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CHANGES IN REGIONAL CEREBRAL BLOOD FLOWS DURING CHRONIC EXPERIMENTAL PERINEPHRITIC HYPERTENSION IN THE DOG

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CHANGES IN REGIONAL CEREBRAL BLOOD FLOWS DURING CHRONIC EXPERIMENTAL PERINEPHRITIC HYPERTENSION IN THE DOG

By

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ABSTRACT

CHANGES IN REGIONAL CEREBRAL BLOOD FLOWS DURING
CHRONIC EXPERIMENTAL PERINEPHRITIC
HYPERTENSION IN THE DOG

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The current study compares regional cerebral hemodynamics in the same dogs before and during chronic perinephritic hypertension as well as acute Angiotensin II induced hypertension. The radioactive microsphere (15μ) distribution technique was used to measure regional cerebral blood flow (rCBF) in anesthetized dogs.

Following six weeks of chronic hypertension, mean aortic blood pressure increased from 129 mm Hg to 177 mm Hg. Regional CBF measured at this time was significantly elevated above control ($p < 0.05$) in the medulla, pons, hypothalamus, thalamus, cerebellum and cortex. Regional cerebral vascular resistance (rCVR) decreased significantly in the medulla and hypothalamus.

The acute elevation of blood pressure to moderate and severe levels resulted in no change in rCBF with the exception of the cortex, where it was elevated. The maintenance of normal rCBF was associated with increased rCVR.

It is concluded that the cerebral circulation maintains normal rCBF during acute hypertension, but increased rCBF is found during chronic hypertension.

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This thesis is dedicated to my family, for their unfailing love and support.

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INTRODUCTION

The effect of chronic hypertension on the cerebral circulation has not been clearly established. The majority of the research up to now has dealt with changes in cerebral hemodynamics in response to acute elevations in arterial blood pressure. Such data could prove to be quite different from the effects of chronic hypertension on the cerebral circulation.

Two basic theories have evolved to explain the response of the cerebral circulation to sustained, increased arterial blood pressure. The first theory, as supported by Kety et al. (1948) and Byrom (1954) suggests that increased arterial blood pressure causes a sustained autoregulatory response (vasoconstriction) in the cerebral vasculature, which maintains cerebral blood flow at normal levels. A sustained increase in cerebral vascular resistance can lead to segmental arteriolar vasospasm, producing a reduction in local blood flow, focal ischemia and tissue damage. It is therefore suggested that this mechanism may be a factor in the genesis of hypertensive encephalopathy.

A second theory, which draws experimental evidence from Strandgaard et al. (1974) and Johansson (1974 a, b, c) suggests that the increase in arterial blood pressure during acute hypertension exceeds the ability of the cerebral vasculature to autoregulate (also described as a possible exhaustion of the Bayliss response), causing a forced, passive dilation of the resistance vessel, which is thought to cause vessel wall damage, increased permeability, net filtration, focal cerebral edema and

damaged brain tissue. Under these conditions, blood flow increases in proportion to the increase in pressure.

The purpose of this research is to examine and compare chronic perinephritic hypertension and acute Angiotensin II induced hypertension in relation to their effects on regional cerebral blood flow and regional cerebral vascular resistance as measured by the radioactive microsphere distribution technique. Regional studies of this nature have not appeared in the literature to date. The effects of chronic hypertension on the cerebral circulation is not only of interest from a physiological standpoint; it is also of clinical importance in such conditions as human essential and renovascular hypertension.

SURVEY OF THE LITERATURE

Essential Hypertension

Essential hypertension accounts for over 90% of all cases of human hypertension. Hypertension is defined as an elevation of arterial blood pressure, and is characterized in its chronic form by a normal cardiac output and an elevated total peripheral resistance (Frohlick et al., 1967; Varnaukas, 1955).

Cardiac Output

In the early or borderline stage of human hypertension, cardiac output is believed to be elevated, accompanied by a normal or even decreased total peripheral resistance. In a relatively recent report, a group of patients with borderline hypertension were found to maintain a significant elevation of cardiac output for more than fifty months (Julius and Schork, 1971). However, this period of elevated cardiac output in the initial stages of essential hypertension is for the most part a transient one, as there is a tendency for cardiac output to return to normal as total peripheral resistance increases, thereby maintaining arterial pressure at an elevated level (Eich et al., 1966).

The mechanism of initial increase in cardiac output in borderline hypertension is unknown. Cardiac output is increased by an increase in heart rate and/or an increase in stroke volume. There are several suggested mechanisms which could increase cardiac output. Autonomic disturbances could increase heart rate above normal. Increases in intravascular fluid volume with unchanging vascular capacitance, or decreased

venous capacitance with unchanging intravascular fluid volumes would lead to increased venous return and thereby increase cardiac output.

Vascular Compliance

Changes in vascular compliance have been implicated in playing a role in the genesis and/or maintenance of essential hypertension. Compliance is described in terms of unit of volume change per unit of pressure change.

$$C = \frac{\Delta V}{\Delta P}$$

The structural components of the vessel wall, smooth muscle, elastic collagen, and ground substance determine the relative distensibility of the vessel and therefore contribute to compliance.

Changes in arterial pressure-volume relationships were studied by Green et al. (1966) in normotensive and hypertensive subjects, using the isolated, temporarily occluded segment of the brachial artery. These direct measurements of compliance during stepwise increments of intravascular pressure determine the hypertensive group to have a decreased compliance as compared to normotensive. This finding may be explained on the basis of structural vascular changes involving medial (smooth muscle) hypertrophy, thickening of the elastic intima and increased electrolyte and water content. Such changes have been observed in both large and small arteries in hypertensive patients (Pickering, 1972).

Measurements of venous compliance in human essential hypertension have been made by indirect methods by Caliva et al. (1963) in the digit and by Walsh et al. (1969) in the forearm. Both author's results indicate that in addition to decreased arterial compliance, venous compliance

is probably decreased as well. It is noted that a decreased venous compliance would decrease the capacitance of the veins, and thereby increase venous return and cardiac output, contributing to the genesis and/or maintenance of the hypertensive state.

On the other hand there is evidence which indicates that venous compliance is not decreased in hypertension. Abramson and Fierst (1942) studied venous distensibility in the hypertensive human. Their results were similar; they found no difference in venous distensibility in hypertensives as compared to normotensives.

Decreased arterial compliance in essential hypertension has been well established. The underlying mechanism appears to be increased smooth muscle tone and medial hypertrophy. However, the evidence for decreased venous compliance is inconclusive.

Blood Volume

Investigations into the role of blood volume in human essential hypertension seem to indicate that blood volume is related to the degree of severity of the hypertension. In hypertensive men with a supine diastolic blood pressure of greater than 105 mm Hg, blood volume was found to be reduced, and continued to decrease with increasing diastolic pressures (Bello et al., 1965; Tibblin et al., 1966; Dustan et al., 1973). It was also reported by Dustan et al. (1973) that extracellular fluid volume was normal, but the ratio of plasma volume to interstitial fluid volume was significantly reduced in essential hypertension. It was suggested that this may reflect increased capillary hydrostatic pressure.

Regional Hemodynamics

Efforts to determine which regions of the body are associated with the increase in total peripheral vascular resistance in human subjects with essential hypertension suggest that increased vascular resistance is distributed uniformly throughout the systemic circuit, with the exception of the kidneys which exhibit a greater increase in resistance, and skeletal muscle beds, which exhibit a relatively lesser increase or even a decrease in resistance.

Renal, splanchnic, skin and muscle blood flows and resistance were measured simultaneously in men with essential hypertension, and whose cardiac outputs were found to be similar to normotensives (Brod et al., 1960, 1962). Renal blood flows were measured by the para-amino-hippurate clearance method, splanchnic flows by the rose-bengal disappearance method, skin flows by the heated thermocouple, and muscle flows by the occlusion plethysmograph method. The results indicate that compared to normotensives, the hypertensive group had higher resistances at rest in the renal, skin and splanchnic circuits, and lower vascular resistances in the muscle beds. This would suggest a shunting of blood flow from viscera and skin to muscle. It was further suggested by the authors that an autonomic nervous system dysfunction may contribute to these hemodynamic derangements in human essential hypertension.

Studies by Overbeck et al. (1969), using an indicator dilution technique to measure blood flow in the entire forearm and hand of essential hypertensive and normotensive subjects, determined blood flows to the forearm to be similar in the two groups. However, calculated mean forearm vascular resistance was significantly greater in the hypertensive group.

Amery et al. (1969) conducted a study of muscle blood flow in the tibialis anterior muscle using the ^{133}Xe clearance method in hypertensive and normotensive male subjects. Their results indicate that at rest, the hypertensive group exhibits both increased muscle blood flow as well as increased muscle vascular resistance. This suggests that the muscle vasculature plays a role in the increase in total peripheral resistance, but to a lesser degree than the majority of the systemic circuit.

It is well documented that renal blood flow is reduced in essential hypertension. It has also been shown that the reduction of renal blood flow is directly related to the severity of the hypertension. Reduction of renal blood flow is related to an increase in renal vascular resistance which is greater than the increased resistances seen in other regional vascular beds (Goldring et al., 1941; Ladefoged et al., 1969; Hollenberg et al., 1969).

In regard to other regional vascular beds, results have shown normal blood flows and increased vascular resistances in essential hypertension in the skin (Brod et al., 1962), the digit (Caliva et al., 1963), the hand (Stead et al., 1940) and the splanchnic bed (Culbertson et al., 1951).

Neurogenic Mechanisms

Neurogenic dysfunction has been implicated as a possible trigger mechanism for the genesis of hypertension. Dickenson (1965) is a strong supporter of the theory that a steadily increased sympathetic discharge is responsible for the genesis of the hypertensive state. The increased heart rate and cardiac output of those patients with early borderline hypertension could reflect involvement of the sympathetic nervous system.

Daily environmental stress and consequent cortico-hypothalamic influences on cardiovascular control has also found support from several studies (Cruz-Coke et al., 1964; Henry and Cassel, 1969). Englemann et al. (1970) and Louis (1973) have reported increased levels of catecholamines in patients with essential hypertension, and Nestel (1969) reported increased urinary excretion of catecholamines after mental stress in a group of borderline hypertensive patients, which may also indicate a possible neuro-humoral mechanism.

Humoral Mechanisms

The renin-angiotensin system has been under investigation as a possible contributor to the genesis or maintenance of essential hypertension. The release of renin by the renal juxtaglomerular cells is normally suppressed by increased pressure in the afferent arteriole. Therefore renin levels should be suppressed in patients with essential hypertension. However, renin levels in patients with hypertension are equal to those in normotensive patients (Kaplan, 1973). Catt et al. (1971) have shown increased circulating angiotensin II in the blood of approximately 50% of their patients with essential hypertension. Sambhi et al. (1975) reported increased rates of angiotensin generation in response to renin in patients with essential hypertension. This data would indicate that there may be some disturbances in this system during hypertension, and that the hypertensive patient may be more sensitive to released renin than the normotensive, however, there is no evidence that this system is directly involved in the pathogenesis of this condition.

Disturbances of the renin-angiotensin system might also be reflected in altered plasma levels of aldosterone. Increased levels of aldosterone could increase sodium retention, increase intravascular fluid

volumes and thus contribute to the hypertensive condition. Lommer et. al. (1972) reported normal urinary excretion and secretion rates as well as normal plasma levels of aldosterone in a large group of patients with essential hypertension. Aldosterone has since been essentially eliminated as a prime mediator in the pathogenesis of essential hypertension.

Experimental Renovascular Hypertension

Goldblatt et al. (1934) pioneered an experimental model for the study of hypertension which involved the constriction of one or both renal arteries. By constricting only one renal artery he was able to produce a mild, transient elevation of arterial blood pressure in dogs. This is known as two kidney Goldblatt hypertension. Constriction of both renal arteries, or constriction of one renal artery accompanied by the removal of the contralateral kidney produced a chronic, severe form of hypertension known as one kidney Goldblatt hypertension.

Page (1939) was responsible for a similar method of producing experimental renal hypertension in animals. By wrapping one kidney in silk, he produced an inflammatory reaction around the kidney and with or without contralateral nephrectomy, a state of hypertension developed. This is referred to as perinephritic hypertension, and proved to be an excellent experimental model. The mechanism by which both Goldblatt and perinephritic methods produce arterial hypertension is still unclear. The Goldblatt method of producing hypertension behaves in the same manner as the perinephritic method developed by Page (Pickering, 1972).

Cardiac Output

Cardiac output has been studied extensively in recent years, and has been found to increase in the early stage of hypertension, and gradually return to normal.

Ferrario et al. (1970) studied cardiac output in unanesthetized dogs with the use of an electromagnetic flowmeter implanted around the aortic arch. The cardiac output was measured before and after the induction of perinephritic hypertension. One to two weeks following the wrapping of one kidney, cardiac output was found to be elevated, and total peripheral vascular resistance was slightly decreased. Arterial blood pressure was normal. Following contralateral nephrectomy (two weeks after wrapping), arterial blood pressure was elevated, associated with a rise in total peripheral vascular resistance. Cardiac output at this time was also continuing to rise, and reached a level 18% greater than control at two weeks post-nephrectomy. Cardiac output returned to normal in the fourth to sixth week post-nephrectomy, while peripheral resistance remained elevated, apparently the major sustaining factor of the hypertension.

Ferrario (1974) performed similar studies in unanesthetized dogs with one kidney Goldblatt hypertension. He found that following the induction of the hypertension, the cardiac output increased and remained elevated for four weeks. This rise in cardiac output was associated with an increased heart rate and increased stroke volume. Three weeks following the induction of hypertension, total peripheral vascular resistance began to rise, and by the fifth week post-induction, this rise was the main cause of the elevated arterial blood pressure.

Coleman and Guyton (1969) studied hypertension in partially nephrectomized, salt loaded dogs. The authors reported an early, transient rise in cardiac output and decreased total peripheral vascular resistance. This was followed by a rise in total peripheral resistance and the return of cardiac output to control. These findings lead Coleman and Guyton to the proposal of the "autoregulation theory" for the development of arterial hypertension (Coleman and Guyton, 1969; Coleman et al., 1971). This theory proposes that hypertension causes increased blood flow to most vascular beds, and this increase in flow evokes an autoregulatory response (vasoconstriction) to decrease flows to normal ranges. This response is equated to the rise in total peripheral vascular resistance seen in hypertension.

Autoregulation is a well known phenomenon associated predominantly with the renal, hepatic, intestinal, coronary and cerebral vascular beds. However, the literature deals with this phenomenon only as a short term, transient response. Little is known about the autoregulatory response over a long term period of weeks, months or years. Therefore, how the autoregulatory response relates to extended periods of hypertension is yet undefined.

Vascular Compliance

Changes in arterial compliance during chronic experimental hypertension were reported by Goldblatt (1938). His studies showed decreased vascular compliance of the arterioles and small arteries due to medial hypertrophy and thickening of the elastic intima. It has since been well established that medial hypertrophy is a common feature of arterial hypertension.

Changes in venous compliance in experimental perinephritic hypertension were studied by Overbeck (1972). The author studied pressure-volume relationships in the isolated, temporarily occluded segment of the jugular and femoral vein in dogs during the early (less than four weeks) stage of hypertension. He found that only the femoral vein pressure-volume curve suggested a decreased distensibility.

Greenburg and Bohr (1975) showed an increased contractility and a decreased extensibility of the isolated portal vein in spontaneously hypertensive rats. Such decreases in compliance could contribute to the elevated cardiac output observed in experimental renovascular hypertension.

Blood Volume and Extracellular Fluid Volume

Changes in extracellular fluid volume in experimental hypertension were studied by Grollman et al. (1953) using the mannitol infusion method in dogs with chronic one kidney Goldblatt hypertension. In these experiments, extracellular fluid volume was found to be increased compared to a normotensive control group. These results were corroborated by Bianchi et al. (1970) using the thiocyanate and Evan's blue dye technique to measure extracellular fluid volume in conscious dogs with one kidney Goldblatt hypertension. The authors reported a significant increase in extracellular fluid volume and plasma volume during the first week following renal artery constriction. By the end of the second week, both plasma volume and extracellular fluid volume had returned to normal. These results would indicate the rise in extracellular fluid volume and plasma volume to be of a transient nature in one kidney Goldblatt hypertension.

Ferrario et al. (1970) studied plasma volume and total blood volume in dogs with perinephritic hypertension and contralateral

nephrectomy using the radioiodinated serum albumin method. These parameters were measured during three experimental stages: 2 weeks after wrapping of one kidney, 2 weeks after contralateral nephrectomy, and 10-17 months of chronic hypertension. Extracellular fluid volume was not measured. Results showed no significant change in plasma volume or total blood volume at any stage of the experimentation. It is possible that a rise in plasma volume did occur during the first two weeks after wrapping, and had returned to normal by the time the measurements were made.

Ferrario (1974), using the Evan's blue dye dilution technique in dogs with one kidney Goldblatt hypertension found a transient rise in plasma volume and total blood volume which occurred during the first two weeks following renal artery constriction.

Regional Hemodynamics

Changes in regional hemodynamics during experimental renovascular hypertension seem to indicate an overall increase in regional vascular resistances.

Total coronary vascular resistance was reported to be elevated in dogs with perinephritic hypertension (West et al., 1959).

Limb hemodynamics were studied by Overbeck et al. (1971, 1972) in the early (less than four weeks) and chronic (more than four weeks) stages of perinephritic hypertension in dogs. The authors reported normal blood flows and increased vascular resistances in the limb of both the early and chronic groups. Skin and muscle venous resistances were found to be normal in both the early and chronic stages of perinephritic hypertension.

Ferrario and McCubbin (1973) studied renal blood flow in unanesthetized, unilaterally nephrectomized dogs (one kidney Goldblatt hypertension), before and after constriction of the renal artery. The technique employed the chronic implantation of electromagnetic flowmeters. Mild stenosis of the renal artery (20%) produced a decreased renal blood flow for approximately one week, thereafter flow returned to normal (control) values. Renal vascular resistance was initially elevated, but returned toward normal after the first week. Severe stenosis (45%) led to a chronic decrease in renal blood flow and a chronic increase in renal vascular resistance.

Neurogenic Mechanisms

Evidence of a neurogenic involvement in experimental renovascular hypertension has centered around the baroreceptor reflex. McCubbin (1958) showed that a change in the "set point" for the carotid sinus baroreceptor's control of arterial blood pressure occurred within one to two days after clamping of the renal artery in dogs. It had been shown previously that the baroreceptor "set point" is reset at a higher level, and that the baroreceptor reflex operates in a decreased range of response to changes in arterial blood pressure in dogs with chronic renal hypertension (McCubbin et al., 1956). It was suggested that this change in baroreceptor "set point" would serve to maintain arterial blood pressure at an elevated level.

Humoral Mechanisms

It has been established that during renovascular hypertension, the initial rise in blood pressure following renal artery constriction is produced by a humoral mechanism (Pickering, 1968).

Ayers et al. (1969) studied renin release in dogs with one kidney Goldblatt hypertension. Following initial constriction of the renal artery, renal vasodilation occurred, associated with an increase in plasma renin activity and a rise in mean aortic blood pressure. This response endured for one week, and was followed by renal vasoconstriction, increased renal vascular resistance (decreased renal blood flow and increased renal artery pressure). This was associated with a decline in plasma renin activity to normal levels, where it remained for the three week duration of the experiment.

Using conscious dogs with one kidney Goldblatt hypertension, Bianchi et al. (1970) reported that in the first two hours following renal artery constriction, a sharp increase in plasma renin concentration, systemic blood pressure, and total peripheral resistance was seen. In the period of day 1-14 following renal artery constriction, plasma renin concentration gradually returned to control, total peripheral resistance declined but systemic arterial blood pressure remained at an elevated level. It was suggested by the authors that the hypertension might be produced by initial increased plasma renin levels followed later by an increased vascular sensitivity to angiotensin.

Hypertension and the Cerebral Circulation

The cerebral circulation exhibits excellent local regulation of its blood flow (active hyperemia, reactive hyperemia, autoregulation). Autoregulation was first observed by Fog in 1938, who noted that the pial vessels in the brain responded to changes in arterial blood pressure by altering their resistance to oppose the changes in pressure. Autoregulation has been defined as the capability of an organ or

vascular bed to regulate its blood supply, maintaining it constant in the face of changes in the perfusion pressure (Purves, 1972; Haggendal and Johansson, 1965).

Cerebral Blood Flow in Essential Hypertension

It has long been of interest how the cerebral circulation responds to chronic human essential hypertension. This was first studied by Kety et al. (1948) in thirteen patients of both sexes. Cerebral blood flow was measured by the nitrous oxide clearance method. These patients had a mean arterial blood pressure 89% above normal levels. The authors reported cerebral blood flow to be normal, as was cerebral oxygen consumption. This normal blood flow was associated with a marked and consistent elevation of cerebral vascular resistance of 88% above normal. This finding is suggestive of the cerebral vascular circuit participating in the increased vascular resistance seen in other systemic vascular beds in patients with essential hypertension.

Strandgaard et al. (1973) studied the cerebral autoregulatory phenomenon in ten male patients with essential hypertension. Cerebral blood flow was measured using the arteriovenous oxygen difference method. Arterial blood pressures were altered with the use of angiotensin amide (a vasopressor) and trimetaphan camsylate (a vasodepressor), neither of which have a direct effect on the cerebral vasculature. The author's results indicated that all ten patients autoregulated well during moderate changes in blood pressure above and below resting levels. It was also reported that the lower limit for autoregulation was elevated above that established for normotensives, and that increases in blood pressure above 160 mm Hg produced no change in cerebral blood flow in seven of the

patients, while three showed increased flows. These results indicate a shift of the brain autoregulation curve to higher blood pressure levels. The authors suggested this demonstrated shift may be due to hypertrophy of the cerebral arterial walls.

Folkow (1958) has reported hypertrophy of the media in the vessel wall during hypertension, however, this has not been clearly established for the cerebral vasculature.

Hypertensive Encephalopathy

Investigations into the genesis of hypertensive encephalopathy have yielded much information on the role of cerebral vascular autoregulation during hypertension.

Byrom (1954) conducted extensive studies into the nature of hypertensive encephalopathy in rats. Hypertension was induced by renal artery constriction and contralateral nephrectomy (one kidney Goldblatt hypertension), and the cranial window technique was employed for observation of the pial vessels. His results strongly support the ischemic theory, which suggests that increased arterial blood pressure causes excessive arteriolar constriction and vasospasm. He found the pial arterioles to exhibit segmental constriction, producing a sausage string effect. Byrom was of the opinion that these areas of segmental vasospasm reduce local cerebral blood flow, thus producing areas of focal cerebral ischemia.

Rodda and Denny-Brown (1966) evaluated the cerebral arterioles in the monkey with chronic one kidney Goldblatt hypertension. Using the cranial window technique, they observed segmental constriction in the meningeal arterioles as well as in the cortical branches of the pial

arterioles. Histologic examination verified that these segmental constrictions were caused by smooth muscle contraction in the vascular wall.

Meyer et al. (1960) induced hypertension acutely in monkeys by clamping the aorta, which produced blood pressure increases of 75-100% above control. Utilizing the cranial window technique, the authors found constriction of the secondary and tertiary branches of the middle cerebral artery, but no evidence of vasospasm was seen. After a prolonged period of this hypertension (more than 24 hours), severe brain swelling occurred causing the pial vessels to be pressed against the cranial window, producing a vasospasm. However, a true arteriole vasospasm was never seen in response to the hypertension alone.

Farrar et al. (1976) also examined the effects of acute increases in arterial blood pressure on the cerebral arterioles. Angiotensin II amide was used to increase blood pressure in cats, and the effects on the cerebral arterioles were studied with the cranial window technique. Areas of segmental constriction (sausage string effect) were observed in the arterioles at pressures above 170 mm Hg. At pressures above 180 mm Hg, this segmental narrowing gave way to progressive vasodilation and increased cerebral blood flow (as measured by the hydrogen clearance method). The sausage string appearance persisted, however this was found to be due to areas of normal vessel caliber surrounded by areas of passive, forced vasodilation.

Johansson (1974a) examined the effects of Aramine (metaraminol bitartrate) induced hypertension on the blood brain barrier (BBB) in cats after papaverine induced vasodilation. Blood brain barrier permeability changes were analyzed with the use of Evans blue dye, which binds to

plasma albumin. Increases in the permeability of the BBB are seen by extravasation of the albumin-Evans dye complex, and consequent staining of the tissue. Their results indicate that acutely induced hypertension causes vessel wall damage and BBB dysfunction by rapid distension. Regional blood flows, as measured by the I-125 antipyrine method, are higher in areas with BBB dysfunction. These findings support a hypothesis that a failure occurs in the autoregulatory response during acutely induced hypertension.

Johansson and Linder (1974b) reported BBB dysfunction in 10 of 13 dogs with acute hypertension, induced by clamping of the aorta. BBB dysfunction was revealed by extravasation of Evans blue-albumin. These findings support the hypothesis that it is only the high intravascular pressure that causes increases in permeability to protein tracers.

Johansson (1974c) studied the relationship between regional cerebral blood flow and areas of BBB dysfunction during acute metaraminol induced hypertension in cats. Regional blood flows were measured using the I-125 antipyrine method. Areas with BBB dysfunction (as evidenced by Evans blue-albumin extravasation) had higher blood flows than the non-damaged areas, supporting the hypothesis that acute increases in blood pressure evokes a local failure of autoregulation.

Ekstrom-Jodal et al. (1971) studied cerebral blood flow autoregulation in dogs at high arterial pressures and varied levels of carbon dioxide tensions. Cerebral blood flows were measured using the Kr-85 gas elimination technique, and increased blood pressures were induced by clamping of the aorta. Their results showed that the upper limit of autoregulation is decreased by hypercapnia. These findings suggest that

the role of autoregulation of cerebral blood flow during hypertension, and its relationship to the genesis of hypertensive encephalopathy is not completely understood.

Cerebral Blood Flow in Experimental Hypertension

Flohr et al. (1971) studied cerebral blood flow and cerebral vascular resistance in female Wistar rats in response to three types of hypertension: two kidney Goldblatt, one kidney Goldblatt, and deoxycorticosterone with salt loading. These groups were compared to a normotensive control group. Cerebral blood flow was calculated as a fraction of the cardiac output as determined by the microsphere particle distribution technique. Their results showed total cerebral blood flows in all three hypertensive groups to be the same as the normotensive group. Cerebral vascular resistance was increased in exact proportion to the increased systolic blood pressure in all three groups with experimental hypertension. These results indicated that the brain participates in the rise in total peripheral resistance in response to hypertension.

Nishiyama and Frohlich (1976) examined cerebral blood flow using the microsphere particle distribution technique in a group of spontaneously hypertensive rats (SHR), and compared them to two groups of normotensive rats, Wistar-Kyoto (WR) and Wistar (NR). The authors reported the SHR groups' cerebral blood flow was significantly increased when compared to the NR group. Cerebral vascular resistances were not reported.

Strandgaard et al. (1974) studied the effects of acute hypertension on the cerebral circulation of baboons. Changes in blood pressure were induced by the infusion of angiotensin II, and cerebral

blood flow was measured by the ^{133}Xe injection method. A stepwise increase of mean arterial blood pressure up to 120-150 mm Hg (30-40% above control) was associated with increases in cerebral vascular resistance, and cerebral blood flow was maintained at normal levels. As mean arterial blood pressure was increased above 40% of control, cerebral vascular resistance decreased. This fall in resistance was said to be due to passive, forced dilation, a possible exhaustion of the Bayliss response. This is termed autoregulatory breakthrough. These same studies were repeated with cervical sympathetic denervation, and the results were no different than the group with intact sympathetic innervation, indicating that the sympathetics probably do not effect the breakthrough of the upper limit of autoregulation in the cerebral circuit.

A study by Strandgaard et al. (1975) was done to compare the upper limits of cerebral blood flow autoregulation in a group of normotensive baboons against a group of baboons with renovascular hypertension (8-12 weeks duration). Cerebral blood flow was measured using the intracarotid ^{133}Xe clearance method. Blood pressure was raised in increments of 10-20 mm Hg with the intravenous infusion of angiotensin II amide. Their results showed that the cerebral blood flow remained constant in the normotensive group until the mean arterial blood pressure had risen to the level of 140-154 mm Hg. Above this level, cerebral blood flow increased as the mean arterial blood pressure was increased. In the hypertensive group, cerebral blood flow remained constant until a range of 155-169 mm Hg (MABP) was reached. Above this level CBF increased as MABP increased. These data suggest the upper limit for cerebral

blood flow autoregulation is elevated to a higher level of mean arterial blood pressure in the group with renovascular hypertension (two kidney Goldblatt). It is possible that this change could be due to structural changes in the cerebrovascular wall which would decrease its capacity for maximal dilation, yet increase its ability to withstand increased blood pressure.

Summary

There are essentially two current theories concerning the effects of hypertension on the cerebral circulation.

The first theory proposes that increases in blood pressure during hypertension evokes an autoregulatory response which produces a sustained increase in the resistance of the cerebral vessels to maintain cerebral blood flow at normal levels. It is further hypothesized that increased blood pressure causes excessive arteriolar constriction and vasospasm. These areas of segmental vasospasm greatly reduces local blood flow, thus producing areas of focal cerebral ischemia and tissue damage.

The second theory proposes that as systemic arterial blood pressure increases, the upper limit of autoregulation is reached, at which point a forced, passive dilation occurs, increasing blood flow in proportion to the pressure change. This is termed autoregulation breakthrough. The consequent increase in intravascular pressure causes vessel wall damage, increased permeability, local net filtration, focal cerebral edema and damaged brain tissue.

Since most of the research in this field has dealt with acute changes in blood pressure, more research is needed to understand how

chronic hypertension relates to the cerebral circulation, which will better enable us to understand human essential hypertension and thus provide a rational approach to therapy.

The purpose of the current study is to examine the effects of chronic renal hypertension on the regional cerebral circulation and compare these results to the effects of acute hypertension in order to examine the differences and/or similarities between these two types of hypertension and their effect on cerebral blood flow and cerebral vascular resistance.

METHODS

Series I. Chronic Renal Hypertension

Healthy, conditioned male mongrel dogs (N=7), weighing 24 $\pm$ 1 kg were trained to lie quietly during femoral arterial punctures for blood pressure measurements, which were conducted weekly during the study. Each animal was documented as having a resting arterial blood pressure of less than 140 mm Hg on two separate occasions prior to the surgical induction of hypertension. Conditioning included examination of the stool for parasites, examination of the blood for microfilaria, and vaccination against rabies, distemper, leptospirosis and hepatitis. During the course of the study, the dogs were maintained on a diet of standard dog chow (Wayne Dog Food, Allied Mills, Inc., Chicago, Ill.) and water ad libitum.

Surgical Procedures

Seven dogs were given one dose of procaine penicillin (600,000 units) and steptomycin (0.5 gm) intramuscularly as a prophylactic measure against wound infection on the day of surgery. This treatment was continued once a day, for three days postoperatively. Following a fasting period of 24 hours, the animals were anesthetized with sodium pentobarbitol (25 mg/kg i.v.) and a cuffed endotracheal tube was inserted. Artificial ventilation was maintained with a Harvard positive pressure respirator. Respiratory rate was set at ten per minute and tidal volume adjusted according to body weight. The animals were allowed to stabilize and arterial blood gases (pO_2, pCO_2) were measured using a radiometer blood

gas analyzer and recorded (pH was not measured). Blood hematocrit was determined using a centrifuged, heparinized capillary tube. Room temperature was held constant at 23°C.

The dogs were positioned in a right lateral recumbency. Under sterile conditions, a polyethylene cannula (PE 240) was inserted into the abdominal aorta via the right femoral artery for the measurement of mean arterial blood pressure, and for the withdrawal of reference blood after the microsphere injection. A similar cannula was inserted into the left ventricle of the heart via the left common carotid artery for microsphere injection. Placement in the ventricle was confirmed by the appropriate (ventricular) pressure recording. Pressure recordings were made using Statham pressure transducers (Model P23Gb) connected to a Sanborn direct writing recorder (Model 7700).

Measurement of Cerebral Blood Flow

Regional cerebral blood flow was measured using the radioactive labeled microsphere distribution technique (Wagner et al. 1969). The microspheres were 15 $\pm$ 5μ in diameter (3M Company, St. Paul, Minn.), and were labeled with ^{85}Strontium, ^{51}Chromium, and ^{141}Cerium. Specific activities for these isotopes were 13.73 millicuries/gm for ^{85}Sr, 7.61 mCu/gm for ^{141}Ce, and 10.42 mCu /gm for ^{51}Cr. One milligram of the microspheres contained approximately 440,000 microspheres. The stock microspheres were suspended in a solution of 10% dextran (1 millicurie/10 ml), and a drop of Tween 80 (polyoxyethylene sorbitan mono-oleate) was added to the solution to prevent aggregation. One ml of each type of microsphere was injected into each dog, which represented an injection

of 3.2 x 10^6 microspheres with the ^{85}Sr label, 4.2 x 10^6 microspheres with the ^{51}Cr label, and 5.7 x 10^6 microspheres with the ^{141}Ce label.

Control Micropshere Injection

One ml of ^{85}Sr microspheres was withdrawn from a preagitated 10 ml vial using a 3 ml syringe, and thoroughly mixed in a glass tube with 2 ml of 20% dextran using an ultrasonic sonifier cell disruptor to achieve uniform dispersion of the microspheres. The suspension was then drawn into a 3 ml syringe and injected as a bolus into the left ventricle. The injection cannula was flushed with 5-8 ml of saline to insure that all microspheres reached the left ventricle. At the time of injection, a three minute reference blood sample was withdrawn from the right femoral artery at a rate of 3.88 ml/min using a Harvard withdrawal pump. The reference blood was heparinized, divided into 12 gamma counting tubes (5 ml capacity) at 1 ml/tube, and frozen for later counting. The cannulae were removed and the arteries repaired with 7-0 polyester cardiovascular suture. The incisions were closed with vetafil suture.

Surgical Induction of Hypertension

Immediately following the microsphere injection, the right kidney was approached retroperitoneally through a flank incision, dissected free and stripped of its perirenal fascia and fat. The kidney was wrapped in silk to produce perinephritic hypertension (Page, 1939) and wrapped again in Saran Wrap to minimize the degree of adhesions to surrounding tissue. The kidney was restored to its normal anatomical position and the wound closed by suturing the tissues by layer.

One week following the first surgery, a contralateral nephrectomy was performed under sodium pentobarbitol anesthesia (25 mg/kg i.v.) and

the same sterile conditions and antibiotic treatment as described above. These animals were allowed to recover, and were maintained for a period of 5-6 weeks following the first evidence of arterial hypertension, as documented by a pressure greater than 140 mm Hg, recorded via direct puncture of the femoral artery.

Experimental Microsphere Injection

Following a 5-6 week period of documented hypertension, the terminal experiment was performed. After a fasting period of 24 hours, the dogs were anesthetized with sodium pentobarbitol (25 mg/kg i.v.) and a cuffed endotracheal tube was inserted. Ventilation was maintained by a Harvard positive pressure respirator at the same settings used during the initial surgery. If necessary, the respirator was adjusted to obtain the same arterial pCO_2 as measured during the initial (^{85}Sr) microsphere injection. The dogs were allowed to stabilize (60-90 min) and arterial blood gases, hematocrit and room temperature were determined. The second microsphere injected was ^{141}Ce or ^{51}Cr ($15 \pm 5\mu$; 3M Co.), the selection being random. As in the initial microsphere injection, a polyethylene cannula (PE 240) was inserted into the abdominal aorta via the right femoral artery for the measurement of mean arterial blood pressure and for the withdrawal of the three minute reference blood sample. A different procedure was used for the 2nd and 3rd microsphere injection. The left common carotid artery was found to be occluded as a result of the prior surgery. Unsuccessful attempts at placing the cannula in the heart via the right common carotid and brachial arteries necessitated opening the chest for subsequent microsphere injections. The left common carotid artery was clamped (to insure that no blood flow was allowed in this artery as in the initial injection), and the chest was opened in the fourth,

left intercostal space. A similar cannula with a 13 gauge needle tip was inserted directly into the left ventricle via a puncture wound for the second microsphere injection. The same protocol was used for the mixing and injection of the Cr or Ce microspheres as was used for the initial Sr injection.

Measurement of Radioactivity

The animals were sacrificed, and the skin, muscle and connective tissues were removed to expose the superior portion of the skull. This portion of the skull was removed with a Stryker saw and the brain was exposed. The cranial nerve and spinal cord attachments were cut and the entire brain removed. Duplicate tissue samples weighing approximately one gram each were taken from the medulla, pons, hypothalamus, thalamus, cerebellum, and cerebral cortex. These samples were placed into pre-weighed plastic gamma counting tubes and weighed again to obtain tissue weights. The tubes containing tissues and the reference blood samples were placed in a Searle (Model 1185) gamma counter and counted at the following settings:

	Base	Window	Attenuation
^{85}Sr	464	100	8
^{141}Ce	380	400	2
^{51}Cr	preprogrammed setting by Searle Co.		

Raw counts were entered into Wang Model 700 preprogrammed computer which removed any overlap of isotope energy peaks which occurred between counting channels.

Calculation of Results

Regional cerebral blood flow (rCBF) was calculated by dividing corrected counts per minute (cpm) per gram of brain tissue by counts per minute of the reference blood sample, and multiplied by the reference blood withdrawal rate (3.88 ml/min).

$$rCBF = \frac{\text{cpm/gm tissue}}{\text{cpm ref blood}} \times RBWR$$

After calculation of each tissue sample blood flow, the two blood flows from each region were averaged into one regional blood flow (ml/min/100 gm). Regional cerebral vascular resistance (mm Hg/ml/min/100 gm) was calculated by dividing the arterial pressure at the time of injection (Pa) by the average rCBF.

$$rCVR = Pa/rCBF$$

Statistical Analysis

The experimental design was such that regional cerebral blood flow could be analyzed before and after chronic perinephritic hypertension, with each dog acting as its own control, thereby eliminating inter-animal variance. Regional cerebral blood flows, cerebral vascular resistances and arterial pressures were analyzed using Student's t test modified for paired replicates. A "p" value of less than 0.05 was considered significant.

Series II. Acute (Angiotensin II Induced) Hypertension

Surgical Procedures

Male, mongrel dogs (n=9), weighing 22 $\pm$ 2 kg were anesthetized with sodium pentobarbitol (25 mg/kg i.v.) and a cuffed endotracheal tube

was inserted into the trachea. Artificial ventilation was maintained with a Harvard positive pressure respirator. Respiratory rate was set at 15 per minute and tidal volume adjusted according to body weight. The animals were positioned in a right lateral recumbency. Polyethylene cannulae (PE 240) were inserted into the abdominal aorta via the right femoral artery for the withdrawal of reference blood (Harvard withdrawal pump), into the left common carotid artery for the measurement of mean arterial blood pressure, and into the right femoral vein for drug infusions. Pressures were measured with Stratham pressure transducers and a Sanborn direct writing recorder. The chest was opened in the fourth, left intercostal space and a cannula (PE 240) with a 13 gauge needed tip was prepared for injection of microspheres directly into the left ventricle via a puncture wound. This cannula was connected to a pressure transducer for confirmation of the presence of the needle in the ventricular chamber by the appropriate ventricular pressure recording. The animals were allowed to stabilize, and arterial blood gases (pO_2, pCO_2) and pH were measured using a radiometer blood gas analyzer, recorded and held constant throughout the course of the experiment.

Preparation of Microspheres

The microspheres used for Series II were labeled with isotopes of ^{85}Sr, ^{51}Cr, ^{141}Ce. These microspheres had diameters of 13.7 ± 1.0, 13.6 ± 0.7 and 14.1 ± 0.8 respectively. They also had specific activities of 11.89 ^{mCu}/gm, 40.76 ^{mCu}/gm and 8.57 ^{mCu}/gm respectively, and each stock solution contained a drop of Tween 80. One milligram of the microsphere stock solution contained approximately 440,000 microspheres.

Nine tenths (0.9) ml of each isotope was injected into each dog, which represented 3.3×10^6 microspheres labeled with ^{85}Sr, 9.9×10^5 microspheres with the ^{51}Cr label, and 4.6×10^6 microspheres with the ^{141}Ce label.

Experimental Procedure

The experimental procedure for Series II consisted of an initial microsphere injection at normal (anesthetized) blood pressure (approximately 130 mm Hg) to obtain a control regional cerebral blood flow measurement (microsphere particle distribution technique). The first microsphere injection was randomized between ^{85}Sr and ^{141}Ce. The same procedure for microsphere preparation, injection and reference blood sample withdrawal was used in Series II as was used in Series I.

The first microsphere injection was followed by the infusion of angiotensin II amide into the femoral vein (Harvard infusion pump) to achieve a mean arterial blood pressure in the approximate range of 170-180 mm Hg. A second microsphere (^{51}Cr) was then injected and a reference blood sample obtained. The ^{51}Cr labeled microsphere was used consistently as the second injection since this isotope had a very high specific activity, and therefore contained a smaller number of microspheres per injection (990,000).

The small number of microspheres injected could be a possible source of error in blood flow measurement, so this isotope was used for the measurement that was felt to be the least important data point.

The infusion rate of angiotensin II amide was increased to obtain a mean arterial blood pressure of 200 + mm Hg. Once the

animals stabilized at this pressure, a third injection of microspheres (^{85}Sr or ^{141}Ce) was made and a reference blood sample obtained.

The animals were then sacrificed, the brain removed and duplicate samples of medulla, pons, hypothalamus, thalamus, cerebellum and cerebral cortex were taken, weighed and the radioactivity measured in the same manner as described in Series I.

Calculations

Average regional cerebral blood flow and vascular resistance was calculated in the manner described in Series I and in the following equations:

$$rCBF = \frac{\text{cpm/gm tissue}}{\text{cpm reference blood}} \times RBWR$$

$$rCVR = {}^{Pa}/_{rCBF}$$

Statistical Analysis

Regional cerebral blood flow, regional cerebral vascular resistances and mean arterial blood pressures were analyzed using a Student's t test modified for paired replicates. A "p" value of less than 0.05 was considered significant.

Series III. Control

This series was completed to determine whether the order of microsphere injection or the different surgical procedures employed could be a possible source of error in the previous two series. Results of injections of three differently labeled microspheres in each dog,

given in a random order and under different surgical conditions (open chest, carotid clamped vs. closed chest, carotid patent), were compared.

Microsphere Preparation

Microspheres labeled with ^{85}Sr, ^{51}Cr and ^{141}Ce were used in this series, and had the same diameters and specific activities as described in Series II. Six tenths (0.6 ml) of each type of isotope was injected, which represents approximately 2.22×10^6 microspheres with the ^{85}Sr label, 6.6×10^5 microspheres with the ^{51}Cr label and 3.08×10^6 microspheres with the ^{141}Ce label. The same procedure used in Series I and II was used in Series III for microsphere preparation and reference blood withdrawal.

Surgical Procedures

Three mongrel dogs weighing 18 $\pm$ 1 kg were anesthetized with sodium pentobarbital (25 mg/kg i.v.), intubated and maintained on a Harvard positive pressure respirator with tidal volume set according to body weight and rate set at 15/minute. The right femoral artery was cannulated (PE 240) for mean arterial blood pressure and blood gas measurements and for reference blood withdrawal. Blood pressures remained at normal (anesthetized) levels throughout the course of the experiment. Arterial blood gases (pO_2, pCO_2) and pH also were maintained at constant (normal) levels throughout the experiment. Mean arterial blood pressure and ventricular pressures were measured with Stratham pressure tranducers and a Sanborn direct writing recorder. Arterial blood gases were measured with a radiometer blood gas analyzer.

The first microsphere injection was done under closed chest condition (with both carotid arteries unoccluded) with a cardiac needle

and PE 240 cannula inserted directly through the chest wall into the left ventricle. The cannula was connected to a pressure transducer and recorder to confirm that the needle was placed in the ventricular chamber by the appropriate ventricular pressure recording.

The second and third microsphere injections were done under open chest conditions (via ventricular puncture) with the left common carotid artery clamped, so that we could examine the effects of this surgical preparation versus the surgical preparation used with the first microsphere injection. This information will be useful in evaluating the data from Series I. Reference blood samples were obtained for each microsphere injection.

Calculations

The animals were sacrificed, the brains removed, and duplicate samples taken of the medulla, pons, hypothalamus, thalamus, cerebellum and cerebral cortex. The same methods were used for measurement of radioactivity and calculations of average regional cerebral blood flow and vascular resistance as was used in Series I and II.

Statistical Analysis

A two way analysis of variance and Student's t test modified for paired replicates were employed in the analysis of the data. A "p" value of < 0.05 was considered significant.

RESULTS

Series I. Chronic Perinephritic Hypertension

Average values for arterial (aortic) blood pressure in the normotensive control and at each week following the induction of hypertension are shown in Figure 1. On the average, mean aortic blood pressures were significantly greater than control (129 mm Hg) at 2 weeks (166 mm Hg), 3 weeks (177 mm Hg), 4 weeks (181 mm Hg), 6 weeks (185 mm Hg) and 8 weeks (176 mm Hg) following surgical induction of hypertension by 28%, 37%, 40%, 43% and 37%, respectively ($p < 0.05$).

Average values for regional cerebral blood flows, regional cerebral vascular resistances, and arterial blood pressures are shown in Figure 2. The cross hatched bars denote values in the normotensive state, the open bars denote values after 6 weeks of hypertension. Average blood flows were increased significantly ($p < 0.05$) after six weeks of hypertension in the medulla, pons, hypothalamus, thalamus, cerebellum and cortex. The percent increase in regional blood flows were: medulla, 61%; pons, 59%; hypothalamus, 106%; thalamus, 57%; cerebellum, 56%; cortex, 35%. Regional cerebral vascular resistances were decreased significantly ($p < 0.05$) in the medulla and hypothalamus by 20% and 35% respectively, however resistances were not significantly different from control ($p > 0.05$) in the pons, thalamus, cerebellum and cortex.

Average values for blood hematocrit (Table 1) did not change significantly ($p > 0.05$) from a control value of 42% to a six week hypertensive value of 43%.

Individual and average arterial blood gases (pO_2, pCO_2) are shown in Table 2, and were adjusted at the time of the second microsphere injection to correlate as closely as possible with the values obtained at the time of the control microsphere injection.

Series II. Acute Antiotensin II Induced Hypertension

Average (mean) values for regional cerebral blood flows, regional cerebral vascular resistances and arterial blood pressures during acute Angiotensin II induced hypertension are shown in Figure 3. Bar #1 denotes the first microsphere injection at normal (anesthetized) blood pressures. Bar #2 denotes the second microsphere injection during moderate Angiotensin II induced hypertension. Bar #3 denotes the third microsphere injection during severe Angiotensin II induced hypertension. On the average, mean aortic blood pressures were significantly greater than control (136 mm Hg) during both moderate hypertension (176 mm Hg) and severe hypertension (202 mm Hg) by 29% and 49% respectively.

The average value for regional cerebral blood flow was found to increase significantly in the cortex during severe hypertension by 46% ($p < 0.05$) when compared to control. Regional cerebral blood flows were not significantly different from control ($p > 0.05$) in the medulla, pons, hypothalamus, thalamus and cerebellum during both moderate and severe hypertension.

Average values for calculated regional cerebral vascular resistances were increased significantly ($p < 0.05$) when compared to control in the medulla during both moderate and severe hypertension by 43% and 33% respectively, in the pons during severe hypertension by 22%, in the hypothalamus during both moderate and severe hypertension by 53% and

33% respectively, in the thalamus during severe hypertension by 23% and in the cerebellum during moderate hypertension by 28%. Resistance in the cortex was not significantly different from control at both levels of hypertension.

Individual and mean arterial blood gases (pO_2, pCO_2) and pH values taken at the time of each microsphere injection are shown in Table 3. There was no significant difference ($p > 0.05$) between control and experimental values.

Series III. Controls

A two way analysis of variance (randomized complete blocks) was employed in analyzing the blood flow data for each region of the brain sampled. Arterial blood gases (pO_2, pCO_2), pH and arterial blood pressures (Table 4) were not significantly different ($p > 0.05$) from each other at the time of each of the three microsphere injections (paired t test). In the ANOVA, dogs were used as blocks and surgical procedures used as treatments. The ANOVA tables are shown in Table 5. A significant difference ($p < 0.05$) was found for blocks (dogs) in the medulla and thalamus, where as no significant difference ($p > 0.05$) existed in the pons, hypothalamus, cerebellum and cortex for blocks. There was no significant difference ($p > 0.05$) between treatments (surgical procedures) in any of the regions sampled.

A Student's paired t test was used to test for differences between microspheres during the surgical conditions used in the experiment (Table 6). For each microsphere, the blood flows from each region of the brain sampled were used collectively as data points for comparison to each of the other microspheres' data points. In Dog #1, the order of microsphere injection was Sr, Cr, Ce. No significant difference

($p > 0.05$) was found when comparing Sr vs. Cr, Sr vs. Ce, or Cr vs. Ce. In Dog #2 the order of microsphere injection was Ce, Cr, Sr. No significant difference ($p > 0.05$) was found when comparing Ce vs. Cr, Ce vs. Sr or Cr vs. Sr. In Dog #3, the order of microsphere injection was Sr, Cr, Ce with no significant difference ($p > 0.05$) was found when comparing Sr vs. Cr, Sr. vs. Ce and Cr vs. Ce.

Further analysis comparing regional cerebral blood flows of Series I control vs. Series II control showed a significant difference ($p < 0.05$) between the two groups in the medulla, pons, hypothalamus, thalamus, cerebellum and cortex, using the Student t test. The Series II mean control flows were consistently higher than the Series I mean control flows by 86% in the medulla, 45% in the pons, 67% in the hypothalamus, 30% in the thalamus, 38% in the cerebellum and 41% in the cortex.

The control flows for both Series I and Series II (together as one group) were compared to the hypertensive flows in Series I using Student's t test. A "p" value < 0.05 was considered significant. The regional cerebral blood flows were significantly higher when compared to control in the hypothalamus, thalamus and cerebellum, whereas flows were not significantly different from control in the medulla, pons, or cortex.

Control flows from Series II were compared to hypertensive flows in Series I using Student's t test. A "p" value of < 0.05 was considered significant. There was no significant difference in any of the regions sampled.

Figure 1.--Changes in mean arterial blood pressures during six week development of chronic experimental perinephritic hypertension.

* $p < 0.05$ when compared to control using Student's t test modified for paired replicates (N=7).
$\frac{1}{2}$ denotes surgical induction of hypertension by wrapping kidney in silk.
↓ denotes contralateral nephrectomy.
MABP denotes mean arterial blood pressure.

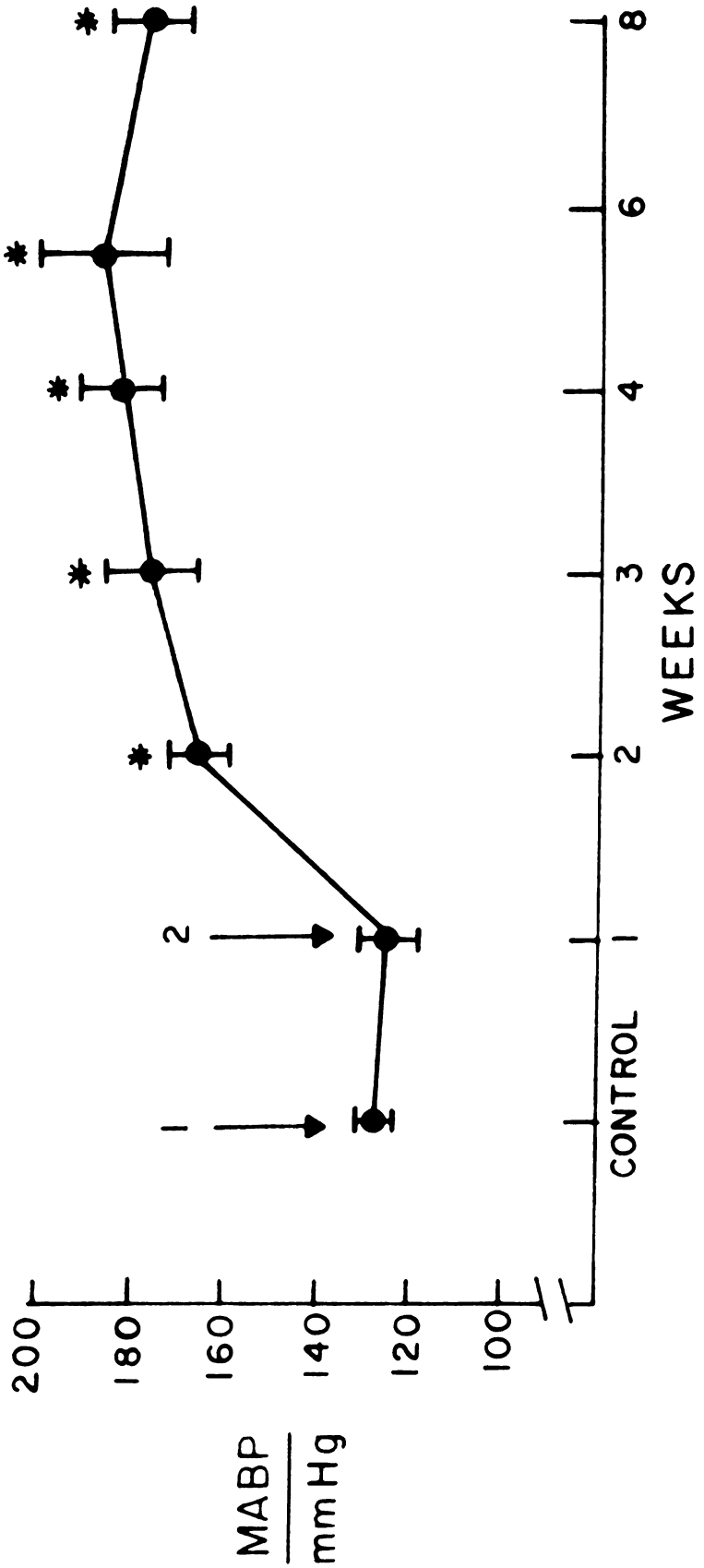
MABP
mm Hg
200
180
160
140
120
100
CONTROL
1
2
3
4
6
8
WEEKS
1
2
*

Figure 2.-- Average values for regional cerebral blood flows, regional cerebral vascular resistances and mean arterial blood pressure (Pa) during normotensive control state (cross hatched bars) and after six weeks of experimental perinephritic hypertension (open bars).

* $p < 0.05$ when compared to control using Student's t test modified for paired replicates (N=7).

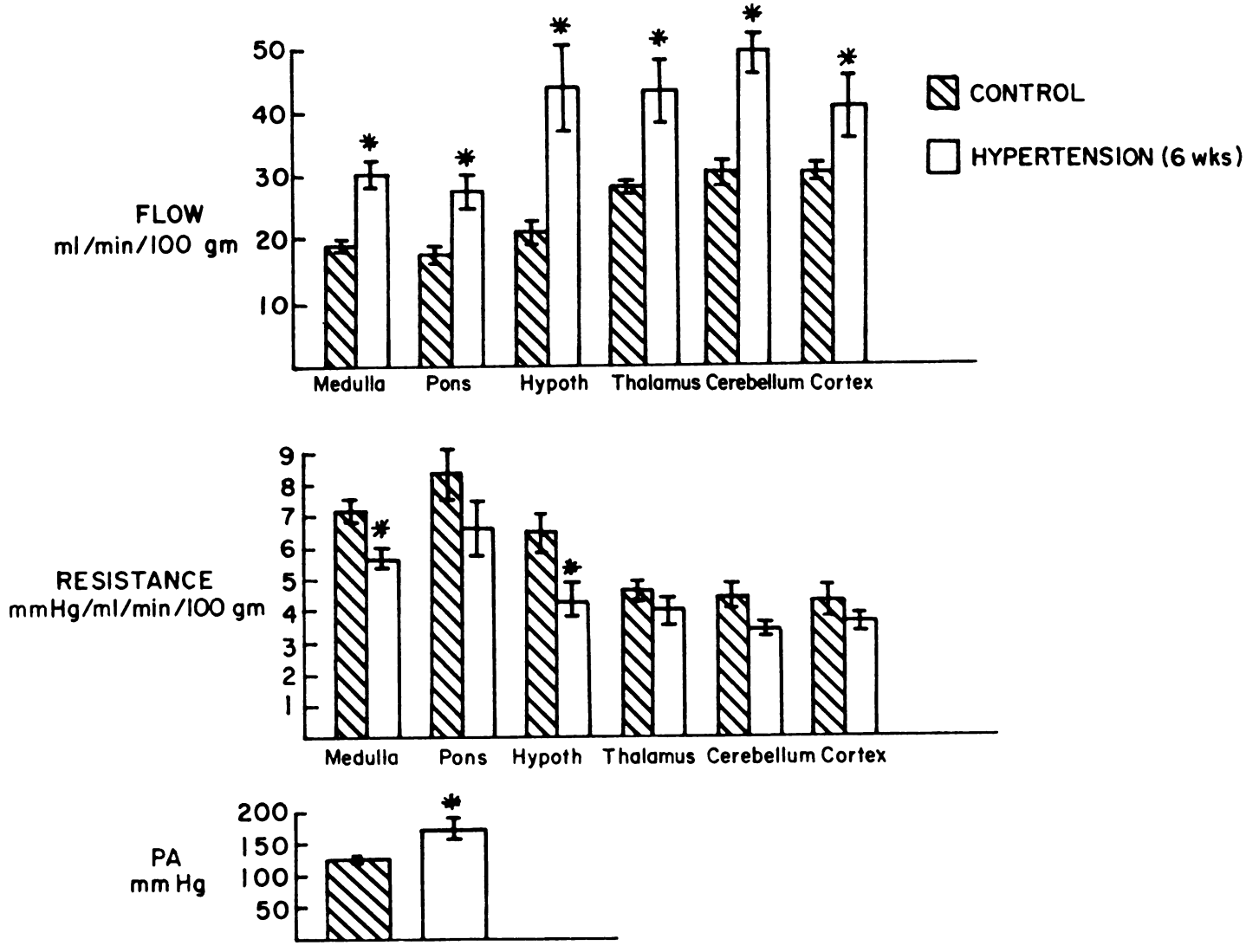
FLOW
ml/min/100 gm
50
40
30
20
10
CONTROL
HYPERTENSION (6 wks)
Medulla
Pons
Hypoth
Thalamus
Cerebellum
Cortex
RESISTANCE
mmHg/ml/min/100 gm
9
8
7
6
5
4
3
2
1
Medulla
Pons
Hypoth
Thalamus
Cerebellum
Cortex
PA
mm Hg
200
150
100
50

Table 1.--Hematocrit determinations, control through six weeks of renovascular hypertension.

Experiment number	(Mean ± S.E.) N=7 Control	N=4 2 weeks	N=3 4 weeks	N=7 6 weeks
1	47	47		46
2	43	40	49	50
3	38			45
4	40	32		46
5	47		41	41
6	41	34		39
7	38		46	34
$\bar{x}$	42	38	45	43
± S.E.	1	2	1	2

$\bar{x}$ = mean
± S.E. = standard error

Table 2.--Arterial blood gases (pO_2, pCO_2) at control microsphere injection and at time of second microsphere injection following six weeks of perinephritic hypertension (N=7).

	pCO_2		pO_2	
Experiment Number	M#1	M#2	M#1	M#2
1	29	28	77	80
2	30	30	95	92
3	30	31	87	85
4	38	38	87	89
5	36	38	85	82
6	36	35	76	77
7	31	31	79	77
$\bar{x}$	33	33	84	83
$\pm$ S.E.	2	2	3	2

M#1 denotes control microsphere injection

M#2 denotes microsphere injection following six weeks of perinephritic hypertension

$\bar{x}$ = mean

+ S.E. = standard error

Figure 3.--Average values for regional cerebral blood flows, regional cerebral vascular resistances and mean arterial blood pressure (Pa) during normotensive (anesthetized) control state (Bar #1), during moderate, acute Angiotensin II induced hypertension (Bar #2) and during severe, acute Angiotensin II induced hypertension.

*$p < 0.05$ when compared to control using Student's t test modified for paired replicates (N=9).

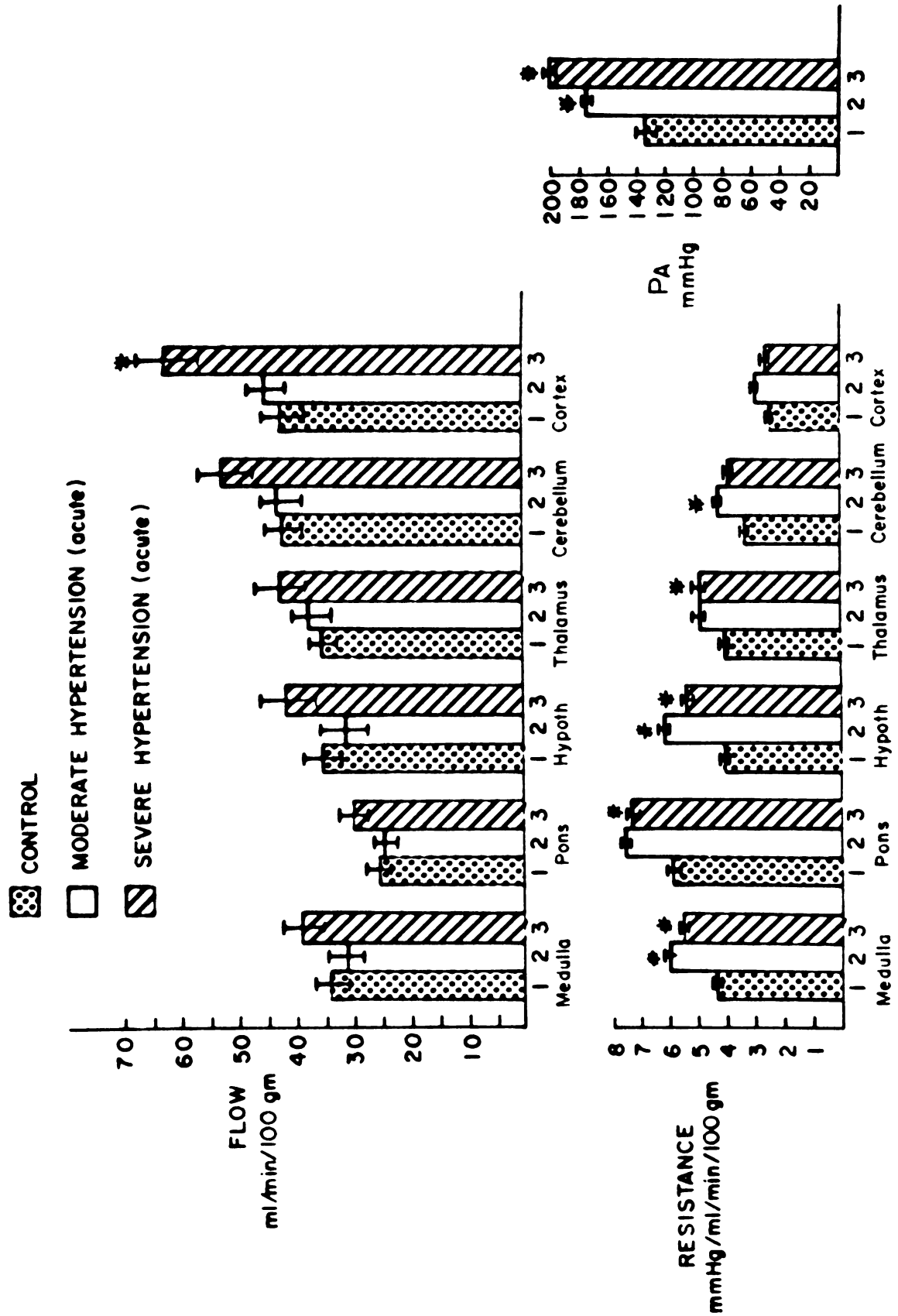
CONTROL
MODERATE HYPERTENSION (acute)
SEVERE HYPERTENSION (acute)
FLOW
ml/min/100 gm
70
60
50
40
30
20
10
1 2 3
Medulla
Pons
Hypoth
Thalamus
Cerebellum
Cortex
PA
mmHg
200
180
160
140
120
100
80
60
40
20
RESISTANCE
mmHg/ml/min/100gm
8
7
6
5
4
3
2
1

Table 3.--Arterial blood gases (pO_2, pCO_2) and pH during normotensive control microsphere injection, during microsphere injection at moderate hypertensive levels and during microsphere injection at severe hypertensive levels (N=9).

	$PaCO_2$			PaO_2			pH		
Dog Number	M#1	M#2	M#3	M#1	M#2	M#3	M#1	M#2	M#3
1	33	34	32	74	78	78	7.38	7.40	7.40
2	28	26	26	81	82	82	7.40	7.40	7.40
3	25	24	24	68	72	72	7.43	7.44	7.44
4	37	37	37	78	77	77	7.39	7.37	7.36
5	30	29	29	87	85	85	7.43	7.40	7.40
6	37	37	36	66	65	66	7.36	7.30	7.30
7	35	35	35	61	60	60	7.40	7.40	7.40
8	32	34	34	77	72	72	7.37	7.32	7.32
9	36	34	34	75	78	77	7.40	7.40	7.40
$\bar{x}$	32	32	32	74	74	74	7.40	7.38	7.38
$\pm$ S.E.	$\pm$2	$\pm$2	$\pm$2	$\pm$3	$\pm$3	$\pm$3	$\pm$0.2	$\pm$0.2	$\pm$0.2

M#1 denotes normotensive control microsphere injection
M#2 denotes microsphere injection during moderate Angiotensin II induced hypertension
M#3 denotes microsphere injection during severe Angiotensin II induced hypertension
$\bar{x}$ = mean
+ S.E. = standard error

Table 4.--Arterial blood gases (pO_2, pCO_2), pH and mean arterial blood pressures during three control injections of microspheres (N=3).

Dog Number	Isotope	pO_2	pCO_2	pH	MABP
1	^{85}Sr	78	30	7.4	155
	^{51}Cr	78	30	7.4	145
	^{141}Ce	72	31	7.4	150
$\bar{x}$		76	30	7.4	150
$\pm$ S.E.		2	--	---	3
2	^{141}Ce	83	33	7.3	140
	^{51}Cr	83	32	7.3	135
	^{85}Sr	80	33	7.3	135
$\bar{x}$		82	33	7.3	136
$\pm$ S.E.		1	--	---	2
3	^{85}Sr	74	36	7.3	110
	^{51}Cr	78	35	7.3	110
	^{141}Ce	78	35	7.3	110
$\bar{x}$		77	35	7.3	110
$\pm$ S.E.		1	--	---	---

MABP = mean arterial blood pressure
$\bar{x}$ = mean
$\pm$ S.E. = standard error

Table 5.--Two way analysis of variance (ANOVA) tables for each region of the brain sampled, computed from brain flow data taken during three control microsphere injections. Individual dogs represent blocks; treatments are represented by two different surgical procedures (closed chest and carotids patent vs. open chest and one carotid occluded) (N=3).

	Source	df	SS	Calc F	Tab F
Medulla	Blocks	2	283	13.68*	10.6
	Treatment	2	14	0.68	10.6
	Error	4	41		
		8	338		
Pons	Blocks	2	55	2.29	10.6
	Treatment	2	26	1.69	10.6
	Error	4	48		
		8	129		
Hypothalamus	Blocks	2	222	2.87	10.6
	Treatment	2	131	1.69	10.6
	Error	4	154		
		8	507		
Thalamus	Blocks	2	504	24.7*	10.6
	Treatment	2	2	0.14	10.6
	Error	4	40		
		8	546		
Cerebellum	Blocks	2	1	0.01	10.6
	Treatment	2	728	4.18	10.6
	Error	4	348		
		8	1077		
Cortex	Blocks	2	40	1.65	10.6
	Treatment	2	11	0.45	10.6
	Error	4	49		
		8	100		

df = degrees of freedom
SS = sum of squares
* = significant at $p < 0.05$

Table 5.--Two way analysis of variance (ANOVA) tables for each region of the brain sampled, computed from brain flow data taken during three control microsphere injections. Individual dogs represent blocks; treatments are represented by two different surgical procedures (closed chest and carotids patent vs. open chest and one carotid occluded) (N=3).

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	Error	4	348		
		8	1077		
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	Treatment	2	11	0.45	10.6
	Error	4	49		
		8	100		

df = degrees of freedom
SS = sum of squares
* = significant at $p < 0.05$

Table 6.--Regional cerebral blood flows (ml/min/100 gm) during three control (normotensive) microsphere injections.

	Dog 1			Dog 2			Dog 3		
Pa =	155 ^{85}Sr	145 ^{51}Cr	150 ^{141}Ce	140 ^{141}Ce	135 ^{51}Cr	135 ^{85}Sr	110 ^{85}Sr	110 ^{51}Cr	110 ^{141}Ce
Medulla	27.8	28.3	27.5	40.0	38.5	39.7	29.0	26.4	29.5
Pons	24.1	20.2	23.2	31.3	28.9	29.4	19.8	22.9	21.8
Hypothalamus	28.5	31.3	29.4	42.3	40.3	40.1	39.9	38.4	41.6
Thalamus	32.9	30.8	28.5	45.7	42.7	45.9	48.5	49.7	49.9
Cerebellum	46.0	48.9	44.6	59.7	56.4	56.3	39.8	37.6	41.4
Cortex	37.4	41.1	38.8	37.8	38.0	39.9	33.4	36.7	34.2
$\bar{x}$	32.7	33.4	32.0	42.8	40.8	41.8	34.5	35.2	36.4
$\pm$ S.E.	3.4	4.1	2.8	3.9	4.0	3.7	4.1	3.8	4.0

Pa = mean aortic blood pressure; $\bar{x}$ = mean; $\pm$ S.E. = standard error; N = 3.

DISCUSSION

This study is unique in that to our knowledge, it is the first in which regional cerebral blood flows have been measured before and after the development of chronic renovascular hypertension in the same animals, which was made possible by the use of radioactive labeled microspheres. The use of microspheres in chronic studies should provide excellent estimates of blood flow in that once they are lodged in the microcirculation, they are not known to become dislodged, metabolized or otherwise disturbed for up to 8 weeks, although they may be incorporated into the vessel wall (Hales, 1974).

The microsphere method of determining regional blood flow is based on the assumption that the microspheres are well mixed at the site of injection, distributed in the same manner as blood, trapped in the microcirculation on the first passage, do not disturb the circulation, and are present in adequate numbers. These assumptions have been proven to be accurate by Buckberg et al. (1971). Buckberg also investigated other possible sources of error in the microsphere technique and reported (1971) that there is essentially no difference in variability of regional distribution of microspheres between left ventricular and left atrial injection sites (with the exception of the heart). Included in Buckberg's publication was evidence that errors in this technique are kept to a minimum if each sample (tissue or blood) contains at least 400 microspheres.

In Series II of the current study the number of microspheres per sample of tissue (approximately 1 gram) and per blood sample were assessed,

and were found in nearly 100% of the samples to contain at least 400 microspheres. This was determined by counting a known quantity of microspheres and obtaining a count per microsphere value. This value was then used to determine microspheres/gram of tissue from counts/gram of tissue.

The microsphere size used in the current study (15 $\pm$ 5 μ) is most efficient for cerebral blood flow measurement in that less than 2% of the microspheres entering the cerebral circulation are found in the cerebral venous outflow (low percentage of microspheres shunted), blood distribution is not distorted and measurements are reproducible (Marcus et al., 1976).

Comparing blood flow measurements in Series I of the present study to similar studies using microspheres shows a favorable correlation. Roth et al. (1970), using 50μ microspheres labeled with ^{85}Sr, ^{51}Cr, and ^{141}Ce in unanesthetized dogs, reported regional cerebral blood flows to be 34.9 ml/min/100 gm in the right anterior cerebrum, and 28.8 ml/min/100 gm in the thalamus. Cerebral blood flows taken from similar regions in Series I of the present study were found to be 31.2 ml/min/100 gm in the cerebellum, 18.7 ml/min/100 gm in the medulla, 30.6 ml/min/100 gm in the right anterior cerebrum and 27.5 ml/min/100 gm in the thalamus. These flows are slightly lower than those reported by Roth et al., however the dogs in the present study were anesthetized with sodium pentobarbitol, and barbiturate anesthesia has been shown to decrease cerebral blood flow (McDowall, 1965). Rapela et al. (1967), through direct cannulation at the confluens of sinuses in anesthetized dogs found cerebral blood flow to be

26 ml/min/100 gm. This flow is primarily representative of cortical and thalamic blood flow, and approximates the cortical (30.6 ml/min/100 gm) and thalamic (27.5 ml/min/100 gm) flows obtained in Series I of the present study.

Results of Series I in the present study shows that chronic renovascular hypertension in the dog is associated with significant and often striking increases in blood flow and decreases or no change in vascular resistance in the medulla, pons, hypothalamus, thalmus, cerebellum and cortex. These results are in conflict with other reports of the state of the cerebral circulation during chronic hypertension. Kety et al. (1948) reported normal cerebral blood flows and elevated cerebral vascular resistances (on the order of 88%) in a group of human patients with chronic essential hypertension. Strandgaard et al. (1973) reported that the cerebral vasculature autoregulated well during moderate changes above and below resting levels in a group of ten male patients with chronic essential hypertension. Nishiyama et al. (1976) using 15 μ microspheres to measure cerebral blood flow, compared a group of spontaneously hypertensive rats to a group of normotensive Wistar-Kyoto rats and to a group of normotensive Wistar rats. The results showed no significant difference in cerebral blood flow when spontaneously hypertensive rats were compared to Wistar-Kyoto rats. However, when comparing spontaneously hypertensive rats to Wistar rats cerebral blood flow was significantly increased in the spontaneously hypertensive group.

Comparing a group of hypertensive animals or patients to a group of so-called "normal" animals or patients is particularly vulnerable to

error in that many other recognized or unrecognized clinical problems may exist concurrently as well as the existing problem of normal variations in arterial pressure caused by age, physical condition, genetic makeup, etc. The problem of species variation and interanimal variance also complicate the between group type of comparison. The present study, in which each animal served as its' own control, effectively reduces such inter-animal variance.

In view of the data from Series I, it appears that the cerebral vasculature may have failed to autoregulate during chronic perinephritic hypertension in that the elevated blood pressure is associated with increased cerebral blood flow in all regions sampled and no change or decreased cerebral vascular resistance. These results find support from investigations by Strandgaard et al. (1974, 1975) and Johansson (1974 a, b, c) who have shown that the upper limit of autoregulation may be exceeded during hypertension, resulting in a forced, passive dilation of the cerebral resistance vessels, causing cerebral blood flow to increase in proportion to the pressure increase.

Although the cerebral vasculature is sensitive to alterations in arterial carbon dioxide tension (Severinghaus and Lassen, 1967) as well as large changes in oxygen tension (Kogure et al., 1970), both arterial carbon dioxide and oxygen tensions were the same at the time of the initial normotensive microsphere injection and at the time of the hypertensive microsphere injection, thereby eliminating differences in blood gas tensions as contributing to the results. The cerebral

vasculature is relatively unresponsive to peripherally active vasoactive stimula such as adenosine (Berne, 1974; Raymond et al., 1976), prostaglandins F_2 α and E_1 (Emerson et al., 1974a; Emerson et al., 1974b), norepinephrine and epinephrine (Emerson et al., 1976), acetylcholine (Raymond et al., 1976), and angiotensin (Olesen, 1972). Although histamine has been shown to have a slight vasodilatory effect (Sokoloff, 1959), there is no reason to suspect that it is present in pharmocological quantities during chronic experimental hypertension. It has also been demonstrated that renin, angiotensin and osmolarity of blood are normal during chronic hypertension (Bianchi et al., 1970) as are plasma Na+ and K+ ionic concentrations (Haddy, 1974). Overbeck (1972) showed a peripheral decrease in sensitivity to the vasodilatory effects of the potassium cation. Traystman and Rapela (1975) have shown sympathetic nerve stimulation to have relatively little effect on the cerebral circulation, and Strandgaard et al.(1974) have shown sympathetic nerve activity to have no effect on the cerebral circulation during hypertension, therefore these factors are also believed to have no role in the results of the present study.

It has been shown in a recent report by Millard et al., (1977) that Tween 80, the surface agent commonly used to prevent aggregation of radionuclide-labeled microspheres, has a significant cardiovascular effect when given in concentrations normally used in microsphere experimentation. Millard et al. (1977) reported that Tween 80 caused a significant degree of hypotension and tachycardia. These changes in response to Tween 80 could cause an autoregulatory vasodilation of the cerebral vasculature and could theoretically cause changes similar to those in Series I, however we saw no cardiovascular or peripheral evidence

of a Tween 80 response in any dog following microsphere injection. It was also reported that the cardiovascular effects of Tween 80 occur between 30 seconds and 2 minutes following injection. Buckberg et al. (1971) have shown that most microspheres (40-98%) are lodged in the first thirty seconds following injection and 98% are lodged in the first sixty seconds, indicating that any cardiovascular effects of Tween 80 would occur after the microspheres have lodged. This relationship, however, has yet to be investigated.

The results of Series II of the present study shows that acute increases in blood pressure by Angiotensin II infusion are associated with increases in regional cerebral vascular resistances and no significant changes in regional cerebral blood flows with the exception of the cortex. These results indicate that the cerebral vasculature is autoregulating its blood flow quite adequately in the face of acute increases in blood pressure, which is contrary to the findings in the Series I chronic study. The region of the cortex demonstrates a significant increase in blood flow during severe hypertension, which is associated with no significant change in resistance. This may indicate that the autoregulatory function of the vasculature in the cortex may not be as resistant to the elevations of arterial pressure as other regions of the brain. It is also noted that for each region sampled, there is not always a significant average increase in resistance at both the moderate and severe levels of hypertension. Although the average resistance values were in each case elevated, individually the resistance values were not in each case elevated, and hence a non-significant statistical finding.

It was shown by Olesen, (1972) that angiotensin has no direct effect on the cerebral vasculature, therefore cannot be responsible

for the changes seen in Series II. The results of Series II are supported by the work of Flohr et al. (1971) who reported that acute increases in arterial blood pressure in Wistar rats with one kidney Goldblatt, two kidney Goldblatt and deoxycorticosterone hypertension resulted in normal cerebral blood flow (as measured by the microsphere distribution technique) and elevated cerebral vascular resistance. Allotey and Klassen (1977) used the microsphere (15μ) particle distribution technique in dogs to examine the acute changes in cerebral blood flow during one kidney Goldblatt hypertension. After 5 days of hypertension cerebral blood flow was normal, with cerebral vascular resistance significantly elevated 47% as compared to pre-hypertensive control values. These data as well as the results of Series II in the present study suggest that an acute increase in arterial blood pressure is associated with an increase in cerebral vascular resistance and normal cerebral blood flow, i.e., autoregulation.

In Series III of the present study, three dogs each received three microsphere injections during normal (anesthetized) blood pressures and during constantly maintained arterial blood gases (pO_2, pCO_2) and pH. The first injection was done under closed chest conditions with both carotid arteries patent. The following two injections were done under open chest conditions with the left carotid artery occluded. A two way analysis of variance was employed, with dogs used as blocks and the aforementioned surgical procedures used as treatments in order to determine whether or not the different surgical procedures had an effect on the results of Series I or Series II. The analysis of variance showed no significant difference ($p > 0.05$) between the surgical procedures, thereby eliminating this factor as a possible source of variance in Series

I or Series II. A significant difference was present in the medulla and thalamus that was attributable to the variance between dogs (blocks) which is to be expected. However, why this significant variance appears only in the regions of the medulla and thalamus and not in the other regions as well remains unclear. In addition, a Student's t test modified for paired replicates was used to compare the results between any combination of two microspheres for each dog. The results of this analysis showed that there was no significant difference ($p > 0.05$) between cerebral blood flows obtained with any combination of two microspheres, indicating a similarity in the distribution of the three types of microspheres.

In Series I (chronic hypertension) of the present study, the ^{85}Sr microsphere was used consistently for the control microsphere injection. This could conceivably introduce error into the results of this series in that the size ($15 \pm 5\mu$) of the ^{85}Sr microsphere may have been different from the size of the ^{51}Cr or ^{141}Ce microspheres ($15 \pm 5\mu$), and could therefore affect the distribution of these different isotopes in the microcirculation. Such non-randomization of order of microsphere injection could thereby introduce error into the experiment. This possibility was evaluated statistically. Comparing the control flows of Series I to the control flows of Series II shows the flows in Series II to be significantly greater ($p < 0.05$) in each of the regions sampled (Student's t test). The microspheres for Series II were randomized (^{85}Sr or ^{141}Ce) for each control injection. This finding could imply the control flows from Series I to contain a degree of error due to non-randomization; this point remains to be a source of speculation. One might also consider the fact that the fate of microspheres

chronically lodged in the microcirculation has yet to be established. It is possible that the microspheres might in someway be transported out of the microcirculation after a period of time. This also would produce results similar to the comparison between Series I and Series II control flows. This possibility is currently under investigation.

In an additional analysis, the control flows from both Series I and Series II were combined as a group (N=16), and compared (Student's t test) to the chronic hypertensive blood flows of Series I (N=7). A significant increase ($p < 0.05$) in blood flow was found in the hypothalamus, thalamus and cerebellum. This may indicate increased cerebral blood flow during chronic renovascular hypertension to be an accurate experimental finding in Series I, and not the result or experimental error. However, comparing the control blood flows from Series II with the chronic hypertensive blood flows from Series I (Student's t test), no significant difference ($p > 0.05$) was found in any region sampled.

The results of the present study shows the cerebral vasculature to autoregulate its blood flow by increasing cerebral vascular resistance during acute Angiotensin II induced hypertension, however the opposite was found to occur during chronic renovascular hypertension, with increased cerebral blood flow and decreased or unchanged cerebral vascular resistance, i.e., a failure to adequately autoregulate. A possible explanation for this finding could conceivably center around a time factor. The autoregulatory function of the cerebral vasculature may diminish with time in the face of a prolonged elevation of arterial

blood pressure. This could be related to a mechanical stretching of the vessel wall, an exhaustion of the smooth muscle's capability to reduce vessel radius, excessive turbulence causing a weakening of the vessel wall and hence dilation, etc.

Before a clear understanding of this complex problem can be reached, further investigation is needed in the field of the usage of microspheres for chronic microvascular research. It is important that we understand the fate of these particles in the microcirculation over long periods of time. A study using sham wrapped kidney (normotensive) animals over a similar six week course of time might also enable us to better interpret the data from the current study. It would also be of particular interest to monitor step by step changes of pressure, flow and resistance in the cerebral circuit during the development of chronic hypertension with the use of multiple microsphere injections. Such data, in conjunction with data on blood volume, cardiac output, histological changes in the vasculature and other pertinent cardiovascular parameters could help to document if changes occur, when they occur, and hopefully how they occur.

SUMMARY AND CONCLUSIONS

The present study was designed to investigate the effects of chronic (6 week) perinephritic hypertension, and acute Angiotensin II induced hypertension on regional cerebral hemodynamics in dogs. In the present study, each dog acted as its' own control to eliminate inter-animal variance. The radioactive particle distribution technique was used to measure regional cerebral blood flows. Three types of 15 $\pm$ 5μ diameter microspheres, labeled with ^{85}Sr, ^{141}Ce and ^{51}Cr, were injected into the left ventricle for cerebral blood flow measurements. The results are summarized as follows:

1. Six weeks of chronic perinephritic hypertension produced significantly increased regional cerebral blood flows in the medulla, pons, hypothalamus, thalamus, cerebellum and cortex. This was associated with significantly decreased resistance in the medulla and hypothalamus, with no change in resistance in the pons, thalamus, cerebellum and cortex.

2. Acute Angiotensin II induced hypertension at moderate and severe levels, were associated with no significant changes in regional cerebral blood flows in the medulla, pons, hypothalamus, thalamus, and cerebellum. The cortex exhibited a significantly elevated blood flow during severe hypertension. Regional cerebral vascular resistance was significantly increased in the medulla, pons, hypothalamus, thalamus and cerebellum. No significant change in resistance was found in the cortex when compared to control.

3. Similar results were obtained with ^{85}Sr, ^{141}Ce and ^{51}Cr labeled microspheres when injected in the same animal under control (normotensive) conditions.

4. Microsphere injections during open chest conditions, with one carotid artery occluded produce the same results as injections during closed chest conditions with both carotid arteries patent.

5. Mean control blood flows from each region of the brain sampled in the chronic study were significantly different when compared to mean control blood flows from each region of the brain sampled in the acute study.

6. Regional control blood flows from both the chronic and acute studies when compared as a group to the regional blood flows after six weeks of chronic perinephritic hypertension showed the hypertensive blood flows to be significantly increased in the hypothalamus, thalamus and cerebellum.

7. Control blood flows from the acute study were compared to the hypertensive flows in the chronic study were not significantly different in any of the regions sampled.

In conclusion, the present study indicates that:

1. The three types of microspheres used in this study produced similar results, therefore one type of radioactive microsphere can be used as a control for the other types.

2. The cerebral vasculature adequately autoregulates during acute Angiotensin II induced hypertension in each region sampled with the exception of the cortex.

3. The cerebral vasculature appears to inadequately autoregulate following six weeks of chronic perinephritic hypertension.

4. Further investigation of the use of microspheres for chronic vascular research is needed.

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APPENDIX

Table A-I. Regional cerebral blood flows (ml/min/100 gm) before and at 6 weeks of renovascular hypertension.

Experiment Number	P_a		Medulla		Pons		Hypothalamus		Thalamus		Cerebellum		Cortex	
	0	6	0	6	0	6	0	6	0	6	0	6	0	6
1	135	175	28.6	51.9	20.5	40.2	29.0	84.1	30.7	71.8	22.7	59.1	34.1	66.8
2	130	195	20.2	31.7	19.8	35.8	23.0	59.2	26.3	62.5	25.1	56.1	31.0	43.9
3	135	145	19.3	22.0	16.4	13.5	28.6	25.4	33.4	30.0	41.1	40.8	31.4	31.1
4	130	200	14.1	29.8	20.5	33.2	13.0	48.0	24.8	41.9	39.7	60.2	35.6	48.5
5	125	170	16.9	25.2	17.4	25.5	22.0	35.2	28.0	39.2	38.9	47.5	30.1	40.1
6	120	125	14.5	27.4	20.5	32.2	16.8	33.0	28.1	30.3	26.3	38.2	29.9	33.6
7	135	140	17.3	23.0	7.5	14.1	16.1	21.8	21.8	27.1	24.8	39.2	22.2	26.6
$\bar{x}$	130	164	18.7	30.1	17.4	27.7	21.2	43.8	27.5	43.2	31.2	48.7	30.6	41.5
$\pm$ S.E.	2	10	1.8	3.8	1.8	3.9	2.3	8.3	1.4	6.5	3.1	3.6	1.6	5.0

P_a = mean aortic blood pressure; 0 = control microsphere injection; 6 = 6th week microsphere injection; $\bar{x}$ = mean; $\pm$ S.E. = standard error; N=7

Table A-II. Regional cerebral vascular resistance (mm Hg/ml/min/100 gm) before and at six weeks of renovascular hypertension.

Experiment Number	Pa		Medulla		Pons		Hypothalamus		Thalamus		Cerebellum		Cortex	
	0	6	0	6	0	6	0	6	0	6	0	6	0	6
1	135	175	4.7	3.3	6.5	4.3	4.6	2.0	4.4	2.4	5.9	2.9	3.9	2.6
2	130	195	6.4	6.1	6.5	5.4	5.6	3.2	4.9	3.1	5.1	3.4	4.1	4.4
3	135	145	6.9	6.6	8.2	10.7	4.7	5.7	4.0	4.8	3.2	3.5	4.3	4.6
4	130	200	9.2	6.7	6.3	6.0	10.0	4.1	5.2	4.7	3.2	3.3	3.6	4.1
5	125	170	7.3	6.7	7.1	6.6	5.6	4.8	4.4	4.3	3.2	3.5	4.1	4.2
6	120	125	8.2	4.5	5.8	3.8	7.1	3.7	4.2	4.1	4.5	3.2	4.0	3.7
7	135	140	7.8	6.0	18.0	9.9	8.3	6.4	6.1	5.1	5.4	3.5	6.0	5.2
$\bar{x}$	130	164	7.2	5.7	8.3	6.6	6.5	4.2	4.7	4.0	4.3	3.3	4.2	3.7
$\pm$ S.E.	2.0	10.0	0.5	0.4	1.6	1.0	0.7	0.5	0.3	0.5	0.4	0.1	0.3	0.2

P_a = mean aortic blood pressure; 0 = control microsphere injection; 6 = 6th week microsphere injection; $\bar{x}$ = mean; $\pm$ S.E. = standard error; N=7

Table A-III. Regional Cerebral blood flows (ml/min/100 gm) during graded levels of acute Angiotensin II induced hypertension.

Expt.	P_a			Medulla			Pons			Hypothalamus			Thalamus			Cerebellum			Cortex		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
1	125	175	200	36.1	36.5	32.5	25.0	25.8	26.0	28.1	24.9	27.0	38.9	41.7	36.8	49.2	40.5	41.3	36.8	35.8	42.4
2	130	175	170	50.5	47.7	42.8	36.2	34.3	31.2	49.0	52.7	35.0	40.3	53.4	33.4	47.4	48.9	40.4	46.6	53.3	41.9
3	130	175	200	22.4	14.0	26.1	27.6	25.5	32.1	23.0	15.7	26.2	26.4	27.1	36.1	31.2	30.5	38.6	29.7	28.6	42.4
4	130	170	215	32.7	42.6	53.8	26.9	32.2	44.1	39.5	41.0	58.0	44.4	48.6	66.8	46.3	65.9	94.4	39.8	50.4	77.7
5	125	175	190	15.9	24.3	21.7	13.1	15.4	17.5	24.5	22.8	29.9	29.3	35.3	34.6	28.5	42.6	40.3	29.0	52.5	77.7
6	160	175	200	37.0	25.3	51.6	37.9	20.6	43.8	41.7	31.5	67.6	39.7	24.4	56.4	54.7	37.7	69.3	61.5	40.7	97.5
7	150	180	225	29.6	36.1	39.4	14.3	26.3	25.5	35.0	44.2	71.5	21.0	36.7	34.2	33.6	46.7	47.8	30.6	41.2	60.2
8	160	175	215	50.6	38.0	46.5	23.1	16.7	22.7	31.3	27.0	28.3	39.3	32.8	41.5	40.2	35.0	46.8	57.3	57.0	79.1
9	120	190	210	39.5	29.0	31.7	25.1	27.3	27.3	47.5	28.8	39.7	44.6	33.4	45.1	58.5	50.0	59.4	58.5	51.2	79.5
$\bar{X}$	136	176	202	34.9	32.6	38.4	25.4	24.9	30.0	35.5	32.0	42.5	35.9	37.0	42.7	43.2	44.2	53.1	43.3	45.6	63.1
$\pm$ SE	± 5	± 1	± 5	3.8	3.4	3.7	2.8	2.1	3.0	3.1	3.9	6.0	2.7	3.1	3.8	3.5	3.4	6.1	4.3	3.1	6.9

P_a = mean aortic blood pressure; 1 = control (normotensive) microsphere injection; 2 = microsphere injection during moderate, acute Angiotensin II induced hypertension; 3 = microsphere injection during severe, acute Angiotensin II induced hypertension; $\bar{X}$ = mean; $\pm$ SE = standard error; N=9.

Table A-IV. Regional cerebral vascular resistances (mmHg/ml/min/100 gm) during graded levels of acute Angiotensin II induced hypertension.

Expt.	P_a			Medulla			Pons			Hypothalamus			Thalamus			Cerebellum			Cortex		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
1	125	175	200	3.4	4.7	6.1	5.0	6.7	7.6	4.4	7.0	7.4	3.2	4.1	5.4	2.5	4.3	4.8	3.3	4.8	4.7
2	130	175	170	2.5	3.6	3.9	3.5	5.1	5.4	2.6	3.3	4.8	3.2	3.2	5.0	2.7	3.5	4.2	2.7	3.2	4.0
3	130	175	200	5.8	12.5	7.6	4.7	6.8	6.2	5.6	11.1	7.6	4.9	6.4	5.5	4.1	5.7	5.1	4.3	6.1	4.7
4	130	170	215	3.9	3.9	3.9	4.8	5.2	4.8	3.2	4.1	3.7	2.9	3.4	3.2	2.7	2.5	2.2	3.2	3.3	2.7
5	125	175	190	7.8	7.2	8.7	9.5	11.3	10.8	5.1	7.6	6.3	4.2	4.9	5.4	4.3	4.1	4.7	4.3	3.3	3.9
6	160	175	200	4.3	6.9	3.8	4.2	8.4	4.5	3.8	5.5	2.9	4.0	7.1	3.5	2.9	4.6	2.8	2.6	4.2	2.0
7	150	180	225	5.0	4.9	5.7	10.4	6.8	8.8	4.2	4.0	3.1	7.1	4.9	6.5	4.4	3.8	4.1	4.9	4.3	3.7
8	160	175	215	3.1	4.6	4.6	6.9	10.4	9.4	5.1	6.4	7.5	4.0	5.3	5.1	3.9	5.0	4.5	2.7	3.0	2.7
9	120	190	210	3.0	6.5	6.6	4.7	6.9	7.6	2.5	6.5	5.2	2.6	5.6	4.6	2.0	3.8	3.5	2.0	3.7	2.6
$\bar{x}$	136	176	202	4.3	6.0	5.6	5.9	7.5	7.2	4.0	6.1	5.3	4.0	4.9	4.9	3.2	4.1	3.9	3.3	3.9	3.4
± SE	5	1	5	0.5	0.9	0.5	0.8	0.7	0.7	0.3	0.7	0.6	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Pa = mean aortic blood pressure; 1 = control (normotensive) microsphere injection; 2 = microsphere injection during moderate, acute Angiotensin II induced hypertension; 3 = microsphere injection during severe, acute Angiotensin II induced hypertension; $\bar{x}$ = mean; ± SE = standard error; N=9.