mm Hg.

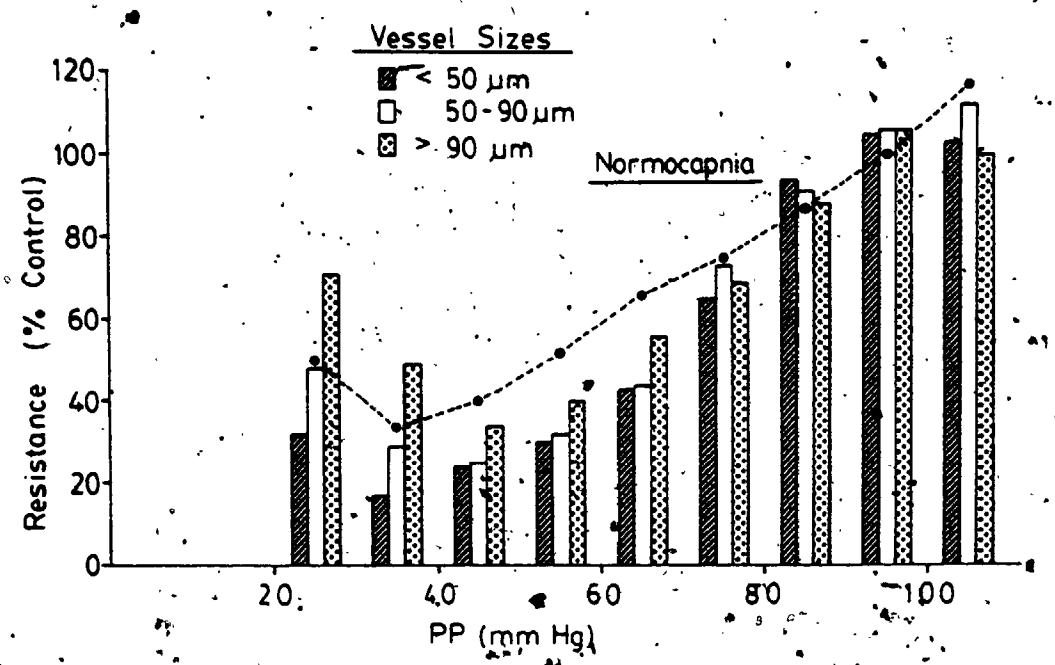
3.3 Vascular Resistance

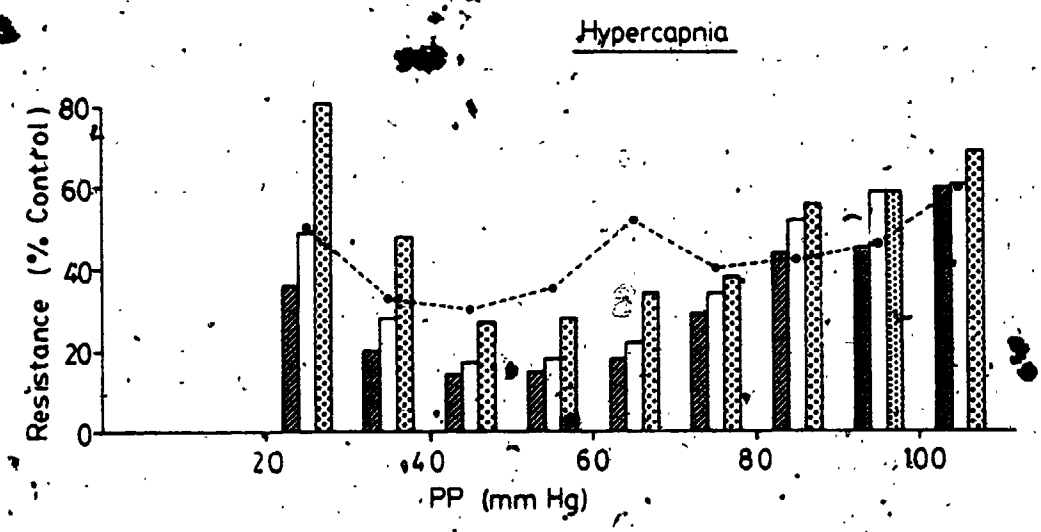
The changes in pial vascular resistance observed during hemorrhagic hypotension are compared to those of total precapillary resistance (PCR) in Figure 13. Under normocapnic conditions the reductions in the resistance of the pial vessels equalled or exceeded the corresponding decreases in total PCR at all perfusion pressures greater than 35 mm Hg (that is, throughout the autoregulatory pressure range). The autoregulatory responses of the pial vessels were size-dependent. As PP was reduced to 45 mm Hg, the decrease in the resistance of the large vessels was proportionately less than that of the smaller vessels. As pressure was reduced further to 35 mm Hg, the resistance of the large and intermediate sized vessels increased. Only the smallest vessels showed a continued autoregulatory decrease in resistance in this range corresponding to the continued decline in total PCR.

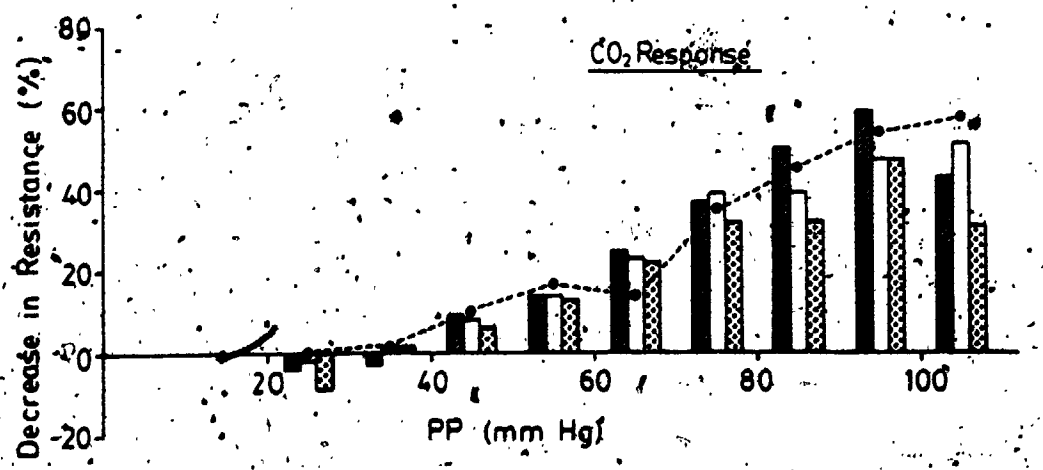
A comparison of total PCR and pial vascular resistance changes during hypercapnia are also included in the Figure. At normotension, all resistances were reduced by an increase in arterial $P_aCO_2$; however, the total PCR decreased to a level similar or slightly less than the resistance of the pial vessels. As the PP was reduced to 35 mm Hg, the pial vascular resistance was decreased (in small vessels more than large) whereas the decline in total PCR was less pro-

Figure 13

This diagram presents the reductions in pial vascular resistance and in total precapillary resistance (--●--) observed during hemorrhagic hypotension. Shown are the resistances at normocapnia (top panel), at hypercapnia (mid panel) and the $CO_2$ responses (lower panel).


Vessel Sizes
< 50 µm
50-90 µm
> 90 µm
Normocapnia
Resistance (% Control)
120
100
80
60
40
20
0
20
40
60
80
100
PP (mm Hg)


Hypercapnia
Resistance (% Control)
80
60
40
20
0
20
40
60
80
100
PP (mm Hg)


$CO_2$ Response
Decrease in Resistance (%)
80
60
40
20
0
-20
20
40
60
80
100
PP (mm Hg)

nounced. Reductions in pial vascular resistance exceeded those of total PCR at PP between 35 and 85 mm Hg. At PP less than 45 mm Hg there was an increase in pial vascular resistance equivalent to that of total PCR.

The additional reductions in resistance produced by hypercapnia ($CO_2$ responses) show that throughout the entire pressure range, the relative decrease in total PCR corresponded very closely with the mean change in pial vascular resistance. At pressures above 75 mm Hg, the $CO_2$ responses were size dependent. However, the reductions in resistance were similar for all vessel groups at pressures below 75 mm Hg.

## 4. Discussion

### 4.1 Methods

#### 4.1.1 Cerebral Blood Flow

The method used to sharpen the platinum electrodes was an important determinant of the reproducibility and reliability of the hydrogen clearance technique. In a recent study, MacKenzie et al.(1979) examined the effects of hemorrhagic hypotension on the cerebral circulation and CBF was measured using platinum electrodes which were sharpened by hand. The flow measurements they obtained using these electrodes showed a relatively high degree of scatter and frequently demonstrated a low proportion of fast-clearing tissue. In addition, "zero flow" or extremely slow hydrogen clearance was observed in approximately 50% of the elec-

trodes at mean arterial pressures ranging from 18 to 59 mm Hg. Although care was taken to avoid compression of the cortex by the electrode flange, the possibility remains that the irregular edges produced by hand-sharpening may have caught on the tissue during insertion and distorted the cortex surrounding the electrode tip. In the present study, the platinum wire was sharpened electrochemically thus producing a very smooth taper and a relatively sharp tip. These electrodes could be inserted directly through the meninges and into the cortex without significant tissue distortion. The flow measurements were much more stable than those obtained using hand-sharpened electrodes (the coefficient of variation of repeated measurements was 7.2% over a 90 minute period) and the average $W_f$ was 60±2%. "Zero flow" was observed in only one electrode (at a PP of 13 mm Hg) out of a total of 69 flow measurements in the 10-19 mm Hg pressure range. Thus, the high degree of scatter, low $W_f$ and frequent occurrence of "zero flow" observed in previous studies are considered to be the result of cortical trauma or compression rather than physiological variability. These difficulties can be minimized or eliminated by careful preparation and insertion of the platinum electrodes.

4.1.2 Pial Vessel Caliber

Recent reports by Navari et al. (1978) and Kuschinsky and Wahl (1980) have indicated that the thickness of the oil layer covering the cortical surface in an open skull preparation is extremely important. Navari et al. found that the

cerebrospinal fluid surrounding the pial vessels became alkalotic within approximately 10 minutes if the vessels were covered with only a thin layer of mineral oil. This resulted in significant alterations in pial vascular reactivity. However, Kuschinsky and Wahl subsequently showed that if the layer of oil is 1 cm or more thick (as in the present study), this alkalosis does not occur.

## 4.2 Measurements at Resting Pressures

### 4.2.1 Cerebral Blood Flow

The control values for the fast and slow components of flow (159±5 and 35±1 ml/100gm/min) obtained in the present study are in close agreement with those measured in the unanesthetized rabbit by deVaIois et al (1975) using the $^{133}Xe$ clearance method (154 and 34 ml/100gm/min, respectively). Similar fast flow values were obtained by Gregory et al. (1977) in chloralose-urethane anesthetized rabbits. The CBF responses to hypercapnia in the present study (2.5, 1.7 and 0.6 ml/100gm/min/mm Hg $P_aCO_2$ for the ISI, fast and slow flow components, respectively) compare closely to those obtained in baboons by Symon et al. (1973,1974). The corresponding $CO_2$ reactivities calculated from their data were approximately 2.3, 1.9 and 0.7 ml/100gm/min/mm Hg $P_aCO_2$.

### 4.2.2 Pial Vessel Caliber

In agreement with previous investigations, I found that the increases in pial vessel caliber induced by hypercapnia were size-dependent (Gregory et al, 1980; Wei et al, 1980).

The $CO_2$ responses decreased with increasing vessel size (1.13, 0.90 and 0.71 %/mm Hg $P_aCO_2$ for groups I, II and III, respectively). These values are similar to those obtained by others in cats (Gregory et al, 1980; Wei et al, 1980). Levasseur et al (1979) reported a significantly higher $CO_2$ reactivity of approximately 2.3%/mm Hg $P_aCO_2$ for 40 μm pial arterioles in awake rabbits. The reason for this discrepancy is uncertain. It is possible that the urethane anesthesia used in my experiments may have depressed the $CO_2$ responses; however, the fact that there was no apparent effect on the resting flow levels or on the CBF response to hypercapnia would argue against this explanation. Alternatively, it may be that the responses measured by Levasseur and colleagues were obtained at a lower PP than those of the present study. The $CO_2$ reactivity for Group I vessels increased to approx. 1.7%/mm Hg $P_aCO_2$ at a PP of 65 mm Hg (see Section 3.2.2).

## 4.3 Responses during Hemorrhagic Hypotension

### 4.3.1 The Lower Limit of Autoregulation

Although other investigators have considered autoregulation to be an "on" or "off" phenomenon, this was not an accurate representation of the pressure-flow relationship in the present study. The pressure at which CBF began to decrease (approx. 65 mm Hg) - traditionally termed the lower limit of autoregulation - represented the transition to a region of incomplete autoregulation in which flow decreased considerably less than the corresponding reductions in PP.

The true lower limit of autoregulation occurred at a PP of 35 mm Hg and was associated with pressure passive reductions in CBF. Differences between the autoregulatory responses obtained in the present series and those reported in the literature are likely related to factors such as the reproducibility of CBF measurements, the number of flow determinations and alterations in the dilative reserve as a result of the particular experimental condition (see Chapters V and VI).

4.3.2 Pial Vessel Dilation

A reduction in PP to 35 mm Hg resulted in a progressive dilation of the pial vessels similar to that observed in other studies (Kontos et al, 1978; MacKenzie et al, 1979). However, in addition to confirming that the intensity of autoregulatory dilation is dependent on vessel size, the present results have shown that large arteries attain their maximum caliber at a higher pressure than small pial arteries. As discussed in Chapter V, this may be related to neurogenic influences.

MacKenzie et al. had found a discrepancy between the lower limit of autoregulation and maximal dilation of the pial vessels. In the present study, CBF autoregulation (although incomplete), continued to a PP of approximately 35 mm Hg, thereby demonstrating a qualitative correspondence between pial vessel and CBF responses. Once the pial vessels were unresponsive to additional pressure reductions (ie. they were maximally dilated), both CBF and pial vessel

caliber responses were pressure dependent.

4.3.3 The Dilative Reserve

The responses of the cerebrovasculature to hypercapnia provided information on the ability of the cerebrovasculature to dilate further following a reduction in PP. The present results confirm that there is a reduction in the CBF response in moderate hypotension and an abolishment of the $CO_2$ response in profound hypotension (Harper and Glass, 1965; Okuda et al., 1976; Gregory et al., 1981). However, in previous studies the relationship between the lower limit of autoregulation, CBF responsiveness to hypercapnia and pial vessel $CO_2$ reactivity were not well defined. Ekstrom-Jodal et al. (1970) found that there was a CBF $CO_2$ response below the "lower limit of autoregulation" but the present results suggest that this reactivity to $CO_2$ occurred in the region of incomplete autoregulation. Wei et al.(1980) found a variation in the pial vessel responsiveness to hypercapnia during hypotension similar to that in the present study; however, CBF was not measured. The combined CBF and pial vessel responses obtained presently demonstrated that there is a close correspondence between CBF autoregulation and the ability of the cerebrovasculature to respond further to hypercapnia.

Within the region of complete autoregulation (PP > 65 mm Hg), the $CO_2$ response of the pial vessels increased with decreasing PP such that the CBF response to hypercapnia was nearly constant. In the region of incomplete autoregulation

(PP=65-55 mm Hg), the CBF and pial vessel response to hypercapnia diminished with decreasing PP and at a PP of 35 mm Hg they were abolished. In the pressure passive region (below the lower limit of autoregulation [ie. 35 mm Hg]), both CBF and the pial vessels were unresponsive to hypercapnia. These results indicate that a functionally intact dilative reserve was associated with a region of complete autoregulation, a progressive decline in the dilative reserve was coupled with a partial autoregulation of CBF and a total loss of this reserve accompanied the onset of pressure-passive flow reductions.

4.4 Changes in Vascular Resistance

The net change in total precapillary resistance (PCR) is determined by the sum of the resistance changes occurring in the various vascular components connected in series (ie. inflow arteries, large and small pial vessels and intraparenchymal arterioles) and the manner in which each component contributes to this change may be assessed by comparing the response (%control) of an individual vessel group to the percentage change in total PCR (see Appendix 1). The autoregulatory responses of the large cerebral arteries may be estimated from data available in the literature. Du Boulay et al (1972) found that the large inflow arteries of baboons decreased in size (ie. resistance increased) when MABP was reduced by "29 mm Hg or more". Kontos et al. (1978) found that inflow artery resistance remained relatively constant during MABP reductions in cats. Their data also showed that

although the large pial arteries (268-384 μm in diameter) were responsive to changes in MABP at relatively high pressures ( > 100 mm Hg), they dilated by only 5% at pressures below this level (ie. an 18% decrease in resistance). Thus it is clear that the autoregulatory responses of the inflow and large pial arteries are extremely limited (when compared to the 65-70% decrease in total PCR seen in the present study) and that the smaller distal arterioles must undergo a pronounced autoregulatory dilation in order to compensate for these lesser responses. This was confirmed by the finding that the autoregulatory reductions in the resistance of the small pial vessels ( < 170 μm in diameter) exceeded the decreases in total PCR at pressures between 35 and 85 mm Hg. The transition from limited to pronounced autoregulatory dilation appears to occur within pial vessels 170-260 μm in diameter.

The responses of the intraparenchymal vasculature cannot be measured directly. However, in view of the marked size-dependence of cerebrovascular autoregulatory behavior, one would postulate that alterations in intraparenchymal vascular resistance would correspond most closely to those of the small pial arterioles of comparable diameter. In support of this statement, I found that only the smallest pial arterioles showed a continued autoregulatory decline in resistance as pressure was reduced from 45 to 35 mm Hg. Total PCR also decreased in this pressure range suggesting that the intraparenchymal vessels had continued to dilate in

parallel with the small pial arterioles. In addition, the close agreement between the changes in pial vascular resistance and total PCR during hypercapnia would argue against any major difference in the response of the intraparenchymal vasculature to this stimulus.

## 5. Summary and Conclusions

(1). During hemorrhagic hypotension, there are three autoregulatory regions: a region of complete autoregulation (at PP > 65 mm Hg); a region of incomplete autoregulation (at PP of 65-35 mm Hg); and a pressure-passive region (at PP < 35 mm Hg).

(2). The onset of flow reductions represented a transition to a region in which there was a gradual decline in CBF. Reductions in flow were proportionately less than reductions in PP due to a continued dilation of the small cerebral vessels. The lower limit of autoregulation was associated with a maximal dilation of these vessels.

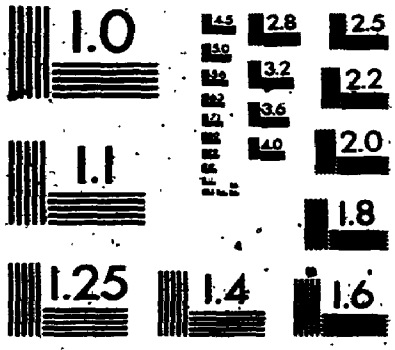
(3). The autoregulatory response is directly related to the residual dilative reserve as measured by the ability of the pial vessels and CBF to respond to a superimposed dilative stimulus. The dilative reserve was not appreciably altered in the region of intact autoregulation; was diminished in the region of incomplete autoregulation; and was completely depleted at a PP of 35 mm Hg - the lower limit of autoregulation.

lation.

(4). The loss of a responsiveness of the cerebrovasculature to hypercapnia is related to a depletion of the dilative reserve by autoregulatory dilation.

(5). Reductions in pial vascular resistance exceeded that of total precapillary resistance at PP between 85-35 mm Hg. Thus the pronounced autoregulatory responses of the small cerebral vessels compensate for the more limited responses of the proximal cerebral arteries.

(6). The decrease in pial vascular resistance evoked by hypercapnia corresponded closely to the reductions in total precapillary resistance at most PP levels. This observation and the preceding conclusion suggest that pial vessel responses were similar to those of the intraparenchymal vessels and were representative of changes in total CVR.


1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0

## V EFFECT OF ALPHA-ADRENORECEPTOR BLOCKADE

### 1. Introduction

Denervation of the sympathetic nervous system has been shown to alter the autoregulatory response of the cerebrovasculature during hemorrhagic hypotension. Fitch et al. (1975) found that CBF began to decrease at a pressure of approximately 65 mm Hg in control baboons subjected to hemorrhagic hypotension. However, in animals pretreated with acute cervical sympathectomy or alpha-adrenergic blockade flow remained at control levels to a pressure of approximately 35 mm Hg. Kovach et al. (1975) also found that the pressure range in which flow remained at control levels during hemorrhage was extended following alpha blockade. Fitch and colleagues concluded that the marked sympathoadrenal discharge which accompanies hemorrhage interferes with autoregulation at low pressures. In accordance with the dual effects hypothesis (Harper et al., 1972), they suggested that hemorrhage had resulted in a sympathetic vasoconstriction of the extraparenchymal vessels and a compensatory dilation of the intraparenchymal vessels which then exhausted the cerebrovascular autoregulatory capacity at a higher pressure in the untreated animals (ie. the dilative reserve was reduced). This ability of the sympathetic nervous system to alter the dilative reserve is supported by several other studies which have demonstrated that following alpha-adrenergic blockade there is a slight increase in

either the CBF $CO_2$ response or the reactivity of large pial arteries to hypercapnia (Kawamura et al., 1974; Wei et al., 1980).

The results of the preceeding group of experiments (Ch. IV) suggest additional ways in which the sympathetic nervous system may have influenced the cerebral circulation during hemorrhage. At PP between 65 and 35 mm Hg, the $CO_2$ response decreased and autoregulation was incomplete (ie. CBF declined). Thus, the sympathetic activation associated with hemorrhage did not appear to have substantially altered the autoregulatory range, rather it seemingly restricted the cerebrovascular autoregulatory response and reduced the dilative reserve at intermediate PP levels. If so, the explanation proposed by Fitch et al. (1975) and the dual effects hypothesis would require some revision (eg. both large and small vessels could be influenced by the sympathetic nervous system). Sympathetic activation during hemorrhage may also have contributed to the differential responsiveness of the pial vessels. Stimulation of the cervical sympathetic ganglion is known to constrict large pial vessels more than small ones. Thus, the size dependence of the autoregulatory dilation observed during hemorrhage may be related to an increasing influence of the sympathetic nervous system with increasing vessel size.

Although alpha-blockade is expected to increase the dilative reserve during hemorrhage, this has not been confirmed experimentally since the effects of sympathetic

denervation on the cerebrovascular $CO_2$ responses during hypotension, are unknown. In addition, the manner in which the pial vessels are affected has not been investigated systematically. A comparison of the responsiveness of the cerebral circulation in animals treated with an alpha adrenoreceptor blocking agent to those in the preceeding control group should indicate the extent to which the sympathetic nervous system infuences CBF and pial vessel responses during hemorrhage.

The specific objectives of the present group of experiments was to:

(1). investigate the effects of alpha-adrenoreceptor blockade on both the CBF and pial vessel responses to hemorrhagic hypotension in the rabbit.

(2). determine the effects of alpha- adrenoreceptor blockade on the dilative reserve (ie. the cerebrovascular responses to hypercapnia) during hemorrhagic hypotension.

## 2. Methods

### 2.1 Animal Preparation

Rabbits were prepared for the measurement of CBF (13 rabbits), pial vessel caliber (7 rabbits) or both CBF and pial vessel caliber (4 rabbits) using the procedures des-

cribed in Chapter III. The effects of phenoxybenzamine(PBZ) on the cerebral metabolic rate of oxygen consumption ($CMRO_2$). were investigated in an additional 3 rabbits. In this latter group of animals, three small burr holes were made over the cortex and electrodes were inserted into the brain for the measurement of CBF. A small craniectomy was made over the superior sagital sinus and the tip of a 23 gauge needle was positioned (using a microdrive) within the sinus for the withdrawal of cortical venous blood. Each determination of $CMRO_2$ required the measurement of CBF and the sampling of blood from both the sagital sinus and from a femoral catheter positioned in the aorta. Arterial and venous blood samples were analyzed for hemoglobin, $O_2$ saturation and $PO_2$ in order to determine their $O_2$ contents. $CMRO_2$ was calculated as CBF times the cerebral arteriovenous oxygen content differences.

2.2 Protocol

Several measurements were made under resting conditions and their average served as the control. Phenoxybenzamine hydrochloride (Dibenzyline; Smith,Kline and French Laboratories) stored as a 1% solution was diluted (x10) in saline and infused intravenously (1.5 mg/kg). The animal was allowed to stabilize for at least 20 minutes following the infusion of PBZ.

PBZ infusion reduced the MABP by 35±3 mm Hg. A measurement of CBF or pial vessel caliber was made at normocapnia and then MABP was raised to pre-infusion pressure

levels. Angiotensin II amide (Hypertensin-CIBA) was infused intravenously in a concentration of 0.025 mg/ml in saline at the rate required to increase PP to normal (.15-1.0 ml/min). Angiotensin has been found to have no effect on CBF if the blood brain barrier is intact (Pickard et al., 1977). At least 5 minutes were allowed for the preparation to stabilize prior to measurements at normocapnia and hypercapnia. The PP was reduced in 10-20 mm Hg steps: initially by decreasing the rate of angiotensin infusion; and subsequently by inducing hemorrhage. With the above exceptions, the experimental protocol was identical to that described in Ch. III-Sect.4. Measurements were made at each PP level and the responses were organized into 10 mm Hg PP ranges.

## 3. Results

### 3.1 CBF

The results from rabbits with both CBF and pial vessel data were identical to those in which only CBF or pial vessel caliber were measured and therefore they have been included in the appropriate sections. Satisfactory clearance curves were obtained from 52 of 66 elecrodes. CBF (ISI) was 102±7 ml/100gm/min under resting conditions (MABP=92±2 mm Hg, PP=82±2 mm Hg, $P_aCO_2$=40.3±0.3 mm Hg) and these values are similar to those obtained in control animals. Treatment with phenoxybenzamine caused a 38% reduction in MABP to 57±3 mm Hg and a 32% decrease in CBF to 68±4 ml/100gm/min. As shown in Table 3, $CMRO_2$ also decreased by approximately 2[illegible]%.

TABLE 3

Effect of Phenoxybenzamine on $CMRO_2$

| Condition | Animal number | n* | $O_2$ content[x] (ave.) A | V | CBF[t] (ave.) | $CMRO_2$[t] (ave.) |
|---|---|---|---|---|---|---|
| Pre-PBZ | 1 | 2 | 15.0 | 9.4 | 74 | 4.2 |
| (control) | 2 | 2 | 13.9 | 9.0 | 148 | 7.2 |
| | 3 | 2 | 18.1 | 12.7 | 125 | 6.8 |
| Post-PBZ | 1 | 4 | 14.3 | 7.1 | 45 | 3.2 (76%) |
| | 2 | 5 | 12.4 | 7.0 | 96 | 5.2 (72%) |
| | 3 | 4 | 17.1 | 8.5 | 63 | 5.4 (79%) |

* number of $CMRO_2$ measurements, [x] ml/dl, [t] ml/100gm/min

The CBF responses during PP alterations are presented as a percentage of their pre-treatment control in Figure 14. At normocapnia, there was an autoregulation of CBF at a reduced flow rate (approx. 70% of control) over the 85-35 mm Hg PP range. At PP less than 35 mm Hg there were marked decreases in CBF. Under hypercapnic conditions, CBF increased to between 100 and 120% of control in the upper pressure range (45-85 mmHg). At PP less than 45 mm Hg, decreases in PP resulted in reductions in CBF. The additional increases in CBF evoked by hypercapnia were approximately 30-40% control at PP between 45-85 mm Hg. The $CO_2$ response at 35 mm Hg was reduced substantially to 10% and at PP less than 35 mm Hg $CO_2$ reactivity was abolished.

3.2 Pial Vessel Caliber

The 57 pial vessels (26-195 μm) examined under resting conditions (MABP=93±3 mm Hg and $P_aCO_2$=39.7±0.4 mm Hg) had mean diameters in Groups I,II, and III of 38±2 μm (n=22), 63±2 μm (n=16) and 118±7 μm (n=19) respectively. These were similar to the resting calibers of the control animals.

The responses of the pial vessels to reductions in PP are shown in Figure 15. Under normocapnic conditions, decreases in PP between 85-35 mm Hg resulted in a progressive dilation of all vessels. The intensity of the response was dependent on vessel size. Group I vessels dilated to 163±10%, Group II to 142±4% and Group III to 129±4% of their control values. All groups achieved their maximal dilation

Figure 14

The CBF responses following phenoxybenzamine infusion are presented in this diagram. Shown are CBF at normocapnia, at hypercapnia and the CBF $CO_2$ response during hypotension. The symbol + indicates that the difference between CBF at normocapnia and hypercapnia is not statistically significant.

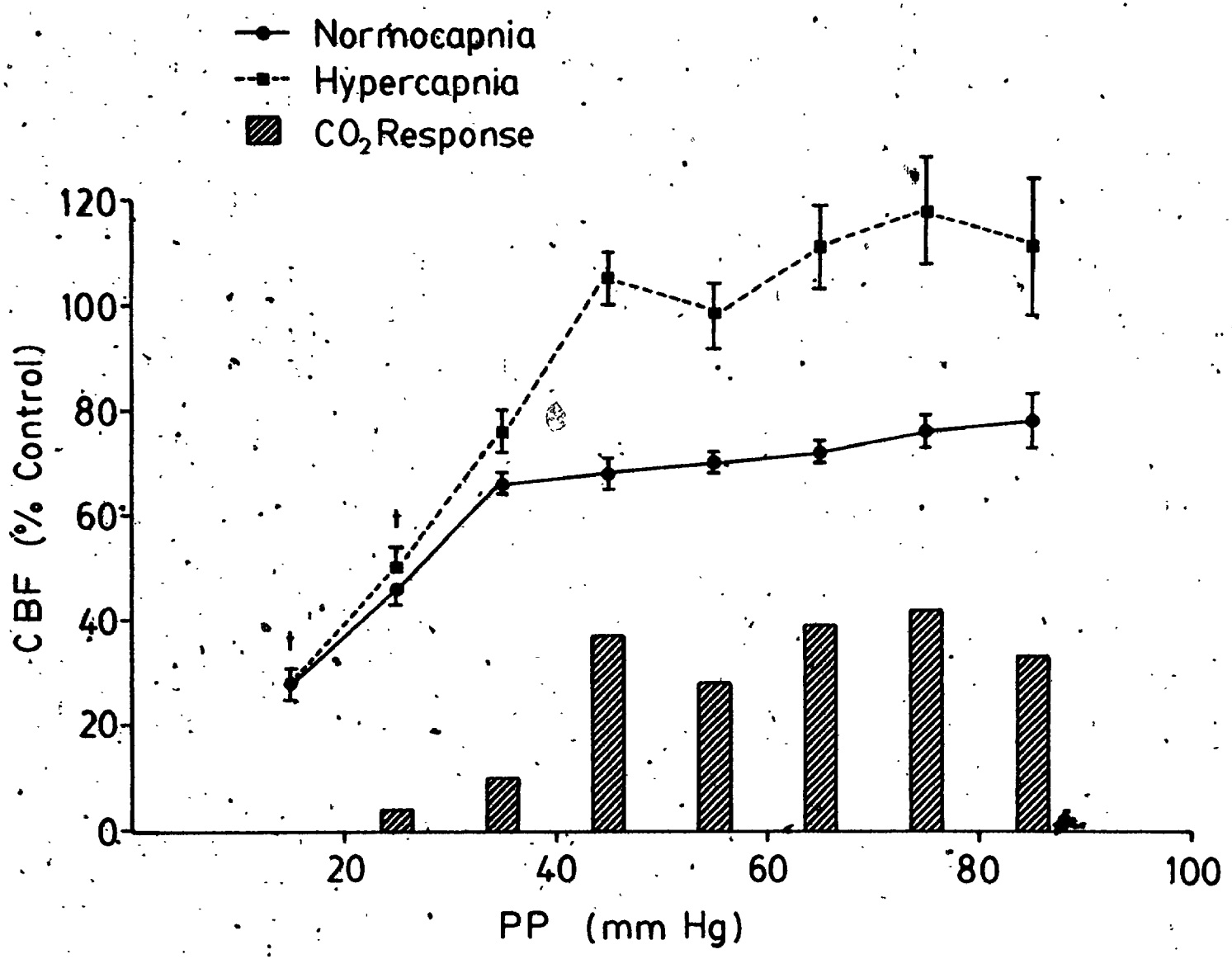
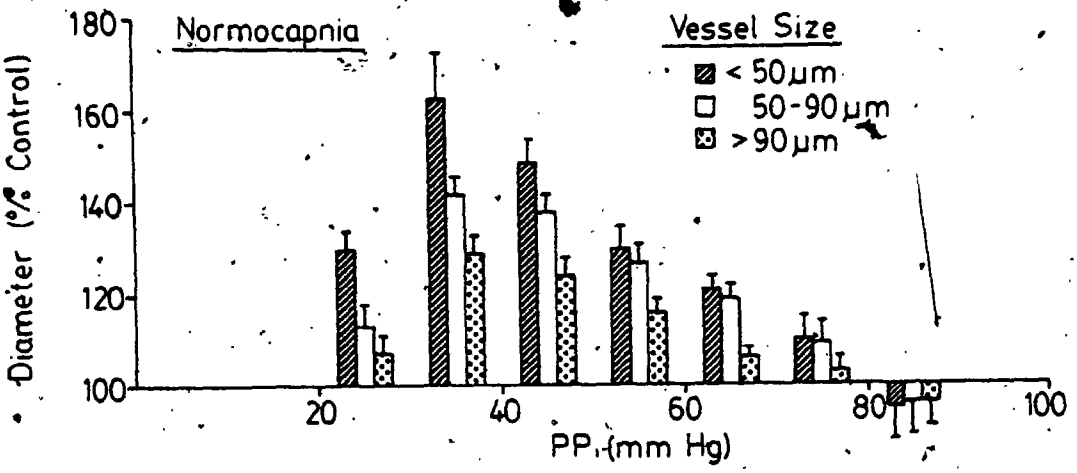
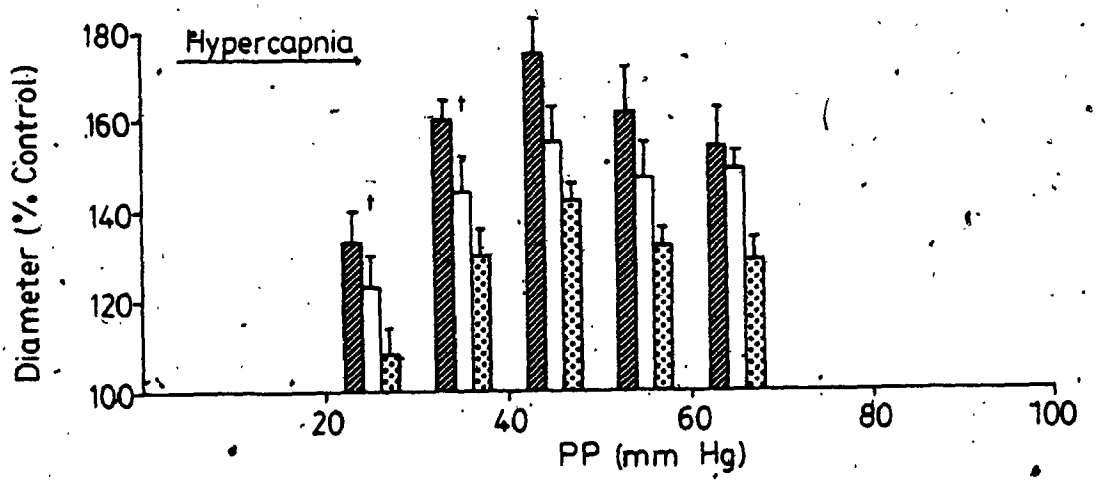
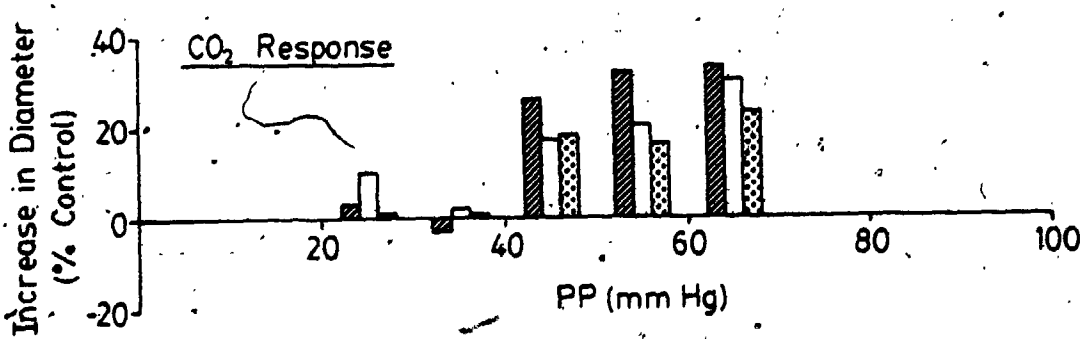

Normocapnia
Hypercapnia
$CO_2$ Response
CBF (% Control)
120
100
80
60
40
20
0
20
40
60
80
100
PP (mm Hg)

Figure 15

This diagram presents the pial vessel caliber data obtained following phenoxybenzamine treatment. Shown are the vessel responses to hemorrhagic hypotension at normocapnia, at hypercapnia and the $CO_2$ responses. The symbol + indicates that the difference in caliber at normocapnia and hypercapnia is not statistically significant.


Normocapnia
Vessel Size
< 50µm
50-90µm
>90µm
Diameter (% Control)
180
160
140
120
100
20
40
60
80
100
PP (mm Hg)


Hypercapnia
Diameter (% Control)
180
160
140
120
100
20
40
60
80
100
PP (mm Hg)


$CO_2$ Response
Increase in Diameter (% Control)
40
20
0
-20
20
40
60
80
100
PP (mm Hg)

at a PP of 35 mm Hg. At pressures less than 35 mm Hg, vessel diameters decreased pressure passively.

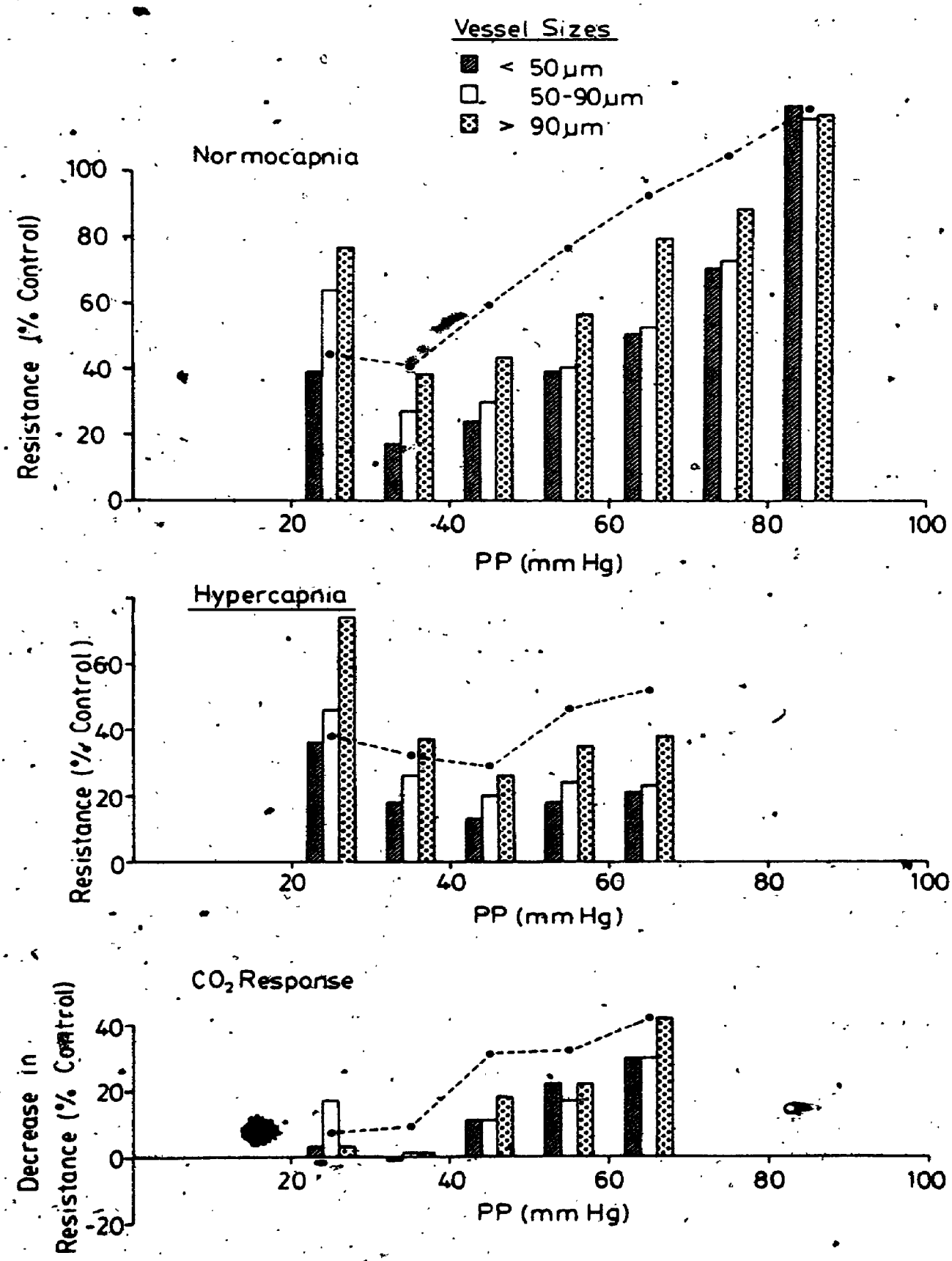
The vessels dilated in response to hypercapnia at all pressure levels above 35 mm Hg. The pial vessel responses to hypercapnia were obtained predominantly at PP levels less than 75 mm Hg as the development of either brain swelling or a tachyphylaxis to angiotensin made it technically difficult to obtain measurements at higher pressures. Under hypercapnic conditions, the calibers of the vessels gradually increased as PP was reduced between 65 and 45 mm Hg. At the 45 mm Hg PP level the vessels achieved a maximum dilation of 175±8% for Group I, 155±8% for Group II and 142±4% for Group III vessels. At pressures less than 45 mm Hg vessel calibers decreased pressure passively. The $CO_2$ response evoked at PP > 35 mm Hg was relatively independent of PP over the range of pressures examined. The magnitude of the $CO_2$ response varied from approximately 20% for Group III vessels to 30% for Group I vessels. At PP of less than 45 mm Hg the $CO_2$ response was abolished.

### 3.3 Vascular Resistance

The changes in resistance corresponding to the pial vessel and CBF responses obtained in the treated animals are shown in Figure 16. At normocapnia, autoregulatory reductions in both pial vascular resistance and total precapillary resistance (PCR) were observed over the 85-35 mm Hg pressure range and vascular resistances increased at PP less than 35 mm Hg. The resistance decreases of Group III ves-

Figure 16

This figure shows the changes in pial vascular resistance and the alterations in total precapillary resistance (--●--) obtained following phenoxybenzamine infusion. Presented are the resistance reductions in response to hypotension at both normocapnia and hypercapnia. The additional decreases in resistance resulting from hypercapnia are included in the lowest panel.


Vessel Sizes
< 50µm
50-90µm
> 90µm
Normocapnia
Resistance (% Control)
100
80
60
40
20
0
20
40
60
80
100
PP (mm Hg)
Hypercapnia
Resistance (% Control)
60
40
20
0
20
40
60
80
100
PP (mm Hg)
CO2 Response
Decrease in Resistance (% Control)
40
20
0
-20
20
40
60
80
100
PP (mm Hg)

sels were less pronounced than those of Group I. At PP between 75-35 mm Hg the reduction in total PCR was approximately 20% less than that of pial vascular resistance. During hypercapnia, the resistances of the pial and precapillary vessels decreased over the PP range 45-65 mm Hg and increased at PP less than 45 mm Hg. All resistances exhibited a $CO_2$ response (a reduction in response to hypercapnia) at PP greater than 35 mm Hg and the change in total PCR surpassed that of pial vascular resistance by approximately 10% in this pressure region.

3.4 Comparison with Control Responses

The variation of CBF with PP in the PBZ treated animals as compared to that of control animals in Figure 17. CBF following alpha-receptor blockade was less than that of the control series at all PP levels greater than 35 mm Hg under normocapnic conditions and at PP levels greater than 65 mm Hg under hypercapnic conditions. The $CO_2$ response in the treated group was greater than that of controls at pressures less than 75 mm Hg. A least squares regression analysis was performed on the flow values obtained at PP of 30-69 mm Hg in the control series (the region of incomplete autoregulation) and at PP between 30-89 mm Hg in the PBZ series. The rate of decline in CBF in the control group (0.7±0.1%/mm Hg) was significantly greater ($p < 0.02$) than that of the PBZ group (0.2±0.1%/mm Hg).

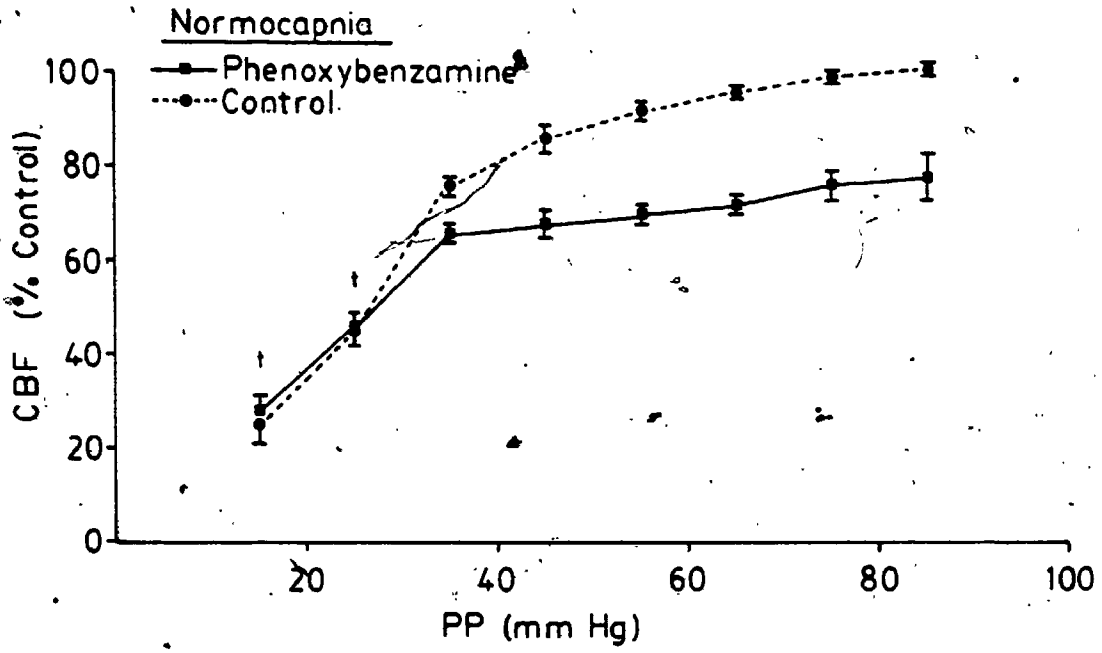
The responses of the pial vessels in groups I, II and III (PBZ treated) are compared to those of controls in Fig-

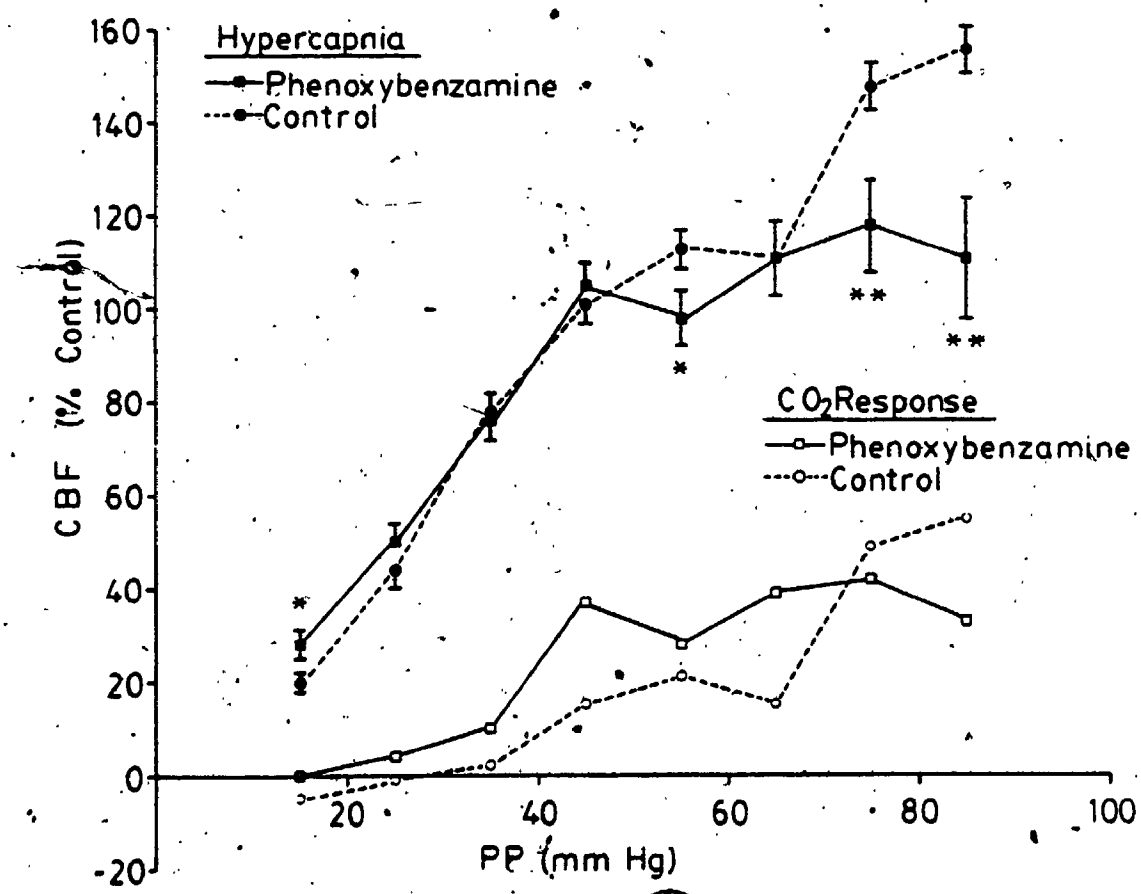
Figure 17

These graphs compare the CBF responses obtained following phenoxybenzamine treatment with the corresponding responses of the control group. Shown are CBF at normocapnia, at hypercapnia and the $CO_2$ response.

* - $p < 0.05$, statistically different from control

** - $p < 0.01$, statistically different from control


Normocapnia
Phenoxybenzamine
Control
CBF (% Control)
PP (mm Hg)


Hypercapnia
Phenoxybenzamine
Control
CBF (% Control)
PP (mm Hg)
$CO_2$ Response
Phenoxybenzamine
Control

ures 18, 19 and 20, respectively. The calibers measured during hypercapnia and the $CO_2$ responses obtained were similar in the two experimental series. In comparison to controls, autoregulatory responses of vessels in the PBZ series were depressed at PP levels of 45-85 mm Hg. This difference reached statistical significance only in the Group III vessels. As PP was reduced from 45 to 35 mm Hg, the large pial vessels (Groups II and III) continued to dilate whereas these vessels had decreased in caliber in the control series.

## 4. Discussion

### 4.1 Direct Effects of Phenoxybenzamine

PBZ infusion in the rabbit reduced MABP by 35 mm Hg (38%), CBF by 32% and $CMRO_2$ by 24%. Previous studies in the cat, dog and primate have reported similar MABP decreases of 23-35 mm Hg (21-34%) following PBZ treatment (Hernandez-Perez et al., 1975; Kawamura et al., 1974; James and MacDonnell, 1975; Fitch et al., 1975; Davis and Sundt, 1980). Several investigators examining the cerebrovascular effects of phenoxybenzamine have also found reductions in flow or metabolism. James and MacDonnell (1975) [in dogs] and Davis and Sundt (1980) [in cats] have shown that CBF is decreased by 13% and 22%, respectively. James and MacDonnell also found that cortical $O_2$ consumption following PBZ treatment was reduced in one out of four dogs. Meyer et al. (1974) demonstrated that intracarotid injection of PBZ in man

Figure 18

Comparison of the Group I ( $< 50$ μm) vessel responses following phenoxybenzamine infusion with the corresponding responses of the control group.

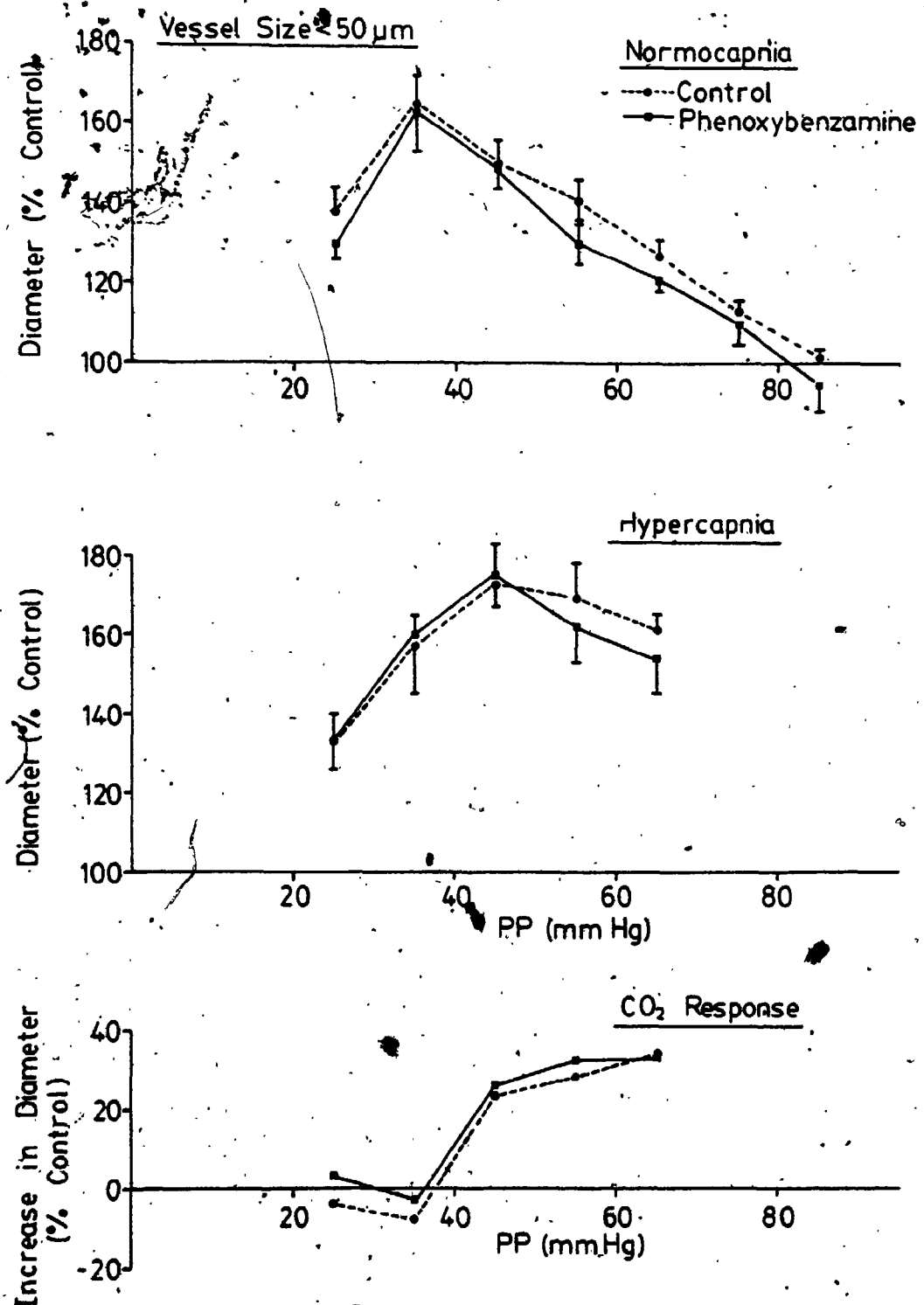

Vessel Size ≤ 50 µm
Normocapnia
Control
Phenoxybenzamine
Diameter (% Control)
180
160
140
120
100
20
40
60
80
Hypercapnia
Diameter (% Control)
180
160
140
120
100
20
40
60
80
PP (mm Hg)
CO2 Response
Increase in Diameter (% Control)
40
20
0
-20
20
40
60
80
PP (mm Hg)

Figure 19

Comparison of the Group II (50-90 μm) vessel responses of the phenoxybenzamine treated group with the corresponding responses of the control group.

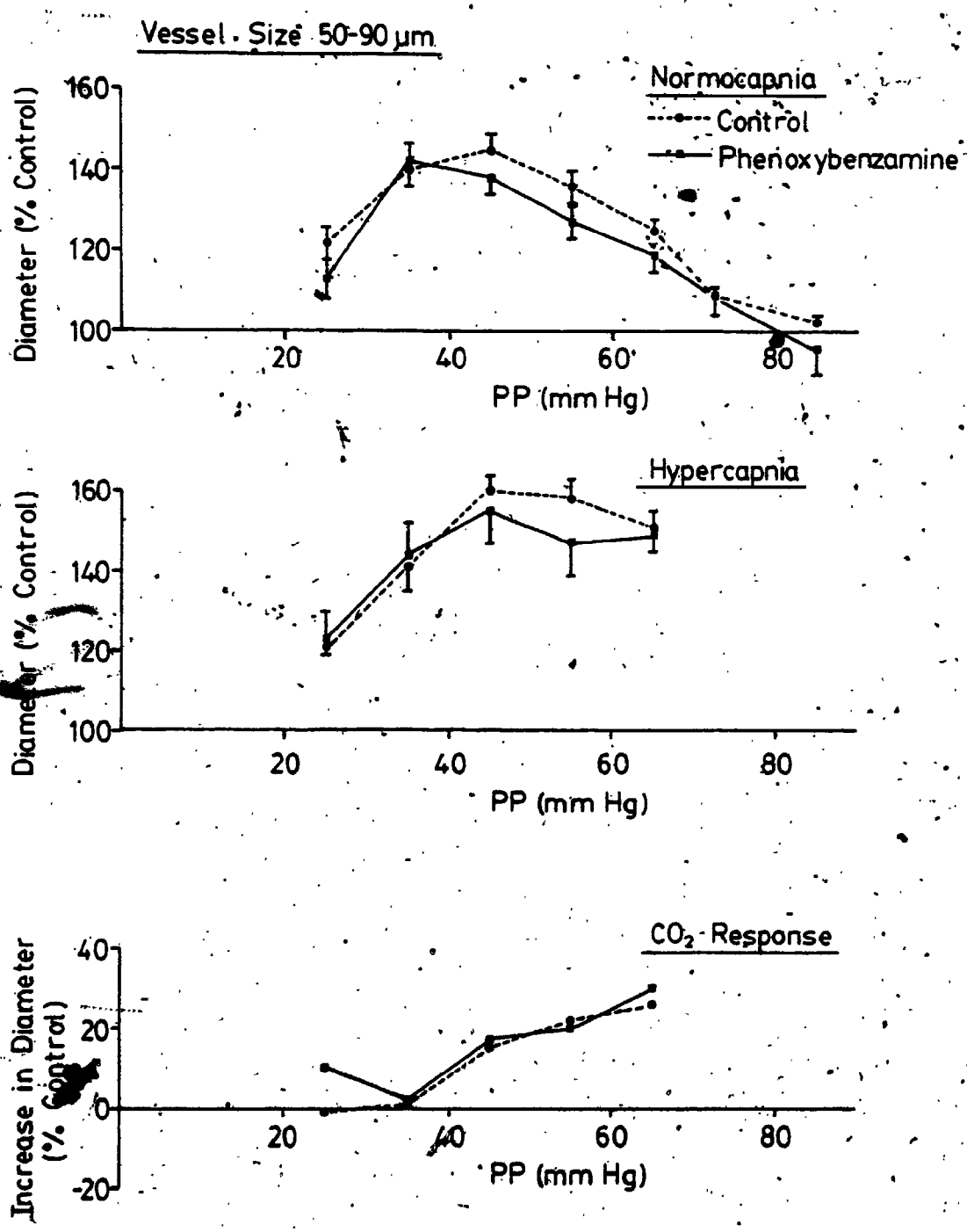
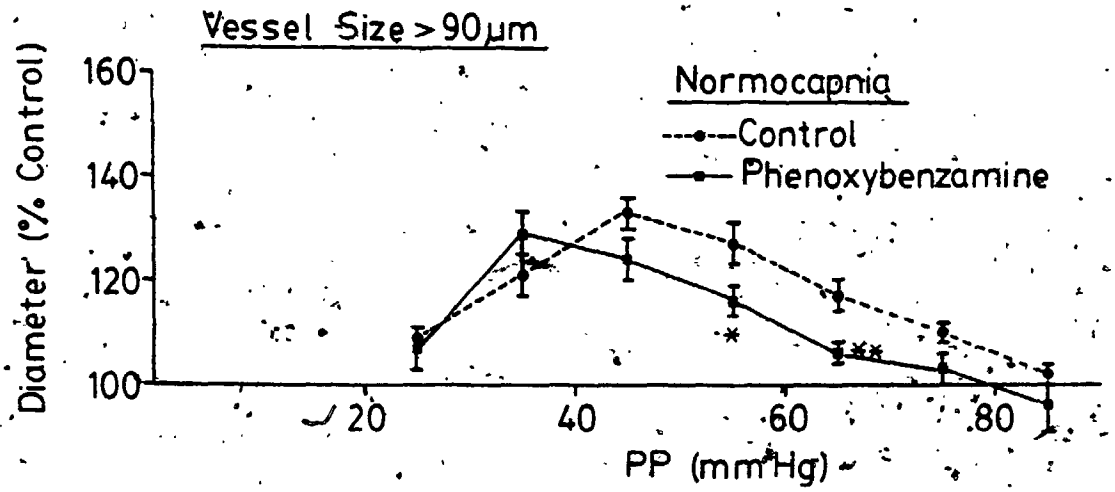

Vessel - Size 50-90 µm
Normocapnia
Control
Phenoxybenzamine
Diameter (% Control)
160
140
120
100
20
40
60
80
PP (mm Hg)
Hypercapnia
Diameter (% Control)
160
140
120
100
20
40
60
80
PP (mm Hg)
CO2 - Response
Increase in Diameter (% Control)
40
20
0
-20
20
40
60
80
PP (mm Hg)

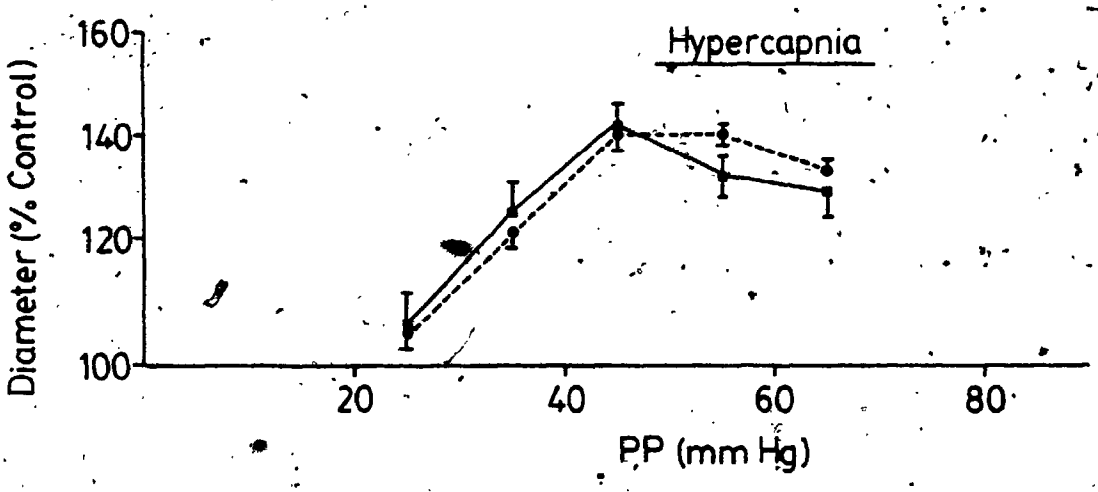
Figure 20

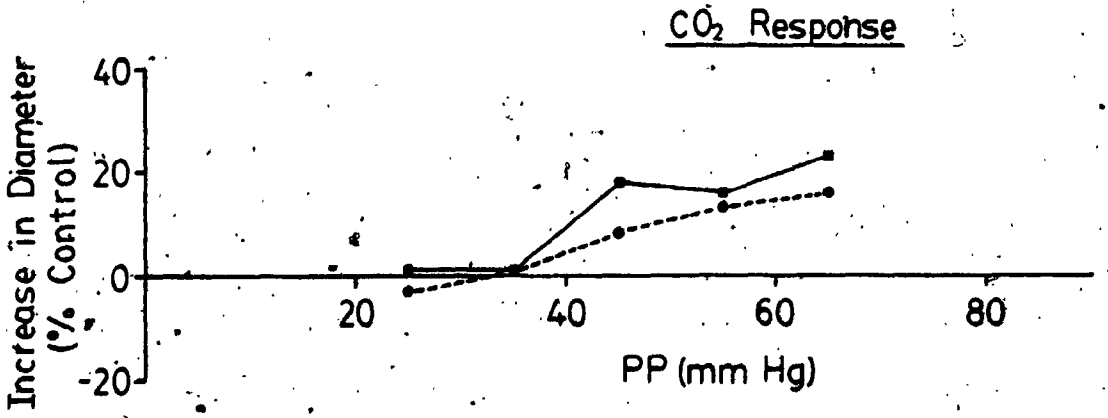
Comparison of the Group III ( >90 μm) vessel responses of the phenoxybenzamine treated group with the corresponding responses of the control group.

* - $p < 0.05$, statistically different from control

** - $p < 0.01$, statistically different from control


Vessel Size > 90µm
Normocapnia
Control
Phenoxybenzamine
Diameter (% Control)
160
140
120
100
20
40
60
80
PP (mmHg)


Hypercapnia
Diameter (% Control)
160
140
120
100
20
40
60
80
PP (mm Hg)


CO2 Response
Increase in Diameter (% Control)
40
20
0
-20
20
40
60
80
PP (mm Hg)

reduced $CMRO_2$. In contrast to these studies, other investigations in primates have found that CBF either remained unchanged (Fitch et al., 1975) or increased by 22% (Hernandez-Perez, 1975) following PBZ infusion. Furthermore, Kawamura et al. (1974) showed that after treatment with PBZ the venous outflow and $CMRO_2$ in the baboon were increased but that these increases were transient. Thus the effects of phenoxybenzamine on CBF and cerebral metabolism are quite variable. Although the reason for this variation is uncertain, it may be the result of the different species and various anesthetics used in the above experiments.

The two most probable causes of the reduction in CBF observed post-PBZ in the present study were the decrease in PP and the reduction in cerebral metabolism. A 38% decrease in PP from 83 to 50 mm Hg could have accounted for the flow reduction if autoregulation had been lost following PBZ infusion but this was not the case. Thus, it would appear that the flow reduction occurred primarily as a result of the decline in $CMRO_2$ induced by PBZ. It is a well established finding that CBF is normally closely coupled to cerebral metabolism (Sokoloff, 1977).

The manner in which PBZ alters cerebral metabolism is uncertain but it is possible that PBZ directly affects cerebral function. There are alpha-receptors present on the cortical neurons and also within deeper brain structures which mediate neural activity (Edvinsson and MacKenzie, 1977). Since PBZ is known to cross the blood brain barrier

(Masuoka et al., 1967), it is possible that PBZ blocks the alpha-receptor mediated synaptic events. In support of this, Bradshaw et al. (1978) found that a topical application of PBZ inhibited the firing rate of cortical cells in the rat. Therefore, the decrease in cerebral metabolism following PBZ infusion could be due to a direct inhibition of normal neural activity.

4.2 CBF Responses Post-PBZ Infusion

There have been indications in previous studies that alpha-adrenoreceptor blockade during hemorrhagic hypotension altered the CBF autoregulatory response of the cerebrovasculature. Both Fitch et al. (1975) and Kovach et al. (1975) had found that during hemorrhage, CBF remained at control levels to a lower pressure in PBZ treated animals than in a group of controls. The preceeding group of control experiments suggested that this might not be entirely correct. Instead of substantially increasing the autoregulatory range, the sympathetic activation associated with hemorrhage appeared to limit the autoregulatory responses of the cerebrovasculature in the region of incomplete autoregulation. In the present study a direct comparison of the results obtained in control and treated animals was complicated by the decrease in CBF following PBZ infusion. The effects of both vascular alpha receptor blockade and the reduction in CBF and metabolism must be considered.

The decline in metabolism accompanying PBZ infusion decreased CBF in the PBZ group over the autoregulatory

pressure range (35-85 mm Hg) under normocapnic conditions and at PP greater than 65 mm Hg under hypercapnic conditions. There was an additional effect of PBZ infusion on CBF. The range over which $CO_2$ reactivity was functionally intact was extended in PBZ animals when compared to the control series and there was an increase in the CBF $CO_2$ response at PP levels of 45-65 mm Hg. It is clear that this increased response was due to the reduction in CBF and metabolism at normocapnia and not a result of increased (absolute) levels of CBF during hypercapnia. Thus, the general depression in CBF/metabolism post-PBZ resulted in an improvement in the dilative reserve.

This increase in the residual capacity for dilation likely had an influence on the autoregulatory responses of the cerebrovasculature. Although the range of CBF autoregulation was not extended by alpha receptor blockade in the rabbit, there was a relative improvement in the autoregulatory responses in the region of incomplete autoregulation (65-35 mm Hg). Regression analysis of the data in this pressure region demonstrated that there was a 0.7±0.1%/mm Hg decline in CBF in the control series. This was reduced to 0.2±0.1%/mm Hg in the PBZ treated group. Either vascular alpha receptor blockade or the decline in CBF and metabolism could account for this change. If the more marked CBF decline in the control series was due to a neurogenic restriction of the autoregulatory responses, then alpha-receptor blockade would have prevented this effect. Alter-

natively, the increase in the dilative reserve due to the decrease in CBF/metabolism could have resulted in a more efficient response of the cerebrovasculature to PP reductions.

[Since most major changes in cerebrovascular responsiveness observed following PBZ infusion appear to be related to the change in CBF/metabolism, the results of the present study may be applicable to other circumstances which reduce either CBF or oxygen consumption. For example, hypocapnia decreases CBF and barbiturate anesthesia is known to depress both CBF and cerebral metaboliam. The present experiments suggest that under these conditions there would also be an increase in the dilative reserve and a relative improvement of autoregulation at low pressures.]

4.3 Pial Vessel Caliber during Hypotension

Fitch et al. (1975) had suggested that during hemorrhage there is a vasoconstriction of the large extraparenchymal vessels (under neurogenic control) and a compensatory dilation of the intraparenchymal vessels (under intrinsic control). The pial vessels in general have been considered to be transitional (under the influence of both neurogenic and local control mechanisms). Since the pial vessels have demonstrated a differential responsiveness to sympathetic stimulation (see Chapter I), it was possible that the size-dependence of their autoregulatory response to hemorrhagic hypotension in control animals may have been related to a greater influence of the sympathetic nervous system on large

pial vessels than small pial vessels. The present study has shown that alpha blockade does not affect this size dependence appreciably. The general responses of the different vessel groups and the maximal dilation attained by these vessels were equivalent to the corresponding groups in the control series. One would conclude that either the level of autoregulatory stimulation or the intrinsic responsiveness of the pial vessels increased with decreasing vessel size.

Some of the differences between the pial vessel responses in the two experimental groups may have been related to neurogenic influences. When compared to controls there was a relative vasoconstriction of the pial vessels in the PBZ group at PP greater than 45 mm Hg. Vascular alpha adrenoreceptor blockade may have decreased the resistance of the large proximal vessels (ie. by preventing an increase in adrenergic tone). This would then have increased the intravascular pial pressure and evoked an autoregulatory constriction of the pial vessels. Alternatively, the decrease in CBF could also have affected the pressure within the pial vessels. A reduction in flow with no change in the resistance of the inflow vasculature would result in an increase in intravascular pial pressure which would be accompanied by vasoconstriction. Finally, the alteration in cerebral metabolism would tend to reduce the concentration of vasoactive metabolites surrounding the pial vessels resulting in a decrease in vessel caliber. It is likely that all of the above effects contributed to some extent to the observed

reduction in pial vascular resistance.

A combination of these effects also appeared to improve the autoregulatory responses of the PBZ group at low PP. The autoregulatory dilation of both the intermediate and large sized vessels (Group II and III) were extended to a lower pressure of 35 rather than 45 mm Hg. A blockade of the vascular alpha receptors could explain these differences if the responses of the pial vessels observed in the control group had been restricted by neurogenic activation. This restriction would then be removed by alpha-blockade, increasing the extent to which they could dilate. However, since CBF and metabolism were reduced, these effects would not be apparent except at very low pressures. The fact that the alteration in the autoregulatory response following PBZ infusion was most pronounced in the large pial vessels would be consistent with the finding by others that sympathetic stimulation constricts large pial vessels more than small ones. Thus a blockade of neurogenic vasoconstriction is a possible explanation for the improved autoregulatory responses of the larger pial vessels. However, this improvement could also be due to the reduction in CBF <u>per se</u>. At a PP of 35 mm Hg, CBF in the PBZ group remained somewhat less than that of controls. This would tend to increase the intravascular pial pressure in the PBZ group at any given PP and therefore reduce the PP at which maximal dilation occurred. Thus the decrease in CBF could also play a role in improving the autoregulatory responses of the pial

vessels at low pressures. The extent to which either effect is involved in the altered pial vessel responsiveness observed following PBZ is not clear.

4.4 Response to Hypercapnia

Alpha receptor blockade has been reported by Kawamura and colleagues (1974) to improve the CBF responsiveness of the cerebrovasculature to hypercapnia at normotension. Their data indicated that after PBZ treatment there was a slight increase in the CBF $CO_2$ reactivity, although this was not statistically significant. They also found that PP decreased 25-35 mm Hg during hypercapnia. They argued that since this decrease in PP was greater following PBZ infusion than under control conditions, a correction for the change in PP was required. Following this correction their data showed a significant increase in CBF $CO_2$ reactivity post-PBZ treatment.

I found that the $CO_2$ response was relatively independent of PP in the upper pressure regions of both animal groups. This indicates that the correction made by Kawamura et al. was likely inappropriate. Furthermore, I found that the $CO_2$ reactivity of the control and PBZ groups were equivalent at high PP levels. This demonstrated that alpha receptor blockade had little effect on the CBF response to hypercapnia at normotension in the rabbit. The possibility remains that the decline in $CO_2$ reactivity in the 45-65 mm Hg pressure range in the control series was due to the sympathetic activation associated with hemorrhage (ie. a

neurogenic restriction of the cerebrovascular responses to hypercapnia). If this was the case, an absolute increase in CBF under hypercapnic conditions would normally be expected following PBZ infusion. However, since there was a reduction in CBF and metabolism, the flow requirements during hypercapnia were reduced and an absolute increase in CBF was not anticipated.

Wei et al.(1975) found that large pial arteries ( $>100\ \mu m$) treated with a topical application of phentolamine (an alpha-receptor blocking agent) showed an increased responsiveness to hypercapnia at normotension such that the response of the large vessels became equivalent to that of the small pial vessels. Normotensive levels of PP were not examined in the present study and therefore this effect of alpha-blockade has yet to be confirmed. Over the pressure range examined presently, the increases in the calibers of the large pial arteries ( $>90\ \mu m$) were less pronounced than those of small pial vessels ( $<50\ \mu m$). Therefore alpha blockade did not remove the size-dependence of the pial vessel responses to hypercapnia in the rabbit at PP levels less than 75 mm Hg.

4.5 Changes in Vascular Resistance

The decrease in CBF and metabolism also affected the changes in resistance of the PBZ group. Comparing total PCR in the control and PBZ series (from Figures 13 and 16) demonstrates that at PP levels above 35 mm Hg, total PCR of the PBZ group was approximately 27% greater than that of the

control group. Pial vascular resistance in the PBZ treated animal was approximately 13% greater than that of controls. The increase in total PCR was related to the decrease in CBF/metabolism and presumably to a change in the concentration of vasoactive metabolites within the brain. However, the observation that total PCR increased more than pial vascular resistance suggests that other cerebral vessels had constricted to a greater extent than the pial vessels. Since the intraparenchymal vessels are closest to the vasoactive metabolites within the brain, it seems most likely that these vessels responded to PBZ infusion with a regulatory increase in resistance exceeding that of the pial vessels.

There was a close correspondence between total PCR $CO_2$ responses and those of pial vascular resistance in control animals. However, in PBZ treated animals, the $CO_2$ response of total PCR exceeded that of pial vascular resistance by an average of 11% at PP greater than 35 mm Hg. One possible explanation for the relatively greater $CO_2$ response of total PCR would be that alpha blockade may have prevented the neurogenic restriction of large cerebral artery responses to hypercapnia thus improving the average response of the cerebrovasculature. However, since the contribution of the large inflow arteries to reductions in resistance during hypercapnia are minimal (see Ch. VI, Sect. 4.2) and the size dependence of the pial vessel responses was not altered substantially by alpha adreno-

receptor blockade, this explanation seems unlikely. Alternatively, it is possible that the intraparenchymal vessels responded to hypercapnia with greater reductions in resistance than the pial vessels. This would imply that the intraparenchymal vessels had a greater dilative reserve following PBZ infusion. The latter possibility would be consistent with the suggestion that intraparenchymal vessels had constricted to a greater extent than pial vessels as a result of the decline in CBF and metabolism.

Although the responses of the pial vessels and those of the intraparenchymal vessels may differ quantitatively following PBZ infusion, their responsiveness to subsequent dilative stimuli appear to be closely interrelated. Alterations in pial vascular resistance generally paralleled both autoregulatory changes in total PCR and the PCR response to hypercapnia. Thus, the pial vascular resistance changes were at least qualitatively similar to both changes in total PCR and intraparenchymal resistance.

4.6 The Dilative Reserve

There were several improvements in the cerebrovascular responses to dilative stimuli following alpha blockade. The CBF $CO_2$ response increased and the range over which the response was functionally adequate was extended to a PP level of 45 mm Hg (ie. there was an increase in the dilative reserve). There was a corresponding extension of the pressure region in which autoregulation was essentially intact. In particular, there was a relative improvement in CBF auto-

regulation and in the pial vessel autoregulatory responses at low PP. Thus the increase in the dilative reserve following PBZ infusion appeared to influence the autoregulatory response.

The CBF $CO_2$ response indicated that the change in the dilative reserve was due primarily to the reduction in CBF/metabolism rather than to an absolute increase in CBF during hypercapnia (ie. increased vasodilation). The close proximity of the intraparenchymal vessels to vasoactive metabolites and the changes in total PCR versus pial vascular resistance obtained following PBZ infusion strongly suggest that intraparenchymal vessels constricted to a greater extent than pial vessels. Resistance analysis also suggested that the intraparenchymal vessels made a major contribution to the increase in the dilative reserve observed in the PBZ group.

Due to the reduction in CBF/metabolism it is difficult to isolate the direct effects of (vascular) alpha blockade (ie. an increase in the limits to which the cerebrovasculature can dilate). Nevertheless, the present results demonstrate that the influence of the sympathetic nervous system during hemorrhage in the rabbit is relatively minor. There were no absolute increases in CBF or pial vessel caliber above those of the control series following PBZ infusion. The autoregulatory range was not altered by alpha adrenoreceptor blockade and the general size dependence of the pial vessels was not dependent on alpha mediated

neurogenic activity. The possibility remains that the reduction in CBF of control animals in the region of incomplete autoregulation was due to a neurogenic restriction of the autoregulatory and $CO_2$ responses. If so, the reductions in CBF were relatively minor under normocapnic conditions (less than 25%) and more pronounced under hypercapnic conditions.

## 5. Summary and Conclusions

(1). Infusion of the alpha adrenoreceptor blocking agent phenoxybenzamine reduced CBF and metabolism in the anesthetized rabbit.

(2). Following PBZ infusion there was an increase in the dilative reserve related to the decline in CBF/metabolism. More specifically, the $CO_2$ response was increased at PP levels of 45-65 mm Hg and the range over which the $CO_2$ response was functionally intact was extended to lower pressures.

(3). There was a relative improvement of CBF autoregulation at PP levels of 35 to 65 mm Hg following PBZ infusion. The autoregulatory response of large pial vessels (50-195 μm) was extended to a lower pressure of 35 rather than 45 mm Hg. These improvements in the autoregulatory responses correlated directly with the observed increase in the dilative reserve.

(4). There was no change in the range of CBF autoregulation or the CBF response to hypercapnia at normotension following

alpha receptor blockade. In addition, the size dependence of the pial vessel responses to hemorrhagic hypotension and to hypercapnia were essentially unaffected by alpha adrenergic blockade. I would conclude that (a) effects of sympathetic activation during hemorrhage are minimal in the rabbit and (b) the size dependence of vascular responses is the result of either intrinsic differences in vessel responsiveness and/or differing levels of dilative stimulation. (5). The responses of the pial vessels were qualitatively representative of changes in total PCR and intraparenchymal resistance. The quantitative comparison of resistances suggests that intraparenchymal vascular responses exceeded those of the pial vessels.

## VI EFFECT OF CAROTID ARTERY OCCLUSION

### 1. Introduction

It is important to understand the effect of carotid artery occlusion on the cerebrovasculature as inflow artery occlusion occurs naturally in occlusive cerebrovascular disease and carotid ligation is often used as a treatment for intracranial aneurysms. Carotid artery occlusion results in a pressure reduction in the Circle of Willis (Bakay and Sweet, 1952; Knapp et al., 1965; Iwabuchi et al., 1971); however there is normally no change in the resting level of CBF (ie. total CVR remains constant) (Sengupta et al., 1973; Hobsen et al., 1974). Since inflow artery resistance [(MABP-Circle of Willis pressure)/CBF] increases following carotid artery occlusion, there must have been a corresponding decrease in the resistance of some other vascular segment. Sengupta et al. (1973, 1974) postulated that the distal vessels dilated to compensate for the initial pressure drop but that this subsequently reduced their ability to respond to other dilative stimuli. In support of this hypothesis they found that the CBF response to both hypotension and hypercapnia were impaired following carotid artery occlusion. Thus it is clear that the dilative reserve is reduced following carotid artery occlusion.

However, several points remain uncertain. The results of the control experiments (Ch. IV) suggest that following occlusion there may be a region of incomplete autoregulation prior to an onset of pressure passive beha-

vior. Although the data of Sengupta et al. (1974) show that the autoregulatory response is impaired, it is not possible to identify clearly a region of incomplete autoregulation due to the considerable scatter of individual flow measurements. Thus the exact manner in which the autoregulatory response is affected is not clear. The preceeding experiments also suggest that there may be a substantial residual dilative capacity at pressures below those at which CBF begins to decrease. However, the extent to which the dilative reserve is reduced throughout hemorrhagic hypotension following occlusion has not been investigated. Furthermore, the manner in which carotid artery occlusion affects pial vessel caliber and their responsiveness to dilative stimuli has not been studied. Finally, although Sengupta et al.(1974) hypothesized that the effects of carotid occlusion were due to the decrease in distal intravascular pressure accompanying occlusion, this has not been tested.

In order to clarify these issues, I have examined the effects of carotid artery occlusion in the rabbit. The specific objectives were as follows:

(1). to determine the effect of carotid artery occlusion on CBF and pial vessel responses to hemorrhagic hypotension.

(2). to examine the effect of carotid occlusion on the dilative reserve (ie. the cerebrovascular responsiveness to hypercapnia) throughout hemorrhagic hypotension.

(3). to determine if the observed effects of carotid artery occlusion are related solely to the change in Circle of

Willis pressure. This was accomplished by comparing the results of the occluded group to control animals at the same level of cerebral PP.

## 2. Methods

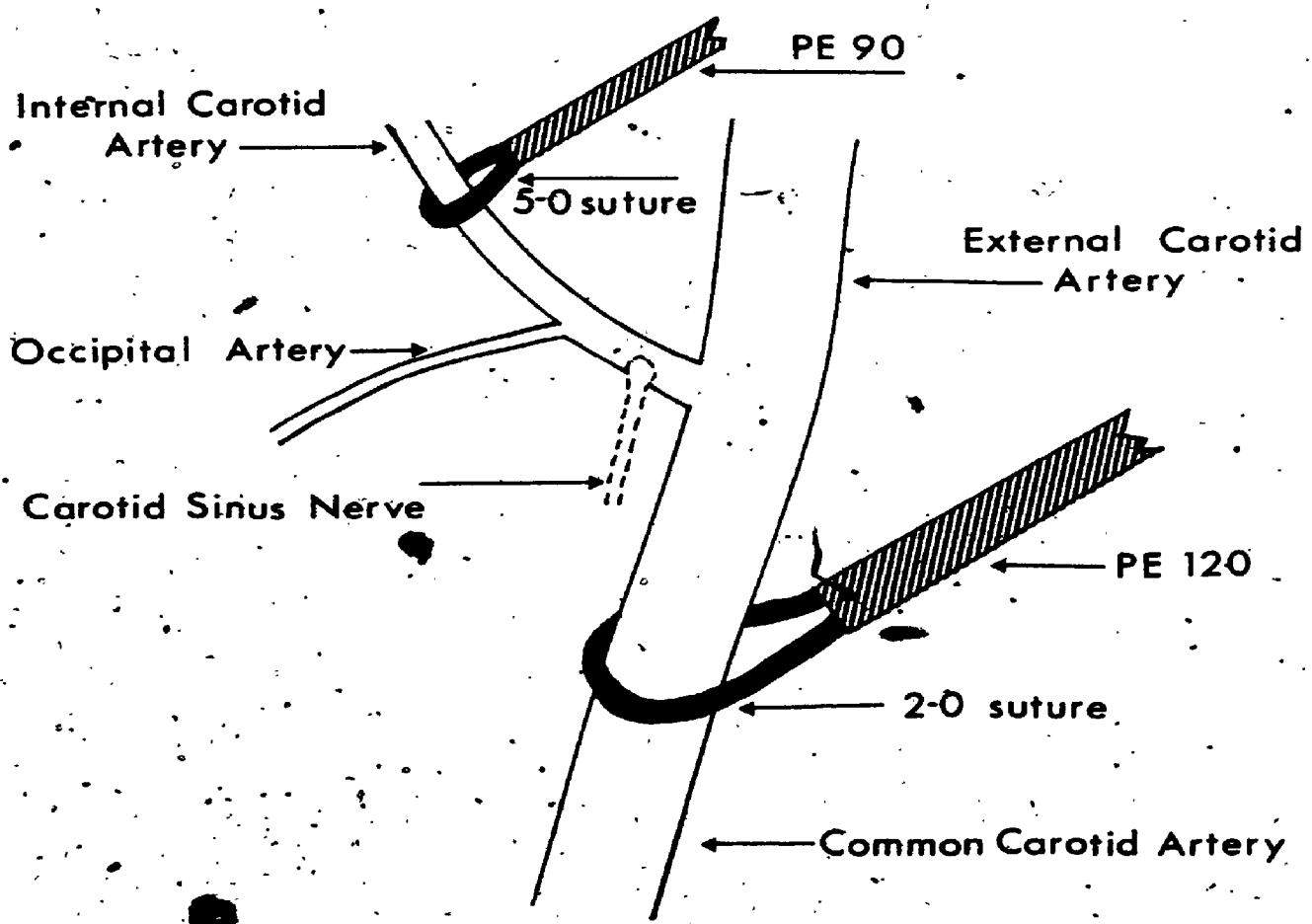
### 2.1 CBF and Pial Vessel Caliber

Rabbits were prepared for the measurement of either CBF (11 rabbits) or pial vessel caliber (10 rabbits) in a manner identical to that described in Chapter 3. Prior to placement of the animal into the headholder, the right common carotid artery was exposed at the level of its bifurcation into the external and internal carotid arteries. As shown in Figure 21, sutures were placed around both the right internal carotid artery (0.5-1.0 cm from the sinus) and the common carotid artery ( > 1 cm from the sinus). The suture was threaded through a 3 cm length of polyethelene tubing (PE 90) which occluded the vessel when the edge of the tubing was compressed against the artery. Occlusion of the internal carotid artery prevented blood flow either from the heart to the brain, or in a retrograde manner from the brain to the external carotid artery. Common carotid artery occlusion eliminated the possibility of blood flow to the brain through anastomotic channels in the eye.

CBF and pial vessel caliber were measured bilaterally following a protocol similar to that outlined in Chapter III. The average control value was determined prior to

Figure 21

This diagram illustrates the anatomy of the carotid artery bifurcation most frequently observed in the rabbit. The figure also shows the positioning of the sutures about the internal and common carotid arteries.


PE 90
Internal Carotid Artery
5-0 suture
External Carotid Artery
Occipital Artery
Carotid Sinus Nerve
PE 120
2-0 suture
Common Carotid Artery

occlusion. Following both right internal and common carotid artery occlusion, measurements were made at normocapnia and hypercapnia and then the PP was reduced by graded hemorrhage. Pial vascular resistance and total precapillary resistance (PCR) were calculated from the data as described previously (Ch. III).

## 2.2 Ophthalmic Artery Pressure Measurements

### 2.2.1 Introduction

Since carotid artery occlusion results in an increase in inflow artery resistance and a pressure reduction in the Circle of Willis (Backay and Sweet, 1952; Knapp et al., 1965; Iwabuchi et al., 1971), the magnitude of this pressure reduction was required to interpret the effects of carotid artery occlusion on the cerebrovasculature. In the rabbit, the internal ophthalmic artery (approx. 0.35 mm in diameter) arises directly from the Circle of Willis or from the internal carotid artery near the Circle and then enters the orbit of the eye without branching (Ruskell, 1962). Therefore, it is possible to measure the pressure in the Circle of Willis by cannulating the internal ophthalmic artery within the orbit. In the present study, techniques were developed to expose and cannulate the internal ophthalmic artery and subsequently measure this pressure.

### 2.2.2 Preparation

The internal ophthalmic artery was approached transorbitally in 14 rabbits. The eye was decompressed by the

removal of the lens, aqueous humor and vitreous body. An incision was made around the upper edge of the orbit, close to the bone and through the cartilage. With the aid of an operating microscope, the periorbita was dislodged gently from the orbit between the frontal artery and the accessory lacrimal artery. These two arteries were coagulated and the lacrimal gland was partly removed. The periorbita was then dissected away from the orbit and retracted. The origin of any hemorrhage occurring during the procedure was visualized by irrigating the area with saline and bleeding was halted using bipolar coagulation or bone wax. Once the optic foramen was visible, the periorbita was cut and the muscle and arteries surrounding the optic nerve were coagulated. The ophthalmic artery was then separated from the optic nerve and the nerve was sectioned. The sheath surrounding 3-4 mm of the artery was dissected free and any branches were coagulated. Two 6-0 silk threads were placed around the ophthalmic artery and the rabbit was heparinized to prevent thrombosis within the vessel following cannulation.

The artery was cannulated using a 31G needle that was positioned with the aid of a microdrive. The suture at the distal end of the vessel was tied and subsequently used to stabilize the artery during cannulation. The microdrive was advanced slowly such that the needle pierced the vessel wall and travelled within the lumen for a distance of 2-3 mm. The second suture was then used to tie the artery to the cannula and achieve a pressure tight seal.

2.2.3 Internal Ophthalmic Pressure

The cannula was connected to a strain gauge transducer using stiff-walled polyethelene tubing. The system was filled with saline and all air bubbles were removed. The patency of the recording system was checked frequently by injecting approximately 0.01 ml of saline. The system was sealed and the tip of the needle was unobstructed if there was a momentary increase in pressure and a return to the preinjection level. The frequency response of this system was such that the arterial pulse pressure was severely damped and only mean pressures could be measured accurately. Therefore, in order to compare the systemic and ophthalmic artery pressures, a continuous recording of mean arterial blood pressure was obtained by filtering the aortic pressure signal electronically to omit all high frequencies. The calibration of aortic and ophthalmic pressure transducers was tested frequently by connecting both to a common pressure source (aortic pressure) and ensuring that there was no difference in pressures recorded.

2.2.4 Data Aquisition

As described in the general protocol (Chapter III), the ophthalmic pressure was measured at resting and then reduced levels of arterial blood pressure at both normocapnia and hypercapnia. The effects of reversible carotid artery occlusion were recorded at each pressure level. The pressure gradient across the large inflow arteries together

with CBF measurements allowed the calculation of the inflow artery resistance.

## 3. Results

### 3.1 Ophthalmic Artery Pressure

#### 3.1.1 Inflow Vessels Intact

The Circle of Willis pressure in the rabbit is composed of arteries which are approximately equal in size (McDonald and Potter, 1951). Therefore, the ophthalmic artery pressure was considered representative of that throughout the Circle of Willis. The mean pressure in the ophthalmic artery (ie. the Circle of Willis) under resting conditions (MABP=92±4 mm Hg, $P_aCO_2$=39±1 mm Hg) was 85±4 mm Hg and the average pressure gradient between the MABP and the Circle of Willis was 7±1 mm Hg. During hemorrhagic hypotension reductions in MABP were accompanied by equivalent reductions in ophthalmic artery pressure (see Figure 22) so that the pressure gradient (aorta to the Circle of Willis) remained essentially constant. Hypercapnia increased this pressure difference at resting and moderately reduced PP. The mean pressure gradient across the inflow arteries for each PP level is shown in Table 4. This Table includes the mean pressure gradients of the capillary-venous pressure component (equal to that calculated in the control series, Ch. IV, Sect. 3.3) and the remaining pressure drop across the cerebral arteries and arterioles. In other words, the entire cerebral perfusion pressure was divided into three

Figure 22

In this graph the pressure measured in the ophthalmic artery (or that in the Circle of Willis) is plotted versus the simultaneous measurement of mean arterial blood pressure. The pressures obtained under normocapnic conditions differ from those obtained at hypercapnia if the blood pressure is either normal or moderately reduced.

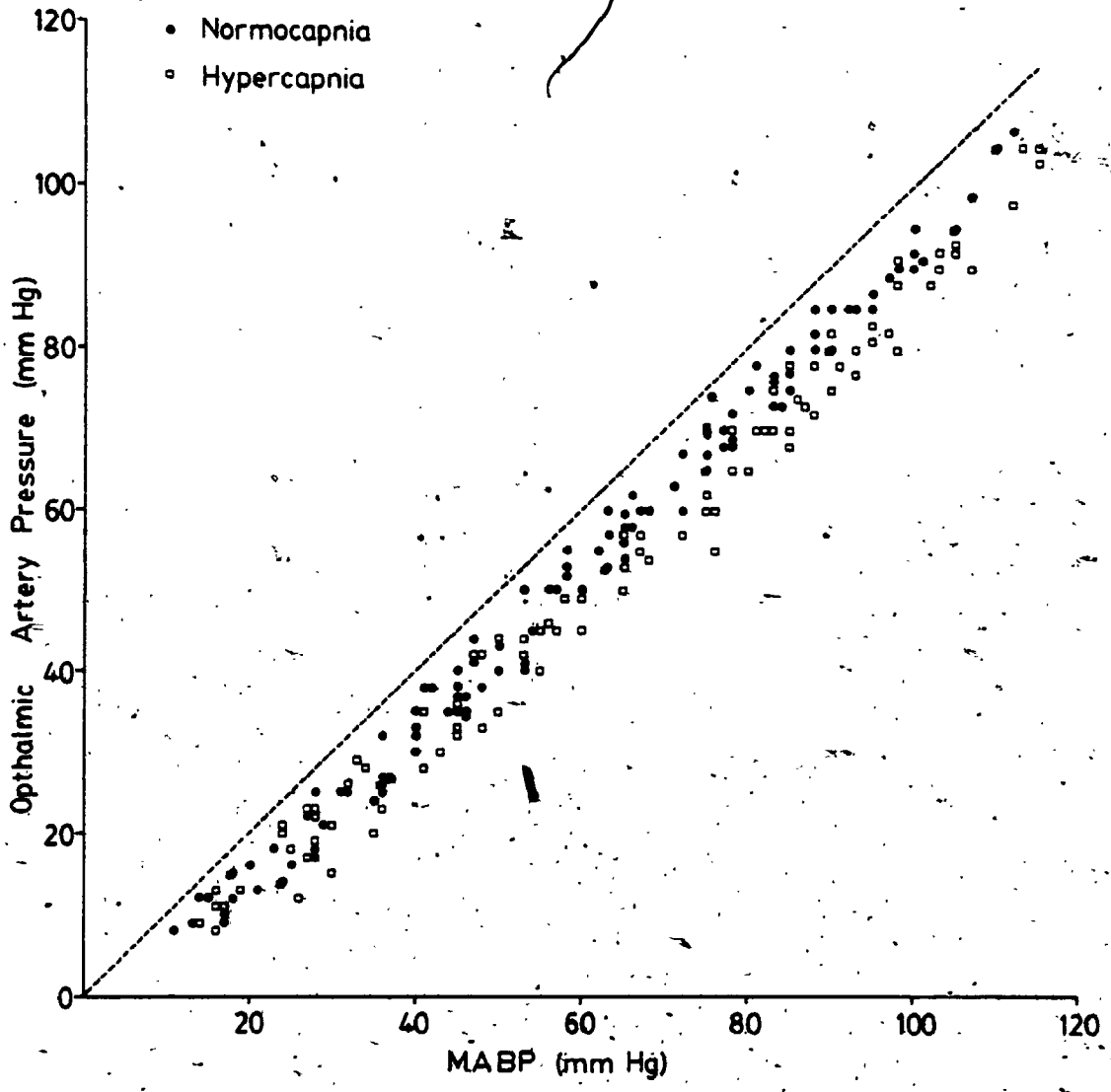

Normocapnia
Hypercapnia
Opthalmic Artery Pressure (mm Hg)
MABP (mm Hg)
0
20
40
60
80
100
120

TABLE 4

Pressure Gradients at Normocapnia(N) and Hypercapnia(H)

| PP Range | Pressure Gradient (mm Hg) | | | | | |
|---|---|---|---|---|---|---|
| | Segment | | | | | |
| | Inflow Arteries+ | | Arteries and Arterioles* | | Capillaries and Veins* | |
| | N | H | N | H | N | H |
| 105 | 8 | 13 | 75 | 57 | 22 | 35 |
| 95 | 8 | 12 | 65 | 46 | 22 | 37 |
| 85 | 7 | 13 | 55 | 38 | 22 | 34 |
| 75 | 7 | 13 | 46 | 29 | 22 | 33 |
| 65 | 8 | 12 | 36 | 29 | 21 | 24 |
| 55 | 7 | 12 | 28 | 18 | 20 | 25 |
| 45 | 8 | 11 | 18 | 12 | 19 | 22 |
| 35 | 8 | 10 | 10 | 8 | 17 | 17 |
| 25 | 7 | 8 | 8 | 7 | 10 | 10 |

+ mean pressure( ± 1 mm Hg), * calculated values (mm Hg)

segments - inflow artery, artery-arteriole and capillary venous pressure gradients. These pressures were used to calculate resistances presented in Section 3.4.

3.1.2 Effect of Carotid Artery Occlusion

There was a 7±1 mm Hg increase in the pressure gradient from the aorta to the Circle of Willis following carotid artery occlusion. A typical example of the effect of temporary carotid artery occlusion on the pressure within the Circle of Willis is shown in Figure 23. The inflow artery pressure gradient during occlusion increased during hypercapnia. Mean values of the total pressure gradient (occluded) and the increase in the presure gradient resulting from occlusion at each PP level are shown in Table 5.

## 3.2 CBF and Pial Vessel Caliber

### 3.2.1 Responses at Normotension

Satisfactory clearance curves were obtained from 46 of 55 electrodes. In order to determine if the location of the electrode was an important determinant of cerebrovascular responsiveness, the responses were grouped according to their location in the left or right(occluded) hemisphere as shown in Table 6. The average MABP, PP and $P_aCO_2$ were not altered by unilateral carotid artery occlusion and the physiological state of these rabbits was similar to that of the control group. CBF was reduced slightly on the right side following occlusion both at normocapnia and hypercapnia although the differences were not significant. The total

Figure 23

Shown are a sample tracing of the ophthalmic artery pressure and mean arterial blood pressure at normocapnia and hypercapnia. The diagram demonstrates that the reduction in the perfusion pressure resulting from occlusion is greater at hypercapnia than normocapnia.

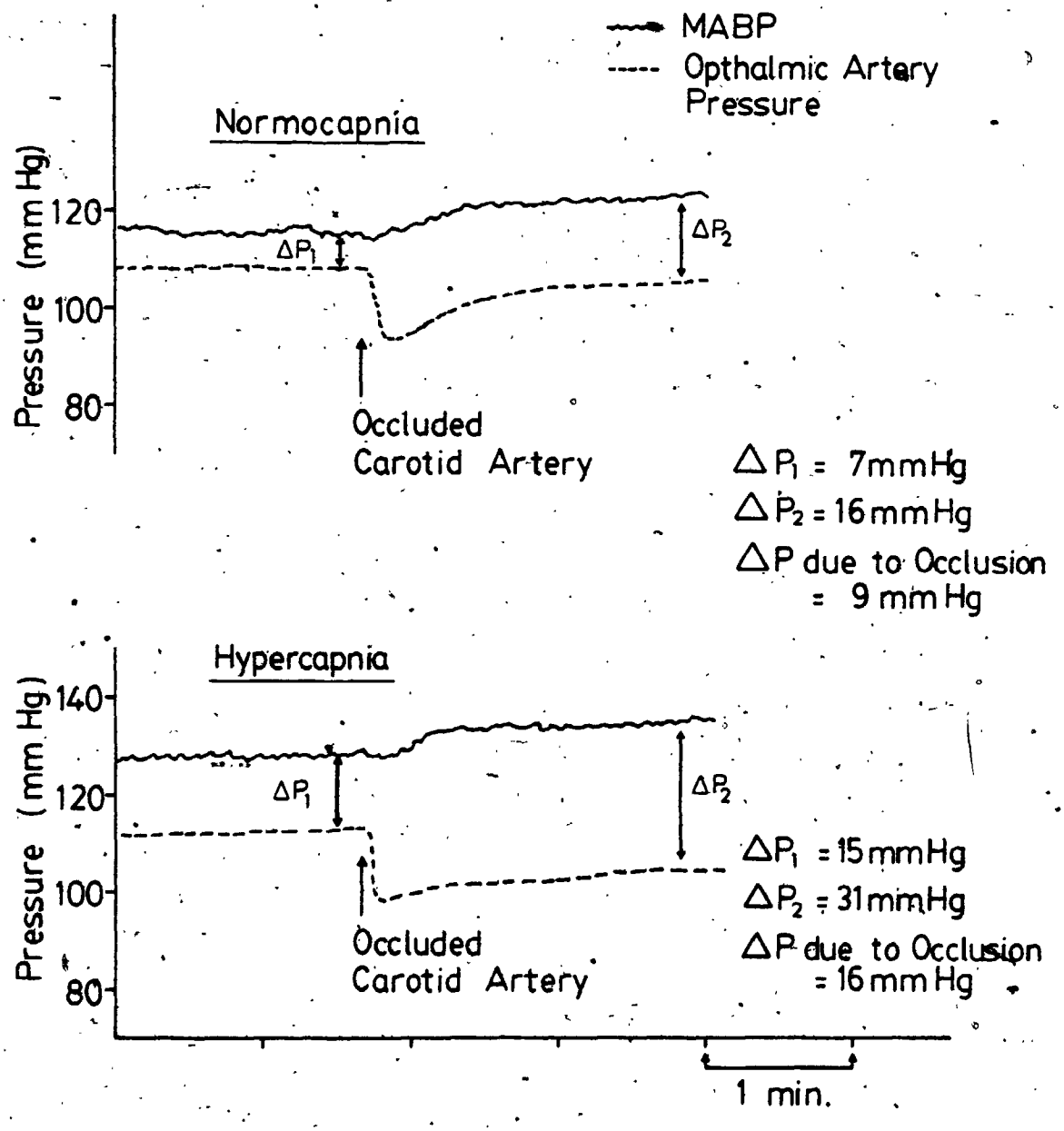

MABP
Opthalmic Artery Pressure
Normocapnia
Pressure (mm Hg)
120
100
80
ΔP1
ΔP2
Occluded Carotid Artery
ΔP1 = 7mmHg
ΔP2 = 16mmHg
ΔP due to Occlusion = 9 mm Hg
Hypercapnia
140
120
100
80
ΔP1
ΔP2
Occluded Carotid Artery
ΔP1 = 15mmHg
ΔP2 = 31mmHg
ΔP due to Occlusion = 16mm Hg
1 min.

TABLE 5

Pressure Gradient across the Inflow Arteries during Unilateral Carotid Artery Occlusion

| PP Range | Pressure Gradient+(mm Hg) | | | |
|---|---|---|---|---|
| | Normocapnia | | Hypercapnia | |
| | Increase due to Occlusion | Total | Increase due to Occlusion | Total |
| 25 | 2±1 | 9±2 | 2±1 | 10±2 |
| 35 | 4±1 | 12±2 | 3±2 | 13±3 |
| 45 | 4±1 | 12±2 | 4±1 | 15±2 |
| 55 | 4±1 | 11±2 | 5±1 | 17±2 |
| 65 | 5±1 | 13±2 | 6±2 | 18±3 |
| 75 | 5±1 | 12±1 | 7±2 | 20±2 |
| 85 | 6±1 | 14±2 | 7±2 | 20±2 |
| 95 | 7±1 | 15±2 | 9±2 | 21±3 |
| 105 | 7±1 | 15±2 | 10±3 | 23±3 |

+ MABP less Internal Opthalmic Artery Pressure

TABLE 6

CBF Following Carotid Artery Occlusion

at Normotension .

| Variables | Pre-occlusion | | Post-occlusion | |
|---|---|---|---|---|
| | N* | H+ | N* | H+ |
| Physiological(n=11) | | | | |
| MABP (mm Hg) | 100±3 | 112±3 | 99±4 | 113±4 |
| PP (mm Hg) | 92±3 | 103±3 | 92±4 | 103±4 |
| $P_aCO_2$(mmHg) | 39.8±.5 | 61.3±.7 | 40.7±.7 | 61.3±.6 |
| CBF(ml/100gm/min) | | | | |
| Left Side (n=22) | 99±8 | 169±12 | 95±7 | 154±11 |
| Right Side (n=24) | 98±7 | 171±9 | 91±7 | 144±13 |
| Total | 99±5 | 170±8 | 93±5 | 149±8 |

* Normocapnia + Hypercapnia

CBF response to hypercapnia was also reduced somewhat following carotid occlusion.

The pre-occlusion diameters (20-152 μm) of the 86 pial vessels examined under resting conditions (MABP=103±2 mm Hg and $P_aCO_2$=39.3±.5 mm Hg) are shown in Table 7. The mean caliber in each vessel group on the right hemisphere was similar to that on the left and the total mean diameters were equivalent to those of the control animals. The effect of unilateral carotid artery occlusion on pial vessel diameter is presented in Table 8. The data shown in the Table were obtained from 5 rabbits that did not exhibit excessive brain swelling during hypercapnia. The average response of all vessels in a given size group were calculated for each animal and used in the determination of the mean responses for that group. Following occlusion, the pial vessels dilated and there was no significant difference between the degree of dilation achieved in the occluded versus the contralateral side. The responses to hypercapnia were similar to those of control animals and the left-right side differences were not significant.

3.2.2 Responses during Hypotension

The cerebrovascular responses were initially combined and analyzed according to the location of the measurement with respect to the left or right (occluded) hemisphere. Figure 24 shows the pial diameters (Group I) and the CBF data organized in this way. The Group II and III vessel responses (not shown) demonstrated slight left-right differ-

TABLE 7

Diameter of the Pial Vessels in each Group Prior to Occlusion

| Group | Left Side | | Right Side | | Total | |
|---|---|---|---|---|---|---|
| | N+ | Caliber* | N | Caliber | N | Caliber |
| I | 20 | 36±2 | 23 | 35±2 | 43 | 35±1 |
| II | 12 | 66±2 | 16 | 60±2 | 28 | 63±2 |
| III | 9 | 112±7 | 6 | 99±3 | 15 | 107±5 |

+ Number of Vessels in each group, * Mean(μm)±SEM

TABLE 8

Pial Vessel Diameter Following Carotid Artery Occlusion

| Vessel Group | Pial Vessel Diameter(% Control) Normocapnia+ Left Side | Right Side | Total | $CO_2$ Response× Left Side | Right Side | Total |
|---|---|---|---|---|---|---|
| I | 106±6 | 108±4 | 107±3* | 32±6 | 26±6 | 29±5 |
| II | 105±2 | 107±4 | 106±2* | 19±7 | 23±4 | 21±4 |
| III | 104±3 | 106±4 | 105±3 | 15±5 | 22±3 | 20±4 |

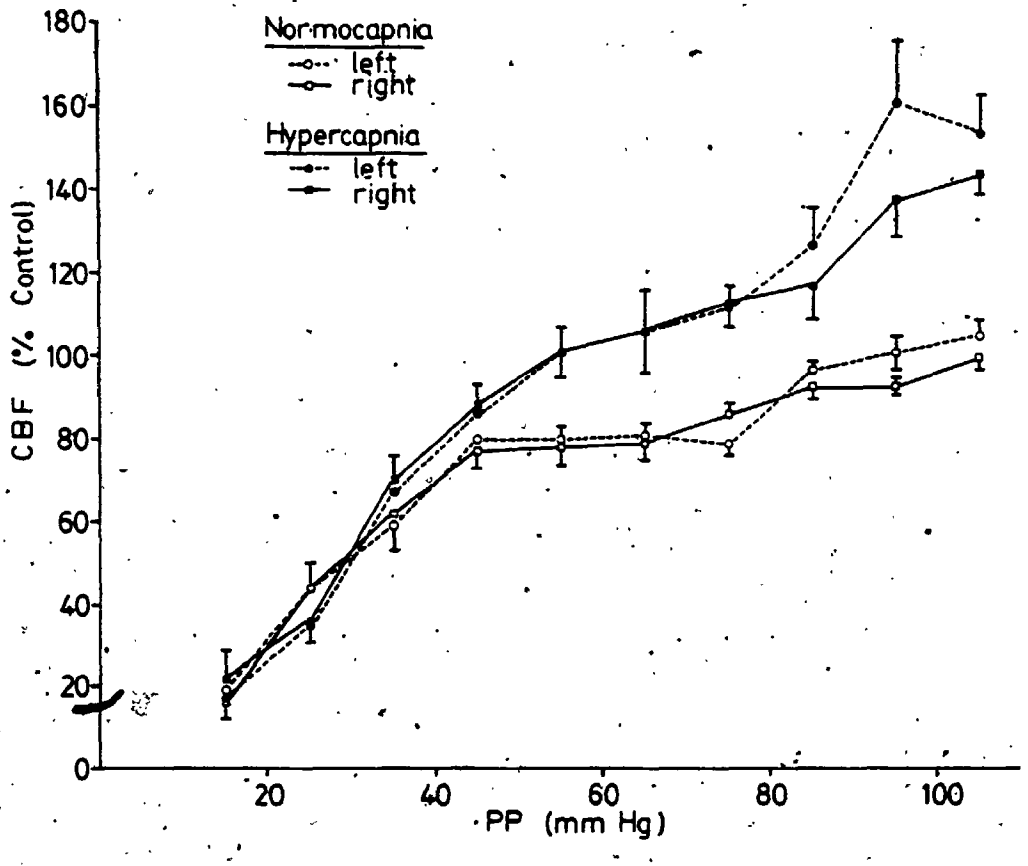
+ MABP=103±3 mm Hg, $P_aCO_2$=39.0±.5 mmHg

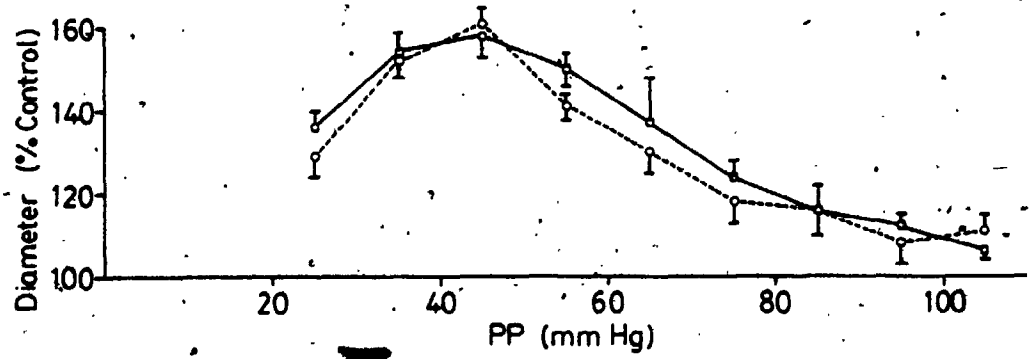
× MABP=104±6 mm Hg, $P_aCO_2$=61±2 mm Hg

* greater than control ($p<.05$)

Figure 24

This figure compares the cerebrovascular responses obtained from the right hemisphere to those obtained from the left side. CBF at normocapnia and hypercapnia are presented in the top section. The calibers of the Group I vessel responses at normocapnia are shown in the lower panel. All differences between right and left sides are not statistically significant.


Normocapnia
left
right
Hypercapnia
left
right
CBF (% Control)
180
160
140
120
100
80
60
40
20
0
20
40
60
80
100
PP (mm Hg)


Diameter (% Control)
160
140
120
100
20
40
60
80
100
PP (mm Hg)

ences similar to those of the Group I vessels. None of the differences between the responses in the occluded and contralateral hemispheres were significant and the slight dissimilarities which did occur were inconsistent. Thus data from the left and right hemispheres were combined.

The CBF responses to hemorrhagic hypotension following carotid artery occlusion are shown in Figure 25. During normocapnia CBF was maintained at control levels between PP of 105-85 mm Hg and CBF declined at PP between 85-45 mm Hg. The lower limit of autoregulation occurred at 45 mm Hg. During hypercapnia, CBF was dependent on PP over the entire range with the possible exception of the uppermost PP levels ($\geq$ 85 mm Hg). As PP decreased, CBF under hypercapnic conditions declined. The $CO_2$ response was approximately 50% at pressures greater than 85 mm Hg and 20-30% at PP of 55-85 mm Hg; it was not significant at pressures less than 55 mm Hg.

The effect of hemorrhagic hypotension on the pial vessel responses are presented in Figure 26. Following the dilation produced by occlusion of the carotid artery at normocapnia, a reduction in PP produced a supplementary dilation of the pial vessels. The arteries dilated progressively until a maximum dilation of 160±3%, 146±3% and 132±3% control was attained in the Group I,II and III vessels, respectively. These maxima occurred at a PP level of 45 mm Hg for small and intermediate sized vessels and at a PP of 55 mm Hg for the larger vessels ( > 90 μm). Further reductions in PP resulted in a decline in vessel diameter. The pial

Figure 25

This diagram presents the CBF responses obtained following unilateral carotid artery occlusion. Shown are the mean responses to hemorrhagic hypotension at normocapnia and at hypercapnia. The additional increases in CBF resulting from hypercapnia are shown in the bar graphs. The symbol + indicates that the difference between normocapnia and hypercapnia is not significant.

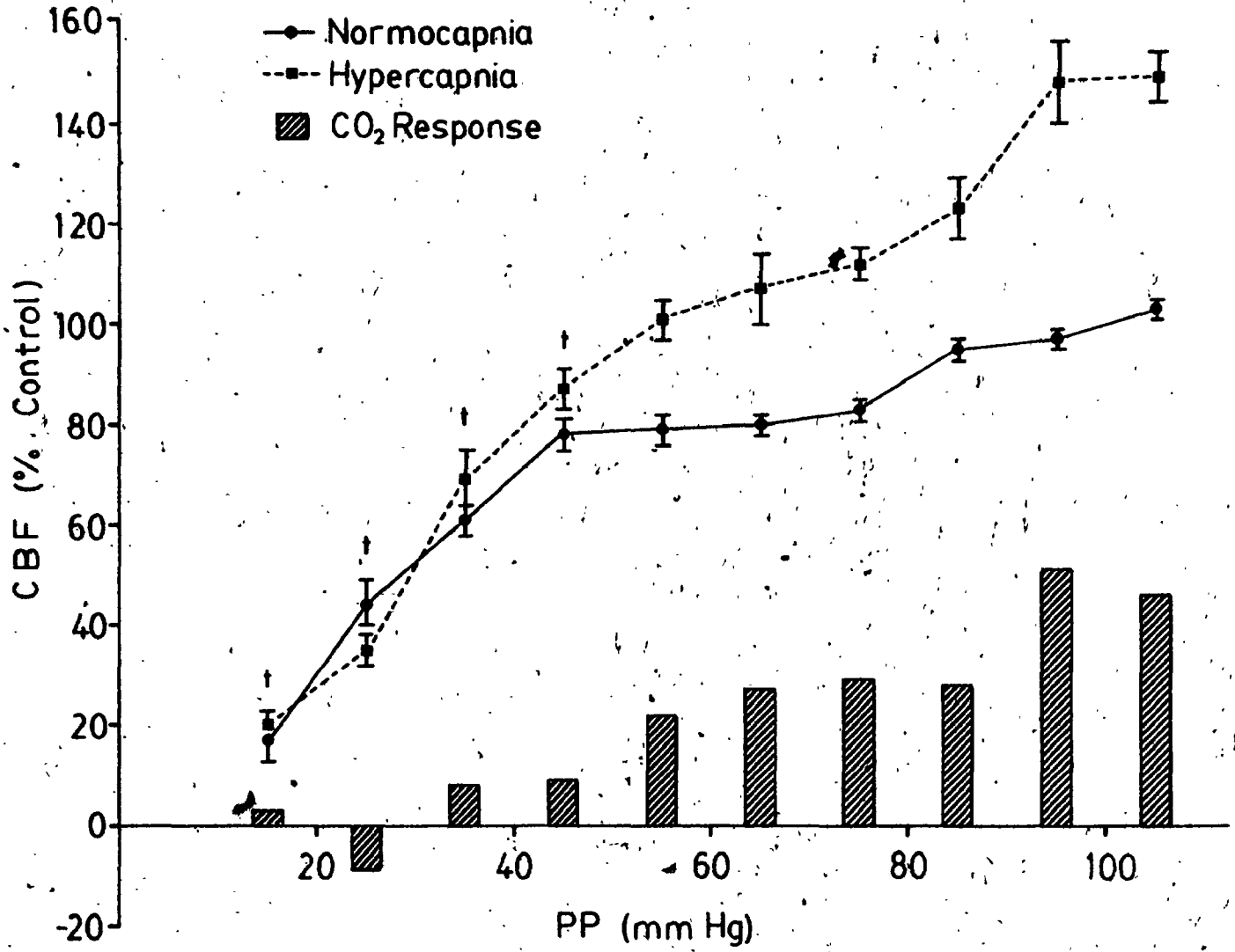
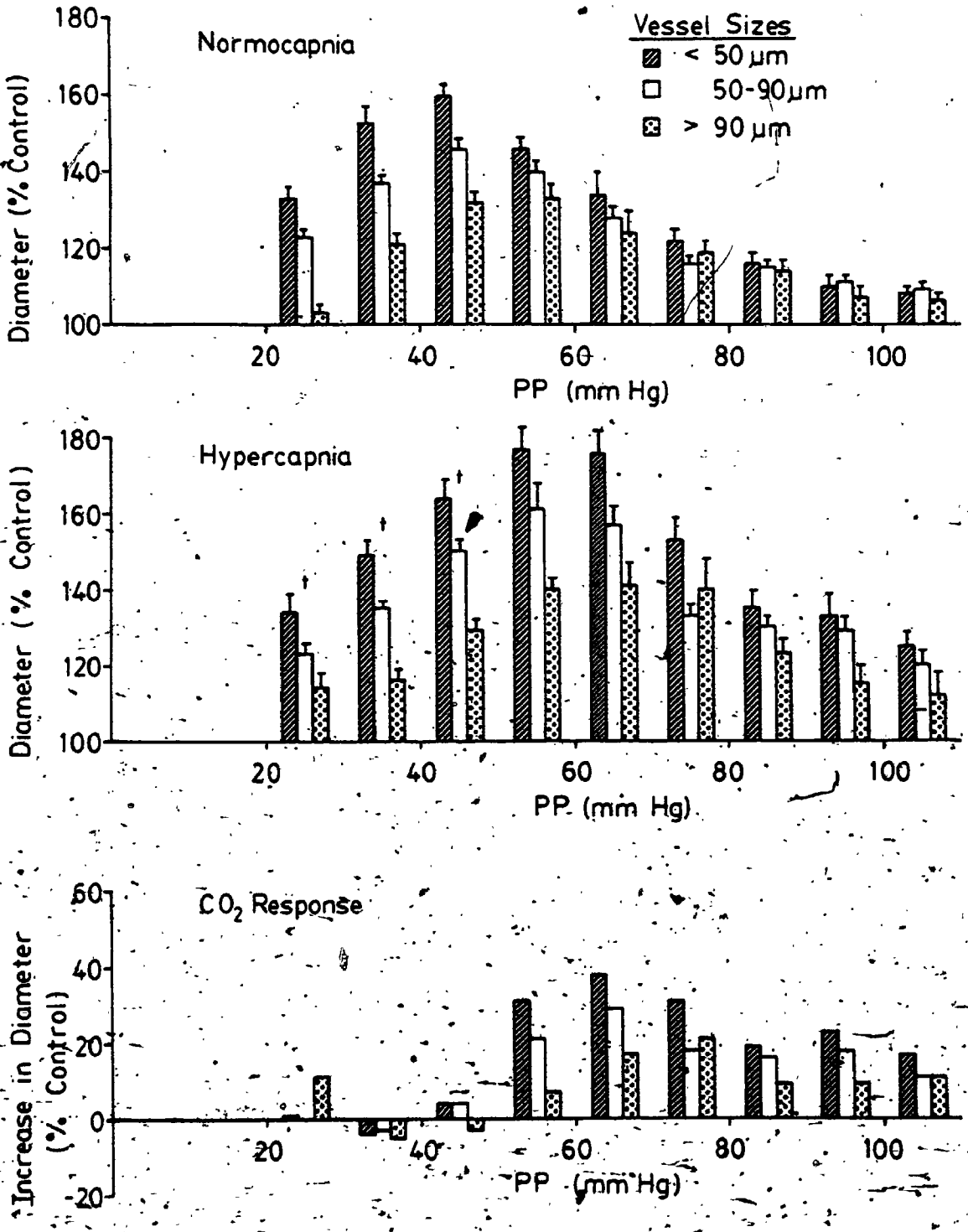

Normocapnia
Hypercapnia
$CO_2$ Response
CBF (% Control)
160
140
120
100
80
60
40
20
0
-20
20
40
60
80
100
PP (mm Hg)

Figure 26

This diagram presents the pial vessel responses obtained following unilateral carotid artery occlusion. Shown are the mean responses to hemorrhagic hypotension at normocapnia, at hypercapnia and the $CO_2$ responses. The symbol + indicates that the differences between normocapnia and hypercapnia are not significant.


Normocapnia
Vessel Sizes
< 50 µm
50-90µm
> 90 µm
Diameter (% Control)
180
160
140
120
100
20
40
60
80
100
PP (mm Hg)
Hypercapnia
Diameter (% Control)
180
160
140
120
100
20
40
60
80
100
PP (mm Hg)
$CO_2$ Response
Increase in Diameter (% Control)
60
40
20
0
-20
20
40
60
80
100
PP (mm Hg)

vessel diameters measured during hypercapnia were greater than those at normocapnia at all PP greater than 45 mm Hg. As PP was reduced, the Group I, II and III vessels dilated continuously to attain maximal values of 177±6%, 161±7% and 141±6% control, respectively. PP reductions below 55 mm Hg resulted in a decrease in vessel diameters to values equivalent to the calibers at normocapnia. The $CO_2$ response of the pial vessels initially increased as PP was reduced from 105 to 65 mm Hg and then declined at pressures below 65 mm Hg.

### 3.3 Comparison with Control Responses

#### 3.3.1 Direct Comparison

The CBF responses following occlusion are compared to those of the control animals in Figure 27. CBF was less than that of control animals at PP of 35-85 mm Hg during normocapnia and at PP of 45-85 mm Hg during hypercapnia. The $CO_2$ response was also reduced following occlusion at PP levels greater than 65 mm Hg.

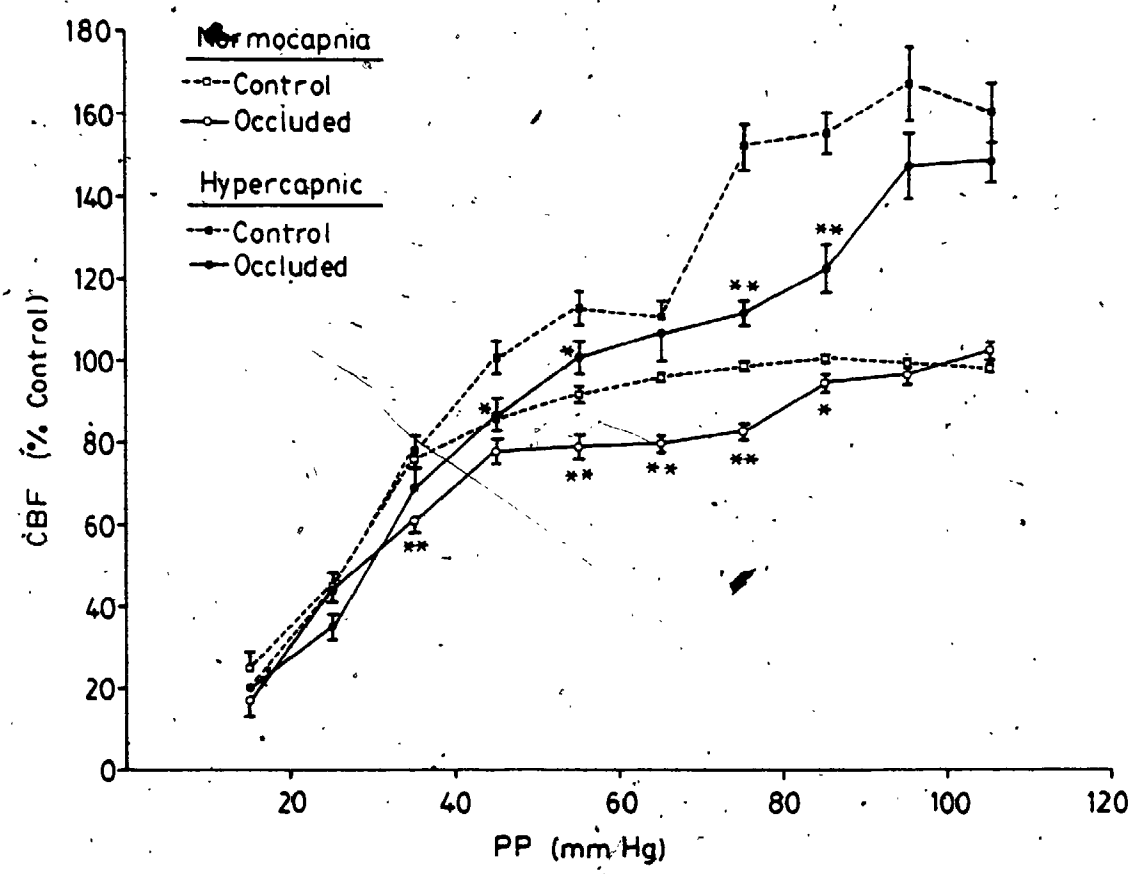
The effect of occlusion on the Group I, II and III vessel responses with respect to those of control are presented in Figures 28, 29, and 30, respectively. Pial vessel dilation at normocapnia was greater (not neccessarily significant) than that of controls at PP above 45 mm Hg. At pressures below this level, pial vessel diameters in the occluded series were less than or equal to those in the control series. Similarly, as PP was reduced to 55 mm Hg

Figure 27

This graph presents a comparison of CBF responses in the occluded group with those in the control group.

* - $p < 0.05$, statistically different from control

** - $p < 0.01$, statistically different from control


Normocapnia
Control
Occluded
Hypercapnic
Control
Occluded
CBF (% Control)
PP (mm Hg)
180
160
140
120
100
80
60
40
20
0
20
40
60
80
100
120
**
*

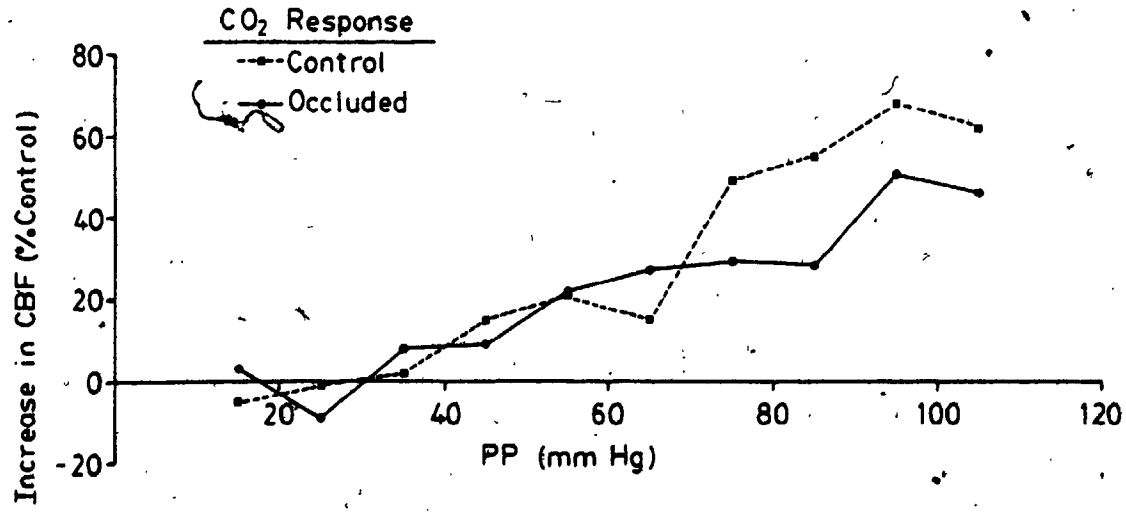

$CO_2$ Response
Control
Occluded
Increase in CBF (%Control)
PP (mm Hg)
80
60
40
20
0
-20
20
40
60
80
100
120

Figure 28

This diagram shows a comparison of the Group I vessel responses in the occluded series with those in the control series.

* - $p < 0.05$, statistically different from control

** - $p < 0.01$, statistically different from control

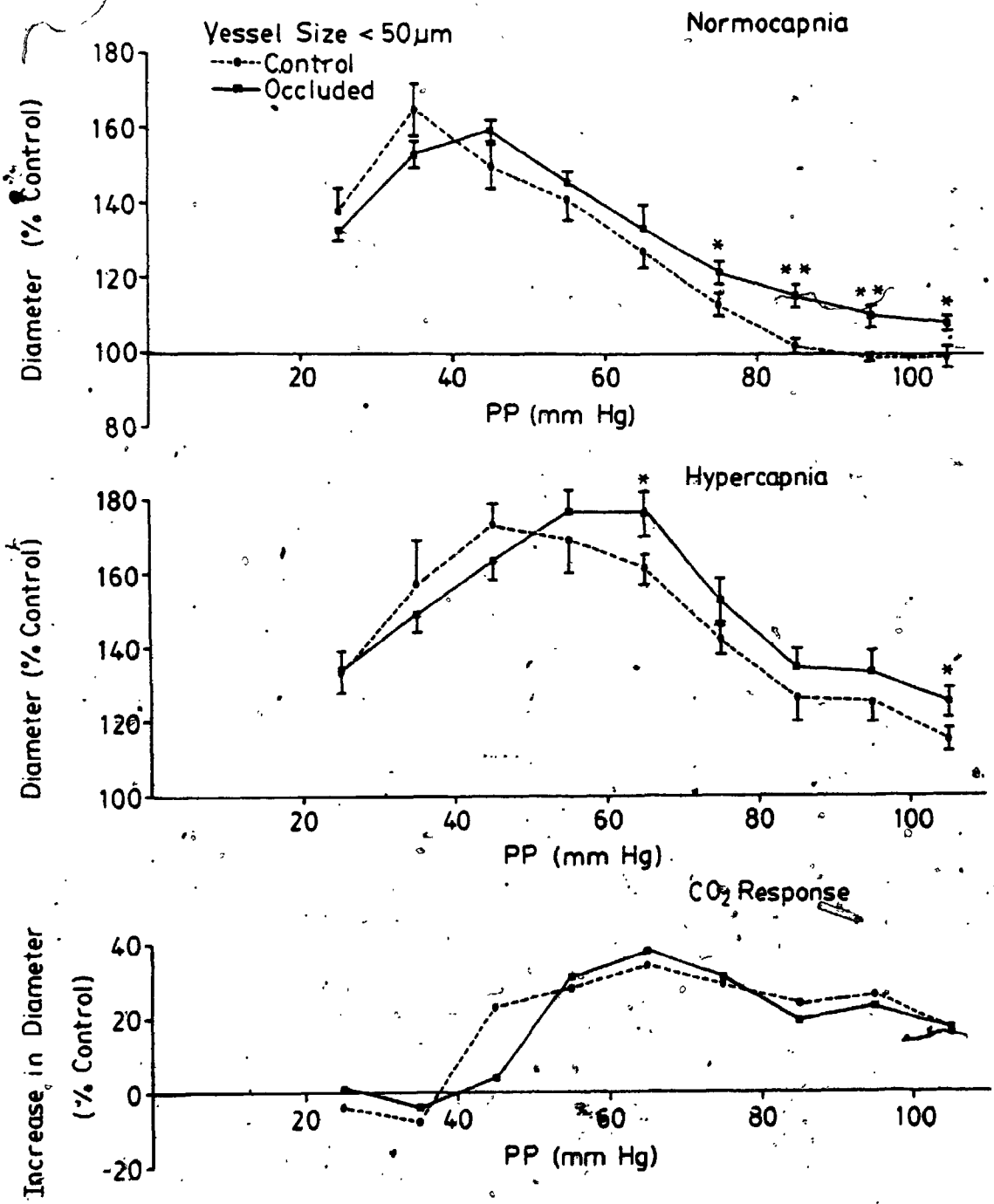

Vessel Size < 50µm
Control
Occluded
Normocapnia
Diameter (% Control)
180
160
140
120
100
80
20
40
60
80
100
PP (mm Hg)
Hypercapnia
Diameter (% Control)
180
160
140
120
100
20
40
60
80
100
PP (mm Hg)
$CO_2$ Response
Increase in Diameter (% Control)
40
20
0
-20
20
40
60
80
100
PP (mm Hg)

Figure 29

This diagram presents the comparison of Group II vessel responses in the occluded series with those in the control series.

* - $p < 0.05$, statistically different from control

** - $p < 0.01$, statistically different from control

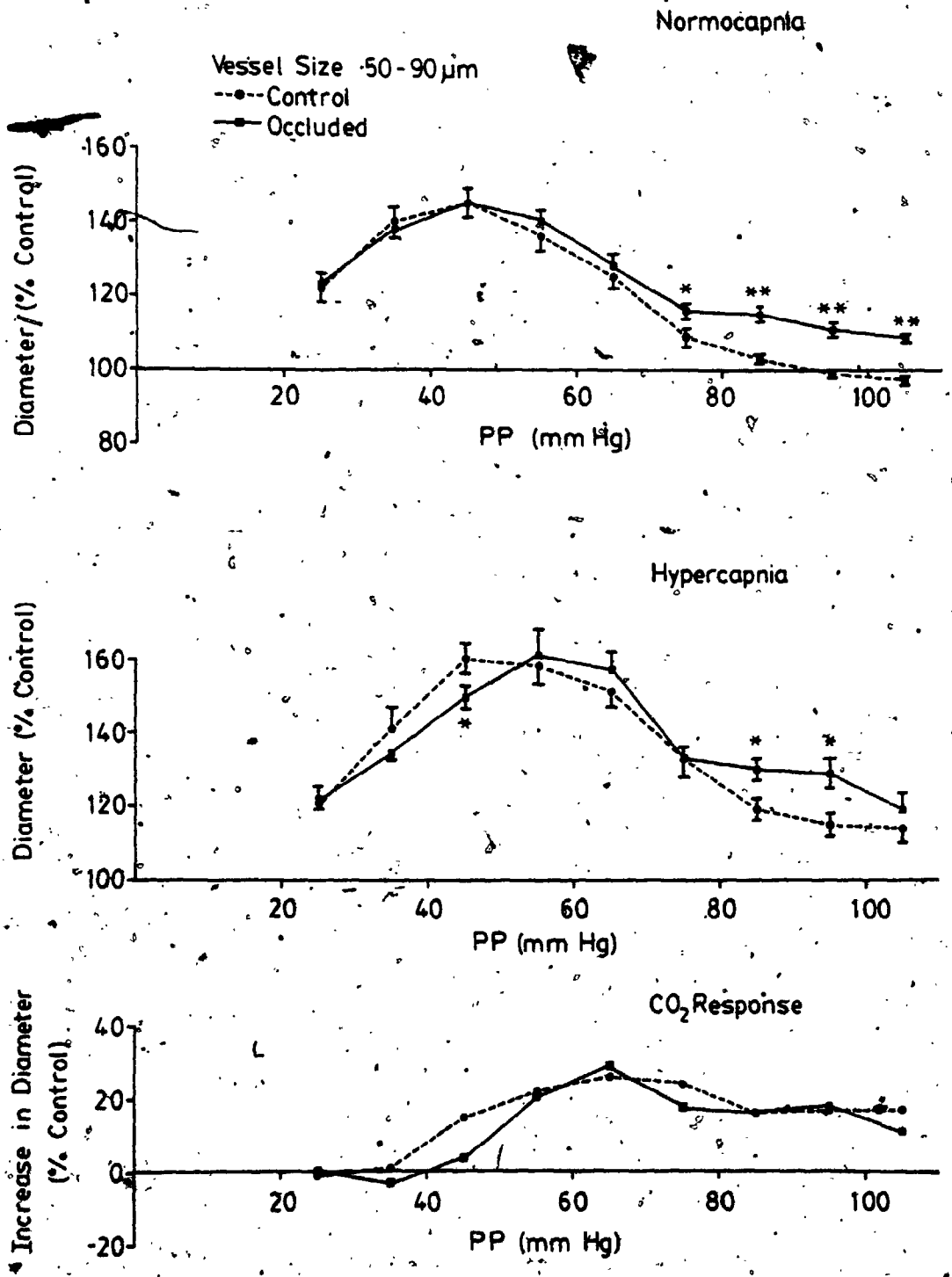
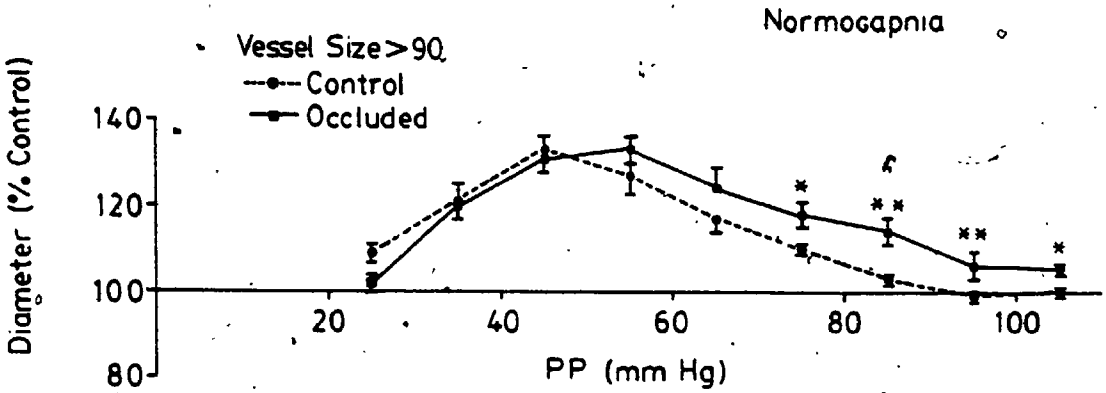

Normocapnia
Vessel Size 50-90 µm
Control
Occluded
Diameter/(% Control)
160
140
120
100
80
20
40
60
80
100
PP (mm Hg)
Hypercapnia
Diameter (% Control)
160
140
120
100
20
40
60
80
100
PP (mm Hg)
CO2 Response
Increase in Diameter (% Control)
40
20
0
-20
20
40
60
80
100
PP (mm Hg)

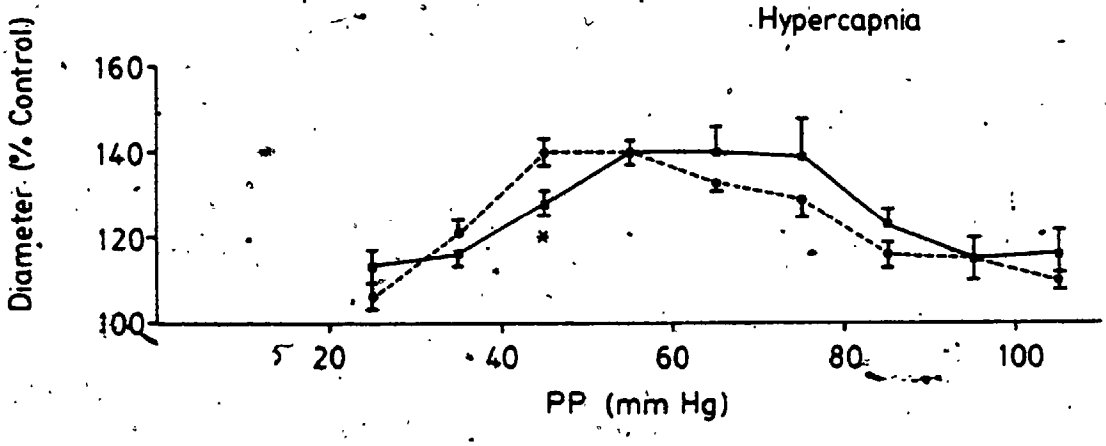
Figure 30

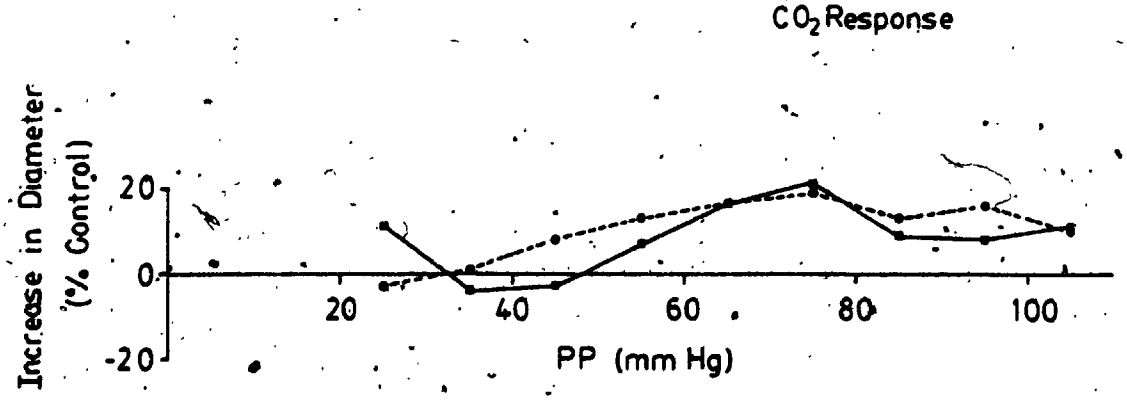
This diagram presents the comparison of Group III vessel responses in the occluded series with those in the control series.

* - $p < 0.05$, statistically different from control

** - $p < 0.01$, statistically different from control


Normocapnia
Vessel Size>90
Control
Occluded
Diameter (% Control)
140
120
100
80
20
40
60
80
100
PP (mm Hg)
*
**
**
*


Hypercapnia
Diameter (% Control)
160
140
120
100
20
40
60
80
100
PP (mm Hg)
*


$CO_2$ Response
Increase in Diameter (% Control)
20
0
-20
20
40
60
80
100
PP (mm Hg)

during hypercapnia, pial vessel calibers were somewhat greater in the occluded series than in the control animals. These differences were most pronounced in small ($< 50\ \mu m$) pial vessels. The autoregulatory responses of the occluded series were similar to or less than those of the control series at PP below 55 mm Hg. The two groups of animals had equivalent $CO_2$ responses at most PP levels. However, at PP of 45 mm Hg the responses of the pial vessels following occlusion were reduced relative to those of the control series.

3.3.2 Correction for Decreases in Cerebral PP

Clearly, carotid artery occlusion affected the autoregulatory and $CO_2$ responses in comparison to those of control animals. There was a reduction in pressure in the Circle of Willis such that the pressure perfusing the cerebral arteries and arterioles following occlusion was less than that calculated as MABP minus ICP. In order to examine the manner in which the altered cerebrovascular responses following occlusion were related to this difference in cerebral PP, the mean Circle of Willis pressure drop in each PP range of the occluded series (from Table 5) was subtracted from the PP for that level. Then the data obtained following carotid occlusion were shifted to a level of cerebral PP which was equivalent to that of the control animals.

The CBF responses of the occluded group (shifted to correct cerebral PP) are compared to the control series in

Figure 31. Many of the differences between the two series of animals were removed by this correction although some dissimilarities remained. CBF was less in the occluded series than in controls at intermediate pressure levels (50-80 mm Hg) during normocapnia and at approximately 75-80 mm Hg during hypercapnia. The $CO_2$ response was also less at approximately 75-80 mm Hg.

The responses of Group I, II and III pial vessels of the occluded series (shifted to appropriate cerebral PP) are compared to those of control animals in Figures 32, 33 and 34, respectively. The autoregulatory responses of the control and occluded series were almost identical at PP less than 85 mm Hg and the $CO_2$ and hypercapnic responses of the control series coincided with those of the occluded series. In the upper PP range, the dilation of the occluded series at normocapnia was significantly greater than that of the control series.

3.4 Pial Vascular and Precapillary Resistance

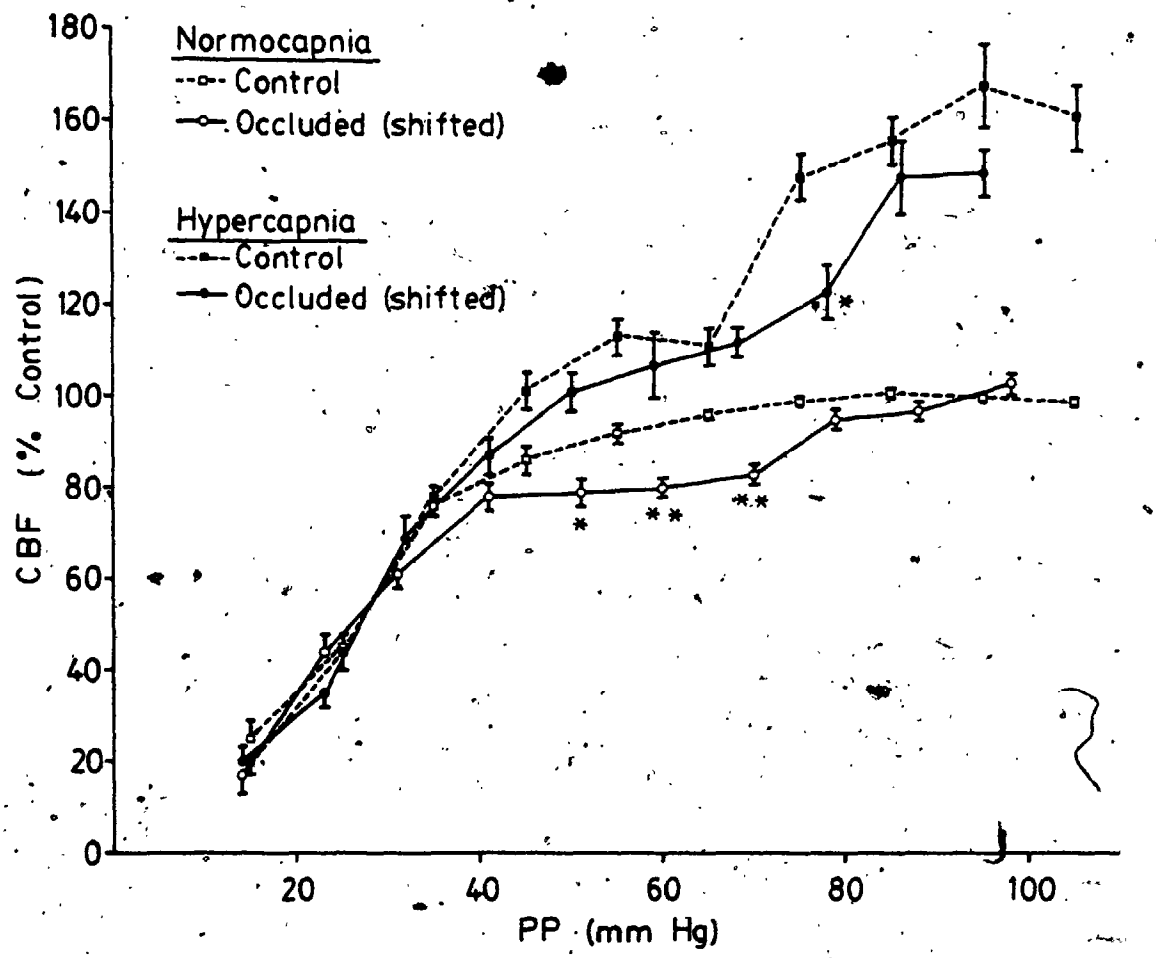
Alterations in total precapillary resistance (PCR) are compared to the changes in pial vascular resistance in Figure 35. Both total PCR and pial vascular resistance exhibited an autoregulatory decline at PP of 45-105 mm Hg. During hypercapnia, total PCR was essentially constant at PP of 105-75 mm Hg, declined at pressures below this PP range and then increased at PP less than 45 mm Hg. Pial vascular resistance during hypercapnia demonstrated a gradual decline over the 105-55 mm Hg pressure region and an increase

Figure 31

In this figure, CBF responses of the occluded series are compared to those of control. Occluded values have been shifted to lower PP to account for the decrease in cerebral PP following occlusion.

* - $p < 0.05$, statistically different from control

** - $p < 0.01$, statistically different from control


Normocapnia
Control
Occluded (shifted)
Hypercapnia
Control
Occluded (shifted)
CBF (% Control)
PP (mm Hg)
0
20
40
60
80
100
120
140
160
180
20
40
60
80
100
*
**
**

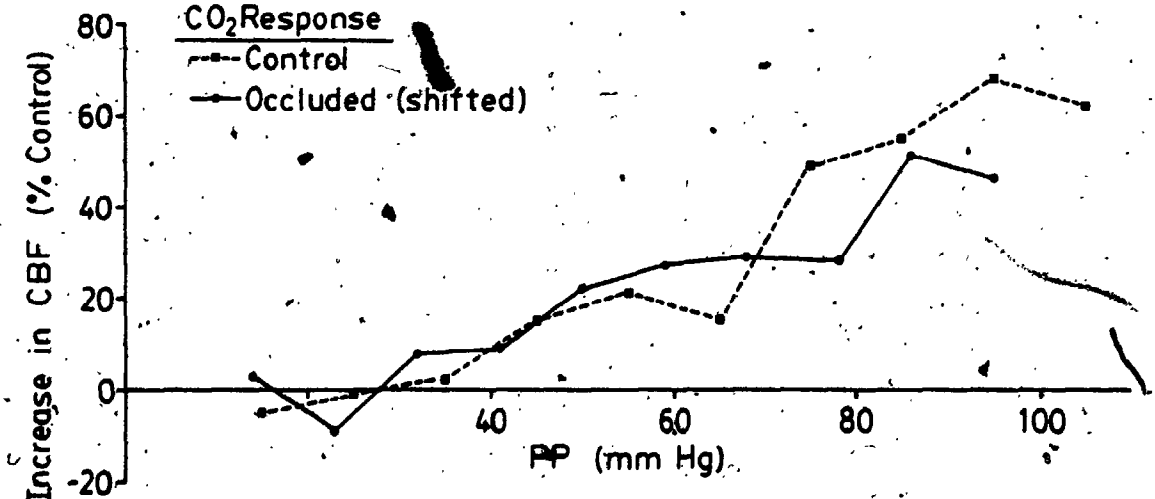

CO2Response
Control
Occluded (shifted)
Increase in CBF (% Control)
PP (mm Hg)
-20
0
20
40
60
80
40
60
80
100

Figure 32.

Group I vessel responses of the occluded series are compared to those of control. Occluded values have been shifted to account for the decrease in cerebral PP following occlusion.

* - $p < 0.05$, statistically different from control

** - $p < 0.01$, statistically different from control

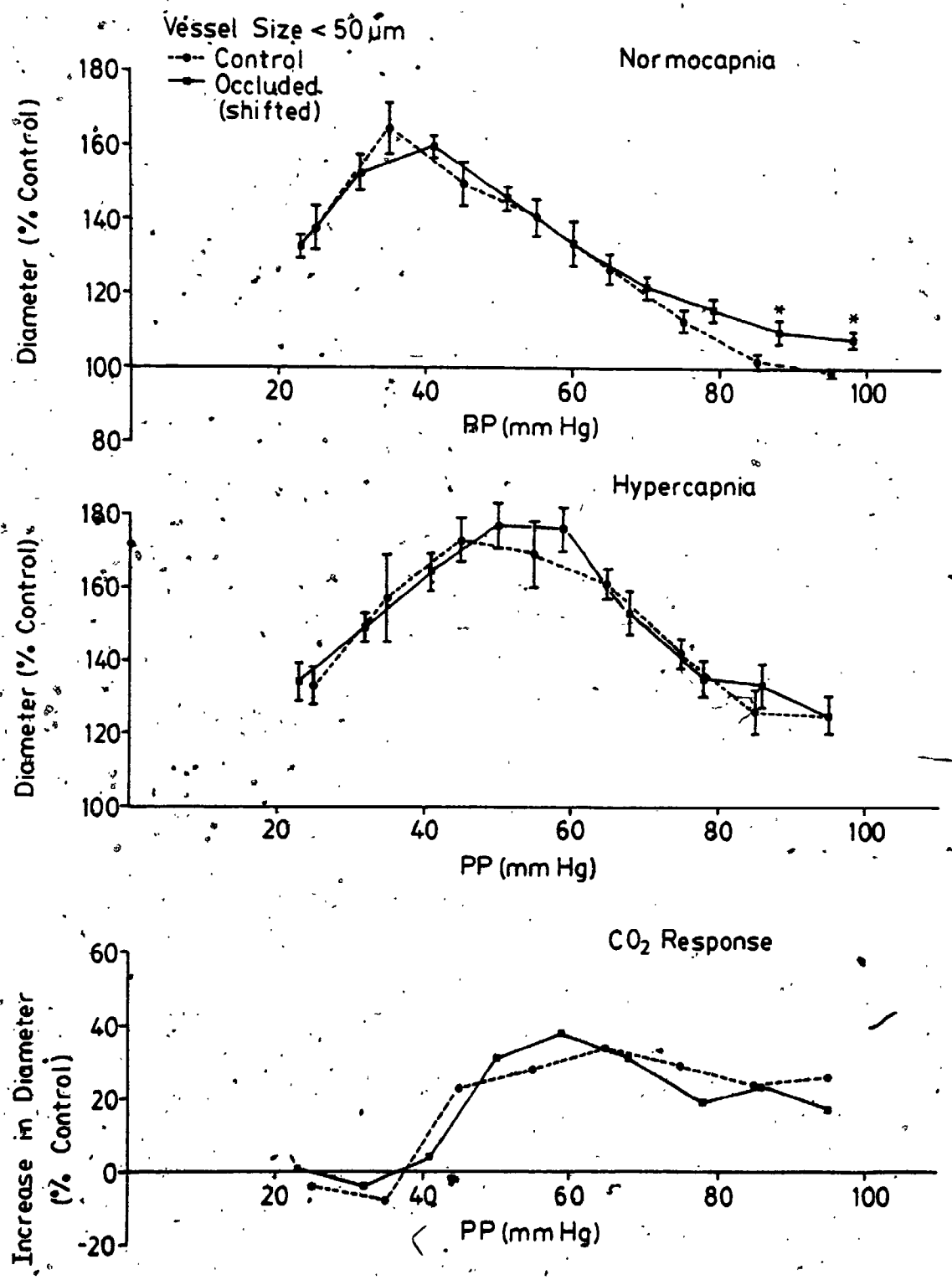

Vessel Size < 50 µm
Control
Occluded (shifted)
Normocapnia
Diameter (% Control)
180
160
140
120
100
80
20
40
60
80
100
BP (mm Hg)
Hypercapnia
Diameter (% Control)
PP (mm Hg)
CO2 Response
Increase in Diameter (% Control)
60
40
20
0
-20
PP (mm Hg)

Figure 33

Group II vessel responses of the occluded series are compared to those of control. Occluded values have been shifted to account for the decrease in cerebral PP following occlusion.

* - $p < 0.05$, statistically different from control

** - $p < 0.01$, statistically different from control

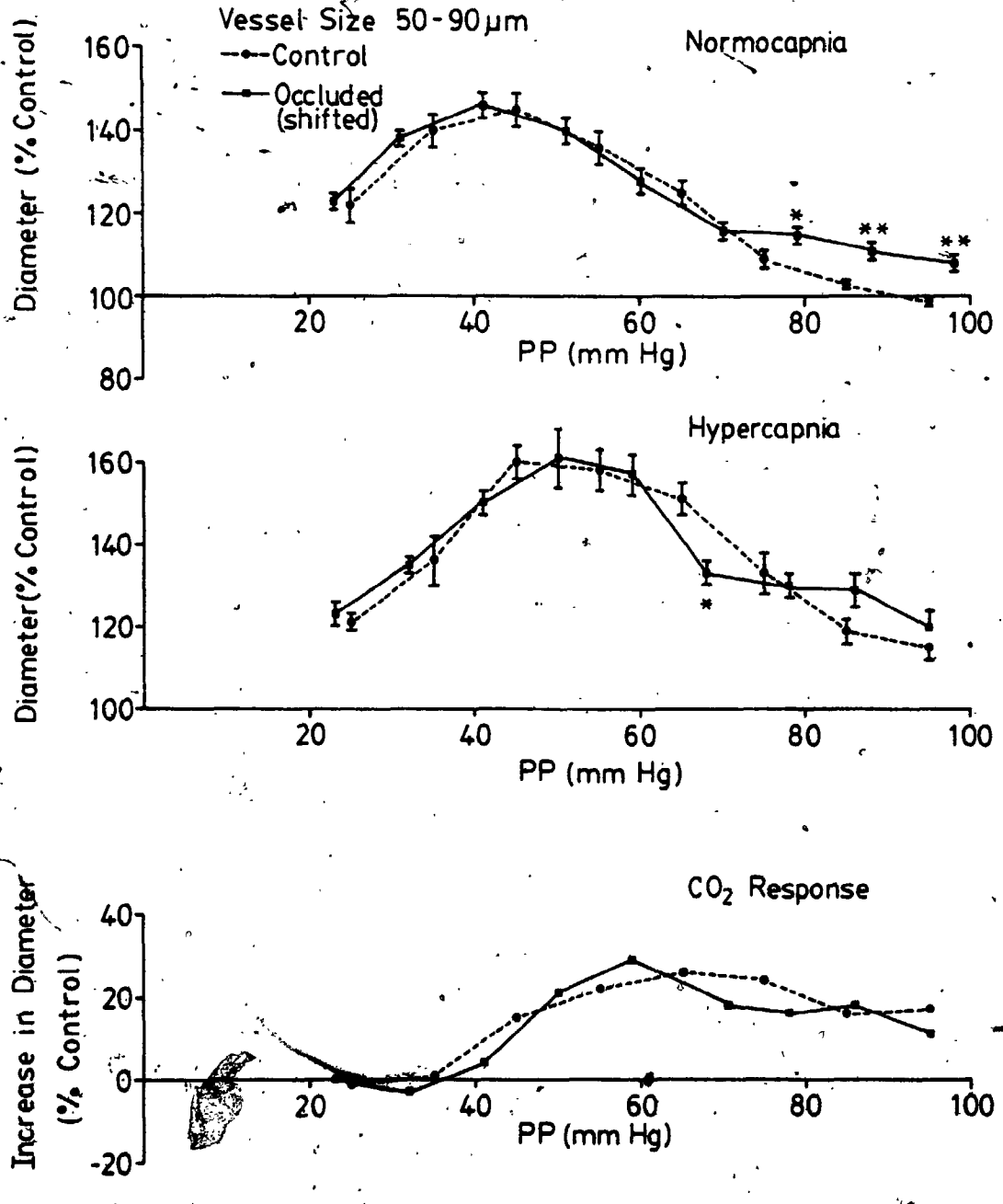
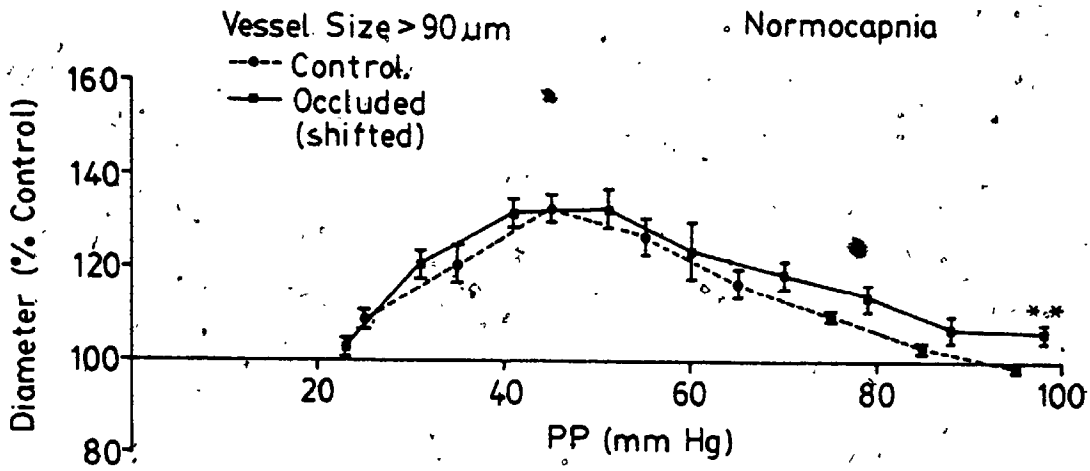
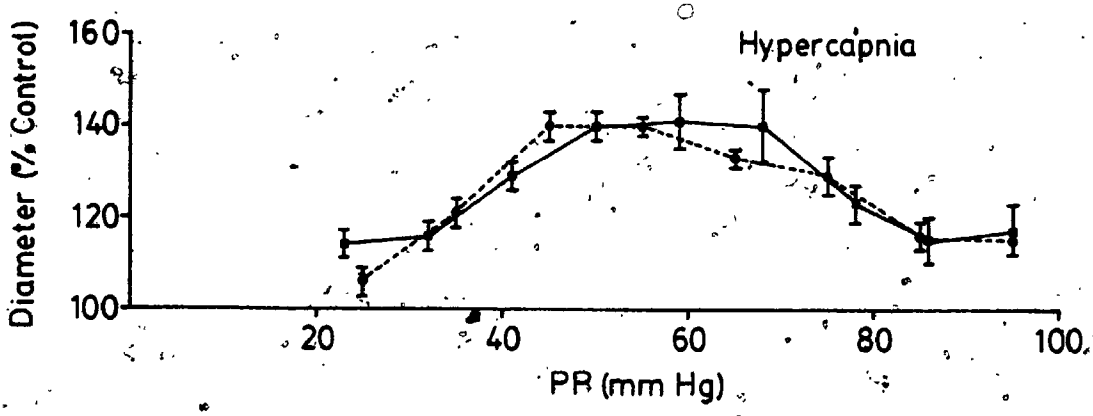

Vessel Size 50-90 µm
Control
Occluded (shifted)
Normocapnia
Diameter (% Control)
160
140
120
100
80
20
40
60
80
100
PP (mm Hg)
*
**
**
Hypercapnia
Diameter (% Control)
160
140
120
100
20
40
60
80
100
PP (mm Hg)
*
CO2 Response
Increase in Diameter (% Control)
40
20
0
-20
20
40
60
80
100
PP (mm Hg)

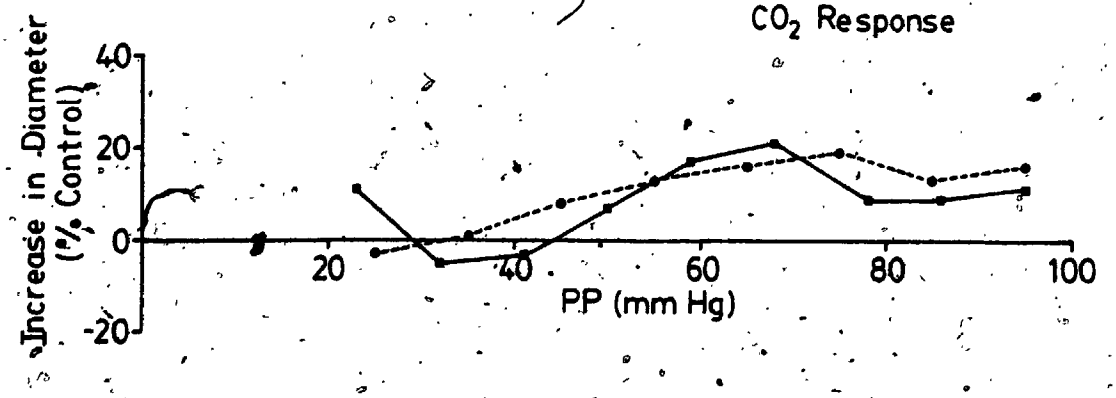
Figure 34

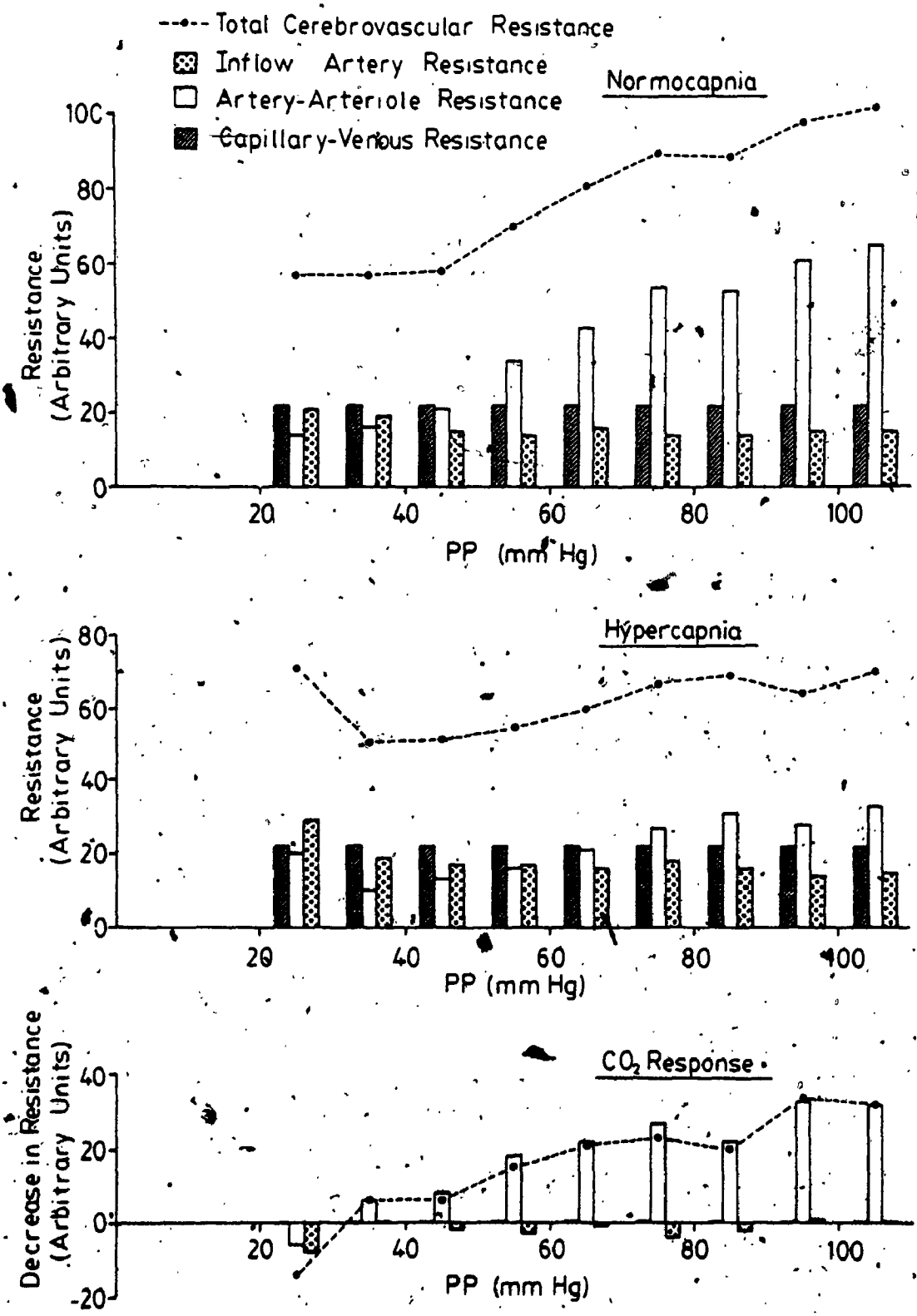
Group III vessel responses of the occluded series are compared to those of control. Occluded values have been shifted to account for the decrease in cerebral PP following occlusion.

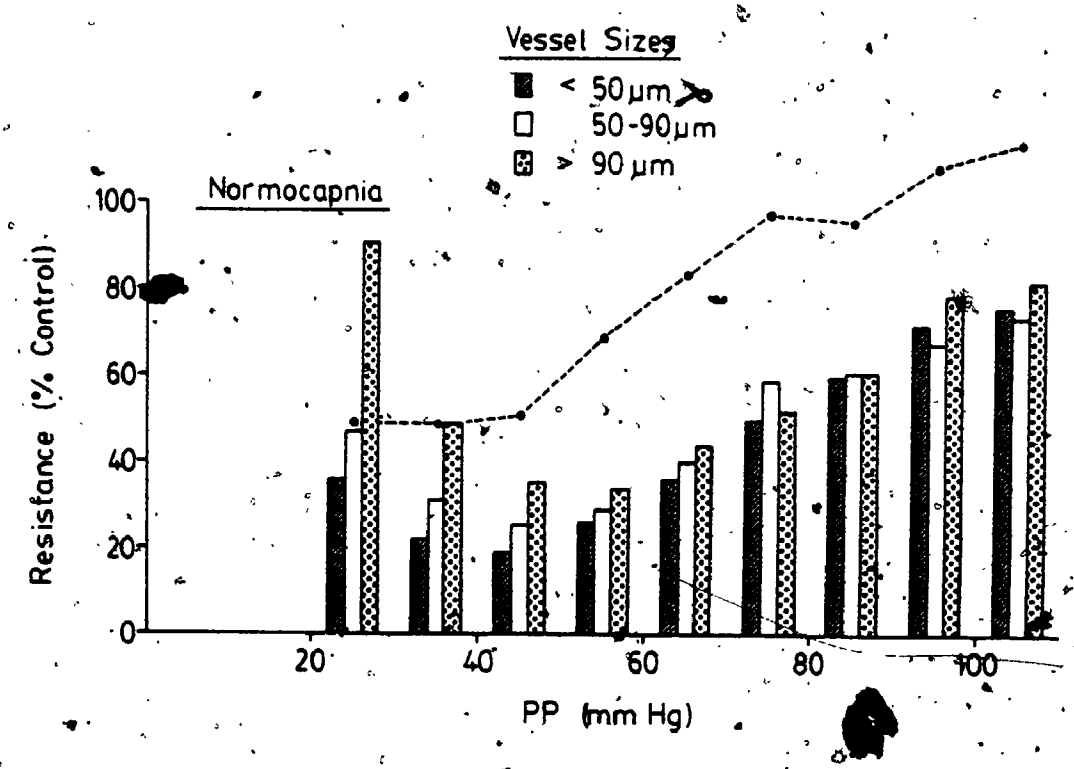
** - $p < 0.01$, statistically different from control

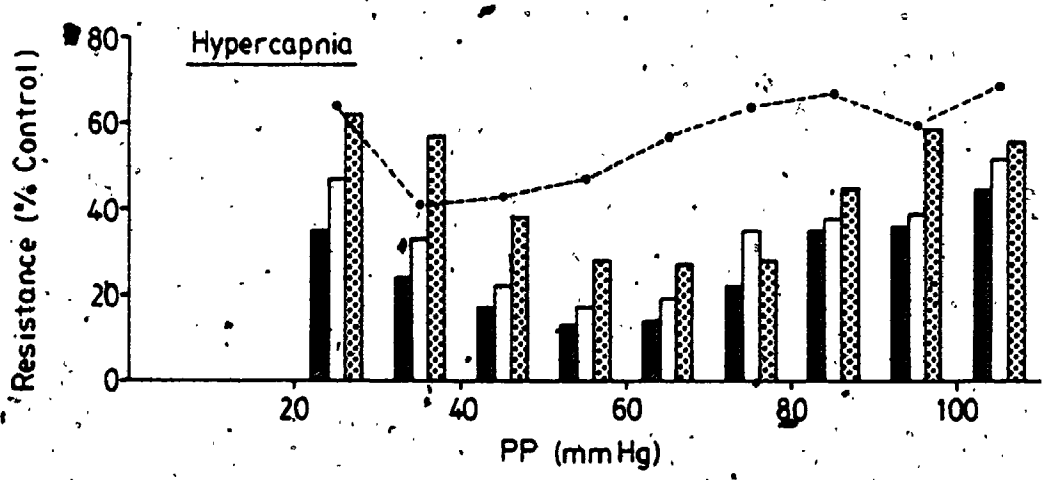

Vessel Size > 90 µm
Control
Occluded (shifted)
Normocapnia
Diameter (% Control)
160
140
120
100
80
20
40
60
80
100
PP (mm Hg)
**

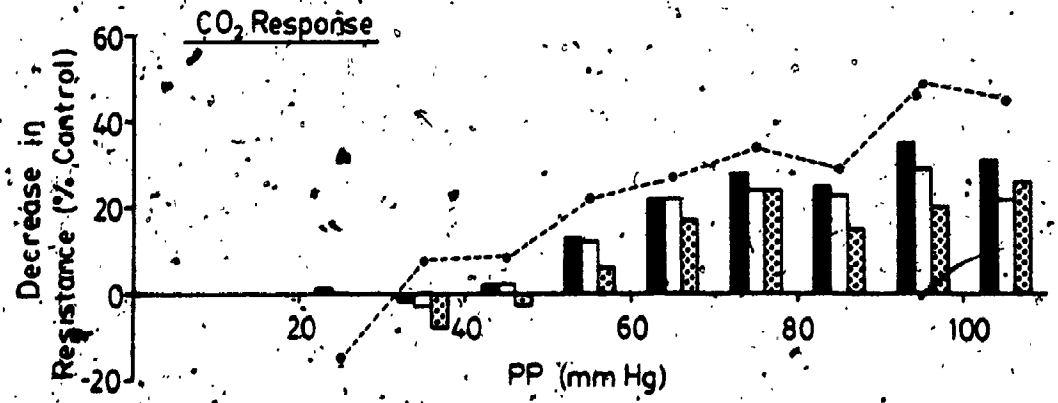

Hypercapnia
Diameter (% Control)
160
140
120
100
20
40
60
80
100
PP (mm Hg)


$CO_2$ Response
Increase in Diameter (% Control)
40
20
0
-20
20
40
60
80
100
PP (mm Hg)


Total Cerebrovascular Resistance
Inflow Artery Resistance
Artery-Arteriole Resistance
Capillary-Venous Resistance
Normocapnia
Resistance (Arbitrary Units)
PP (mm Hg)
Hypercapnia
Resistance (Arbitrary Units)
PP (mm Hg)
$CO_2$ Response
Decrease in Resistance (Arbitrary Units)
PP (mm Hg)


Vessel Sizes
< 50 µm
50-90 µm
> 90 µm
Normocapnia
Resistance (% Control)
100
80
60
40
20
0
20
40
60
80
100
PP (mm Hg)


Hypercapnia
Resistance (% Control)
80
60
40
20
0
20
40
60
80
100
PP (mm Hg)


$CO_2$ Response
Decrease in Resistance (% Control)
60
40
20
0
-20
20
40
60
80
100
PP (mm Hg)

at PP less than 55 mm Hg. All pial vessel groups exhibited a $CO_2$ response at PP greater than 45 mm Hg which paralleled that of total PCR. However, at PP greater than 85 mm Hg, reductions in total PCR substantially exceeded those of pial vascular resistance.

The most apparent difference between the resistance changes following occlusion and those of the control series (see Figure 13) was in the extent to which reductions in pial vascular resistance exceeded those of total PCR. When compared to controls pial vascular resistance was substantially reduced in the occluded series (approx. 25%) and total PCR was higher at intermediate pressures. These changes corresponded to the pial vessel dilation and relatively reduced CBF observed following occlusion. When the two series were compared at equivalent levels of PP (not shown) the majority of these differences were resolved although pial vascular resistance remained lower than control values at high PP and total CVR was greater than that of controls in the intermediate pressure range (50-80 mm Hg).

## 3.5 Inflow Artery Resistance

### 3.5.1 Changes in Vascular Resistance

The pressure measurements of section 3.1 were used to calculate the resistances of three consecutive segments of the cerebrovasculature under unoccluded and occluded conditions. The inflow artery and cerebral artery-arteriole

resistances were calculated from the appropriate pressure gradient (unoccluded or occluded) divided by the corresponding CBF (control or occluded) in each PP range. The capillary-venous resistance was calculated as described in Chapter III Sect. 5.2 - ie. it was assumed to remain constant under the conditions studied.

The resistance changes obtained when all inflow vessels were intact (ie. under conditions equivalent to control) are shown in Figure 36. The resistance of the inflow vessels was essentially constant during hemorrhagic hypotension, increasing slightly at PP less than 45 mm Hg. In contrast, there was an autoregulatory decline in total CVR as a result of a decrease in artery-arteriole resistance. Under hypercapnic conditions the resistance of the large inflow arteries rose slightly as PP was reduced whereas there was a gradual decline in both total CVR and artery-arteriole resistance. The $CO_2$ responses demonstrate that inflow artery resistance either remained constant or increased slightly during hypercapnia whereas both total CVR and artery-arteriole resistance decreased.

The effect of carotid artery occlusion on these vascular resistances is presented in Figure 37. Following occlusion there was an increase in inflow artery resistance from 7 to 15% and a corresponding decrease in artery-arteriole resistance. The subsequent changes in vascular resistance were similar to those described above. Inflow artery resistance did not decrease during hemorrhagic hypo-

Figure 36

Shown are the autoregulatory changes in total CVR and the corresponding alterations in resistance of three different cerebrovascular segments. The resistances obtained at normocapnia, at hypercapnia and the $CO_2$ responses are presented in the upper, mid and lower sections, respectively.

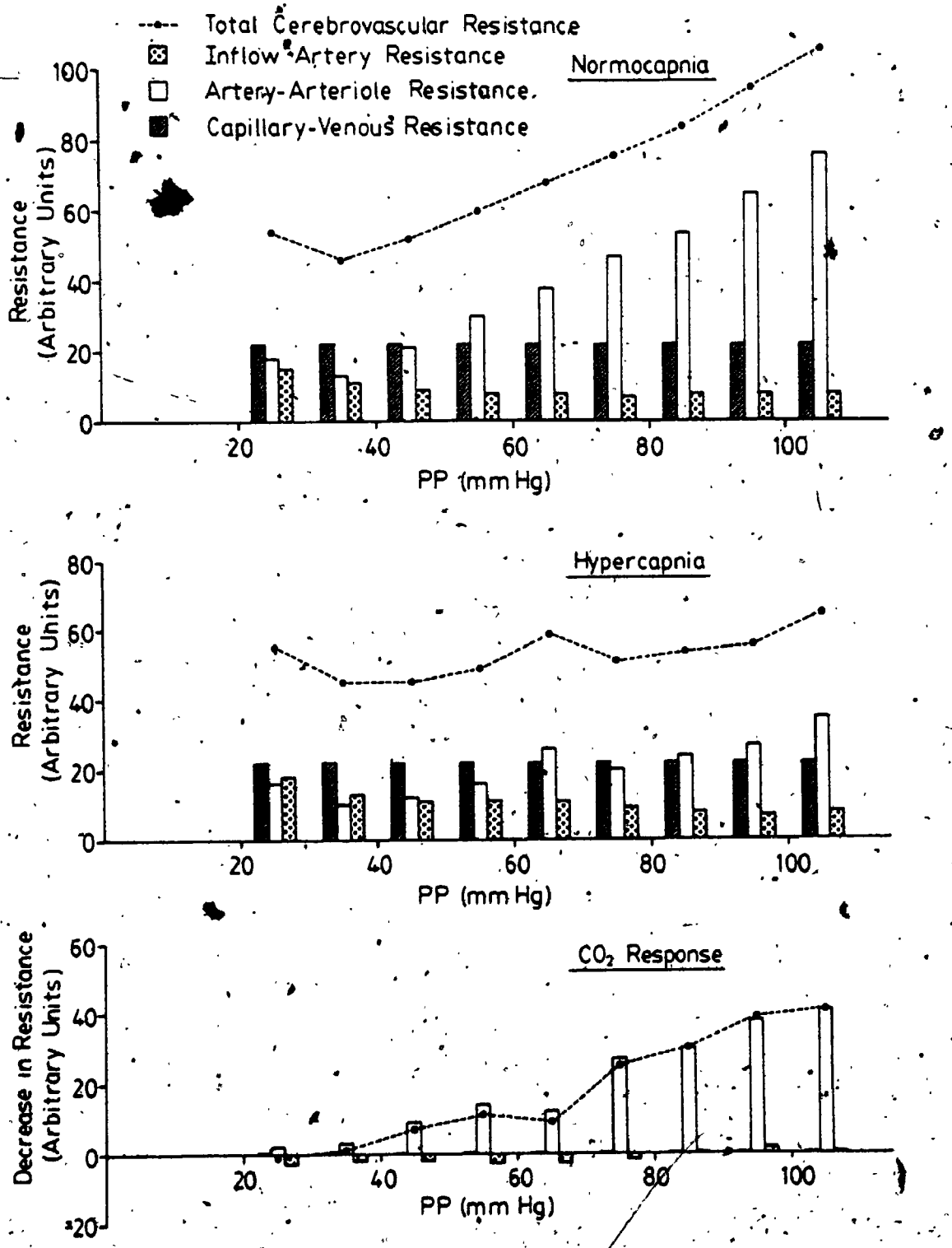
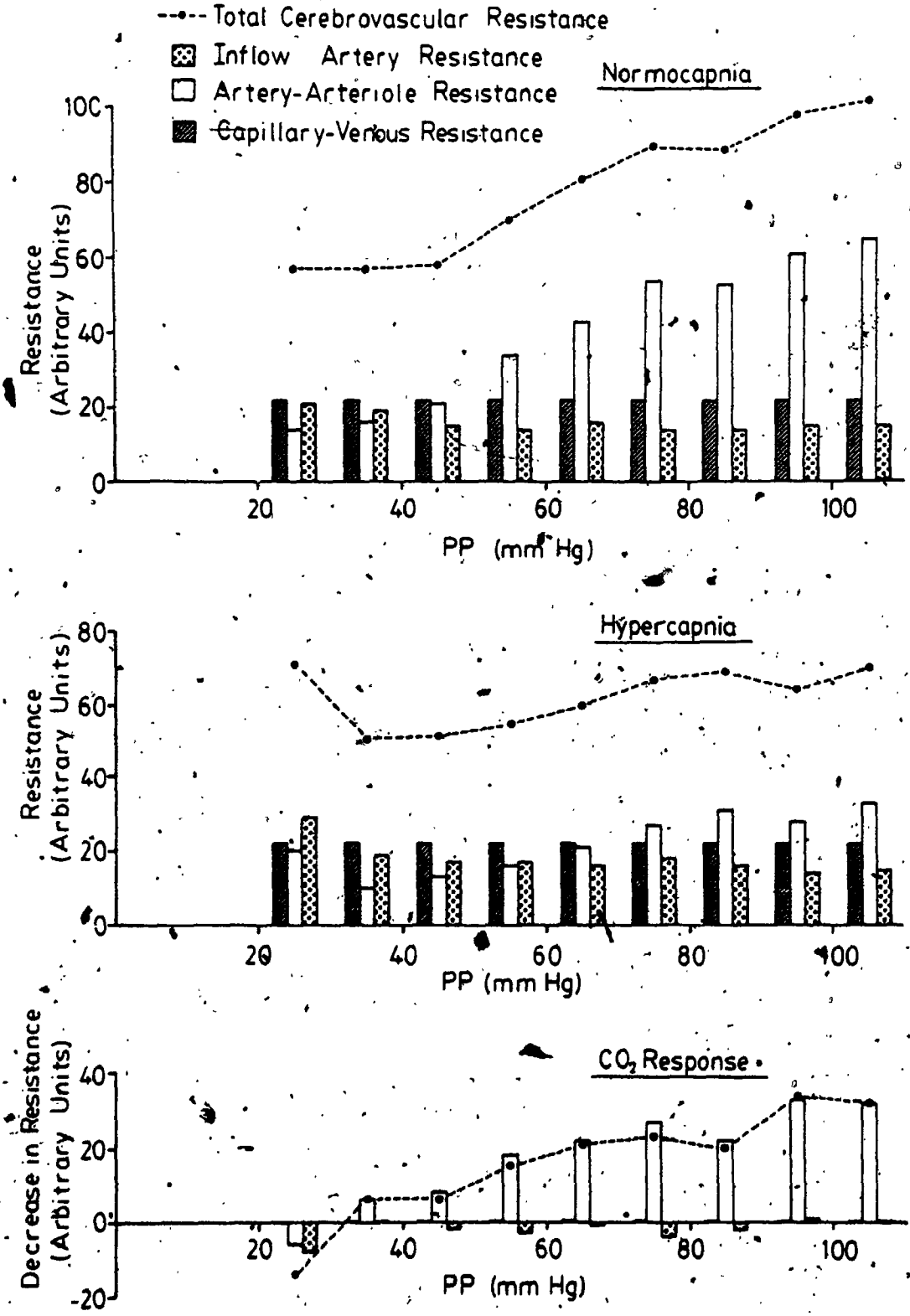

Total Cerebrovascular Resistance
Inflow-Artery Resistance
Artery-Arteriole Resistance
Capillary-Venous Resistance
Normocapnia
Resistance (Arbitrary Units)
PP (mm Hg)
Hypercapnia
Resistance (Arbitrary Units)
PP (mm Hg)
$CO_2$ Response
Decrease in Resistance (Arbitrary Units)
PP (mm Hg)

Figure 37

Shown are the alterations in total CVR and the changes in resistance in each of the three cerebrovascular segments following carotid artery occlusion. Resistances obtained during hemorrhagic hypotension at normocapnia, at hypercapnia and the $CO_2$ response are presented.


Total Cerebrovascular Resistance
Inflow Artery Resistance
Artery-Arteriole Resistance
Capillary-Venous Resistance
Normocapnia
Resistance (Arbitrary Units)
PP (mm Hg)
Hypercapnia
Resistance (Arbitrary Units)
PP (mm Hg)
$CO_2$ Response
Decrease in Resistance (Arbitrary Units)
PP (mm Hg)

tension, hypercapnia or hypercapnia plus hypotension. Rather, the reductions in total CVR were associated with parallel decreases in artery-arteriole resistance.

3.5.2 Distribution of Resistances

Changes in the distribution of resistances (ie. the relative contribution of a particular component to total CVR) are shown in Figure 38 (unoccluded) and Figure 39 (occluded). The resistances in the unoccluded state at normocapnia indicate that at a PP of 105 mm Hg the artery-arteriole component accounted for a major portion of total CVR (72%) whereas the inflow artery and capillary-venous segments made relatively minor contibutions of 7 and 21%, respectively. As PP decreased, a progressively greater portion of total CVR was attributed to the large inflow arteries. At a PP of 35 mm Hg they composed 24% of total CVR and the cerebral arteries and arterioles accounted for only 28%. Under hypercapnic conditions, the initial contributions to total CVR of the artery-arteriole segment decreased whereas that of the other two components increased. The subsequent redistribution of resistances were similar to that at normocapnia. Artery-arteriole resistance accounted for 54% of total CVR at normotension which declined to 22% at a PP of 35 mm Hg. The contribution of the inflow arteries increased from 12 to 29% and that of the capillary venous segment increased from 34 to 49% over this pressure range.

The relative contribution of the inflow vessels was

Figure 38

Diagram presenting the contributions made by the various cerebrovascular components to total CVR. Their resistance redistributions during hemorrhagic hypotension at both normocapnia and hypercapnia are indicated in the bar graphs.

## Distribution of Resistances

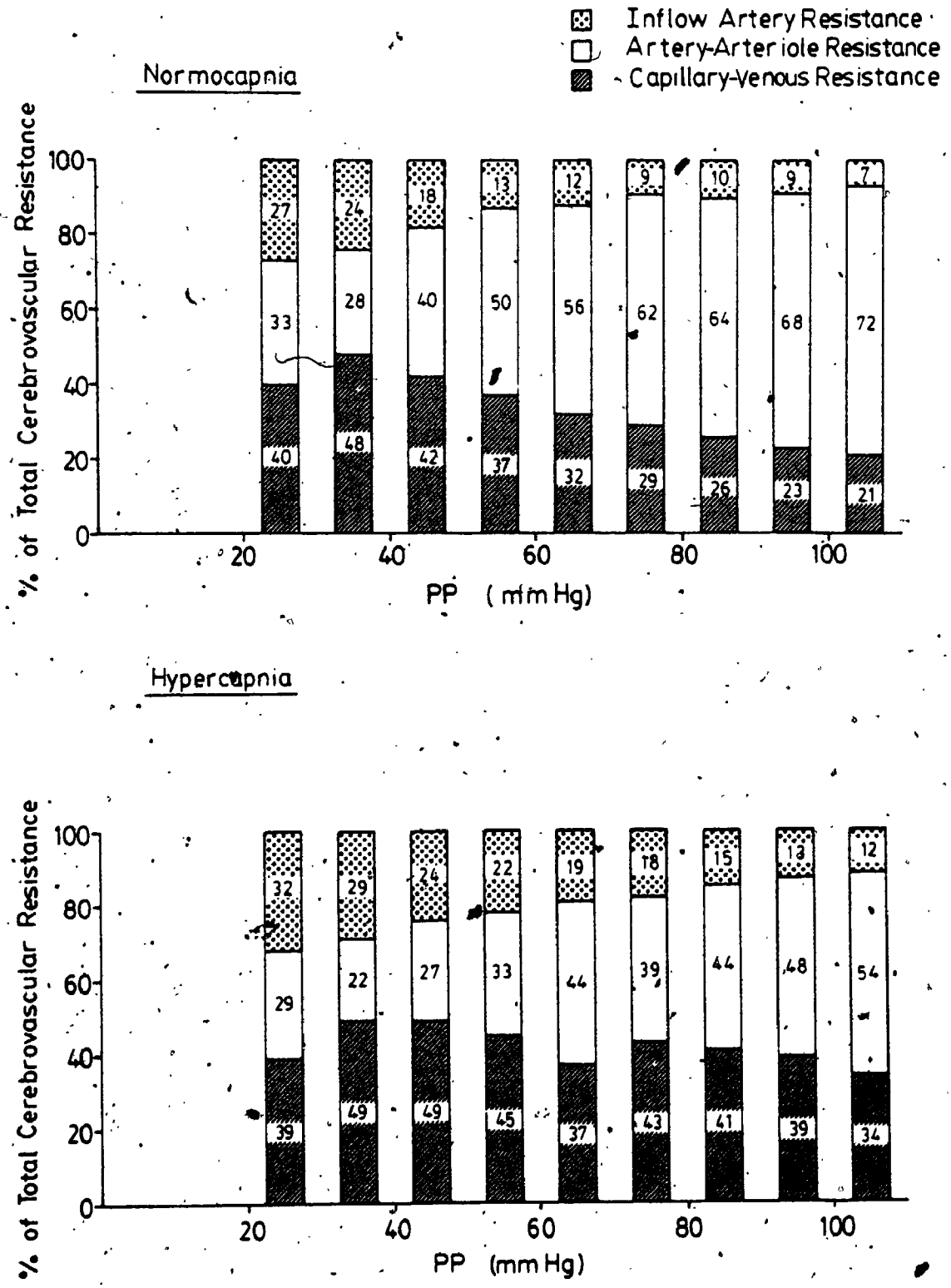
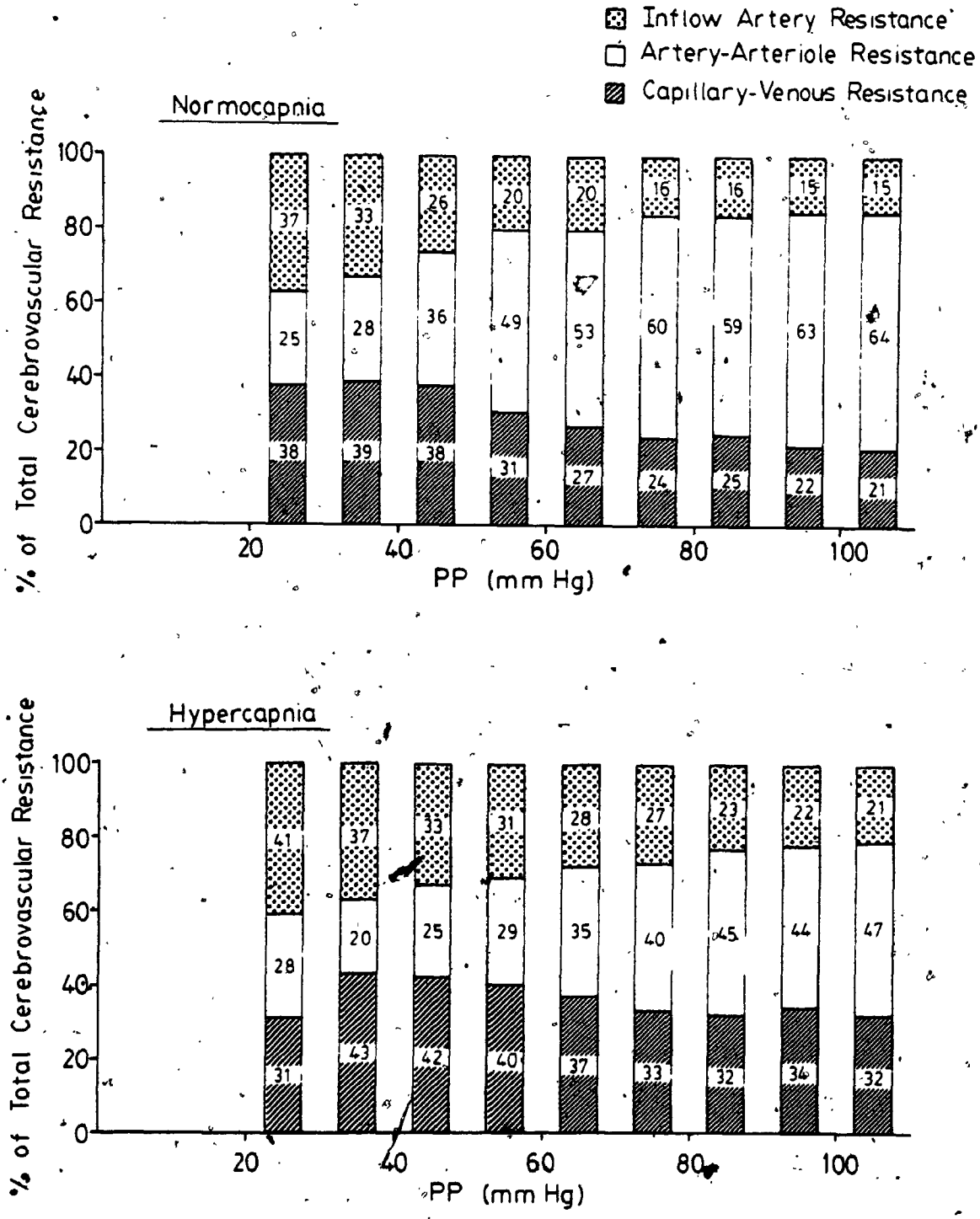


Figure 39

Resistance distributions of the vascular components following carotid artery occlusion. Shown are the contributions made to total CVR at normocapnia and at hypercapnia at each PP level.

## Distribution of Resistances



increased at all PP following carotid artery occlusion (from Fig. 39). This was related to the initial increase in inflow artery resistance and the corresponding decrease in artery-arteriole resistance. During hypotension and hypercapnia the resistances were redistributed in a manner similar to that described in the unoccluded situation.

## 4. Discussion

### 4.1 Carotid Artery Occlusion

#### 4.1.1 Effect of Occlusion at Normotension

Following unilateral carotid artery occlusion in the rabbit there was a 7 mm Hg decrease in the Circle of Willis pressure and inflow artery resistance increased by a factor of two. CBF was maintained at or near control levels by a reduction in total PCR which was reflected in the 22% decrease in pial vascular resistance (ie. a 6% dilation of the pial vessels).

Resistance calculations indicate that the compensatory response of the pial vessels was adequate. Under resting conditions the relative segmental pressure gradients are equivalent to the relative weights (see Appendix 1) of the inflow artery, artery-arteriole and capillary-venous segments (ie. .09, .66 and .25 respectively). If inflow artery resistance increases 100% and capillary-venous resistance is unchanged following occlusion, then total CVR will remain

constant if there is a 14% reduction in artery-arteriole resistance. Therefore the decrease in pial vascular resistance observed would appear to be sufficient to counteract the increase in inflow artery resistance.

There was a slight reduction in the CBF $CO_2$ response and no change in pial vessel reactivity to hypercapnia. Although, the CBF $CO_2$ response following occlusion has been found to be substantially reduced or even abolished following occlusion in man and animals (Pistolese et al., 1971; Dyken, 1972; Sengupta et al., 1973), such a major change in the CBF $CO_2$ reactivity would not be expected in the present study. The change in cerebral perfusion pressure accompanying occlusion was approximately 10 mm Hg during hypercapnia and the control series indicates that CBF is relatively independent of pressure at upper PP levels.

4.1.2 Effects on the Dilative Reserve

The CBF $CO_2$ response during hemorrhagic hypotension was markedly reduced in the occluded group of animals when compared to controls once PP was reduced to 85 or 75 mm Hg. In addition, the PP level at which the CBF and pial vessel $CO_2$ responses were abolished was elevated by 10 mm Hg following occlusion. Both of these observations indicate that there was a reduction in the dilative reserve. Changes in the autoregulatory response also indicated that there was a decrease in the ability of the cerebrovasculature to respond to a dilative stimulus at low pressures. The lower limit of

autoregulation occurred at 45 rather than 35 mm Hg and the pressure at which there was a maximal autoregulatory dilation of the pial vessels was also shifted to a 10 mm Hg higher pressure level. Thus, both the CBF and pial vessel responses demonstrated that there was a reduction in the residual capacity for dilation of the cerebrovasculature following carotid artery occlusion.

4.1.3 The Cerebral Perfusion Pressure

The majority of the changes in the responses of the cerebrovasculature observed following occlusion were associated with the change in the cerebral PP. The lower limit of CBF autoregulation and the pial vessel autoregulatory responses in the control and occluded groups were essentially equivalent following a shift to corrected cerebral PP. Similarily, correcting for reductions in cerebral PP resolved almost all differences between the cerebrovascular (CBF and pial vessel) responses to hypercapnia in the occluded and control groups. In other words, the decrease in dilative reserve following carotid artery occlusion was related to the change in pressure at the Circle of Willis (ie. cerebral PP). The responses of the occluded series were for the most part equivalent to the control series observed at a lower PP level - the pressure change being equivalent to the decrease in the Circle of Willis pressure produced by occlusion.

This analysis demonstrates that the severity of the effects of carotid occlusion will be closely related to the

extent to which the cerebral PP is altered by occlusion. Moderate to severe reductions in the Circle of Willis pressure would cause relatively limited decreases in flow at normocapnia and normotension but would result in a marked decrease in the residual capacity for dilation. A profound reduction in the cerebral PP to levels of 30-40 mm Hg would result in pressure passive changes in CBF and a complete depletion of the dilative reserve. These results also show that CBF could be maintained at control levels to a cerebral PP of approximately 45 mm Hg if the dilative reserve available were utilized fully.

The actual change in cerebral PP resulting from carotid artery occlusion differs greatly from species to species. This variability is a result of variation in the volume flow rate carried by the carotid artery and in the resistance of the collateral vessels. For example, if the occluded vessel had previously supplied a relatively large fraction of the total inflow, then flow in the remaining collaterals must increase substantially resulting in a marked reduction in the Circle of Willis pressure. Similarily, if the collateral arteries are poorly developed or obstructed then these vessels would have a comparatively high resistance to flow which would also result in a profound reduction in cerebral PP.

In many animals with large collateral channels (such as the dog and rabbit) unilateral carotid artery occlusion results in a pressure drop of 20 mm Hg or less at the Circle

of Willis and these animals can survive carotid artery occlusion with no ill effects (Lowe, 1962; Moss, 1974). In contrast, the collateral circulation in some species is poorly developed. The gerbil does not have posterior communicating arteries and may also lack an anastomosis between the right and left anterior cerebral arteries (Berry et al., 1975). In the latter case, unilateral carotid artery occlusion commonly results in cerebral infarction and/or death. Laas et al. (1979) found that a lethal outcome in the gerbil was predictable if the stump pressure (back pressure in the carotid artery) decreased to less than approximately 20 mm Hg. It is clear from the present data that at this pressure level the dilative reserve would be completely depleted and CBF would decrease to ischemic levels.

In the baboon, the pressure in the Circle of Willis is decreased by approximately 15-20 mm Hg following carotid artery occlusion (Jennet et al., 1976). Since this reduction in pressure is relatively minor, one would expect a region of incomplete autoregulation to preceed the onset of pressure passive flow reductions if these animals were subjected to systemic hypotension. The data presented by Sengupta et al. (1974) indicate that a gradual decline in CBF may have occurred at higher pressure levels but the scatter of individual flow measurements makes the positive identification of such a response difficult. Sengupta et al. simply concluded that CBF was pressure passive following carotid artery occlusion in the baboon.

In man, the relationship between cerebral PP and CBF is not well defined. Leech et al. (1974) found that CBF was dependent on the pressure reduction in the internal carotid artery following occlusion, but the large scatter in flow measurements at any one pressure made it impossible to predict CBF based solely on the carotid stump pressure. However, they found that reductions in CBF to less than 20 ml/100g/min (30-40% control) following occlusion were associated with a high incidence of ischemic neurological complications. According to the present study, flow reductions of this magnitude would occur only at pressures below the lower limit of autoregulation and would be associated with a complete loss of the dilative reserve. Clearly, permanent carotid artery occlusion would not be safe under such conditions.

Several factors can contribute to the variability in the relationship between CBF and the carotid stump pressure. For example, patients with occlusive cerebrovascular disease in the distal cerebral vessels would be expected to have a lower CBF than patients with an intact distal vasculature but with equivalent stump pressures. Similarly, individuals with a high intracranial pressure or jugular venous pressure would experience a greater reduction in CBF following occlusion than patients with a normal intracranial pressure. Therefore, the change in the Circle of Willis pressure following occlusion will undoubtedly influence CBF in man but it is not the only factor determining the degree

to which CBF will decrease.

4.1.4 Additional Effects of Occlusion

Following the corrective shift for changes in cerebral PP, several differences between the occluded and control group remained. CBF in the occluded group was less than controls at cerebral PP of 50-75 mm Hg whereas pial vessel dilation exceeded control at cerebral PP greater than 80 mm Hg. Since the CBF $CO_2$ responses were equivalent, the flow decrease at normocapnia was not due to a reduction in the dilative reserve. In addition, since a correction for the change in cerebral PP removed all differences between the pial vessel $CO_2$ responses in the two animal groups, the supplementary dilation at high pressures did not appreciably reduce the residual capacity for dilation. Thus, these changes in cerebrovascular responsiveness did not appear to be related to either decreases in the Circle of Willis pressure or reductions in the dilative reserve.

Although care was taken to avoid disturbing the carotid bifurcation, its manipulation may have altered cerebrovascular responsiveness in one of two ways. It is possible that cerebral metabolism was reduced since a distension of the carotid sinus has been associated with a decrease in the firing rate of cortical pyramidal tract neurones (Coleridge et al., 1976). However, this reduction in metabolism would account only for the CBF decrease and not the supplementary pial dilation observed in the occluded group. [Recall that in the PBZ series there was a reduction

in CBF/metabolism and also a decline in pial vessel caliber.] Alternatively, the baroreceptor and/or chemoreceptors may have been stimulated during occlusion. One would postulate that this neurogenic activation subsequently affected the cerebrovasculature in two ways: by producing a large artery constriction and a compensatory vasodilation distally, thus accounting for the pial vessels responses observed at high PP levels; and by enhancing the effectiveness of the sympathetic activation accompanying hemorrhage which would explain the reduced CBF observed at intermediate PP.

## 4.2 Inflow Artery Resistance

### 4.2.1 Methods

Alterations in the inflow artery resistance in previous studies have been determined using two different methods. Changes in vessel caliber have been measured directly from cerebral angiograms. However, since it is difficult to distinguish the edges of vessels on the X-ray film it is technically difficult to distinguish small changes in caliber. Also many consecutive measurements are not routine or feasible. An alternative method has been to calculate changes in inflow artery resistance based on measurements of the pressure in the Circle of Willis and CBF. In many such studies one or more of the major supply arteries were occluded with a catheter in order to measure the Circle of Willis pressure. The present study has shown that occlusion of an inflow vessel can increase inflow

artery resistance by a factor of two. The present method allows the measurement of the Circle of Willis pressure without interfering with the vascular supply. This pressure provided a determination of inflow artery resistance under normal physiological conditions.

4.2.2 Measurements at Normotension

Although the major component of resistance in most vascular beds is contained in the precapillary arterioles, pressure measurements in the pial arteries (> 150 μm) of the cat, rabbit and monkey have suggested that the large cerebral arteries may contribute substantially (30-40%) to the total CVR (Kahzow and Diekoff, 1969; Fox and Sromberg, 1975; Kontos et al., 1978, Baumbach and Heistad, 1982). This suggested that both the inflow and large pial arteries may play an important role in the cerebrovascular responses to intrinsic dilative stimuli. Studies in which a major inflow vessel was cannulated to obtain the Circle of Willis pressure have reported substantial contibutions (17-30%) of the inflow vessels to total CVR (Heistad et al., 1978; Kontos et al.,1978). The results of the present study indicate that this is probably an overestimate resulting from the measurement technique. I found that the inflow arteries in the rabbit represent only 7% of the total CVR. Other investigators have obtained similar results using a direct puncture of the vessels in the Circle of Willis. These studies showed that inflow artery resistance was approximately 7% in the dog and even less in man (Backay and Sweet, 1952; Knapp et

al., 1965; Ferguson, 1972). The relatively minor contribution of inflow arteries to total CVR under resting conditions indicates that they would not be very effective in subsequently reducing total CVR in response to dilative stimuli.

4.2.3 Responses to Dilative Stimuli

There is some question as to whether or not the large cerebral arteries dilate in response to hypotension. Heistad et al. (1978) found that reductions in inflow artery resistance accounted for 25% of the decrease in total CVR during hypotension. In contrast to these results several studies have shown that the pressure gradient between the aorta and the large cerebral arteries is constant during hypotension (Kanzow and Diekoff, 1969; Kontos et al. 1978). This indicates that inflow artery resistance is stable if one assumes CBF is constant (ie. autoregulation is intact). The present study provided direct evidence that the resistance of the inflow arteries did not decrease dufing hypotension but actually increased at PP less than 45-55 mm Hg. This increase in resistance at low pressures would agree with the results of du Boulay et al. (1972) who found a decrease in the caliber of large inflow arteries during severe pressure reductions of "29 mm Hg or more". It is not clear whether this represented an active vasoconstriction or simply a pressure passive reduction in caliber. One would conclude that the inflow arteries do not participate in the autoregulatory reductions of total CVR.

The responsiveness of the major supply vessels to hypercapnia is also uncertain. The results from angiographic studies suggest that the large basal arteries may be responsive to alterations in $P_aCO_2$ (Kreuger et al., 1963; Petruk et al., 1974). However, Kreuger et al. found that extreme changes in $P_aCO_2$ were required to visualize significant variations in diameter. If $P_aCO_2$ was increased from normocapnia to hypercapnia inflow artery caliber did not increase. Similarily, Petruk et al. (1974) concluded that increases in caliber in response to hypercapnia were most consistent and significant in vessels distal to the inflow arteries (eg. the pericallosal artery). Measurements of inflow artery resistance (from CBF and Circle of Willis pressure) by Levy et al. (1976) demonstrated that resistance did not change during hypercapnia. In the present study the increase in the pressure gradient across the inflow arteries during hypercapnia was proportional to the increase in CBF and inflow artery resistance remained constant. Thus the results of the above studies and those of the present experiments indicate that there is little or no significant dilation of the cerebral inflow arteries following a 20 mm Hg elevation in $P_aCO_2$. In addition, the present data show that the combined dilative stimulus of hypercapnia plus hypotension was also unsuccessful in reducing inflow artery resistance. One would conclude that the inflow arteries are not responsive to hypercapnia (an extremely potent vasodilator) and are unreactive to dilative stimuli in general.

4.2.4 Redistibution of Resistances

The redistibutions in total CBF in response to various dilative stimuli occurred as a result of decreases in the resistance of the artery-arteriole segment and it is these vessels which determine the dilative reserve of the cerebral vasculature. Inflow artery and capillary-venous resistance either remained constant or increased during reductions in total CVR. As a result of this, decreases in total CVR were accompanied by a substantial redistribution of the resistive components. As the contribution of the artery-arteriole component decreased that of the remaining segments increased.

The relatively minor contribution of inflow artery resistance to total CVR was augmented substantially during hypercapnia and hypotension. This indicates that increases in inflow artery resistance (ie. vasoconstriction) would be more likely to cause flow reductions under these conditions. This is supported by the fact that sympathetic stimulation and carotid artery occlusion (both of which increase large artery resistance) have been found to reduce CBF during hypercapnia but not under normocapnic conditions. The greater influence of the large cerebral arteries during PP reductions is evident in patients with arterial spasm (ie. increased large artery resistance). Although CBF was normal in such patients at resting blood pressures, hypotension to a blood pressure of 40 to 50 mm Hg resulted in a 35-65% reduction in CBF whereas in patients without spasm CBF was ob-

served to remain relatively constant (Farrar et al., 1981). Thus increases in inflow artery resistance do not appear to reduce CBF until their contribution to total CVR increases substantially.

## 5. Summary and Conclusions

1. Carotid artery occlusion in the rabbit resulted in a 7 mm Hg reduction in cerebral PP and a dilation of the pial vessels. The 22% reduction in pial vessel resistance compensated for the twofold increase in inflow artery resistance such that total CVR and CBF were essentially constant.

2. At intermediate PP levels, CBF was reduced following occlusion but autoregulation was not abolished. There was sufficient dilative reserve available to return CBF to control levels at all PP above 45 mm Hg.

3. There was a reduction in the dilative reserve following occlusion which was directly related to the change in cerebral PP. Occlusion resulted in a decrease in the CBF $CO_2$ response at high PP and a decrease in the pial vessel $CO_2$ response at 45 mm Hg. In addition, the lower limit of CBF autoregulation and that of pial vessel dilation were shifted to a 10 mm Hg higher PP level.

4. There were additional alterations in cerebrovascular responsiveness following occlusion unrelated to changes in either the Circle of Willis pressure or the dilative reserve. In the occluded group, CBF was reduced at intermediate pressures and there was a greater pial vessel dilation

at high pressures. Both of these effects presumably occurred as a result of manipulation of the carotid bifurcation.

5. The inflow vessels did not dilate in response to reductions in PP, hypercapnia or hypercapnia plus hypotension. The dilative reserve appeared to be contained entirely within the cerebral artery-arteriole component.

6. The contribution of the large inflow arteries to total CVR at normocapnia and normotension was relatively minor under control conditions and doubled following carotid artery occlusion. The proportional resistance of these vessels increased substantially during hypotension and/or hypercapnia and it was suggested that under these conditions changes in inflow artery resistance may significantly influence CBF.

## VII GENERAL DISCUSSION

### 1. Autoregulation of the Cerebrovasculature

In the present study the cerebrovascular response to reductions in PP could be described by the characteristic autoregulatory responses observed in one of three pressure regions. (1) During moderate reductions in PP, the pial vessels dilated progressively and CBF autoregulation was complete. The CBF $CO_2$ response was constant and that of the pial vessels increased. (2) At intermediate PP, autoregulation was incomplete (or impaired). CBF decreased despite a continued autoregulatory dilation of the pial vessels but the decrease in CBF was proportionately less than the reduction in PP. Both pial vessel and CBF $CO_2$ responses diminished progressively as the PP was reduced. (3) The lower limit of autoregulation occurred at a cerebral PP of approximately 35 mm Hg. This pressure level was associated with the onset of pressure passive reductions in both CBF and pial vessel caliber and with a complete loss of cerebrovascular reactivity to $CO_2$.

Previous studies have identified the lower limit of autoregulation as the pressure at which significant reductions in CBF commence. This manner of identification may account for some of the variation in the lower limit of autoregulation reported in the literature. The present study has shown that the onset of flow reductions during hemorrhage merely represents a transition to a region of

incomplete autoregulation. The true lower limit of autoregulation occurs at a considerably lower pressure.

The cause of the autoregulatory impairment at intermediate PP is uncertain. However, the results presented by Fitch et al. (1975) indicate that CBF could have been maintained at control levels during hemorrhage to a blood pressure of approximately 35 mm Hg following alpha adrenergic blockade or cervical sympathectomy. This suggests that the sympathetic activation accompanying hemorrhage may have contributed to the decline in CBF observed at intermediate PP levels.

It is clear that all vessels do not participate equally in the autoregulatory response since there is a marked dependence of vascular responsiveness on vessel size. The large inflow arteries were totally unreactive to dilative stimuli as shown by the essentially constant inflow artery resistance observed during hypotension and/or hypercapnia. Large pial arteries ( $>200$ μm) were not studied. However, Kontos et al. (1978) found that these vessels constricted in response to hypertension but showed very little autoregulatory dilation. I found that the autoregulatory responses of small ( $<200$ μm) pial vessels to hypotension increased with decreasing vessel size. Similar findings have been reported by others (Kontos et al., 1978; MacKenzie et al., 1979). In additon, I showed that the decrease in pial vascular resistance compensated for lesser responses of the more proximal vessels and that the responses of the

smallest vessels ($< 50\ \mu m$) appeared to be representative of those occurring in the intraparenchymal vasculature. Reductions in total CVR closely paralleled the observed changes in pial vascular resistance and one would conclude that the small cerebral vessels play a dominant role in the autoregulatory control of CBF during PP reductions. However, there was a substantial redistribution of resistances during hypotension and/or hypercapnia suggesting that the influence of alterations in inflow vessel resistance on total CVR and CBF would be increased under these conditions.

The majority of current models describing the control of the cerebral circulation are based on the basic concepts contained in the dual effect hypothesis as developed by Harper and colleagues (1972). They proposed that the cerebral circulation behaved as two resistances in series, each under a different control system. They suggested that the extraparenchymal vessels would be influenced by the sympathetic nervous system while the intraparenchymal vessels would be regulated by intrinsic autoregulatory mechanisms. They also suggested that vasoconstriction of the inflow tract arteries would be accompanied by a compensatory (autoregulatory) vasodilation of the intraparenchymal vessels. The present study provides direct evidence that "compensatory" vasodilation does occur in the small cerebral vessels both during hemorrhagic hypotension and following carotid artery occlusion. However, the responses of the small pial vessels appeared to parallel closely those of the

intraparenchymal vasculature under all conditions studied. One would conclude that the division of cerebrovascular resistance into extraparenchymal or intraparenchymal components on the basis of differing control mechanisms does not appear to be justified. The location of the vessels may not be as important a determinant of vascular responsiveness as the size of the vessels under consideration (a similar suggestion has been made by Kontos et al., 1978). As shown by this study and others, the effectiveness of neurogenic and dilative stimuli in altering cerebral vessel caliber is most clearly dependent on cerebral vessel diameter. Large cerebral arteries are influenced to a greater extent than small vessels by neurogenic vasoconstrictive stimuli whereas small vessels are much more reactive to intrinsic dilative stimuli.

There are several possible explanations for the size dependence of the vascular responses to neurogenic versus autoregulatory stimuli. There are a greater number of adrenergic fibers surrounding the large cerebral vessels and this suggests that these vessels may be more sensitive to neurogenic influences due to a higher density of innervation. However, Edvinsson and MacKenzie (1977) have emphasized that small vessels have less smooth muscle and would require fewer nerve fibres to achieve the same density of innervation as the larger vessels. In support of this statement, Kuschinsky and Wahl (1975) found that the response of pial vessels to the perivascular application of

norepinephrine was independent of vessel size. This would suggest that large and small cerebral vessels are equally sensitive to sympathetic stimulation. It is important to note that a generalized vasoconstriction affecting all cerebral vessels (as would be expected during hemorrhage or stimulation of the cervical sympathetic ganglion) would tend to reduce CBF and decrease intravascular pressure in the distal vessels. Therefore, the size dependent responses observed under such conditions could be interpreted as a greater autoregulatory dilation on the part of the smaller vessels in response to metabolic and/or myogenic stimuli. I showed that alpha adrenergic blockade had only a relatively minor effect on pial vascular responses to hemorrhagic hypotension. Thus, one would conclude that the pial vessels exhibit a differential susceptibility to autoregulatory stimuli and that neurogenic influences had contributed very little to this size dependence.

It is possible that the differential autoregulatory responsiveness of the pial vessels is a result of differences in their accessibility to vasoactive substances. The degree of stimulation in small arteries located close to the brain may be more intense than that in large pial arteries which are further removed from the cerebral tissue and vasoactive metabolites. Alternatively, the greater dilative capacity of the small cerebral vessels may be the result of a greater inherent sensitivity to autoregulatory stimuli.

However, since the resistance decreases resulting from hypercapnia (an equivalent dilative stimulus for all vessels) was shown to be much less dependent on size than the autoregulatory response, an inherent differential responsiveness of the pial vessels would seem to be of less importance in determining the autoregulatory response than the proximity of the vessels to vasoactive metabolites in the brain. It is clear that both autoregulatory and neurogenic mechanisms are able to influence vessel caliber and I would suggest that the control of vessel diameter is achieved through a competitive interaction between intrinsic and extrinsic regulatory mechanisms.

2. The Dilative Reserve

The concept of dilative reserve was introduced in this study and has been shown to be a useful indicator of the autoregulatory capability of the cerebrovasculature. The dilative reserve was defined as the cerebrovascular response to a standardized dilative stimulus (a 20 mm Hg increase in $P_aCO_2$) and was thus a relative rather than an absolute measure of the residual capacity for dilation. This fixed stimulus also decreased total CVR (ie. increased CBF) a standard amount, if the neccessary reduction in vascular resistance was possible. A constant CBF response indicated that the dilation required to reduce total CVR in response to hypercapnia was less than the maximal extent to which the cerebral vessels could dilate (ie. the absolute

cerebrovascular reserve). A decrease in the $CO_2$ response indicated that the residual dilative capacity was no longer sufficient to allow the cerebrovasculature to respond fully to this stimulus (ie, the vessels were approaching their maximum degree of dilation). The dilative reserve as discussed below will refer to changes in the residual dilative capacity determined from alterations in the cerebrovascular response to hypercapnia.

The dilative reserve can be increased either by an elevation in the maximal level to which the cerebrovasculature can dilate or by a reduction in the resting caliber of the cerebral vessels. The latter method would increase the residual capacity for dilation but not the maximal dilation attainable. I found that phenoxybenzamine infusion increased the dilative reserve by decreasing the resting CBF and metabolism (ie. reducing vascular diameter). In addition, alpha receptor blockade may have increased the maximal dilation achievable by removing adrenergic tone. However, this was a relatively minor effect.

A decrease in the dilative reserve can occur if vascular dilation is restricted or the resting vessel caliber is increased. I found that carotid artery occlusion increased inflow artery resistance resulting in a compensatory vascular dilation and a reduction in the residual dilative capacity.

The autoregulatory response observed was closely related to the residual capacity for dilation available. Under all experimental conditions examined, depletion of the dilative reserve was associated with a complete loss of CBF autoregulation and a pressure passive decrease in pial vessel caliber. An increase in dilative reserve following alpha-receptor blockade resulted in a relative improvement in CBF autoregulation at intermediate PP. A reduction in dilative reserve following carotid artery occlusion raised the lower limit of autoregulation and decreased the autoregulatory range. Thus, changes in the dilative reserve closely paralleled alterations in the autoregulatory capabilities suggesting that the residual dilative capacity was an important factor in determining the autoregulatory response.

The present study showed that the dilative reserve of the cerebrovasculature is contained entirely within the small cerebral arteries and arterioles. I also found that the responses of the small pial vessels ($< 200$ μm) were closely representative of the dilative reserve of the cerebrovasculature as a whole. Reductions in $CO_2$ reactiviy of both CBF and pial vessel caliber accurately reflected the decline and subsequent depletion of the dilative reserve during hypotension. However, CBF and pial vessel caliber differed in their ability to distinguish the effectiveness of the autoregulatory response. The region of incomplete autoregulation could be identified only from a gradual decline in CBF and not from the pial vessel response. Yet,

in any given animal, it was difficult to determine the lower limit of CBF autoregulation due to the gradual decrease and variability in CBF. The continuous dilation of the pial vessels and the reproducibility of their response allowed the lower limit of autoregulation to be more readily identified from the pressure at which maximal dilation occurred. In summary, I have shown that the small pial vessel responses accurately reflect the dilative reserve and the autoregulatory capability. Therefore, I would conclude that these vessels provide a suitable model for the study of mechanisms involved in the control of cerebral perfusion.

Certain aspects of the present study may be of importance in the treatment of cerebrovascular disease. The results have shown that in the region of incomplete autoregulation CBF decreased despite a substantial residual capacity for dilation. The $CO_2$ responsiveness of the cerebrovasculature indicated that over most of this pressure region, CBF could have been maintained at control levels if the autoregulatory stimuli would have fully evoked the available dilative reserve. Thus, it is possible that in patients with ischemia resulting from cerebrovascular disease, there is a dilative reserve available which, if utilized, could result in a lessening of the CBF reduction and the ischemic deficit. Clearly, the mechanisms responsible for the impairment of CBF autoregulation and the availability and control of the dilative reserve, under normal conditions and during ischemia, are worthy of further investigation.

## APPENDIX 1. CALCULATION OF VASCULAR RESISTANCE CHANGES

### 1. Components of Resistance

The total resistance of a vascular bed ($R_t$) is defined as the ratio of the pressure drop ($\Delta P_t$) to the total flow ($F_t$). As indicated by Burton (1972), successive components of the bed (arteries; large arterioles, small arterioles etc.) are effectively connected in series such that total resistance may also be expressed as the sum of the resistances of the individual components ($R_c$). Thus:

$$R_t = \Delta P_t / F_t = \sum_c R_c \quad \ldots\ldots\ldots (1)$$

where $\sum_c$ represents a summation over all components. Each component will consist of a number of vessels ($N_c$) arranged in parallel such that $R_c$ will be ($1/N_c$) times the resistance of a single vessel ($R_v$). If we assumed that $R_v$ may be described according to Poiseuille's equation (see below), then $R_c$ will be given by:

$$R_c = R_v/N_c = (8/\pi).(L/N_c).(\mu/r^4) \ldots (2)$$

where L = average vessel length, $\mu$ = viscosity and r = vessel radius. Substituting (2) in (1) yields:

$$R_t = \Delta P_t/F_t = \sum_c (8/\pi).(L/N_c).(\mu/r^4) \ldots (3)$$

It is theoretically possible to calculate the total cerebrovascular resistance from measurements of perfusion pressure and flow and to compare these measurements directly to the responses of the individual pial vessel groups. However, in practice, it is often not possible or practical to obtain absolute measurements of many of the above para-

meters. For example, the calculation of total CBF (ml/min) from measurements of mean flow (in ml/gm/min) requires that the total weight of the brain is known. Similarly, the calculation of $R_c$ requires that the average length and total number of vessels of a given size are known for each vascular component. However, since these factors are constant, the resistance relative to a control value is readily calculated.

Converting the values to percentages of control:

$$R_t(\%) = 100 \cdot R_t(\text{test}) \,/\, R_t(\text{control})$$

Substituting for $R_t = PP/(CBF.W_b)$ gives:

$$R_t(\%) = 100 \cdot \frac{[PP/(CBF.W_b)]_{test}}{[PP/(CBF.W_b)]_{control}}$$

where $W_b$ = total weight of the brain (a constant). Thus:

$$R_t(\%) = 100 \cdot \frac{(PP/CBF)_{test}}{(PP/CBF)_{control}} = (PP/CBF)\% \quad \ldots(4)$$

In terms of the individual components, we may write:

$$R_t(\%) = \sum_c \frac{100. R_c(\text{test})}{R_t(\text{control})}$$

and substituting for $100.R_c(\text{test}) = R_c(\text{control}).R_c(\%)$ gives:

$$R_t(\%) = \sum_c \left[ \frac{R_c(\text{control})}{R_t(\text{control})} \cdot R_c(\%) \right] \quad \ldots(5)$$

The first term on the right hand side of equation (5) is a constant equal to the relative contribution of an individual vascular component to the total resistance under control conditions. This term is analogous to a weighting factor since $\sum_c R_c/R_t = 1$ (from equation (1)). Thus, equation (5) states that changes in total resistance will represent the average (weighted mean) response of all cerebral vessels to a given stimulus.

The response of an individual group of vessels will be given by:

$$R_c(\%) = 100 \cdot \frac{[(8/\pi).(L/N_c).(\mu/r^4)]_{test}}{[(8/\pi).(L/N_c).(\mu/r^4)]_{control}}$$

which reduces to:

$$R_c(\%) = (\mu/r^4)\% \quad \ldots\ldots\ldots\ldots(6)$$

Therefore, the resistance of the vascular components may be calculated from measurements of $\mu$ and r.

## 2. Viscosity

It is important to note that viscosity cannot be considered as constant in these experiments since the viscosity of blood decreases with decreasing vessel radius

(the Fahraeus-Lindquist effect). The relationship between the effective viscosity in a tube of radius r ( $\mu_r$) to that in a tube of infinite radius ( $\mu_\infty$) was given by Burton (1965) as:

$$\mu_r = \mu_\infty / (1 + d/r)^2 \quad \ldots\ldots\ldots (7)$$

where d is the diameter of the particles in the perfusate. This correction was applied in the calculation of pial vascular resistance using a value of d=6 microns.

The effect of this correction on the calculation of pial vascular resistance is shown in the following example. The diameter of Group I vessels increased from a control value of 38 microns at a PP of 95 mm Hg, to 62 microns at a PP of 35 mm Hg. According to equation (6), the uncorrected resistance ( $\mu = \mu_\infty$ = constant) would decrease from the control value ($R_c$) to 0.13 $R_c$ as a result of the dilatation. Correcting for the Fahraeus-Lindquist effect according to equation (7) decreases the control resistance to 0.58 $R_c$. This corrected resistance ($R_c^1$) would then be reduced to .16 $R_c$ (.09 $R_c^1$) at the lower pressure. Thus, the major effect of this correction was to reduce the absolute value of vascular resistance whereas its effect on the calculation of changes in resistance as a percent of control was relatively minor.

It is also well known that changes in hematocrit will alter the apparent viscosity of blood. In three animals in which hematocrit was measured over the entire pressure range, we found that hematocrit decreased from approximately

0.40 to 0.34 in the latter stages of hemorrhage (PP = 55-35 mm Hg). According to the equations given by Charm and Kurland (1974) (pages 32-33), this would reduce viscosity by a factor of 0.90 (at a PP of 35 mm Hg) and the corresponding decrease in resistance (from the previous example) would be approximately 1.5%. Since we did not monitor hematocrit routinely in the present experiments, the data were not corrected for this factor. However, such corrections would be small and would affect only the lower pressure ranges.

### 3. Applicability of the Poiseuille Equation

Poiseuille's equation was developed to describe the steady flow of a Newtonian fluid through a rigid cylindrical tube (McDonald, 1974). That is:

$$F = \pi . \Delta P . r^4 / (8L . \mu)$$

In order to use this equation for the calculation of pial vascular resistance (i.e. in equation (2) above), one must first examine the extent to which the assumptions made in its derivation will apply to the pial vasculature. The following assumptions were required:

1. The fluid does not slip at the wall. It is generally agreed that the fluid velocity is zero at the vessel wall and, as discussed in detail by McDonald(1974), the validity of such an assumption is assured.

2. The tube is rigid. Although the diameter of small vessels does vary throughout the cardiac cycle, the fluctuations are very small and are much less than those of the

larger vessels (the largest fluctuation being approximately ± 2.5% of the mean diameter in the proximal aorta) (McDonald, 1974). Thus, any error arising from this approximation would be insignificant when compared to the changes in diameter resulting from active dilatation (30-60%).

3. Flow within the tube is fully developed and laminar. This condition will be satisfied providing the Reynolds number ($Re = 2.r.\bar{v}.\rho / \mu$) is less than approximately 500 and the entrance length ($Le = 0.16.r.Re$) is small compared to the length of the vessel (where $\bar{v}$=mean velocity and $\rho$ = density of the fluid) . The mean velocity of flow in the largest vessels of the present study (r = 0.008 cm) would be approximately 1-2 cm/sec (Gaehtgens et al., 1970). Assuming a viscosity of 0.02 poise and a density of 1.05 g/cm$^3$ for blood (Charm and Kurland, 1974), the calculated Reynolds number would be less than 2 and the entrance length required to establish a parabolic velocity profile would be less than 30 microns. Therefore, the assumption of fully developed laminar flow is justified for the pial vessels.

4. The viscosity of the fluid is constant and independent of the shear rate. As discussed above, the viscosity of blood decreases in small vessels (the Fahraeus-Lindquist effect) and this must be taken into account when calculating an "absolute" value for vascular resistance. When resistance is expressed as a percentage of control, the effect is relatively minor. Blood also exhibits anomolous viscous properties at low rates of shear. For blood with a cell

volume fraction (hematocrit) of 0.40, the apparent viscosity increases at shear rates less than 100 $sec^{-1}$ (Charm and Kurland, 1974; McDonald, 1974). The shear rate ($\dot{\gamma}$) within the pial vessels may be estimated by $\dot{\gamma} = 4.\bar{v}/r$ and will be approximately 500-1000 $sec^{-1}$. Thus, providing flow remains above 20% of control values, viscosity may be considered independent of the shear rate.

## APPENDIX 2. ANALYSIS OF THE HYDROGEN CLEARANCE CURVE

The theoretical model upon which the calculation of CBF is based was developed by Kety (1951). It considers the exchange between tissue and blood of a freely diffusible tracer that is neither utilized nor produced in the tissue. The increase in the amount of tracer substance within a tissue compartment per unit time is equal to the rate at which the tracer is brought to the tissue in the arterial blood less the rate at which it is removed in the venous blood. This is the Fick priciple, a law of conservation of mass, which can be stated mathematically as

$$dQ_i/dt = F_i(C_a - C_{vi}) \quad \ldots\ldots\ldots\ldots(1)$$

where $Q_i$ is the quantity of tracer in the tissue compartment i, $F_i$ is the rate of blood flow in that compartment, $C_a$ is the arterial concentration of tracer and $C_{vi}$ is the venous concentration of tracer.

If it is assumed that the tissue compartment is instantaneously in equilibrium with the blood, then the venous concentration and tissue concentration of the tracer are proportional, or

$$C_{vi} = C_i/\lambda_i \quad \ldots\ldots\ldots(2)$$

where $\lambda_i$ is the tissue :blood partition coefficient. According to Kety, $\lambda_i = V_i/W_i$ where $V_i$ is the volume of distribution and $W_i$ is the weight of the tissue in which the tracer is distributed. Note that the tracer concentration in the tissue compartment is just the quantity of tracer

divided by the weight of the tissue. That is

$$C_i = Q_i/W_i \quad \ldots\ldots\ldots(3)$$

Substituting the last two equations into equation (1) yields,

$$dC_i/dt = (F_i/W_i)\,(C_a - C_i/\lambda_i) \quad \ldots\ldots\ldots(4)$$

Analysis: The tracer in the present experiments, hydrogen gas, is delivered such that the arterial concentration of tracer is constant. During saturation the solution to (4) is:

$$C_i(t) = \lambda_i\, C_a(1-e^{-k_i t}) \quad \text{where } k_i = F_i/\lambda_i W_i.$$

Following saturation of the tissue, ie. for t large,

$$C_i = \lambda_i C_a.$$

Since $\lambda = 1$ for hydrogen, the concentration($C_o$) in the tissue of all compartments at the start of desaturation is equal to the arterial concentration. During desaturation, the hydrogen is rapidly cleared from the lungs such that the arterial concentration falls to zero within 10-20 sec. Under these conditions (ie. $C_a = 0$), the differential equation (4) is reduced to

$$dC_i/dt = -k_i C_i \quad \ldots\ldots\ldots(5)$$

The solution is

$$C_i(t) = C_o\, e^{-k_i t} \quad \ldots\ldots(6)$$

where $k_i = F_i/\lambda_i W_i = F_i/W_i = f_i$ the flow per unit weight of tissue and $C_i(t)$ is the tissue concentration within the compartment at time t. Clearly a semilog plot of $C_i(t)$ versus time would be linear.

Frequently, using the hydrogen clearance technique, the total concentration $C_t(t)$ within a tissue is obtained from more that one compartment. In general, if all compartments are assumed to be in parallel then $C_t$ is just a weighted sum of the concentrations within each compartment. That is

$$C_t(t) = \sum_i w_i C_o e^{-k_i t} \quad \ldots\ldots\ldots(7)$$

where $w_i$ is the relative weight of each compartment such that $\Sigma w_i = 1$. In the present study, the clearance of tracer was from tissue containing compartments with a fast flow ($f_1$) and a slow flow ($f_2$). Equation (7) for two compartments would be

$$C_t(t) = w_1 C_o e^{-f_1 t} + w_2 C_o e^{-f_2 t} \quad \ldots\ldots\ldots(8)$$

(as $\lambda = 1$ for hydrogen). Since $f_1$ is greater than $f_2$ (approx. 3 times), the first term of equation (8) approaches zero for t large, ie.

$$C_t(t) \sim w_2 C_o e^{-f_2 t} \quad (t \text{ large})$$

$$\text{or } \ln C_t(t) \sim \ln(w_2 C_o) - f_2 t \quad \ldots\ldots\ldots(9)$$

Thus a semilog plot of the clearance curve, $C_t(t)$ versus t is linear (for large t) with a slope of $-f_2$ and a log intercept of $I_2 = \lambda_2 C_o$ (see Figure 7). Regression analysis of points in the final 2-3 minutes ($t \geq 5$ min) of the semilog plot determines this slope and intercept. The values of the second term of equation (8) are then calculated for small t. Rearranging equation (8) yields,

$$C_t(t) - w_1 C_o e^{-f_1 t} = w_2 C_o e^{-f_2 t} \quad \ldots\ldots\ldots(10)$$

where the left hand side is the original clearance curve

less the extrapolated values of the slow flow component for all t. Taking the logarithm, equation (10) becomes

$$\ln[(C_t(t) - w_1 C_o e^{-f_1 t}] = \ln(w_2 C_o) - f_2 t \quad .....(11)$$

Thus a semilog plot of the left hand side of (10) is linear and $f_2$ and $w_2 C_o$ are determined from the slope and intercept respectively. The mean flow $f_m$ is just

$$f_m = w_1 f_1 + w_2 f_2$$

or substituting the values of the intercepts determined from the semilog plots

$$f_m = (I_1 f_1 + I_2 f_2)/(I_1 + I_2)$$

where the relative weights are

$$w_1 = I_1/(I_1+I_2) \quad \text{and} \quad w_2 = I_2/(I_1+I_2).$$

An alternative analysis of the clearance curve was introduced by Symon et al. (1974). This analysis considers only the initial 1-2 minutes of the clearance curve, as the initial clearance can be represented by a monoexponential. A semilog plot of the curve has a linear segment with a slope equal to the initial slope index of flow. Since biexponential analysis requires 8-10 minutes of stable flow conditions and clearance, the initial slope analysis is suitable for relatively short periods (2-3 min) of stability.

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