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Autoregulation of Cortical Blood Flow in Response to Phenylephrine Induced Hypertension in the Normocapnic and Hypercapnic Cat

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Abstract

AUTOREGULATION OF CORTICAL BLOOD FLOW IN RESPONSE TO PHENYLEPHRINE INDUCED HYPERTENSION IN THE NORMOCAPNIC AND HYPERCAPNIC CAT

by

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The purpose of this research was to determine the degree of autoregulation of cortical blood flow in the cat, and to evaluate the usefulness of the heated thermocouple technique for measurement of local cortical blood flow. We determined the relationship between local flow and voltage output from our thermoelectric flow probe by in vitro experiments with an artificial kidney. We measured local cortical blood flow in 17 cats during episodes of phenylephrine-induced hypertension, under conditions of normocapnia and, in some cases, hypercapnia. Arterial blood pressure and voltage output from the flow probe thermocouples were recorded continuously with a Physiograph-six monitor.

We found the heated thermocouple flow probe to be useful for qualitative description and for estimation of

relative changes in local cortical blood flow. The relationship between the flow probe thermocouple voltage and local flow was shown to be a hyperbola.

We found active regulation of local cortical blood flow in the presence of acutely induced hypertension. This autoregulation does not completely prevent change in local cortical blood flow but it does limit the change. Within the autoregulatory range, an increase in mean arterial blood pressure of 10 percent was associated with an increase in local cortical blood flow of 8 percent. This is in agreement with other studies of cortical blood flow autoregulation in the cat, and represents less complete autoregulation than is found in other species. Breakthrough of autoregulation was found in some cats with mean arterial blood pressures of 180-230 mmHg.

We found intact autoregulation of local cortical blood flow in the hypercapnic cat. The upper arterial blood pressure limit of autoregulation was apparently shifted downward from the normocapnic level by hypercapnia.

LOMA LINDA UNIVERSITY

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

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INTRODUCTION

An organism must be able to differentially adjust blood supply to its various organs and tissues. Autoregulation is the adjustment of bloodflow in an organ in response to change in perfusion pressure. Cortical blood flow autoregulation is of particular interest because of the critical importance of maintaining the brain homeostasis. The increasing popularity of manipulating blood pressure and blood flow for medical and surgical purposes requires thorough understanding of the basic regulatory mechanisms. The purpose of this research was to determine the degree of autoregulation of the local cortical blood flow in the normocapnic and hypercapnic cat; and to evaluate the usefulness of the heated thermocouple technique for blood flow measurement in this context.

We used a thermoelectric blood flow probe to investigate the regulation of local cortical blood flow in the cat during episodes of phenylephrine (Neo-synephrine) induced hypertension. These measurements were made under conditions of normocapnia (Series I) and, in some cases, hypercapnia (Series II).

The relationship between local flow and voltage output from the thermoelectric flow probe was determined by in

vitro studies with a mechanical model constructed from an artificial kidney. The results were used as a basis for interpretation of flow probe data from the in vivo experiments.

BACKGROUND

Cerebral blood flow is regulated by the modification of cerebrovascular resistance in response to changes several different factors including: a) perfusion pressure (autoregulation), b) cerebral blood volume, c) arterial oxygen and carbon dioxide content and d) local metabolic rate (Mchedlishvili 1980). Cerebrovascular resistance is modified by several mechanisms including: a) reflex contraction of vascular smooth muscle in response to increased wall tension (the myogenic response, Bayliss 1902); b) direct local effects on vascular smooth muscle tone of CO_2, O_2, H+, K+, adenosine, and other metabolic factors (Kontos 1981); and c) neurogenic mechanisms, which seem to play a role in the regulation of vascular smooth muscle tone of the major pial and intracerebral arteries as well as the carotid arteries (Mchedlishvili 1980).

Bayliss (1902) presented the first reported evidence for autoregulation of blood flow. He observed changes in blood volume in response to changes in blood pressure in the hind limbs of cats and dogs. Bayliss concluded that vascular dilatation with decreasing blood pressure and vascular constriction with increasing blood pressure were acting to minimize changes in blood flow.

Autoregulation of the cerebral circulation was systematically documented by Fog (1937, 1938, 1939a, 1939b). In a classic series of experiments, using the cranial window technique perfected by Forbes (1928), Fog was able to measure changes in pial arteriole diameter in the cat with changes in arterial blood pressure. Consistent dilatation with decreasing blood pressure and constriction with increasing blood pressure was interpreted as an autoregulatory response of the pial arterioles.

Study of the regulation of cerebral blood flow has been limited by measurement difficulties. The nitrous oxide technique, developed by Kety and Schmidt (1945, 1946, 1948a, 1948b) was the first practical method for quantitative measurement of cerebral blood flow. This technique is an application of the Fick principle: the quantity of a substance in the inflowing arterial blood is equal to the quantity of that substance removed by the perfused tissue plus the quantity in the outflowing venous blood. The nitrous oxide technique and its numerous variations provided safe, quantitative and relatively non-invasive methods for cerebral blood flow measurement, and opened the door for a variety of studies on cerebral circulation. Studies of cerebral blood flow autoregulation have typically shown relatively stable blood flow over a wide range of blood pressures. In general, cerebral blood flow tends to fall

off with mean arterial blood pressures below 40 to 80 mmHg and tends to increase with pressures above 150 to 200 mmHg. The regulation of cerebral blood flow has been well reviewed by a number of investigators including Lassen (1959), Betz (1972), Kuschinsky and Wahl (1978), Strandgaard (1978), Larsen and Lassen (1979), Mchedlishvili (1980) and Kontos (1981).

Measurement of blood flow by techniques based on the Fick principle is limited to intermittent measurement during steady flow states. The most widely studied technique for continuous measurement of cerebral blood flow is the heated thermocouple technique. This technique was introduced by Gibbs (1933), who described a heated thermocouple in the form of a needle which could be inserted into relatively inaccessible tissue with minimal trauma. The temperature of the heated thermocouple reflects the balance between the generation of heat by the probe and the dissipation of heat by conduction and convection. The rate of heat dissipation by convection (the transport of heat by movement of blood in the vasculature of the tissue) is proportional to the magnitude and velocity of local blood flow. Therefore, the temperature difference between the probe thermocouple and a reference thermocouple placed in adjacent tissue will be inversely proportional to blood flow; an increase in blood flow will decrease the probe temperature, and a decrease in

blood flow will allow the probe temperature to rise. Gibbs demonstrated this relationship by concomitant measurement of flow probe temperature in the cortex of the cat kidney and direct measurement of venous outflow. He assumed that local renal cortical blood flow was proportional to total organ blood flow in the cat kidney. Gibbs suggested that the probe would be most useful for continuous qualitative measurement of blood flow and for rough quantitative measurement when in vivo calibration was possible.

MATERIALS AND METHODS

Surgical Preparation and Monitoring

We anesthetized 28 mongrel cats with 10 to 20 mg ketamine (Vetelar) intramuscularly. Following endotracheal intubation, ventilation was controlled with a Harvard mechanical respirator which was adjusted to maintain normocapnia and normoxia (respiratory rate 14 to 16 per minute, tidal volume 60 to 100 cc, inspired gas mixture 75 percent nitrous oxide, 25 percent oxygen; arterial PCO_2 30 mmHg, PO_2 120 mmHg, pH 7.33). Muscular relaxation was achieved with intravenous gallamine (Flaxidil) 20 mg initially, followed by periodic 15 mg injections as needed. Eleven experiments are not included in this study because of technical problems or change in technique; the results presented here are based on experiments with 17 cats.

We placed femoral arterial and venous catheters for blood sampling, blood presure measurement and intravenous injection of drugs. Arterial blood pressure was monitored with a Statham strain gauge transducer and recorded on one channel of a Physiograph-six monitor. Arterial blood was drawn frequently for measurement of PO_2, PCO_2, and pH (at 37 degrees Celsius). With 4 experiments, end-expired PCO_2 was measured continuously with a Beckman LB-III monitor.

The cats were placed in a stereotaxic head holder and unilateral or bilateral craniotomies were made in the parietal regions. The dura mater was opened to expose the cortex and the thermoelectric flow probe (described in detail below) was placed against the cortex in a position allowing maximum contact with the cortical surface. This interface was stabilized with mineral oil which effectively filled any gaps and prevented drying. The voltage output from the flow probe thermocouples was continuously recorded on one channel of a Physiograph-six monitor.

Acute increases in perfusion pressure were produced by raising the mean arterial blood pressure with a continuous intravenous infusion of phenylephrine (0.2 mg/ml) with a "Harvard Pump" motor driven syringe. The dosage ranged from 0.2 to 10.0 mg/hr; most cats responded satisfactorily to infusion rates less than 5.0 mg/hr.

Thermoelectric Flow Probe

The flow probe used in this study was based on a modification of Gibbs' heated thermocouple technique (Brawley 1968, 1969, Carter and Atkinson 1973a, 1973b). A Peltier device (a small thermoelectric heat pump) was used to heat and cool 2 small gold plates which were applied directly to the exposed cerebral cortex. The temperature difference between the 2 plates was measured with a pair of

thermocouples connected in series and attached to the top surface of the plates. With this arrangement only change in the temperature difference between the plates effects the output voltage; change in ambient temperature does not effect the temperature difference or output voltage. The use of a thermoelectric heat pump allows differential temperatures of 2 to 5 degrees Celsius while keeping the temperature of the warm plate less than 3 degrees Celsius above the brain temperature. This effectively minimized the disturbance of local blood flow and neural function which results when brain tissue is heated (Brodkey (1964) showed a substantial disturbance in blood flow and neural function when brain tissue was heated above 42 degrees Celsius).

The flow probe was designed around a Borg-Warner model 130-12 thermoelectric module (Peltier device) as shown in Figure 1. Thirty gauge, 14K gold plates were attached with silver-impregnated silicone rubber to both sides of the thermoelectric module. The sections of gold plate extending beyond the surface of the thermoelectric module were bent outward to approximately 92 degrees, providing two flat surfaces each 6 mm square, the entire contact surface measuring 6 by 16 mm. On the top surface of each plate a miniature "Zig/Zag" copper-constantan thermocouple (Hy-Cal Engineering Co.) was affixed with adhesive coated Kaptan. After assembly the components of the flow probe were encased

in epoxy cement. The flow probe was mounted on an adjustable phonographic tone arm which held it in position against the cortical surface with a constant force of approximately 0.01 to 0.02 newtons (1 to 2 grams). With this arrangement, movement of the brain did not disturb the contact between the flow probe and the cortex.

The current flow through the thermoelectric module was maintained at 300 mA with 2, "D" size, 1.35 volt mercury batteries connected in series with a variable resistor and microammeter. This current maintained a plate temperature difference of 2 to 4 degrees Celsius under the usual operating conditions. The voltage output from the thermocouple (150 to 450 microvolts for a 2 to 5 degrees Celsius temperature range) was amplified by a thermocouple amplifier with a DC gain of 1,000 (designed and built by Larry Aamodt, Department of Medical Electronics, Loma Linda University), and continuously recorded on one channel of a Physiograph-six monitor.

Artificial Kidney Model

We used an artificial kidney (Cortis-Dow) as a model organ to determine the relationship between plate temperature and flow, in vitro. The artificial kidney consists of a hollow plastic casing approximately 3.5 cm in diameter and 12 cm in length which is packed with

longitudinal capillary exchange tubes. A 2 by 3 cm opening was made in the plastic casing and covered with a single layer of latex rubber (Schmid Labs, Inc.) to prevent leakage of water from the system. We placed the flow probe firmly against the latex in both parallel and perpendicular orientations; the latex was in turn pressed against the capillary tubes. Blood flow was simulated by water flow through the capillary tubes, and the output voltage from the flow probe thermocouples was recorded with a Physiograph-six monitor.

Analysis of Data

Artificial Kidney Experiments. The notation used for description and analysis of flow probe data is summarized in Figure 2 and Table 1. Analysis of data from thermoelectric flow probes has traditionally been based on principles of internal calorimetry (Grayson 1951, 1952). The apparent thermal conductivity K is determined from the equation:

$$I^2 \times R = 12.6 \times r \times K \times dT \qquad (1)$$

where $I^2 \times R$ is the power through a spherical heat source radius r, and dT is the temperature increment maintained between the heated and reference thermocouples. When blood flow is present the apparent thermal conductivity is increased from the zero flow state by convection (the transport of heat by the movement of blood in the vascular

bed). This observed difference in apparent thermal conductivity is designated the "conductivity increment" and has been shown to be a linear function of the rate of local blood flow, in some circumstances.

Carter and Atkinson (1973a, 1973b) initially reported a direct linear relationship between the voltage output from the probe thermocouples and local cortical blood flow, as measured simultaneously with a xenon-133 wash out technique. Subsequently, Carter and Erspamer (1980) reported (in an abstract) that it was the apparent thermal conductivity increment that was proportional to local cortical blood flow, as described by the equation:

$$\Phi c = Y \times (1/V - 1/V0) \qquad (2)$$

where Φc is the local cortical blood flow, V is the voltage output from the probe thermocouples, V0 is the voltage output (V) when the local blood flow is zero, and Y is a proportionality constant. As shown in equation 1 the apparent thermal conductivity is inversely proportional to the temperature difference between the probe thermocouples, hence (1/V-1/V0) is directly proportional to the apparent conductivity increment.

In the present study this is compared with an alternative equation derived by Grangsjo et al. (1965). With theoretical deduction, the relationship between local

blood flow and voltage output from a thermoelectric flow probe is shown to be a hyperbola which can be represented as:

$$\Phi g = Z \times (dV / (dVmax - dV)) \qquad (3)$$

where Φg is relative local blood flow, dV is the difference between V and V0, dVmax is the value of dV which is approached with very large flow rates and Z is a constant. For calculation of the relative magnitude of local flow, we have given the constants Y and Z the value 1.0.

The most significant difference between equations 2 and 3 is the inclusion of dVmax in the calculation of Φg. With very large local flow, the transfer of heat between the plates of the flow probe and the flowing fluid becomes a limiting factor and dV approaches a maximum. This dVmax corresponds to the minimum temperature difference between the probe plates. In the calculation of Φc (Equation 2) very large values for local flow are obtained only as the temperature difference between the probe plates, or V, approaches zero (i.e. dV approaches V0). Since in practice the limit of dV is significantly less than V0, the calculation of Φc as an estimate of local flow would be expected to underestimate the actual local flow at higher flow rates. We analyzed the data from the artificial kidney experiments with both Equation 2 and 3.

In Vivo Experiments. Flow probe voltage and blood pressure data were analyzed in the following manner: analog to digital conversion (by hand) from the graphic record (one minute increments); calculation of mean arterial blood pressure (diastolic pressure plus one third the pulse pressure); calculation of relative local cortical blood flow (Φg by equation 3); and graphical representation of relative local cortical blood flow versus mean arterial blood pressure. The ratio of the fractional change in flow versus fractional change in pressure was calculated as:

$$RS = A \times (mMABP / m\Phi g) \qquad (4)$$

where RS is the relative slope ratio, A is the slope of Φg versus mean arterial blood pressure, and $m\Phi g$ and mMABP are the mean values for relative local cortical blood flow and mean arterial blood pressure respectively. The relative slope ratio is a numerical representation of the relative change in flow for a given change in pressure. For example if the relative slope equals 1.0, a 10% increase in pressure is associated with a 10% increase in flow, if the relative slope equals 0.8, a 10% increase in pressure is associated with an 8% increase in flow. The slopes were calculated by standard "least squares" linear regressions. Data processing was done with a Radio-Shack TRS-80 computer.

RESULTS

Artificial Kidney Model

Data from the artificial kidney experiments (with several different orientations of the flow probe relative to the column of capillary tubes) are illustrated in Figures 3, 4 and 5, as dV, Φc and Φg respectively, versus flow through the artificial kidney. We used multiple probe orientations in an attempt to minimize the effects of unidirectional flow and variation in surface contact. Closer contact was made (between the flow probe plates and the capillary tubes) when the probe was perpendicular to the column than when parallel to the column. The combined results from different orientations approximate the in vivo relationship between the flow probe, the surface of the cortex, and the multidirectional blood flow in the cortical tissue.

In Figure 3 the data from the artificial kidney is represented graphically as dV versus flow through the artificial kidney. The maximum dV, as estimated from this data, is shown as a line across the top of the graph. In Figures 4 and 5 the estimated local flow, Φc by Equation 2 and Φg by Equation 3 respectively, has been plotted versus flow through the artificial kidney. It is apparent from comparison of these Figures that Φg is a more accurate

estimate of relative flow in the artificial kidney than is Φc, which underestimates the actual flow with higher flow rates.

For the in vivo experiments, Φg has been used as an estimate of relative local cortical blood flow. A single value for dVmax has been estimated from the artificial kidney data. In practice dVmax is variable: a complex function of a) the physical relationship between the flow probe and the flowing fluid, and b) the thermal properties of the fluid and the surrounding matrix. In the artificial kidney a thin layer of latex and the walls of the capillary tubes are interposed between the flow probe and the flowing fluid. These elements correspond to the non-perfused zone between the flow probe plates and the exposed cortex, and the structural elements of the perfused tissue, in the in vivo situation.

Autoregulation in Normocapnic Cats

In 17 normocapnic cats, the mean arterial blood pressure was gradually increased over a period of 2 to 23 minutes from resting values of 95 to 180 mmHg (mean 135, SD 24) to maximum values of 158 to 247 mmHg (mean 202, SD 24). At these levels further moderate increases in the rate of phenylephrine infusion had little effect on the arterial blood pressure. The mean arterial blood pressure was maintained greater than 90 percent of the maximum for 2 to

15 minutes (mean 5) and was subsequently allowed to return gradually to the resting level. These hypertensive episodes ranged in total length from 5 to 43 minutes (mean 15). The resting arterial blood pressures are well within the wide range of values (100/60-200/145 mmHg) reported by other investigators and compiled in the Biology Data Book, Volume III (Altman and Dittmer 1974).

The response of Φg to changes in mean arterial blood pressure during 33 hypertensive episodes in 17 cats is represented in Figure 6. We found four basic patterns of response: linear, hysteresis, two-stage, and breakthrough. These patterns will be discussed below.

The mean relative slope ratio for the initial response of Φg to increasing arterial blood pressure is 0.8 (SD 0.3, n=33). This can be appreciated visually by comparing the experimental results to the lines of proportional increase which have been drawn on the graph. Along the lines of proportional increase the relative slope ratio is equal to 1.0 and the increase in flow is proportional to the increase in pressure. The relative slope ratios from these experiments are represented in histogram form in Figure 7.

With complete autoregulation, an increase in arterial blood pressure is associated with a compensatory increase in vascular resistance maintaining constant blood flow and a

relative slope ratio of zero. If the compensatory increase in vascular wall tension is only enough to maintain constant resistance, there is a proportional increase in blood flow and a relative slope ratio of 1.0. The relative slope ratio mean of 0.8 indicates an autoregulatory response to arterial hypertension which was not complete, but was adequate to maintain the vascular resistance constant or increase it slightly.

The response of Φg to acutely induced arterial hypertension was of several different forms. A simple linear response was found in 10 hypertensive episodes in 7 of 17 cats. In these cases Φg increased in a more or less linear fashion in response to increasing mean arterial blood pressure as illustrated in Figures 8 and 12.

A hysteresis response was found in 12 hypertensive episodes in 8 of 17 cats. This response was very similar to the simple linear type except that the return of Φg lagged behind the return of the mean arterial blood pressure to pre-infusion levels. This effect was somewhat variable with different animals, but quite repeatable within the same animal (Figures 9 and 13).

A two-stage response was found in 6 hypertensive episodes in 6 of 17 cats. In 5 of these cats simple linear or hysteresis responses were also found. With the two-stage response there was an initial linear response of increasing

Φg with increasing mean arterial blood pressure. As the mean arterial blood pressure continued to rise (above pressures ranging from 140-195 mmHg, mean 173) the response of Φg was proportionally larger than the initial response. This is illustrated in Figures 10 and 11.

A breakthrough type response was found in 5 hypertensive episodes in 4 of 17 cats. In these cases there was an initial linear response of increasing Φg with increasing mean arterial blood pressures. With sustained high mean arterial blood pressures (180-230 mmHg, mean 210), there was an increase in Φg above the initial plateau level (Figures 12 and 13). During the return of the mean arterial blood pressure to pre-infusion levels and during hypertensive episodes which immediately followed, Φg remained at relatively higher levels. In one case, after waiting 20 minutes for Φg to return to pre-infusion levels, a subsequent hypertensive episode again showed the breakthrough response (Figure 13).

Autoregulation in Hypercapnic Cats

We induced hypertensive episodes in 6 cats under conditions of hypercapnia (in addition to control periods with normocapnia). Hypercapnia was produced with an inspired gas mixture of 5 or 10 percent carbon dioxide, 25 percent oxygen and 65 or 70 percent nitrous oxide. In this

series the mean arterial blood pressure was gradually increased over a period of 2 to 10 minutes from resting values of 95 to 150 mmHg (mean 122, SD 15) to maximum values of 146 to 214 mmHg (mean 186, SD 15). At these levels further moderate increases in the rate of phenylephrine infusion had little effect on the arterial blood pressure. The mean arterial blood pressure was maintained greater than 90 percent of the maximum for 2 to 5 minutes (mean 3, SD 1) and was subsequently allowed to return gradually to the resting level. These hypertensive episodes ranged in total length from 5 to 18 minutes (mean 10, SD 4).

The response of Φg to changes in mean arterial blood pressure during 14 hypertensive episodes in 6 cats is represented in Figures 14 and 15. During the hypercapnic periods, which ranged in duration from 23 to 39 minutes, the arterial PCO_2 was increased from a baseline mean of 27.6 mmHg (SD 4.9) to a hypercapnic mean of 65 mmHg (SD 19). Associated with the induction of hypercapnia, there was an increase in Φg to 140 to 360 percent (mean 260, SD 80) of the baseline levels.

Comparison of the hypercapnic hypertensive episodes with the pre-hypercapnic control hypertensive episodes shows no detectable difference in the shape of the resulting Φg versus mean arterial blood pressure curves, the degree of autoregulation, or the resulting relative slope ratios

(Figure 7). For the initial control hypertensive episodes the relative slope ratio mean was 0.7 (SD 0.4). For the hypercapnic hypertensive episodes the relative slope ratio mean was 0.8 (SD 0.5). These variations in Φg and relative slope ratio are illustrated in Figure 15.

During hypercapnia, the upper limit of autoregulation (observed in 3 of 6 cats) was apparently shifted downward from the normocapnic level (Figure 14). Pre-hypercapnic control hypertensive episodes did not show an upper limit of autoregulation in these cats.

During the control hypertensive episodes following hypercapnic periods, Φg remained approximately 50% higher than during the pre-hypercapnic controls. The autoregulatory response of Φg to induced hypertension and the resulting relative slope ratios were not significantly different from the controls (relative slope ratio mean 0.9, SD 0.3).

DISCUSSION

Experimental Design

In this study the cats were lightly anesthetized with nitrous oxide. This avoids the impairment of autoregulation which has been observed with deep anesthesia (Zwetnow 1968, Smith et al. 1969). Although there is considerable inconsistency in the investigational reports, the effects of nitrous oxide on cerebral blood flow and metabolic rate seem to be relatively small (Adriani 1970, Vickers et al. 1978, Hemmingsen et al. 1979, Oshita et al. 1979). Smith et al. (1979) have shown intact cerebral blood flow autoregulation to both arterial hypertension and hypotension in the presence of nitrous oxide anesthesia. Gallamine has little effect on the cardiovascular and cerebrovascular systems (Vickers et al. 1978). Ketamine, which is rapidly metabolized, produces a transient (10-15 minute) rise in blood pressure, cardiac output and cerebral blood flow (Chen 1969, Szappanyos et al. 1969, Vickers et al. 1978). In the present study, we waited two to three hours after the administration of ketamine before commencing flow measurement.

The mean blood pressure in the abdominal aorta was used as an estimate of mean cerebral perfusion pressure. With an

open craniotomy preparation the intracranial pressure is essentially zero. With the cat in the "sphinx" position the venous blood pressure at the level of the cerebral cortex is very small relative to the arterial blood pressure. The magnitude of the cerebral perfusion pressure is therefore very close to that of the peripheral arterial blood pressure.

In this study, we produced acute increases in cerebral perfusion pressure by increasing the arterial blood pressure with an intravenous infusion of phenylephrine. Phenylephrine was chosen because of its potent, selective, alpha adrenergic agonist properties. When infused intravenously, phenylephrine causes a substantial peripheral vasoconstriction associated with an increase of both diastolic and systolic arterial blood pressures and of the pulse pressure. In vivo, intravenous phenylephrine has very little direct effect on the cerebral vasculature; its action is limited by the blood brain barrier, which limits the accessibility of cerebrovascular smooth muscle to circulating amines. In vitro, the effect of phenylephrine on cerebral vessels is to stimulate a small dose related vasoconstriction which is one-tenth the response of vessels from other tissues, and is proportionally less than with other adrenergic agonists such as epinephrine, norepinephrine, isoprenaline and isoproterenol (Lowe and

Gilboe 1971, Edvinsson and Owman 1974, Hobson et al. 1975, Edvinsson and MacKenzie 1977).

Heated Thermocouple Technique

A number of investigators have used the heated thermocouple technique for qualitative measurement of blood flow (Schmidt and Pierson 1934, Norcross 1938, Lubsen 1941, Field, Grayson and Rogers 1951, Scher 1951, Brawley 1968, 1969, Kogure et al. 1969). In an effort to more accurately measure local blood flow Grayson (1951, 1952) developed the method of internal calorimetry for the quantitative measurement of local blood flow in certain situations. Using a thermocouple probe which was maintained at a constant temperature increment from the reference junction, and a series of gelatin solutions with known thermal conductivities, he was able to calibrate the measurement of thermal conductivity. With artifical perfusion of isolated rabbit and sheep kidneys and sheep spleens he demonstrated a linear relationship between the local conductivity increment and total organ blood flow.

There is considerable disagreement concerning the general application of the principles of internal calorimetry for the quantitative measurement of local blood flow with the heated thermocouple technique. In an effort to further characterize the relationship between apparent thermal conductivity and local blood flow, investigators

have developed numerous theoretical and physical models including: a) various mathematical descriptions (Bill 1962, Perl 1962, Kastella and Fox 1971), b) isolated organ perfusion (Grayson 1952, Linzell 1953, Hensel and Ruef 1954, Graf, Golenhofen and Hensel 1957, Seylaz 1965, Grangsjo et al. 1966) and c) mechanical models including tubes of varying sizes, gelatin, sponges, cotton wool, glass wool, and glass beads (Gibbs 1933, Linzell 1953, Mowbray 1959, Brawley 1969). Others have resorted to in vivo calibration with independent methods including: a) direct measurement of arterial inflow or venous outflow (Gibbs 1933, Tada 1977), b) radioactive gas clearance (Betz et al. 1966, Carter and Atkinson 1973a, 1973b), c) hydrogen clearance (Betz et al. 1966, Cusick and Myklebust 1980) and even d) heat clearance, by the measurement of transient responses from a heated thermocouple (Grayson 1952, Muller-Schauenburg and Betz 1969, Muller-Schauenburg et al. 1975).

Many of these investigators found the apparent thermal conductivity increment, or its equivalent, to be more or less directly proportional to local flow, within physiological limits. This makes possible qualititive or quantitative (with in vivo calibration) measurement of local blood flow (Grayson 1951, 1952, Hensel and Ruef 1954, Hensel and Bender 1956, Graf and Rosell 1958, Mowbray 1959, Dosekun, Grayson and Mendel 1960, Seylaz 1965, Carter and

Atkinson 1973a, 1973b, McCaffrey and McCook 1975, Carter and Erspamer 1980, Cusick and Myklebust 1980). Other investigators report conflicting results. Linzell (1953) made studies with simple tubes, a sponge model, and dead and living isolated organs. He found that at lower flow rates the apparent thermal conductivity was proportional to flow, but as flow increased (to greater than 50 to 100 ml/100gm/min) the response tended to level off. Similar results are reported by Gibbs (1933), Hensel and Ruef (1954), Graf, Golenhofen and Hensel (1957), Bill (1962), Perl (1962), Grangsjo et al. (1965), Betz et al. (1966), Brawley (1969) and Muller-Schauenberg et al. (1975).

Several theories have been offered to explain why so many investigators find linear relationships between apparent thermal conductivity measurements and local flow. Bill (1962) suggested that in many cases the flow probe is placed so that predominately very small vessels influence the probe, in which case local blood flow velocity is relatively low and the curvature of the corresponding relationship between apparent thermal conductivity and blood flow will be very slight. Also, as the flow increases more vessels open up and tiny vessels tend to dilate; this may give a small extra boost to the apparent thermal conductivity. Perl (1962) suggested that fluctuations in local flow due to arteriolar vasomotion, and an instrument

correction factor based on the distance between the heat source and the thermocouple hot junction could increase the apparent thermal conductivity increment with higher flow rates.

It is apparent that with certain specific applications the apparent thermal conductivity increment will be approximately proportional to flow within physiologic limits. However, with a thermoelectric flow probe with relatively large surface area, like ours, the apparent thermal conductivity will be influenced by a relatively large area of tissue with vessels of many different calibers. In this situation the expected relation between the apparent thermal conductivity increment and local blood flow will be hyperbolic in nature (Grangsjo et al. 1966, Brawley 1968, 1969).

Our in vitro experiments with an artificial kidney demonstrated the expected hyperbolic relationship between the apparent thermal conductivity increment and local fluid flow. This result contradicts Carter and Atkinson (1973a, 1973b), who initially reported a direct linear relationship between the voltage output from the probe thermocouples and local cortical blood flow. Subsequently Carter and Erspamer (1980) reported that it was the apparent thermal conductivity increment (the difference between 1/V and 1/V0) that was proportional to local cortical blood flow. In

either case, the validity of the method is not well supported. Their conclusions are based on cumulative data from in vivo calibration with a xenon-133 clearance technique during multiple experiments on cats. They have assumed that the relationship between local cortical blood flow measured by thermoelectric flow probe and cortical blood flow measured by xenon-133 clearance is the same for different probe placements within the same animal or in different animals; once the thermoelectric flow probe is calibrated, quantitative measurement of local cortical blood flow is possible, without individual in vivo calibration. We found substantial variation in relative local cortical blood flow with different probe placements both intra- and inter-animal. The physical relationship between the flow probe and vessels of various calibers in the perfused tissue had a large effect on the apparent thermal conductivity increment. For quantitative measurement, in vivo calibration is clearly required for each probe placement position. This requirement has been reported by several other investigators (Gibbs 1933, Bill 1962, Betz et al. 1966, McCaffrey and McCook 1975).

Cortical Blood Flow Autoregulation

The results of this study are in agreement with the wide range of results in published reports on the

autoregulation of cortical blood flow in response to acutely induced hypertension in the cat (Table II). Waltz (1968) estimated cortical blood flow by measuring the clearance of radioactive krypton-85, and altered blood pressure by intravenous injection of phenylephrine or sodium nitroprusside. In his study there was no overall tendency for cortical blood flow to change with alteration of mean arterial blood pressure over the range of 25 to 175 mmHg. From the examples shown there seems to be a small increase in cortical blood flow with arterial blood pressure in at least some cases (estimated relative slope ratio 0.2-0.4).

MacKenzie et al. (1976) reported on the autoregulation of local cortical blood flow in response to acute hypertension induced by intravenous infusion of angiotensin II. Local cortical blood flow was estimated by the hydrogen clearance technique (which is a measure of blood flow in the small volume of tissue within approximately 1 mm of the surface of a 0.2 mm diameter platinum wire electrode). Of 38 electrodes in 19 cats, 29 showed an "autoregulatory plateau" over the mean arterial blood pressure range of 90 to 160 mmHg; 9 did not. Over this pressure range, the reported slopes of 0.45%/mmHg and 0.97%/mmHg correspond to estimated relative slope ratios of 0.6 and 1.3 respectively with a weighted mean relative slope ratio of 0.7. With experiments of similar design, Boisvert et al. (1977) showed

that the local cortical blood flow was relatively stable with the mean arterial blood pressure range of 110 to 130 mmHg. Overall, the local cortical blood flow was found to increase with mean arterial blood pressures above 130 mmHg. The slope was 0.4 ml/100g/min/mmHg (estimated relative slope ratio 1.2) for the mean arterial blood pressure range 130 to 170, and even larger with mean arterial blood pressures above 170 mmHg. Kontos et al. (1978) showed relatively stable blood flow over the mean arterial blood pressure range of 80 to 170 mmHg (0.37%/mmHg, estimated relative slope ratio 0.4).

Heistad and Marcus (1977) measured cortical blood flow with labeled microspheres during normotensive control periods (mean arterial blood pressure 92 mmHg, cortical blood flow 30 ml/100g/min), after infusion of angiotensin II or norepinephrine (mean arterial blood pressure 208 mmHg, cortical blood flow 98 ml/100g/min) and after barodenervation and vagotomy (mean arterial blood pressure 226, cortical blood flow 99 ml/100g/min). These values correspond to estimated relative slope ratios of 1.4 and 1.3. Busija, Heistad and Marcus (1980) subsequently studied the response of cortical blood flow to an acute increase in arterial blood pressure produced by occluding the descending aorta. The cortical blood flow was measured with labeled microspheres during normotensive control periods (mean

arterial blood pressure 83 mmHg, cortical blood flow 75 ml/100g/min) and 150 seconds following the induction of stable hypertension (mean arterial blood pressure 133 mmHg, cortical blood flow 100 ml/100g/min). This corresponds to an estimated relative slope ratio of 0.6.

It is clear from the above discussion that the regulation of blood flow in the cat cerebral cortex is quite variable. Much of this apparent variation may result from methodological differences. In addition, there appears to be considerable variation within different animals and even between different local cortical areas in the same animal. This has been shown in other species by several investigators (Metzger 1969, Kuschinsky and Wahl 1978, Larsen et al. 1978, Larsen and Lassen 1979, Heiss 1981). With cats, most investigators have shown an increase in cortical blood flow with increasing arterial blood pressure at any level. This response is often relatively small at near baseline blood pressures and becomes more pronounced with large increases in blood pressure.

Studies of the regulation of cortical blood flow in response to acutely induced hypertension in several different species are summarized in Table 2. Some investigators have shown essentially no change in cerebral blood flow with increasing blood pressure, others have shown substantial changes. Although the number of studies

is not large, the degree of the autoregulatory response to hypertension seems to be less complete in the cat (mean relative slope ratio 0.7) than in the other species studied (rat 0.3, dog 0.1, monkey 0.3, baboon 0.1, and man 0.0).

In this study we have described several different patterns of local cortical blood flow response to acutely induced arterial hypertension. The term hysteresis has been used to describe the cases where the return of local cortical blood flow to pre-infusion levels is slower than the return of arterial blood pressure. This effect was previously noted by Waltz (1968) in a similar study, but the mechanism by which this occurs has not been well described.

When arterial blood pressure increases above the upper limit of cortical blood flow autoregulation, forceful dilatation of cortical vessels occurs allowing large increases in cortical blood flow (Ekstrom-Jodal et al. 1972, Strandgaard 1974, Edvinsson et al. 1976, MacKenzie et al. 1976, Morita et al. 1977, Kontos 1981). In a series of experiments on 126 cats, Kontos et al. (1978) made quantitative measurements of vessel caliber and (in 5 cats) local cortical blood flow. They showed gradually increasing vasoconstriction of the larger cortical vessels (200 to 400 micrometers) in response to acutely induced arterial hypertension; the calibers of the smaller cortical vessels were essentially unchanged. With increasing arterial blood

pressure beyond the upper limit of cortical blood flow autoregulation, forced dilatation of the smaller vessels occured, in an uneven sausage-shape pattern. Dilatation of the larger cortical vessels occured only at very high arterial blood pressures. In approximately 50 percent of the smaller vessels, dilatation persisted 5 minutes or more after arterial blood pressure had returned to the resting level.

In our experiments, when the upper limit of autoregulation was exceeded, the response of local cortical blood flow was either the two-stage or the breakthrough pattern. With the two-stage pattern, the increase in local cortical blood flow was proportionally greater than the increase in arterial blood pressure beyond the upper limit of autoregulation. With the breakthrough response, sustained high arterial blood pressure was associated with increasing local cortical blood flow, above the initial plateau level. The mechanism by which this occurs is not clear but may be related to stress relaxation or creep of the vascular tissue.

Cortical Blood Flow Response to Hypercapnia

The measurement of the response of relative local cortical blood flow to induced hypercapnia provides additional information on the validity of local blood flow measurement with the thermoelectric flow probe. An increase

in arterial PCO_2 from 28 to 65 mmHg was associated with an increase in Φg of 160 percent. Other investigators have reported similar results (with proportionally larger increases in cerebral blood flow (CBF) at higher levels of arterial PCO_2): a) in cats--increasing PCO_2 25 to 40 mmHg, increased CBF 125% (Flohr et al. 1969), increasing PCO_2 30 to 50 mmHg, increased CBF 80% (Gregory et al. 1981); b) in dogs--increasing PCO_2 30 to 80 mmHg, increased CBF 100% (Haggendal and Johansson 1966), increasing PCO_2 37 to 53 mmHg, increased CBF 200% (Heistad et al. 1977); c) in monkeys--increasing PCO_2 30 to 70 mmHg, increased CBF 150% (Reivich 1964); d) in baboons--increasing PCO_2 41 to 58 mmHg, increased CBF 120% (Harper et al. 1972), increasing PCO_2 33 to 49 mmHg, increased CBF 160% (Kawamura et al. 1974).

Hypercapnia has generally been found to decrease the autoregulatory capacity of the cerebral circulation. Several investigators have suggested a complete absence of cerebral blood flow autoregulation (to decreased perfusion pressure) in the presence of hypercapnia (in dogs--Harper 1965, 1966, Rapela and Green 1968; and in monkeys--Hernandez 1972, Hernandez-Perez 1975). Conflicting results are reported by Ekstrom-Jodal et al. (1970) who show nearly complete autoregulation of cortical blood flow (to decreased arterial blood pressure) in the hypercapnic dog over a wide

range of mean arterial blood pressures (70 to 150 mmHg). They did not observe the lower arterial blood pressure limit of autoregulation however.

Studies of the upper and lower arterial blood pressure limits of autoregulation have shown that hypercapnia (and the associated vasodilatation and increased blood flow) reduces the range of arterial blood pressures over which autoregulation occurs. Haggendal (1965) and Haggendal and Johansson (1965) showed a shift of the lower arterial blood pressure limit of cortical blood flow autoregulation from a mean arterial blood pressure of less than 60 to mean arterial blood pressures of 80 to 100 mmHg, with 5 to 7 percent inspired carbon dioxide in dogs. Raichle and Stone (1972) demonstrated a stepwise increase in the lower arterial blood pressure limit of cerebral blood flow autoregulation with increasing concentration of inspired carbon dioxide in monkeys (90 mmHg with normocapnia, 110 mmHg with 6% inspired CO_2, and 130 mmHg with 9% inspired CO_2).

Ekstrom-Jodal et al. (1972) studied cortical blood flow autoregulation at high arterial blood pressures in normocapnic and hypercapnic dogs. They found no difference in the degree of autoregulation, but a shift downward in the upper arterial blood pressure limit of autoregulation with hypercapnia (greater than 200 mmHg with normocapnia, 150 to

170 mmHg with arterial PCO_2 40 to 60 mmHg, and 100 to 140 mmHg with arterial PCO_2 greater than 60 mmHg). We found similar results in the present study. The degree of cortical blood flow autoregulation, as shown by relative slope ratios, was not altered by hypercapnia. In several cases the upper limit of autoregulation was demonstrated with hypercapnia when it had not been found at similar mean arterial blood pressures in the normocapnic animal.

CONCLUSIONS

The thermoelectric flow probe methodology described here provides a useful experimental technique for qualitative description and for estimating relative changes in local cortical blood flow. Furthermore, quantitative determination of local blood flow would be possible with independent in vivo calibration in each experiment.

The data presented show active regulation of the local cortical blood flow in response to acutely induced hypertension in the cat. This autoregulation does not completely prevent changes in blood flow, but it does limit those changes by maintaining or slightly increasing the vascular resistance in response to increasing perfusion pressure. When the upper arterial blood pressure limit of autoregulation is exceeded, forceful vascular dilatation occurs, and the vascular resistance drops, allowing large increases in local cortical blood flow.

With moderate levels of hypercapnia there is a substantial increase in the local cortical blood flow. Autoregulation of local cortical blood flow in response to acutely induced hypertension is intact, but the upper arterial blood pressure limit of autoregulation is apparently shifted downward from the normocapnic level.

Figure 1. Diagram of thermoelectric flow probe: (A) Borg-Warner model 130-12 thermoelectric module, (B) 30-gauge, 14K gold plates, (C) "Zig/Zag" copper-constantan thermocouple junction.

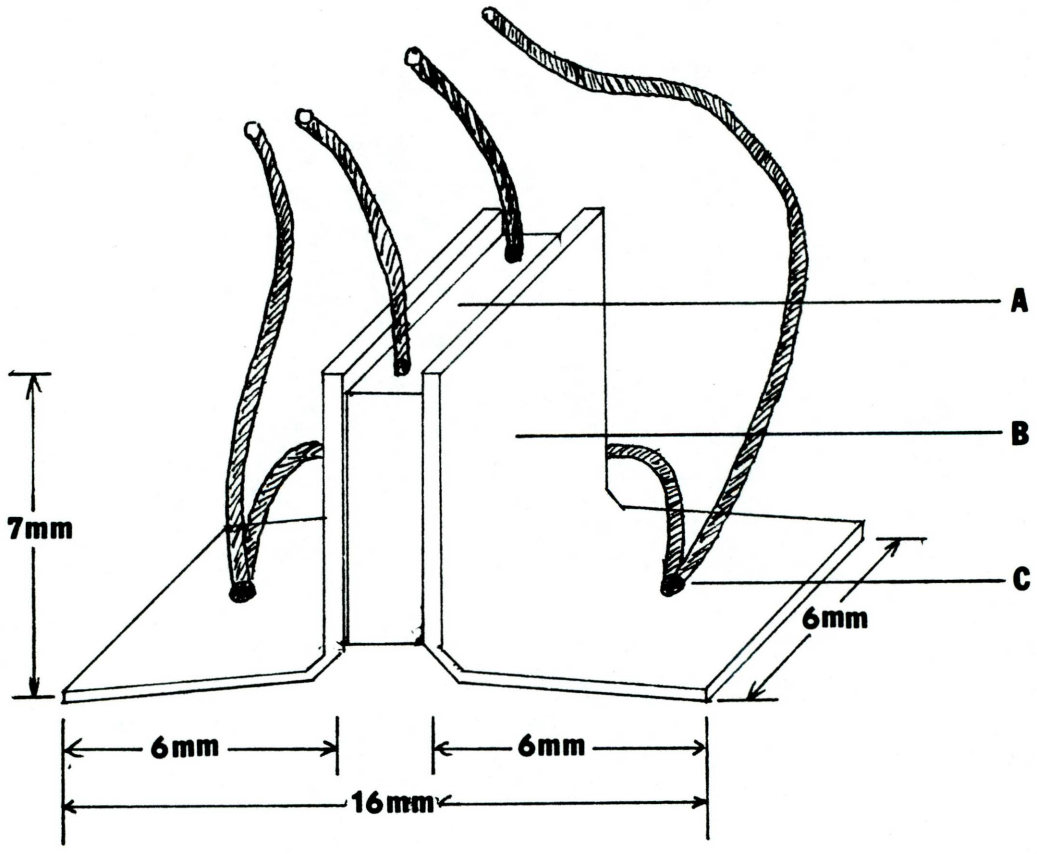
A
B
C
7mm
6mm
6mm
6mm
16mm

Figure 2. Illustration of flow probe notation. With no current through the thermoelectric module (probe off) there is zero temperature difference between the plates and V=0. With current flow through the termoelectric module, but zero local flow, the maximum temperature differential occurs and V=V0. As local flow is increased from zero, heat clearance by convection occurs, the temperature differential (hence V) decreases, and dV increases. As local flow becomes very large, the temperature differential approaches a minimum level and dV approaches the maximum value dVmax.

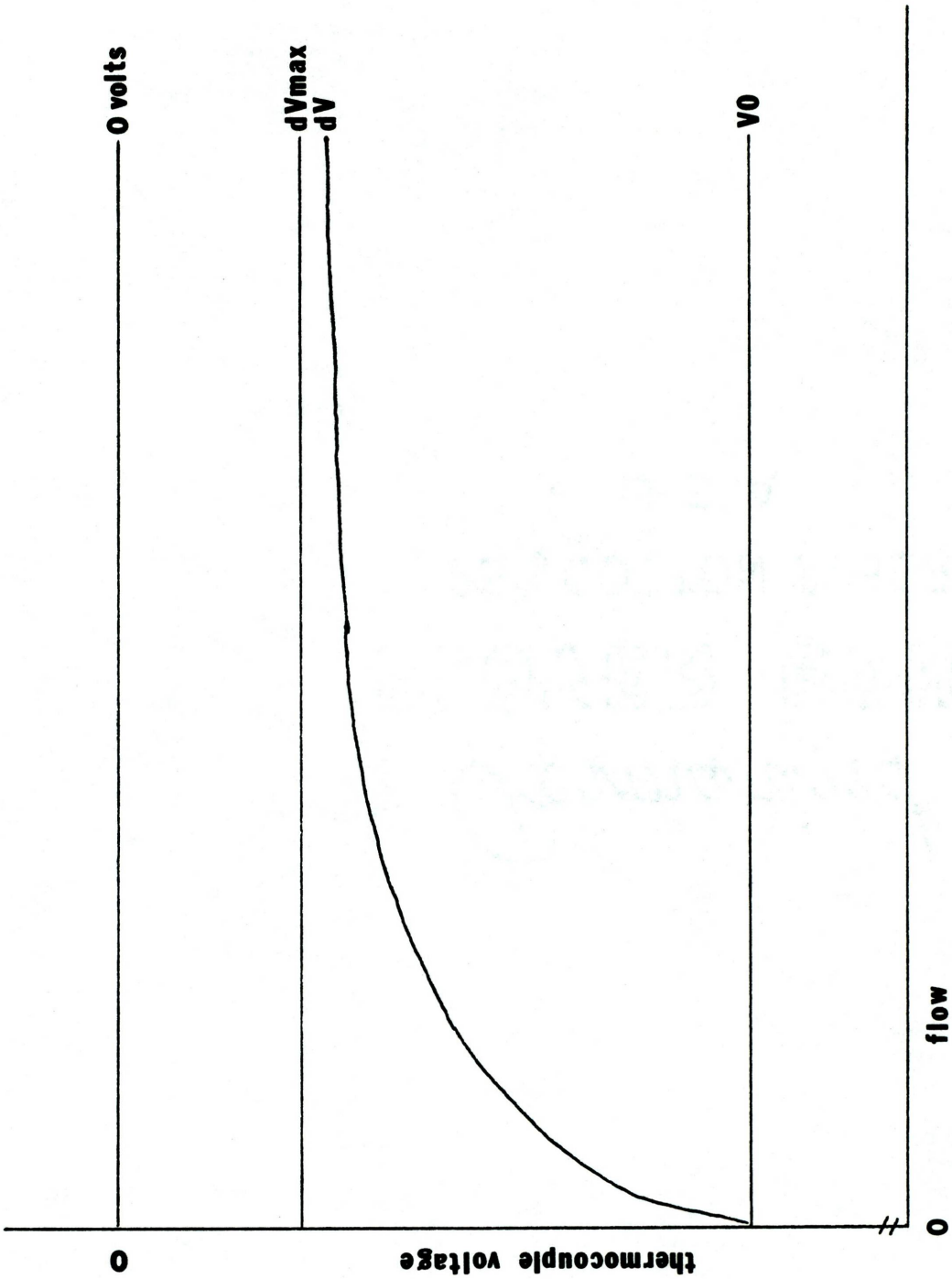
0 volts
dVmax
dV
V0
flow
0
0
thermocouple voltage

Figure 3. Flow probe voltage dV (microvolts) versus flow (deciliters per minute) in the artificial kidney model. Flow perpendicular to the probe plates (•). Flow from hot to cold plate (x). Flow from cold to hot plate (o).

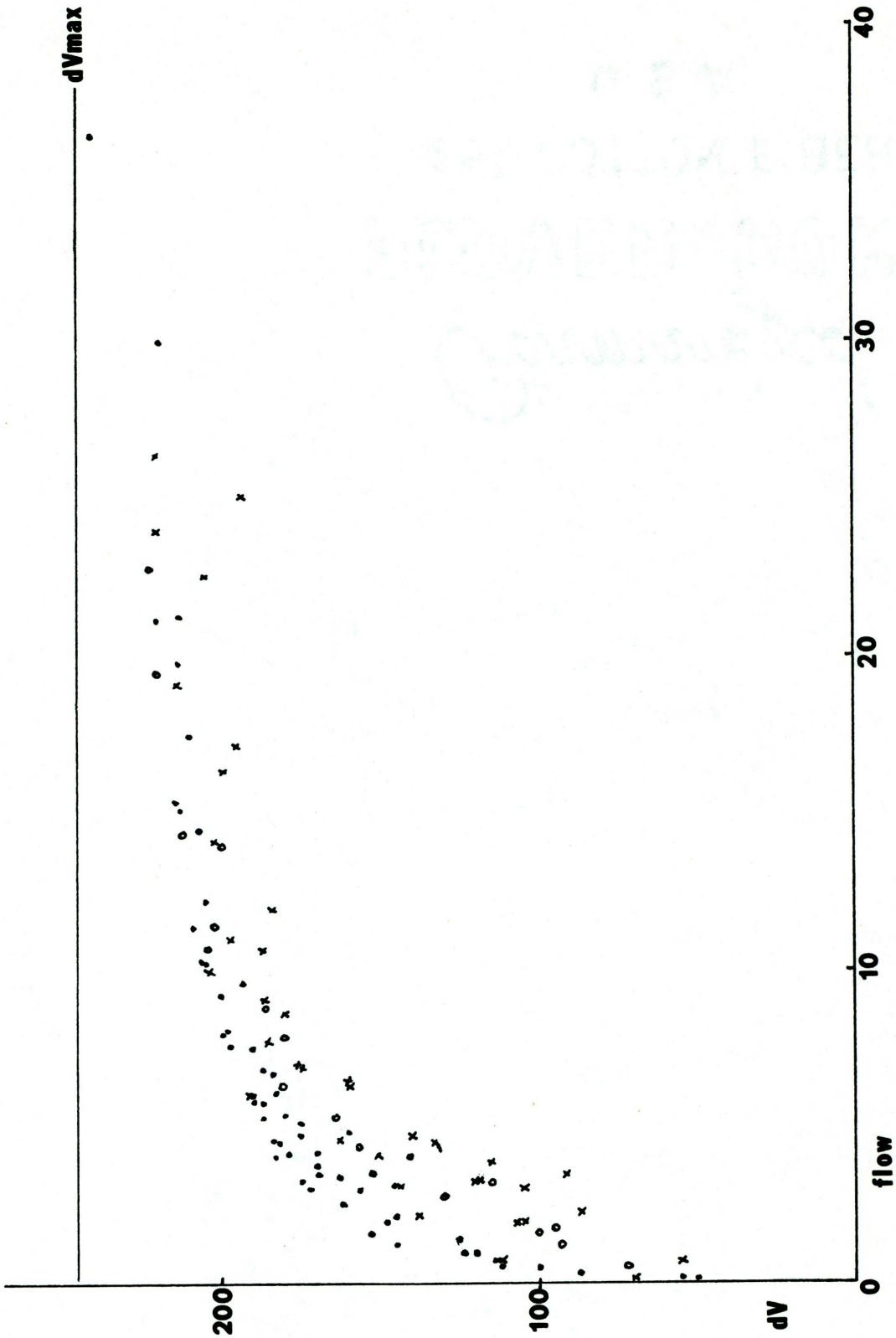
dVmax
200
100
dV
0
10
20
30
40
flow

Figure 4. Calculated relative flow (Φc) versus flow (deciliters per minute) in the artificial kidney model. Flow perpendicular to the probe plates (•). Flow from hot to cold plate (x). Flow from cold to hot plate (o).

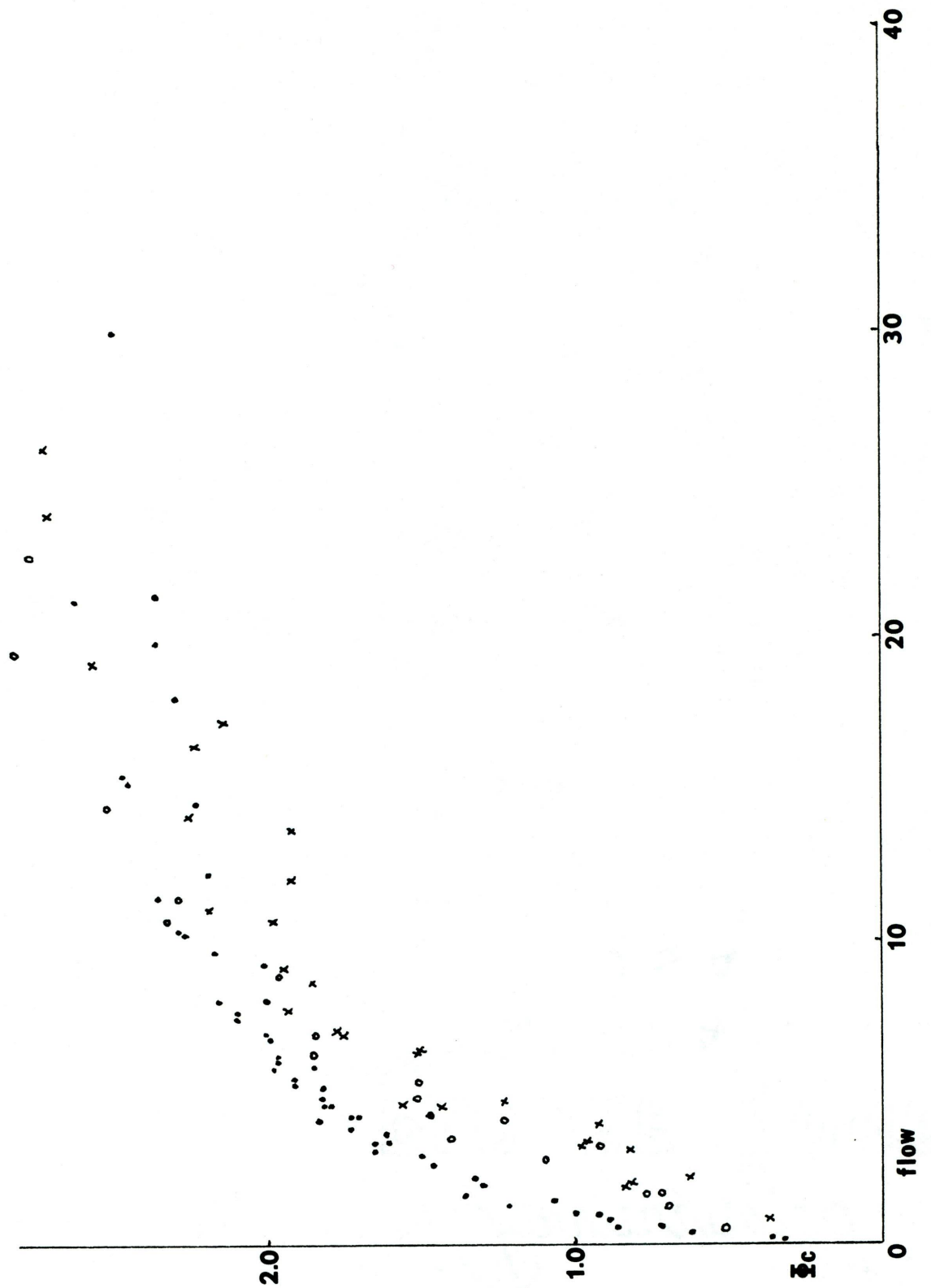
2.0
1.0
Ec
0
10
20
30
40
flow

Figure 5. Calculated relative flow (Φ_g) versus flow (deciliters per minute) in the artificial kidney model. Flow perpendicular to the probe plates (•). Flow from hot to cold plate (×). Flow from cold to hot plate (○).

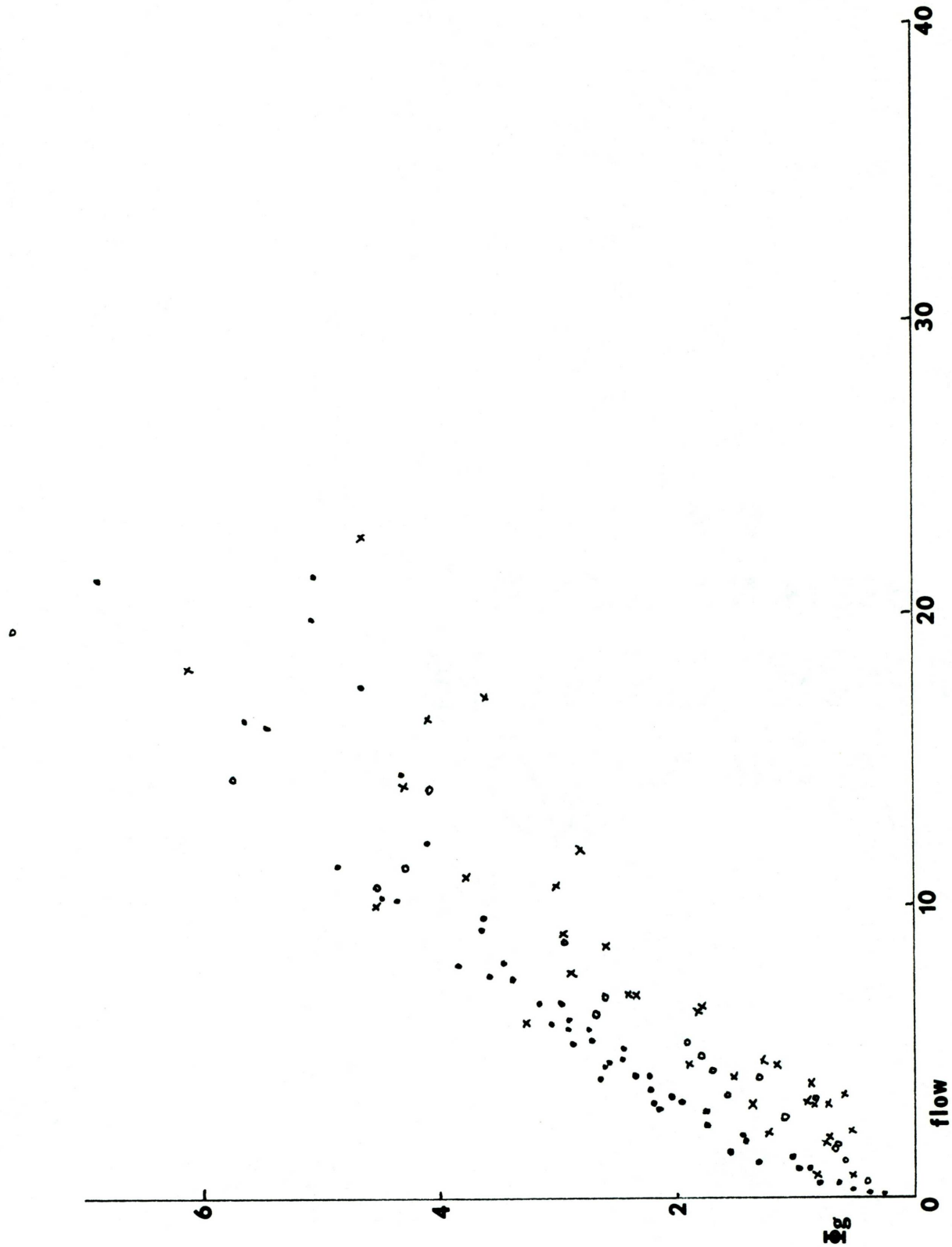
6
4
2
0
Eg
0
10
20
30
40
flow

Figure 6. Local cortical blood flow (Φg) versus mean arterial blood pressure in normocapnic cats. The response of local cortical blood flow with each hypertensive episode is represented here by a single line. Several lines of proportional increase are drawn on the graph. Along these lines the increase in local cortical blood flow is proportional to the increase in mean arterial blood pressure.

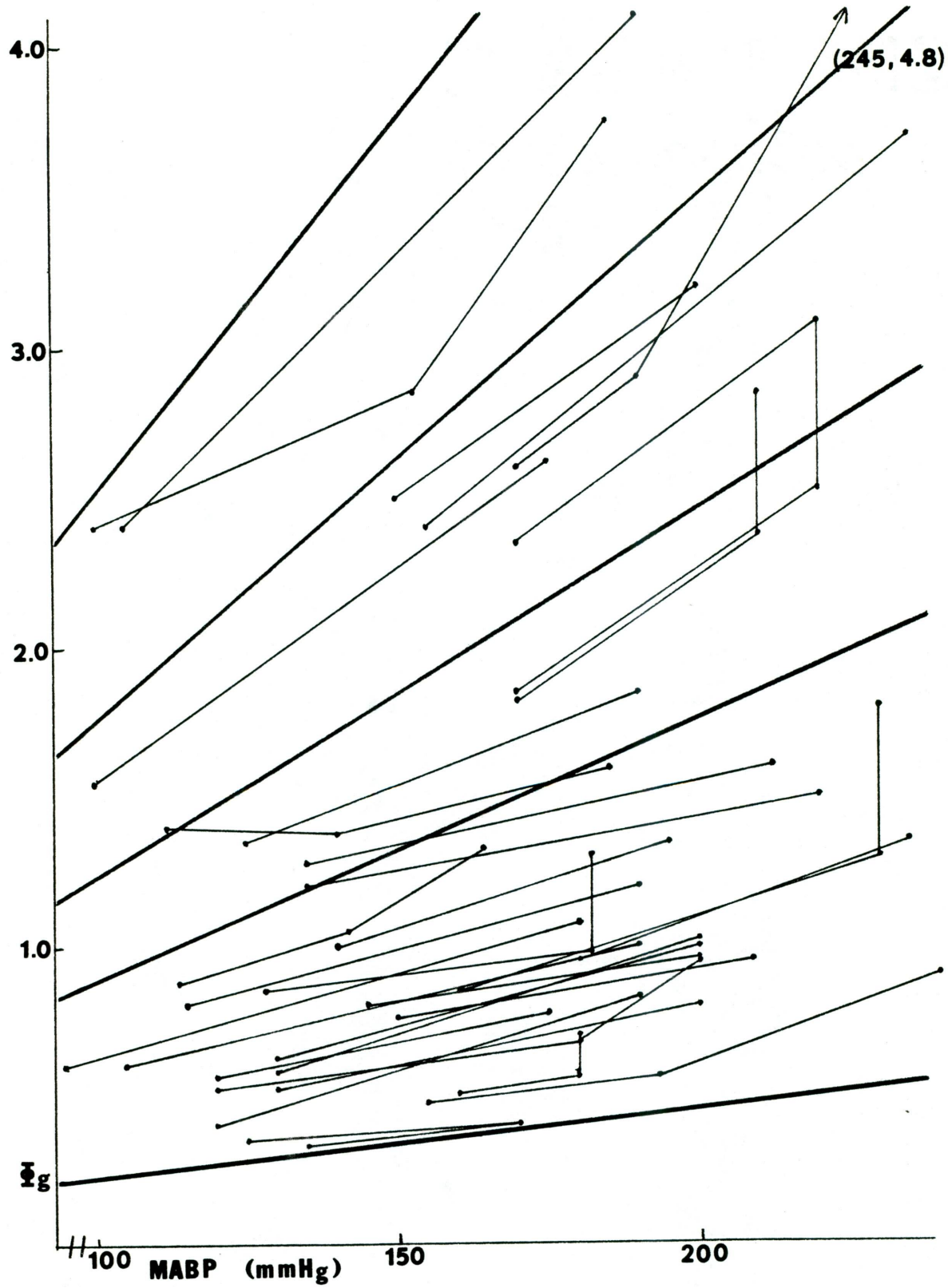
4.0
3.0
2.0
1.0
(245, 4.8)
100
MABP (mmHg)
150
200

Figure 7. Histogram representation of relative slope ratios for local cortical blood flow response to hypertensive episodes in normocapnic and hypercapnic cats.

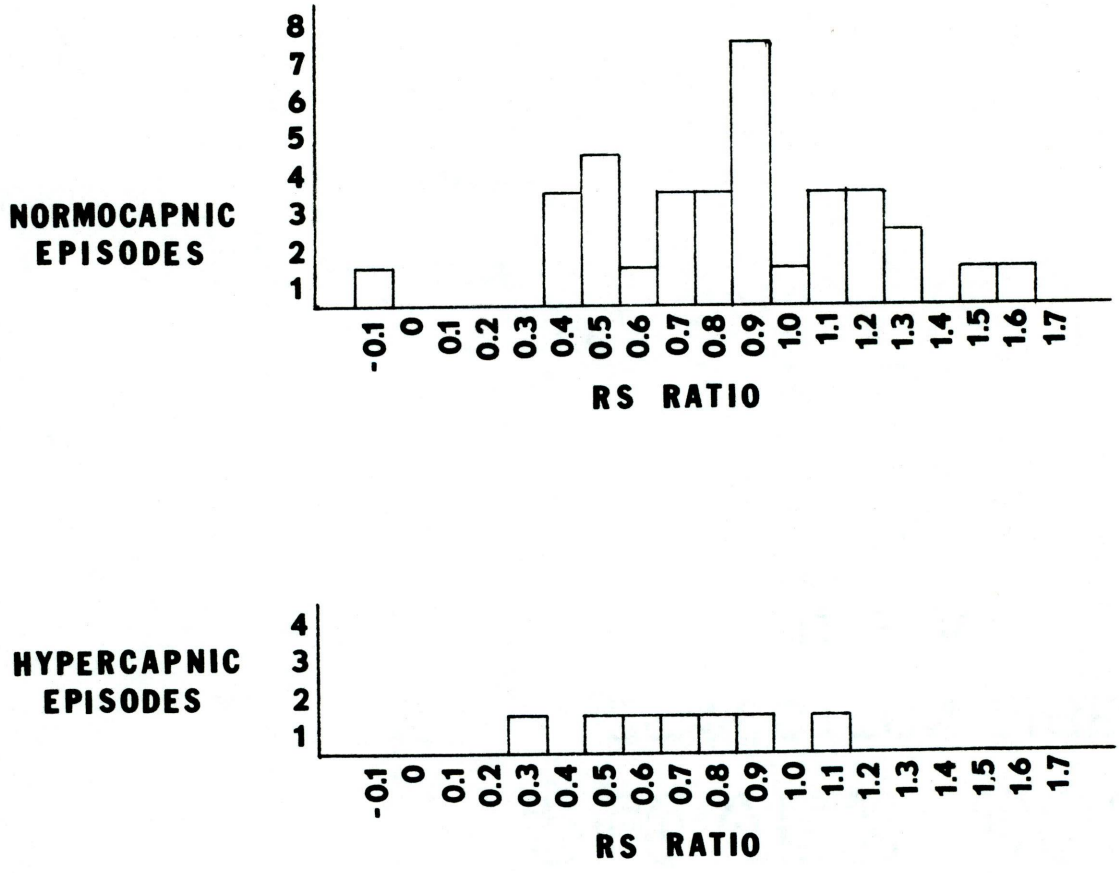
NORMOCAPNIC EPISODES
8
7
6
5
4
3
2
1
-0.1
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
RS RATIO
HYPERCAPNIC EPISODES
4
3
2
1
-0.1
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
RS RATIO

Figure 8. Hypertensive episode with linear response of local cortical blood flow ($\bar{\Phi}g$). Graph of $\bar{\Phi}g$ versus mean arterial blood pressure. Each line segment represents a one minute interval. The arrow shows temporal orientation.

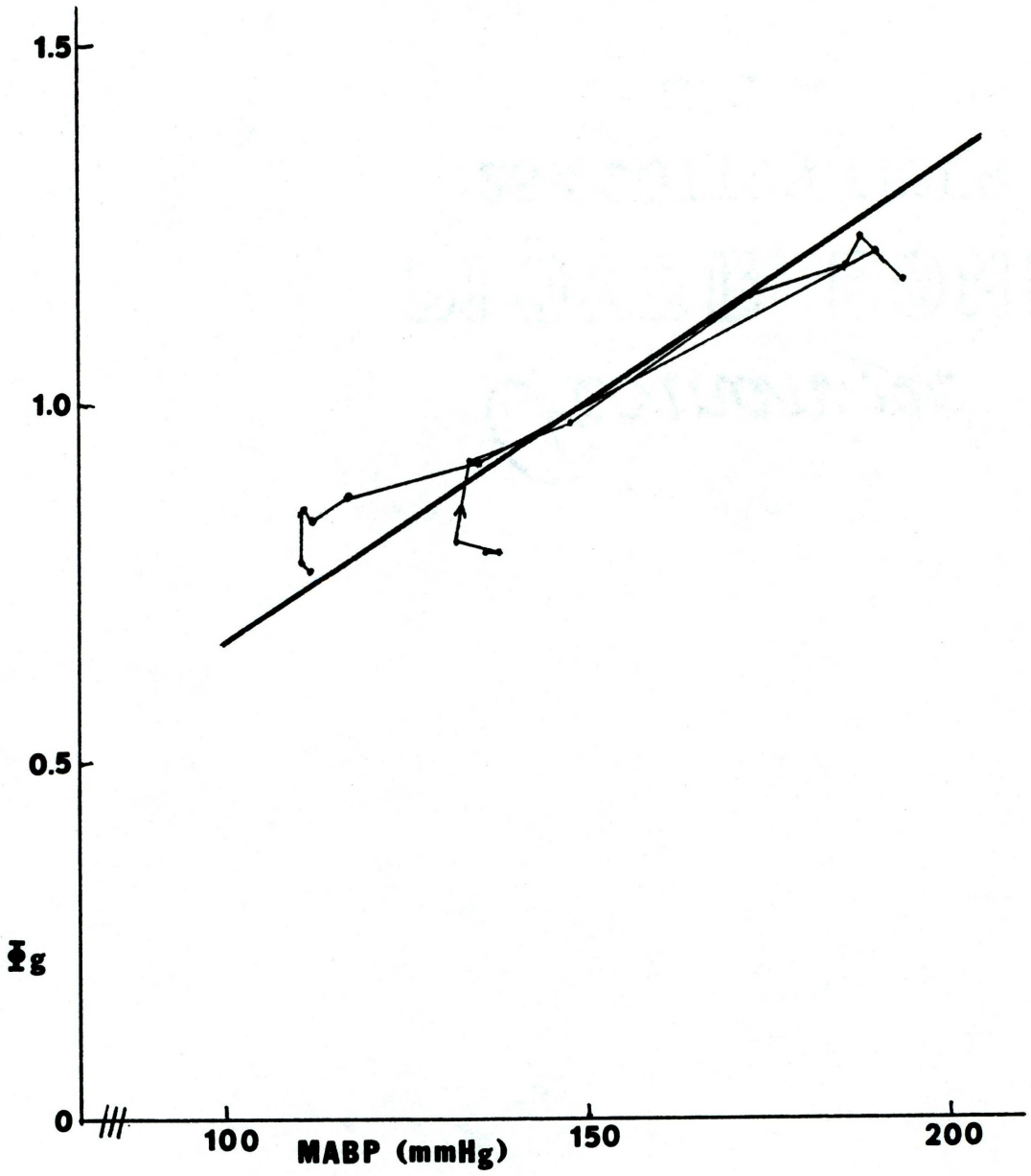
1.5
1.0
0.5
0
100
150
200
MABP (mmHg)

Figure 9. Hypertensive episodes with hysteresis response of local cortical blood flow (Φg). Two subsequent hypertensive episodes from the same cat are shown: episode 1 (•), and episode 2 (∘). Graph of Φg versus mean arterial blood pressure. Each line segment represents a one minute interval. The arrow shows temporal orientation.

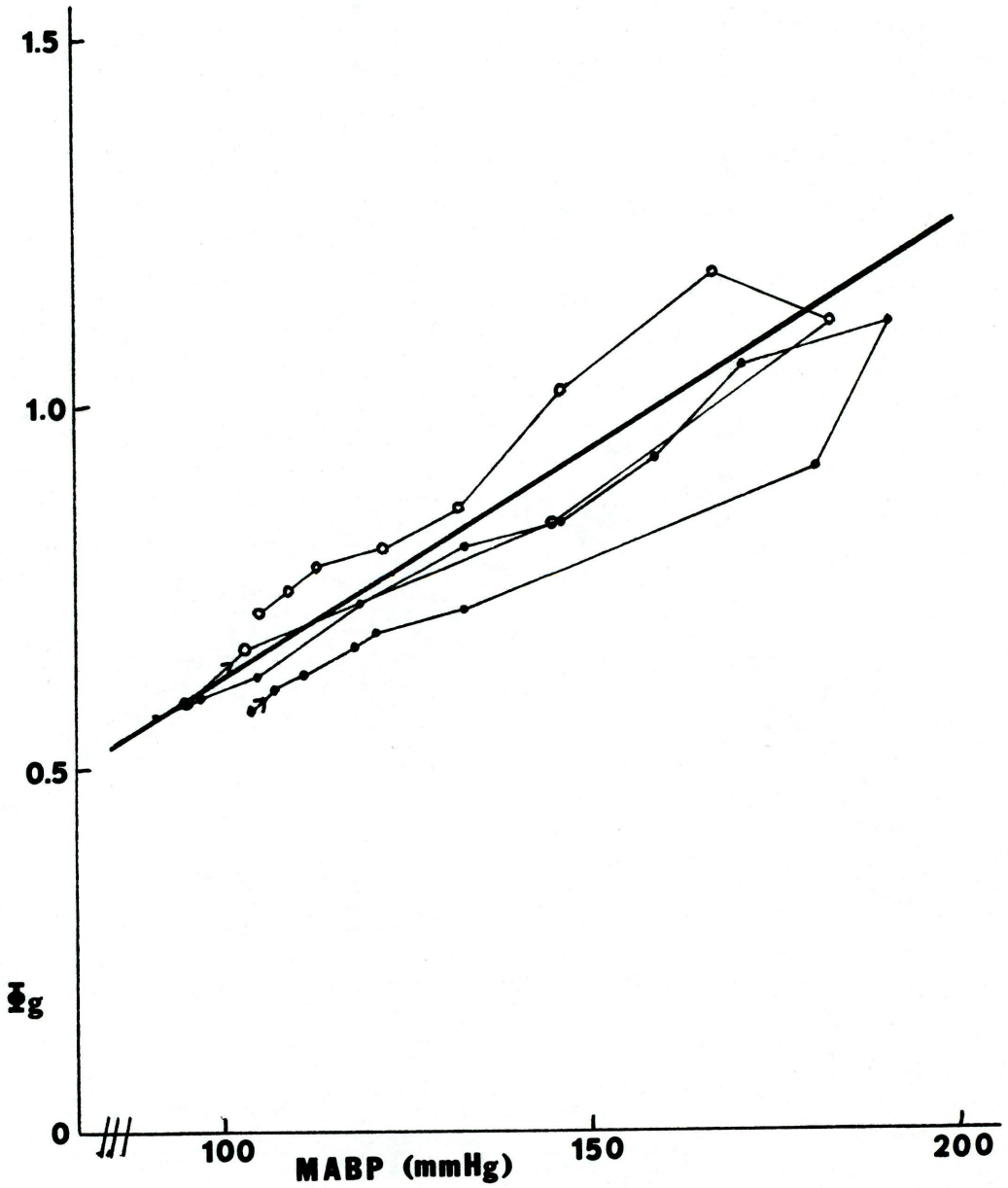
1.5
1.0
0.5
0
$\bar{\Phi}_g$
100
150
200
MABP (mmHg)

Figure 10. Hypertensive episodes with linear and two-stage responses of local cortical blood flow (Φg). Two subsequent hypertensive episodes from the same cat are shown: episode 1 (•), and episode 2 (∘). Graph of Φg versus mean arterial blood pressure. Each line segment represents a one minute interval. The arrow shows temporal orientation.

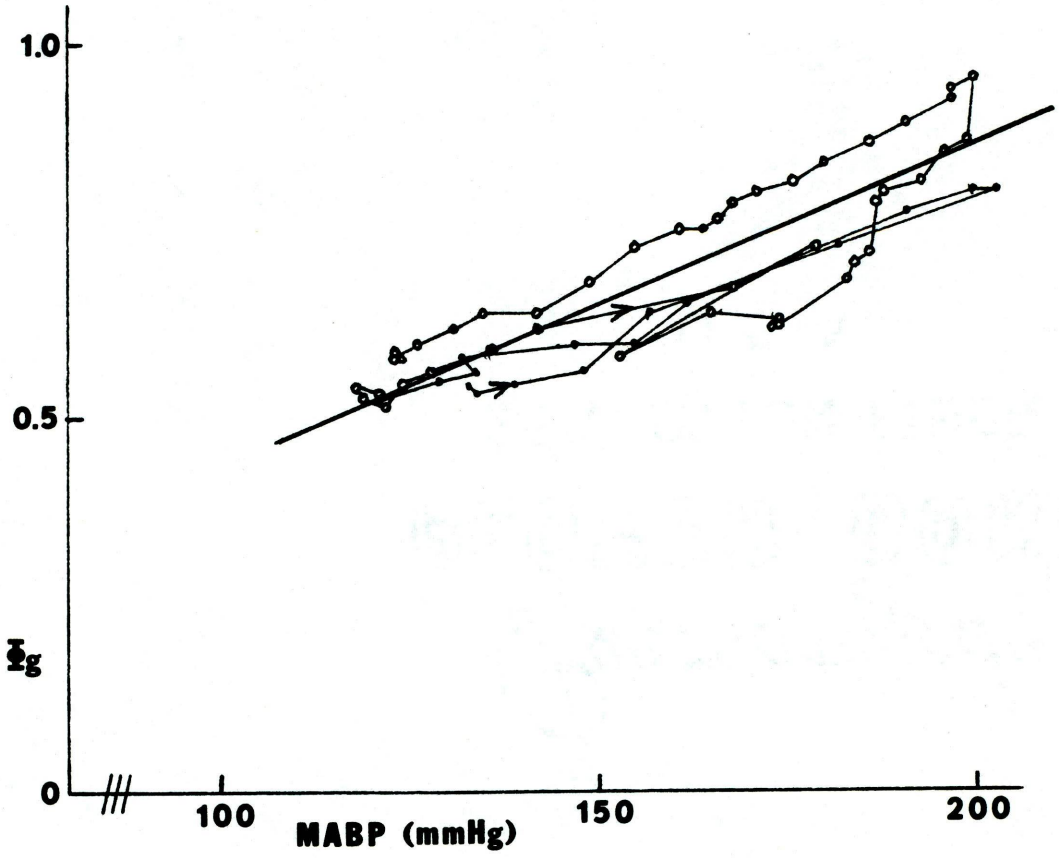
1.0
0.5
0
100
150
200
MABP (mmHg)

Figure 11. Hypertensive episode with two-stage response of local cortical blood flow (Φg). Graph of Φg versus mean arterial blood pressure. Each line segment represents a one minute interval. The arrow shows temporal orientation.

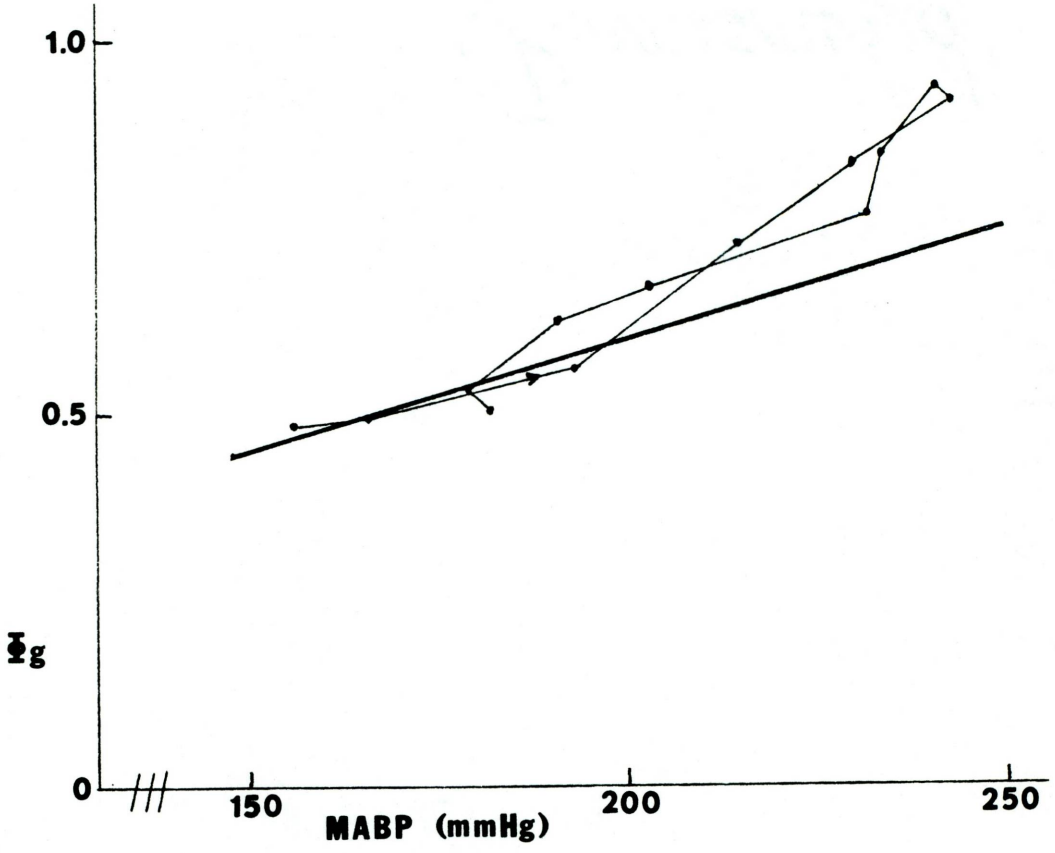
1.0
0.5
0
Φg
150
200
250
MABP (mmHg)

Figure 12. Hypertensive episodes with linear and breakthrough responses of local cortical blood flow. Three subsequent episodes from the same cat are shown: episode 1 (•), episode 2 (x), and episode 3 (○). Graph of Φg versus mean arterial blood pressure. Each line segment represents a one minute interval. The arrow shows temporal orientation.

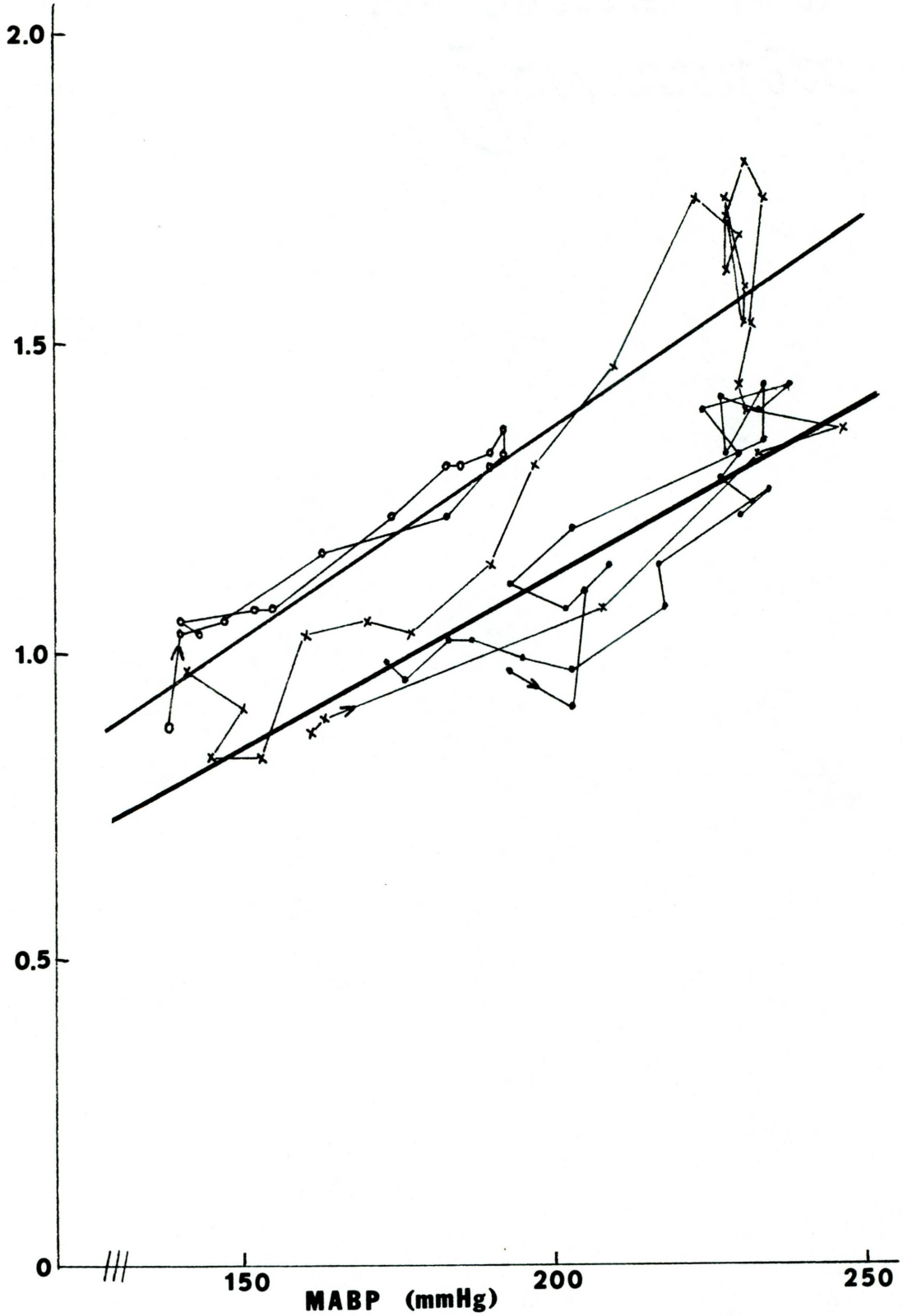
2.0
1.5
1.0
0.5
0
150
200
250
MABP (mmHg)

Figure 13. Hypertensive eisodes with hysteresis and breakthrough responses of local cortical blood flow (Φg). Three subsequent episodes from the same cat are shown: episode 1 (•), episode 2 (∘), and episode 3 (×). Graph of Φg versus mean arterial blood pressure. Each line segment represents a one minute interval. The arrow shows temporal orientation.

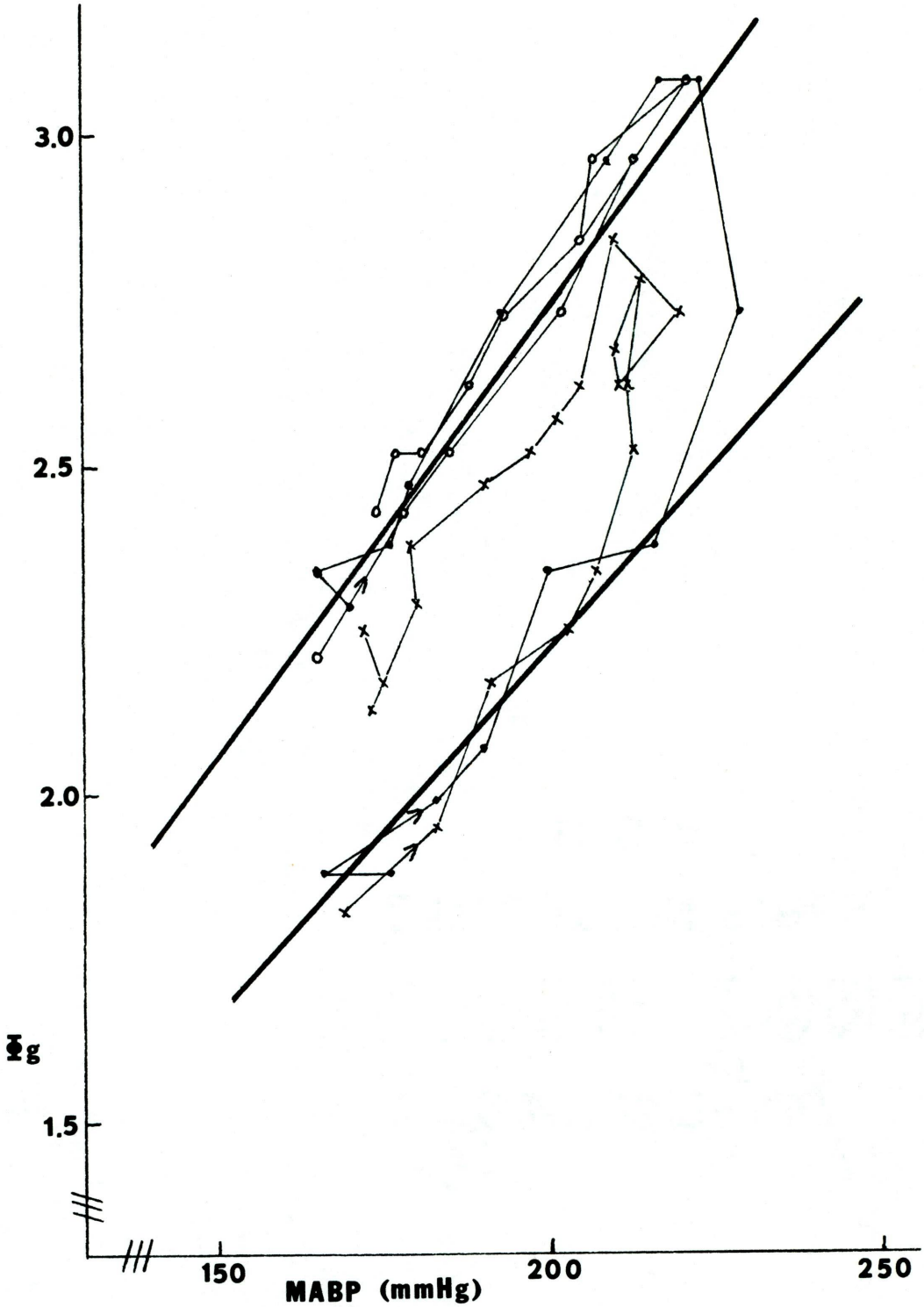
3.0
2.5
2.0
1.5
Φg
150
200
250
MABP (mmHg)

Figure 14. Local cortical blood flow (Φg) versus mean arterial blood pressure in hypercapnic cats. Hypertensive episodes from six cats are represented along with the normocapnic control episodes (**1 2 3 4 5 6 // c**). The response of local cortical blood flow with each hypertensive episode is represented here by a single line. Several lines of proportional increase are drawn on the graph. Along these lines, which intersect the true origin, the increase in local cortical blood flow is proportional to the increase in mean arterial blood pressure.

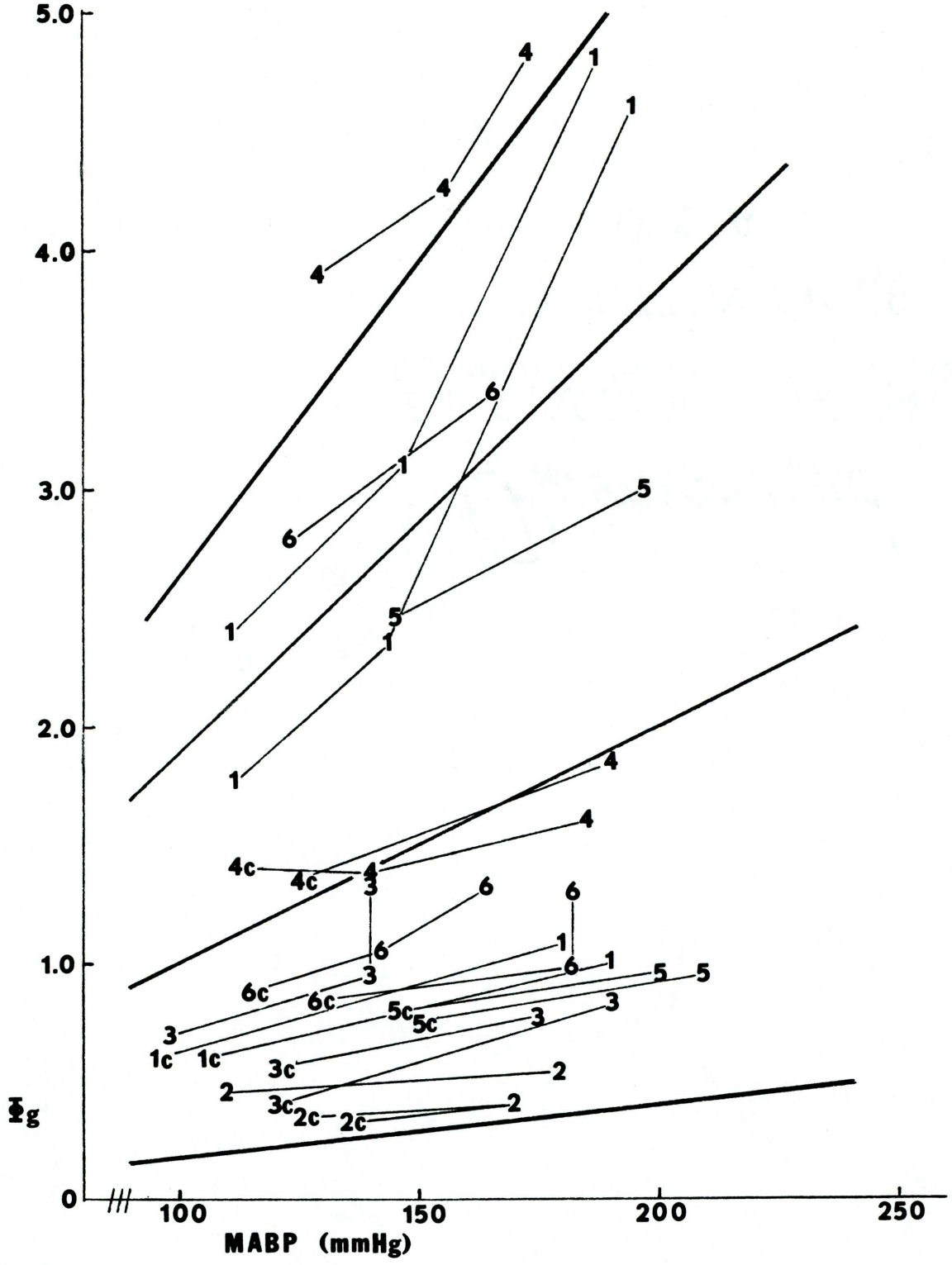
5.0
4.0
3.0
2.0
1.0
0
100
150
200
250
MABP (mmHg)
Σg

Figure 15. Local cortical blood flow (Φg) versus relative slope ratio in hypercapnic cats. On this graph the relative slope ratios for local cortical blood flow response to hypertensive episodes in the hypercapnic cat are represented along with those from normocapnic control hypertensive episodes. Average values from each cat are shown.

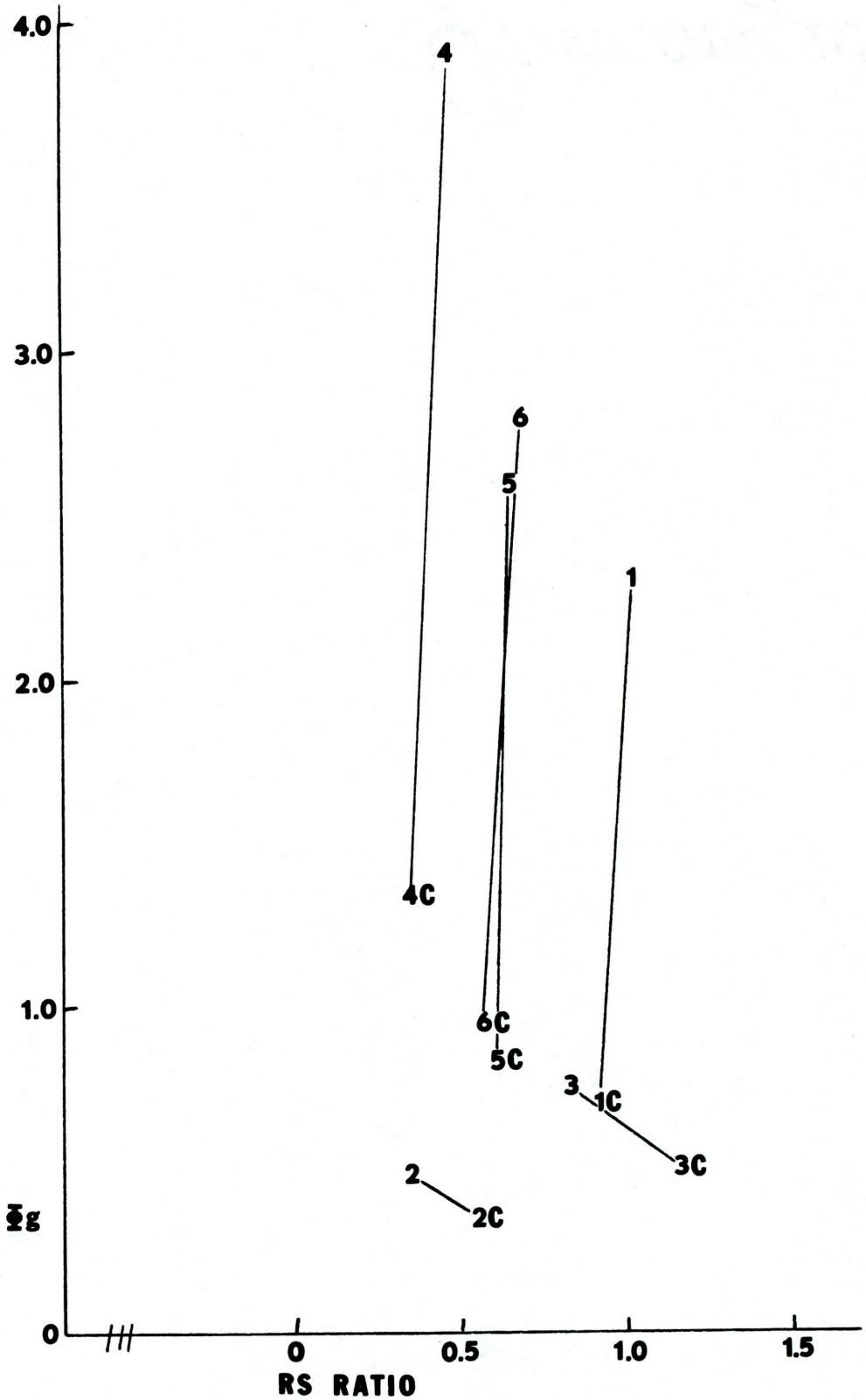
4.0
3.0
2.0
1.0
0
4
6
5
1
4C
6C
5C
3
1C
3C
2
2C
0
0.5
1.0
1.5
RS RATIO

Table 1. Thermoelectric flow probe notation.

K = apparent thermal conductivity as measured with a heated thermocouple, reflects heat clearance by conduction and convection

V = voltage output from the thermocouple pair

V0 = voltage output from the thermocouple pair with zero flow, reflects maximum temperature difference hence maximum V

dV = difference between V0 and V, increases with increasing flow and decreasing V

dVmax = maximum value of dV, approached with high flow, reflects minimum temperature difference hence minimum V

Y = constant, used to relate relative and absolute flow

Z = constant, used to relate relative and absolute flow

Φ = local cortical blood flow

Φc = estimate of relative local cortical blood flow thermal diffusion measurements after Carter and Erspamer (1980)

Φg = estimate of relative local cortical blood flow from thermal diffusion measurements after Grangsjo (1965)

Table 2. Response of cortical blood flow to acutely induced hypertension in several species. The data in this table has been estimated from the references listed. "BP Change" is the range of mean arterial blood pressures observed and whether the change acheived in a single step or in multiple steps. "RS Ratio" is by my calculation from the data presented. "UL" is the upper mean arterial blood pressure limit of autoregulation; a "NO" in this column means an upper limit was not observed, a "NA" (not applicable) appears by those studies with a single step increase in blood pressure.

First Author	Techniques	BP Change	RS Ratio	UL
		Rats		
Edvinsson 1976	Angiotensin A-V O_2 Diff.	Stepwise 140-280	0.3	180
		Cats		
Waltz 1968	Phenylephrine Nitroprusside Kr Clearance	Stepwise 25-175	overall 0.0 examples 0.2-0.4	175
Mackenzie 1976	Angiotensin H_2 Clearance	Stepwise 90-160	0.7	160
Boisvert 1977	Angiotensin H_2 Clearance	Stepwise 110-130	1.2	130
Kontos 1978	Angiotensin or Norepinephrine	Stepwise 81-172	0.5	NO
Heistad 1977	Angiotensin or Norepinephrine Microspheres	One-step 92-208	1.4	NA
Busija 1980	Occlude Aorta Microspheres	One-step 83-133	0.6	NA
		Dogs		
Ekstrom-Jodal 1972	Occlude Aorta Kr Clearance	Stepwise 70-200	0.1	NO
Mueller 1977	Occlude Aorta Microspheres	One-step 99-131	0.0	NA

Table 2, (continued). Response of cortical blood flow to acutely induced hypertension in several species. The data in this table has been estimated from the references listed. "BP Change" is the range of mean arterial blood pressures observed and whether the change acheived in a single step or in multiple steps. "RS Ratio" is by my calculation from the data presented. "UL" is the upper mean arterial blood pressure limit of autoregulation; a "NO" in this column means an upper limit was not observed, a "NA" (not applicable) appears by those studies with a single step increase in blood pressure.

First Author	Techniques	BP Change	RS Ratio	UL
		Monkeys		
Yoshida 1966	Occlude Aorta Carotid Flow	One-step 103-161	0.8	NA
Hernandez 1972	Metaraminol Hemorrhage Carotid Flow	Stepwise 40-180	0.1	NO
Raichle 1972	Metaraminol Hemorrhage Carotid Flow	Stepwise 30-150	0.0	NO
Morito 1977	Phenylephrine Trimethophan Xe Clearance	Stepwise 50-150	0.3	150
		Baboons		
Strandgaard 1974	Angiotensin Xe Clearance	Stepwise 75-130	0.1	130
		Man		
Agnoli 1968	Angiotensin Kr Clearance	One-step 100-135	0.0	NA
Smith 1969	Angiotensin or Phenylephrine Kr Clearance	One-step 84-125	0.1	NA
Skinhoj 1973	Angiotensin Xe Clearance	Stepwise 110-150	0.0	150
Strandgaard 1973	Angiotensin Trimethophan	Stepwise 70-150	0.0-0.1	150

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