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Pressure-flow Relationships In Isolated Major Cerebral Arteries

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PRESSURE - FLOW RELATIONSHIPS IN ISOLATED MAJOR CEREBRAL ARTERIES

by

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ABSTRACT

The narrowing of a major cerebral artery can be caused by an "active" contraction or a "passive" reduction of the force distending the arterial walls. The relative importance of these two mechanisms in determining cerebral arterial diameter and flow has not been established.

The term cerebral perfusion pressure, as used in the literature, was found to be inconsistent with current concepts of vascular resistance. The term transmural pressure (TMP) was defined to indicate this difference between arterial and intracranial pressures. Perfusion pressure (PP) was defined to indicate the total pressure drop across the entire system under consideration.

The flow-PP and flow-TMP relationships were obtained for 26 isolated major human cerebral arteries without smooth muscle tone. A reduction of TMP to 40-60 mm Hg resulted in a decrease in flow to below normal physiological levels. It was argued that this coincides with the loss of autoregulation and that this occurs when the flow-limiting resistance is shifted from the arterioles to the large cerebral arteries.

In five pairs of arteries, cannulated and perfused in parallel, preferential flow reductions of up to 50 percent occurred when both arteries were at the same TMP and PP. Preferential narrowing depended on the relative lumen diameter, degree of atherosclerosis and wall thickness of the two arteries. Therefore, flow

reductions, possibly focal in nature, can occur in the presence of increased intracranial pressure. These flow reductions could originate in the major cerebral arteries in the absence of active contractions.

The TMP at which flow ceased varied from -15 mm Hg for large atherosclerotic arteries to +2 mm Hg for small normal arteries. Calculations based on wall thickness and lumen diameter indicate that major cerebral arteries cannot close by muscle contraction alone.

The flow-pressure relationships of six common carotid and six femoral arteries from rabbits were obtained in the presence and absence of normal smooth muscle tone and in the presence of active vasoconstriction. The TMP at which flow reductions began, increased with increasing vasomotor tone. Similar increases were predicted for human cerebral arteries. It is concluded that the range of TMP over which autoregulatory responses can maintain a normal cerebral blood flow will decrease, with increasing arterial vasomotor tone and increase with decreasing tone.

In the presence of an active constriction, any increase in external pressure resulted in a decrease in flow through the artery. The flow-TMP relationship depended only on the initial degree of constriction and was independent of the vasoconstrictor used, or the artery in which the constriction was produced. A human cerebral artery with a given degree of constriction would exhibit a flow-TMP relationship typical of that constriction.

Phenoxybenzamine relieved and prevented constrictions produced by serotonin and norepinephrine in the rabbit arteries tested.

The improvement in flow produced by this reversal of contraction, decreased with decreasing TMP.

In the presence of a mild constriction, an increase in external pressure to 45 mm Hg resulted in a reduction in flow of up to 50 percent. A mild constriction amplified by the simultaneous occurrence of increased intracranial pressure is proposed as the cause of chronic cerebral arterial spasm.

Decreased transmural pressure appears to be the major cause of diameter and flow reductions in human cerebral arteries.

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I WISH TO EXPRESS MY APPRECIATION
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I. INTRODUCTION AND HISTORICAL REVIEW

1) INTRODUCTION

The importance of the brain circulation has been known since the early 1500's. Leonardo da Vinci suggested that little over half a minute of total circulatory obstruction need elapse before irreversible brain damage would occur, followed shortly by death (da Vinci, trans. by MacCurdy, 1956). Current knowledge suggests that three to five minutes of total cerebral blood flow arrest will produce irreversible brain damage, while a forty percent decrease in flow will result in signs of cerebral ischemia* (Finnerty, Witkin and Fazekas, 1954). Therefore, a constant flow of blood to the brain must be maintained and any reduction of this flow may be detrimental. In view of these facts, it is not surprising that cerebral blood flow and its regulation in health and disease has long been a subject of investigation. In 1901, Cushing described a series of experiments in which he placed "windows" in the skulls of animals and observed the relationship between cerebral blood flow and the pressure of the cerebrospinal fluid which surrounded the brain. He found that increases in this pressure could slow the cerebral circulation and were capable of causing its arrest if sufficiently severe.

Since Cushing's observations, further investigations have

* Ischemia is defined in Dorland's Medical Dictionary as "deficiency of blood in a part, due to functional constriction or actual obstruction of a blood vessel."

revealed that increased intracranial pressure is a common occurrence following intracranial hemorrhage and in the presence of intracranial tumors. A reduction in cerebral blood flow can occur in both instances, if the intracranial pressure is sufficiently high, but the origin of these flow reductions (arterial, arteriolar or venous) has not been established.

2) CIRCULATION OF THE BRAIN AND ITS MEASUREMENT

Thomas Willis (1621-1675), first described the detailed network of vessels at the base of the brain (Willis, 1684):

> "For inasmuch as the carotidick arteries do communicate between themselves in various places, and are mutually ingrafted; from thence a double benefit results, though of a contrary effect: because by this one and the same means care is taken, both lest the brain should be defrauded of its due watring of the blood, and also lest it should be overwhelmed by the too impetuous flowing of the swelling stream or torrent. As to the first, lest that should happen, one of the Carotids perhaps being obstructed, the other might supply the provision of both; then, lest the blood rushing with too full a torrent should drown the channels and little Ponds of the brain, the flood is chastised or hindered by an opposite emissary, as it were a Flood-gate, and so is commanded to return its flood, and haste backwards by the same ways, and to run back with an ebbing Tide."

Since then, the anastomatic vessels at the base of the brain have been known as "the circle of Willis".

The pulsations of the brain were mentioned long before this in the Smith Papyrus, one of the earliest medical texts written around the seventeenth century B.C. (Sarton, 1952). These pulsations, however, were not recognized as being arterial in nature until Realdus Columbus learned that they were synchronous with those of the heart and arteries (Singer, 1957). Two hundred years later Harvey revolutionized the concepts of the circulation (Harvey, trans. 1957) and Willis

published his description of the arteries of the brain.

In 1783, Alexander Monroe deduced that the volume of blood in the intracranial cavity must be nearly constant (Hill, 1896), so that

> "blood must be continually flowing out of the veins that room may be given to the blood which is entering by the arteries."

This fact, later confirmed experimentally in 1824 by Kellie (Hill, 1896), is known as the Monroe-Kellie doctrine. This doctrine was soon employed in the measurement of cerebral blood flow. Knoll (1886) and Dean (1892) measured cerebrospinal fluid pressure changes and inferred from these the relative changes in blood flow due to experimental conditions assuming that increased pressure meant increased blood flow (Hill, 1896).

Roy and Sherrington (1890) proposed that such measurements were of little value unless coupled with simultaneous measurement of arterial and jugular vein pressure. They used cerebral expansion through a trephine opening in the skull as a measure of cerebral blood flow. They found that there was a considerable expansion of the brain both during anoxia, and following the intravenous infusion of strong acids, which was independent of arterial blood pressure and that

> "the blood supply of the brain varies directly with the blood pressure in the systemic arteries".

Although they could find no vasomotor control they concluded that

> "... the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity".

Six years later, Hill (1896) published his book on the cerebral circulation discounting all previous results, including those of Roy and Sherrington, and stating emphatically that:

> "In every experimental condition the cerebral circulation passively follows the changes in the general arterial and venous pressures".

Hill's discoveries and conclusions, though erroneous, were so convincingly presented that they persisted until the late 1920's. Schmidt (1928) and Forbes and Wolff (1928) demonstrated that the earlier observations of Roy and Sherrington were indeed correct. Many investigators have since confirmed these results (Lennox and Gibbs, 1932; Gibbs, Gibbs and Lennox, 1935; Wolff, 1936; Forbes and Cobb, 1938; and others).

Prior to 1943, many methods had been used to measure cerebral blood flow. In addition to those already mentioned, Lennox and Gibbs (1932) used the arterio-venous oxygen and carbon dioxide differences, Schmidt (1934) employed a cooled thermocouple to measure blood velocity in the carotid artery, and Ferris (1941) measured cerebrospinal fluid displacement following venous occlusion, all as indications of total cerebral blood flow. Each method had its own inherent faults and each gave a different value for cerebral blood flow ranging from 60 to 130 mls/100 g/minute in the same species. Finally, in 1943, Dumke and Schmidt obtained the first reliable cerebral blood flow measurements using a "bubble" flowmeter. They obtained a value of 86 mls/100 g/minute in the anesthetized macacque monkey and demonstrated that flow responded to arterial blood pressure, blood gas concentrations and several drugs. Two years later, Kety and Schmidt (1945) developed a method based on the Fick Principle* using nitrous oxide, an inert gas. This method is described in detail in a later publication (1948 (b)), and has since been

* The Fick Principle states that the quantity of a substance in the tissue of an organ after a given time of exposure equals the total amount introduced minus the total amount expelled by the organ (conservation of mass providing none is lost to the tissue).

used extensively in the determination of cerebral blood flow (Kety and Schmidt, 1948 (a); Novack et al, 1953; and others). There are two serious drawbacks to this method: firstly, at least ten minutes are required for each determination and therefore only steady-state total flow may be measured; and secondly, regional flow variations remain undetected. These limitations have since been overcome by slight variations in the method but using essentially the same principles. In 1950, Kety, Landau et al, using a different inert gas (CF_3I^{131}), and with the aid of autoradiography, obtained quantitative estimates of blood flow for 30 regions of the brain of cats. This method, however, required that the animal be sacrificed and was consequently unsuitable for clinical use. A method for the continuous measurement of cerebral blood flow in man was introduced in 1960 by Lewis et al. They used the gamma-ray-emitting inert gas Krypton (Kr^{79}), instead of nitrous oxide, and were able to follow rapid changes in blood flow, but were uncertain of the quantitative accuracy of their measurements. A hydrogen-bolus technique was proposed by Fieschi, Bozzao and Agnoli (1965) and later used to measure hemispheric blood flow and metabolism (Meyer and Shinohara, 1970; and Meyer, Shinohara et al, 1970) but again only steady state flow could be determined. Finally, in 1967, a technique for measuring continuous regional cerebral blood flow using xenon (Xe^{133}) was developed (Høedt-Rasmussen et al, 1967), and is described by Olesen and Paulson (1971 (a), (b)). It is now possible, therefore, to measure regional changes in cerebral blood flow in response to various experimental and clinical conditions. However, these measurements do not indicate the origin of the increase or decrease in flow to a particular area.

3) INTRACRANIAL PRESSURE AND CEREBRAL BLOOD FLOW

> "If its (the skull) osseous walls are efficient in affording resistance to agents from without, they will no less exert repression on the forces operating within its cavity."
>
> (Cappie, 1880).

Cappie (1880) first suggested the current concept of the manner in which intracranial pressure* is maintained. He states further:

> "... as to the origin of intracranial pressure, its balance will depend simply on local alterations in the distribution of blood through the vessels. Every change in its circulation will be accompanied by a change of pressure in or on the brain."

Although the Monroe-Kellie doctrine (1824) stated that the total volume of the intracranial cavity must remain nearly constant, this was the first clear statement that a pressure normally exists in the cerebrospinal fluid and that it can vary with changes in cerebral blood flow. Fifteen years later, Bayliss and Hill (1895) recorded arterial, intracranial, general venous and cerebral venous pressures simultaneously in an attempt to measure cerebral blood flow variations. Although they drew erroneous conclusions concerning flow from their results, they did discover experimentally that cerebral venous pressure was approximately equal to intracranial pressure in all conditions they imposed and that intracranial pressure is not constant but can vary.

Cushing, in 1901 to 1903, published a series of articles (Cushing, 1901, 1902, 1903) describing the response of flow through the

* In strict terms, "Intracranial pressure" refers to any pressure contained within the cranial cavity. For the purpose of this and the following discussion, the common usage as a synonym for cerebrospinal fluid pressure will be assumed.

pial* arteries and that of blood pressure to increased intracranial pressure. He made a trephine** opening in the top of the skull which he fitted tightly with a glass "window" allowing him to observe caliber and flow changes in the underlying arteries. Cushing found that when intracranial pressure is approximately equal to diastolic blood pressure:

> "an increase of intracranial tension occasions a rise of blood pressure which tends to find a level slightly above that of the pressure exerted against the medulla".

He also discovered that the blood pressure varies rhythmically between a value slightly above and one slightly below the level of the increased intracranial pressure. He observed that the flow through pial vessels during this phenomenon was intermittent, stopping when the blood pressure was below the intracranial pressure and flowing when above (Cushing, 1901). When the high level of intracranial pressure was caused by compression of the brain, the same response was observed. As the difference between intracranial and arterial blood pressure decreased, flow in the pial arteries became slower and finally ceased when intracranial pressure was greater than arterial pressure. He demonstrated further that the longitudinal sinus would collapse if intracranial pressure was sufficiently high. (Cushing, 1902). In his paper of 1903, Cushing described patients suffering from intracranial

* The pia mater is the innermost of the three membranes surrounding the brain and spinal cord. The pial arteries mentioned above are small arteries which pass through the pia mater as they enter the brain.

** A trephine is a crown saw used to remove a circular disc of bone, usually from the skull. A trephine opening is a hole provided through its use.

hemorrhage and increased intracranial pressure, one in each of the four stages of cerebral compression described by Duret in 1878. In all but the most severe case of compression, removal of the blood clot and subsequent reduction of intracranial pressure resulted in an immediate improvement of the patient's clinical state. He emphasized that the symptoms of compression were due solely to disturbances in the intracranial circulation caused by a rapid increase in intracranial pressure. He stated that one of the symptoms of such a compression is

> "a progressive increase in arterial blood pressure or a high degree of the same, which has already been reached..."

and that in such cases "early operative intervention" to relieve the intracranial pressure should be attempted.

These discoveries created much interest in the cerebrospinal fluid pressure. Dandy and Blackfan (1913) discovered an experimental method of producing internal hydrocephalus at high intracranial pressures. The normal value of cerebrospinal fluid pressure was established in 1919-1920 as being approximately 125 mm of cerebrospinal fluid (Weed and McKibben, 1919; Becht, 1920; Foley and Putnam, 1920). A method of decreasing the pressure of the cerebrospinal fluid using hypertonic salt solutions was developed at this time (Weed and McKibben, 1919; Foley and Putnam, 1920; Cushing and Foley, 1920; Fay, 1923), and the effects of increased intracranial pressure on the medullary centers were described by Tsubara in 1924.

Wolff and Forbes, in 1928, confirmed Cushing's observations concerning flow in the pial arteries stating that as the intracranial pressure rises, pressure in the cerebral veins and arteries also rises,

thereby lowering the perfusion pressure* and decreasing the flow. Also in 1928, Stopford suggested that increased intracranial pressure associated with intracerebral tumors is most likely due to compression of the great vein of Gallen (Stopford, 1928). This postulate was later supported by Courtice (1940), who found that posterior tumors or compression increased intracranial pressure and slowed the cerebral blood flow more than similar anterior occurrences.

Wolff and Blumgart (1929) measured cerebral blood velocity and found that flow was proportional to blood pressure at normal intracranial pressures. They also found that flow was reduced if the intracranial pressure was elevated, and that cerebral blood flow ceased if intracranial pressure exceeded the arterial pressure. This view was challenged in 1939 by Williams and Lennox (1939), who found that cerebral blood flow was not significantly altered in patients with high intracranial pressure. Kety, Shenkin and Schmidt (1948) suggested that Williams' and Lennox's calculations of blood flow depended on the assumption that the oxygen consumption of the brain is constant. The brain of comatose patients with high intracranial pressure uses oxygen at a lower rate (Kety, Polis, Nadler and Schmidt, 1948), and therefore a normal arteriovenous oxygen concentration gradient suggests that a slow rate of blood flow existed.

With the development of the nitrous oxide technique of measuring cerebral blood flow in 1945 (Kety and Schmidt, 1945), quantitative

* The perfusion pressure is the difference in pressure between the two ends of a tube (artery) or collection of tubes (arteries) and is a measure of the force acting to "push" the blood from the high pressure end to the end of lower pressure.

measurements of changes in total cerebral blood flow were possible. Between 1945 and the present date, investigation of intracranial pressure has proceeded along two major experimental lines:

(i) increased pressure caused by intracerebral masses such as tumors, and

(ii) increased pressure caused by fluid injections to simulate intracranial hemorrhage.

Intracranial Tumors -

In 1948, Kety, Shenkin and Schmidt measured cerebral blood flow and intracranial pressure in 13 patients with brain tumors. They found that if the intracranial pressure exceeded 450 mm of cerebrospinal fluid (approximately 33 mm Hg*), blood flow decreased as intracranial pressure increased. Heilbrun, Jorgensen and Boysen (1972), in a similar study, found that flow decrease began when the difference between arterial and intracranial pressure was less than 50-60 mm Hg. Other investigators have used inflatable balloons to simulate tumor growth in experimental animals. Lovell and Bloor (1971) found that increases in intracranial pressure in excess of 40 mm Hg would reduce flow. Langfitt, Kassel and Weinstein (1965) found that this critical level of increased intracranial pressure was dependent on the time course of the pressure increase. If the balloon was expanded slowly, flow remained constant until intracranial pressure rose above 35-50 mm Hg but if the expansion was fast, flow decreased as soon as the intracranial pressure was increased. Lewis and McLaurin (1971) also found

* A pressure of 1 mm Hg = 13.6 mm of water or cerebrospinal fluid.

that flow decreased with any increase in intracranial pressure. Johnston and his co-workers (Johnston, Rowen, Harper and Jennett, 1973), stated that the relationship between intracranial pressure and cerebral blood flow depended on the location of the tumor or balloon. If the tumor was located above the level of the cerebellum, as in the above studies, they found that flow was maintained until the arterial-intracranial pressure difference fell below 50 mm Hg. If, however, the tumor was situated below this level, any increase in intracranial pressure resulted in decreased blood flow. They stated that infratentorial tumors resulted in the loss of autoregulation* and that this was the reason flow passively followed intracranial pressure. Miller, Stanek and Langfitt (1973), supported this idea and stated that during normal autoregulation, flow remained essentially constant until the arterial-intracranial pressure difference was less than 40 mm Hg. Loss of autoregulation resulted in passive flow decreases with any intracranial pressure increases.

Intracranial Hemorrhage -

A clinical analysis of flow reductions due to increased intracranial pressures, resulting from intracranial hemorrhage, is extremely difficult. The major difficulty lies in determining how much of the cerebral blood flow loss is due to increased intracranial pressure, and how much is the result of active narrowing of the major cerebral arteries due to vascular smooth muscle contraction (often called "spasm"). The major arteries of the circle of Willis can constrict in response to vasoactive chemicals released by blood platelets during clotting (Rapport, 1948;

* Autoregulation of blood flow in the brain is the ability of the cerebral vasculature to maintain a relatively constant blood flow during increases or decreases of perfusion pressure.

1949; Zucker, 1954). The presence of blood in the cerebrospinal fluid, however, does not produce spasm in every instance. Stornelli and French (1964) stated that only 40 percent of their patients with bloody cerebrospinal fluid showed any signs of vasospasm and that diffuse spasm occurred only when the intracranial pressure was elevated. They also stated that all patients who exhibited spasm had an increased intracranial pressure. A similar set of observations were made by Pribram (1961). Allcock (1966) found that only 41 percent of patients with intracranial hemorrhage showed signs of spasm; Griffith, Cummins and Thomson (1972), 35 percent; and Wilkins, Alexander and Odom (1968), 37 percent. Nornes and Magnaes (1972) have recently shown that intracranial pressures between 40-80 cm water were present following their "Type 1" hemorrhage, and pressures of 120-220 cm water with "Type 2" hemorrhage. Nornes (1973) also demonstrated that internal carotid artery blood flow was severely reduced following subarachnoid hemorrhage and was improved if intracranial pressure was reduced. It is well established that major cerebral arteries are occasionally narrowed and blood flow is decreased following subarachnoid hemorrhage but the relative importance of increased intracranial pressure compared to that of arterial spasm is as yet unknown.

Experimental simulation of intracranial hemorrhage is achieved by the injection of fluid into the subarachnoid space*. Greenfield and Tindall (1965) reported that flow remained constant until the arterial-intracranial pressure difference was less than 65 mm Hg. Häggendal and co-workers (1970) and Zwetnow (1970) found this critical value to be approximately 50 mm Hg, but all three investigations indicated that cerebral

* The subarachnoid space is the space between the pia mater and the arachnoid membrane and is filled with cerebrospinal fluid.

blood flow decreased if the arterial-intracranial pressure difference was decreased beyond this critical value. McQueen and Jelsma (1967) found that 8 cc injections of whole blood into the cerebrospinal fluid were capable of producing and sustaining an intracranial pressure of 30 cm water and that a similar injection of red blood cell ghosts* would result in an intracranial pressure of 100 cm water. They suggested that the red blood cell ghosts blocked the absorption of cerebrospinal fluid and that this resulted in the high intracranial pressures.

In summary, increases in intracranial pressure high enough to cause a reduction in cerebral blood flow are known to occur in both intracranial tumor growth and intracranial hemorrhage. It is important to note that these observations are based on total or regional cerebral blood flow measurements and therefore, cannot yield specific information as to the origin of the flow reduction. A narrowing of the large cerebral arteries could produce the same net flow decrease as a narrowing of the arterioles, or veins, and measurement of total blood flow in the affected area would not indicate which situation exists.

4) FLOW DETERMINING FACTORS

If we assume that, in general, flow through the cerebral arteries is non-turbulent or laminar, Poiseuille's law will apply, i.e.:

$$F = \Delta P/R$$

where F is the flow, ΔP is the internal pressure gradient,** and R is

* Red blood cell ghosts are red blood cells from which the hemoglobin has been removed.

** The internal pressure gradient, ΔP, is the difference in intraluminal pressure between the two ends of the vessel.

the resistance of the vessel under consideration. The resistance (R) is inversely proportional to the fourth power of the radius (r) of the vessel so that we may rewrite Poiseuille's law in the form:

$$F \propto \Delta P r^4$$

Flow can therefore be reduced by decreasing either the internal pressure gradient or the radius of the lumen. At a given ΔP, flow through the vessel is extremely sensitive to changes in radius and small reductions in radius are capable of producing large variations in flow. This argument applies equally well to both the large arteries of the circle of Willis and the small arterioles of the brain. The entire systemic circulation of the brain is distributed from the six major branches of the circle of Willis (Figure 1) which, in turn, are supplied by two vertebral and two carotid arteries. Flow decreases in any of these major arteries will therefore cause widespread flow reductions in the cerebral circulation and, if sufficiently severe, large areas of anoxia.*

* Anoxia is a reduction of oxygen in body tissues below normal levels.

FIGURE 1

A line drawing of the human circle of Willis

ACA - anterior cerebral artery

ACoA - anterior communicating artery

BA - basilar artery

ICA - internal carotid artery

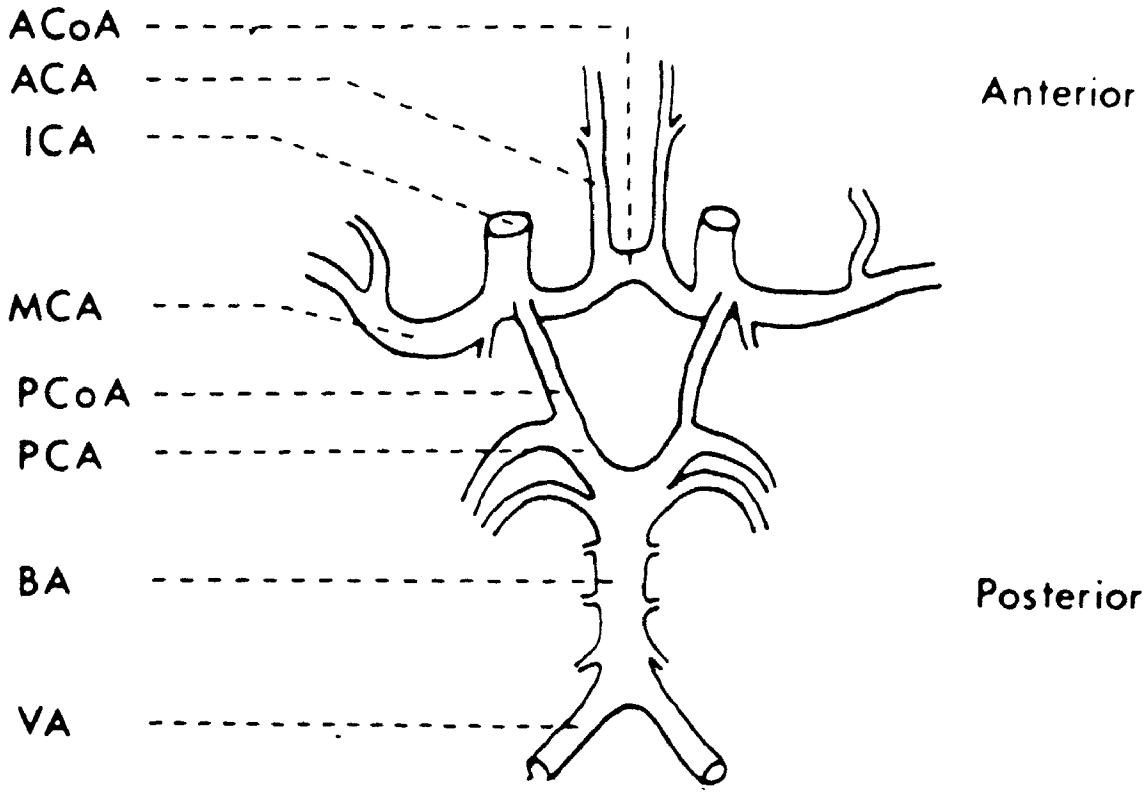
MCA - middle cerebral artery

PCA - posterior cerebral artery

PCoA - posterior communicating artery

VA - vertebral artery

Circle of Willis



II. NARROWING AND CLOSURE OF MAJOR CEREBRAL ARTERIES

1) INTRODUCTION

Since brain arteries behave like distensible tubes (Scott, Ferguson and Roach, 1972), their internal diameter is determined by the difference between the force acting to distend the walls (intraluminal pressure) and the sum of the forces acting to limit this distension (extraluminal pressure, elasticity of the wall and the component of active smooth muscle contraction tending to decrease the circumference/radius of the vessel). These factors clearly fall into two groups: "active", referring only to the action of smooth muscle; and "passive", referring to the other variables. The two are by no means mutually exclusive and represent only the mechanisms by which flow variations may be caused by changes in radius.

2) ACTIVE NARROWING

(a) AUTOREGULATION -

Active control of cerebral blood flow is accomplished by constriction and dilatation of the arteries and arterioles of the brain. The intrinsic tendency of the cerebral vasculature to maintain a constant blood flow despite changes in arterial perfusion pressure is termed autoregulation (Johnson, 1964). There are two major theories describing the nature of autoregulatory control of the cerebral circulation. The metabolic hypothesis states that a decrease in blood flow (caused by a decrease in perfusion pressure) results in an accumulation of vasodilator

metabolites. This results in a dilatation of the artery which tends to decrease resistance and increase flow (Berne, 1964). The myogenic hypothesis states that a reduction of pressure results in a decrease of arterial smooth muscle tone. This causes a dilatation of the artery and subsequent increase in flow (Folkow, 1964).

(1) Metabolic Theory -

The metabolites considered capable of causing autoregulation are carbon dioxide (pCO_2), oxygen(pO_2), and hydrogen ion concentration (pH) (Rapela and Green, 1964).

An increase in carbon dioxide or a decrease in oxygen tension are both capable of producing a dilatation of cerebral arteries and arterioles, and a decrease in pCO_2, or an increase in pO_2 results in a constriction (Gibbs, Gibbs and Lennox, 1935; Forbes and Cobb, 1938; Dumke and Schmidt, 1942; Kety and Schmidt, 1948 (a); Krueger, Rockoff, Thomas and Ommaya, 1963; Häggendal and Johansson, 1965). The cerebral arteries, however, are more responsive to changes in pCO_2 than those of pO_2 (Gibbs, Gibbs and Lennox, 1935; Kety and Schmidt, 1948 (a)). A decrease in blood flow results in a build-up of carbon dioxide and a depletion of oxygen, both of which cause vasodilatation tending to restore the flow to its original level. Changing the carbon dioxide tension, however, also changes the pH of the blood and that of the extracellular and intracellular fluid of the arterial smooth muscle cells. Zwetnow, Kjällquist, Siesjö (1968), and Skinhøj (1966), state that the extracellular pH is the major metabolic factor responsible for autoregulation. This view has been challenged by Harper and Bell (1963), McDowall and Harper (1968), Plum, Posner and Zee (1968), and Rapela and Green (1968).

These investigators all favor pCO_2 as the vasoactive agent. The third theory states that intracellular pH is the regulating mechanism and that pCO_2 and extracellular pH have little effect if the intracellular pH remains constant (Gotoh, Tazaki and Meyer, 1961; Meyer and Gotoh, 1961; Shinohara, 1973). The specific metabolic agent responsible for autoregulation has not been agreed upon, but all three factors are interrelated and will therefore act together.

(ii) Myogenic Theory -

This theory states that arterial smooth muscle reacts to variations of pressure instead of changes in flow. Smooth muscle responds to an increase or decrease in stretch with a contraction or dilatation, respectively (Dobrin and Rovick, 1969; Dobrin, 1973 (a), (b)). A decrease in arterial blood pressure reduces the stretch or tension in the arterial wall which results in a dilatation. This increase in radius will maintain the original flow rate at a reduced perfusion pressure. This hypothesis was introduced by Bayliss (1902) and later supported by Fog (1938), Folkow (1964), Häggendal and Johansson (1965), Häggendal (1968) and others.

(iii) General Viewpoint -

In spite of the different theories proposed, it is generally agreed that autoregulation is accomplished through a combination of some or all of the above-mentioned factors (Lassen, 1964; Harper and Häggendal, 1968; Zwetnow, 1968). It is also agreed that

autoregulation can be lost with severe hypoxia* (Häggendal, 1968), hypercapnia** (Iwabuchi, Kutsuzawa, Ikeda and Nakamura, 1973), increased intracranial pressure (Miller, Stanek and Langfitt, 1973), or subarachnoid hemorrhage (Hashi, Meyer, Shinmaru, Welch and Teraura, 1972). Without autoregulation, there is a passive relationship between cerebral blood flow and perfusion pressure. Under normal conditions autoregulatory responses determine the caliber of the cerebral blood vessels. The large arteries of the circle of Willis exhibit changes in diameter in response to metabolic (Krueger, Rockoff, Thomas and Ommaya, 1963), and myogenic (Echlin, 1942) stimuli. Because of their large radii and consequently small resistances, these arteries probably do not contribute significantly to normal autoregulation. If these arteries become narrower, however, they can severely decrease the blood flow (Allcock, 1966; Ecker, 1945; Ecker and Riemenschneider, 1953).

(b) CEREBRAL ARTERIAL SPASM -

Spasm or narrowing of the major cerebral arteries was first demonstrated angiographically by Moniz in 1942 (Ecker and Riemenschneider 1953), and later confirmed by Ecker (1945), Ecker and Riemenschneider (1951), and others. Spasm is usually associated with an unfavourable prognosis and has often been named as the major cause of morbidity and death following subarachnoid hemorrhage (Ecker and Riemenschneider,

* Hypoxia is a state of low oxygen concentration or availability.

** Hypercapnia is a state of high carbon dioxide concentration in the blood.

1951, 1953; Logue, 1956; Allcock and Drake, 1963, 1965; Allcock, 1966; Zervas, Kuwayama, Rosoff and Salzman, 1973). Severe arterial constrictions have been shown to last for up to three weeks (Marshall, 1973), and appear to be most severe 5-10 days after the hemorrhage (Bergvall and Galera, 1969; Marshall, 1973). Brawley, Strandness and Kelly (1968) found experimentally that spasm was a biphasic phenomenon with an "acute" phase lasting less than an hour and a "chronic" phase beginning 3 to 24 hours after the hemorrhage and lasting for days. This was later confirmed by Echlin (1971) and Kuwayama, Zervas, Shintani and Pickren (1972). Wilkins and Levitt (1970) and Weir, Erasmo, Miller et al (1970) were unable to reproduce these results. Yamaguchi and Waltz (1971) found that spasm was slight following the rupture of cerebral arteries in cats if intracranial pressure was maintained at normal levels.

Many mechanisms have been proposed as causes of spasm, and each has been tested using experimental animals. Mechanical stimulation (stretch) caused by the sudden rupture of a cerebral blood vessel was proposed by Echlin (1942) and Ecker (1945). This idea was supported by Ecker and Riemenschneider (1951), Harvey and Rasmussen (1951) and later by Pool, Jacobson and Fletcher (1958), and Johnson, Potter and Reid (1958). The spasm induced by mechanical stimulation lasts only for a short time (approximately 10-30 minutes), and does not explain the clinical observations of long-lasting contractions.

The nerve supply of the cerebral arteries has also been considered as a cause of spasm. Forbes and Wolff (1928) and Forbes and Cobb (1938) stated that electrical stimulation of the cervical sympathetic nerves produced only 8 to 10 percent constriction of the cerebral arteries. Echlin (1942, 1965), however, found a 30 to 70 percent

reduction of diameter when the basilar artery was directly stimulated at a high frequency. D'Alecy and Feigl (1972) found similar results at a stimulation frequency of 15 per second. They stated that these frequencies were higher than normally occur physiologically, and that constriction decreased with decreasing frequency. Green and Denison (1956) and McClure and Green (1959) found no evidence of a constriction in response to adrenergic stimulators. James, Millar and Purves (1969) reported a 30 percent decrease in flow following sympathetic stimulation. Recent investigations using catecholamine fluorescent techniques (Fraser, Stein, Barret and Pool, 1970), and scanning and transmission electron microscopy (Nelson, Takayanagi, Rennels and Kawamura, 1972; Dahl, 1973) have demonstrated that the arteries of the circle of Willis do have an extensive nerve supply. Fraser et al (1970) have shown, however, that denervation of the basilar artery did not prevent or relieve spasm produced by the external application of blood. In addition, all of the above observations produced only short-term constrictions and therefore do not mimic the spasm seen following subarachnoid hemorrhage. The exact function of the cerebral arterial nerve supply is uncertain at present.

Further attempts to determine the cause of prolonged vasospasm assumed that the blood in the cerebrospinal fluid must contain or release a potent vasoconstrictor. Wilkins and Levitt (1971) found that high potassium ion (K^+) concentrations could produce spasm in the cerebral arteries of dogs, but that the K^+ concentration was not elevated in the cerebrospinal fluid of patients with intracranial hemorrhage. They also observed that the concentrations required to induce spasm were

higher than those expected to result from hemolysis* of a subarachnoid blood clot. In 1948, Rapport, Green and Page isolated a potent vasoconstrictor which was released by platelets during clotting (Zucker and Borrelli, 1954), and named it serotonin. Rapport (1949) later found that this was actually a serotonin creatinine sulfate complex, but that serotonin (5-hydroxytryptamine) was the vasoactive substance. Serotonin was capable of producing a 20-40 percent constriction of cerebral arteries lasting up to 3 hours (Raynor, McMurtry and Pool, 1961; Karlsberg, Elliot and Adams, 1963; Raynor and McMurtry, 1963; Fraser, Stein, Barret and Pool, 1970; White, Denton and Robertson, 1971; Toda and Fujita, 1973). Brawley, Strandness and Kelly (1968) found that serotonin may cause the initial acute phase of spasm. They found no evidence supporting the theory that serotonin was responsible for long lasting, chronic spasm. Another vasoconstrictor, prostaglandin $F_{2\alpha}$ has recently been investigated by White, Denton and Robertson (1971) and Denton, White and Robertson (1972), and was reported to have short-term pressor effects similar to those of serotonin.

Spasm has been demonstrated angiographically to be capable of complete, or nearly complete, closure of large cerebral arteries as well as long-term reductions in vessel caliber and flow (Ecker, 1965; Allcock and Drake, 1963; and others). The cause of these circulatory disturbances has not been determined.

3) PASSIVE NARROWING

The net force acting to distend the arterial wall is the

* Hemolysis is the liberation of hemoglobin from red blood cells.

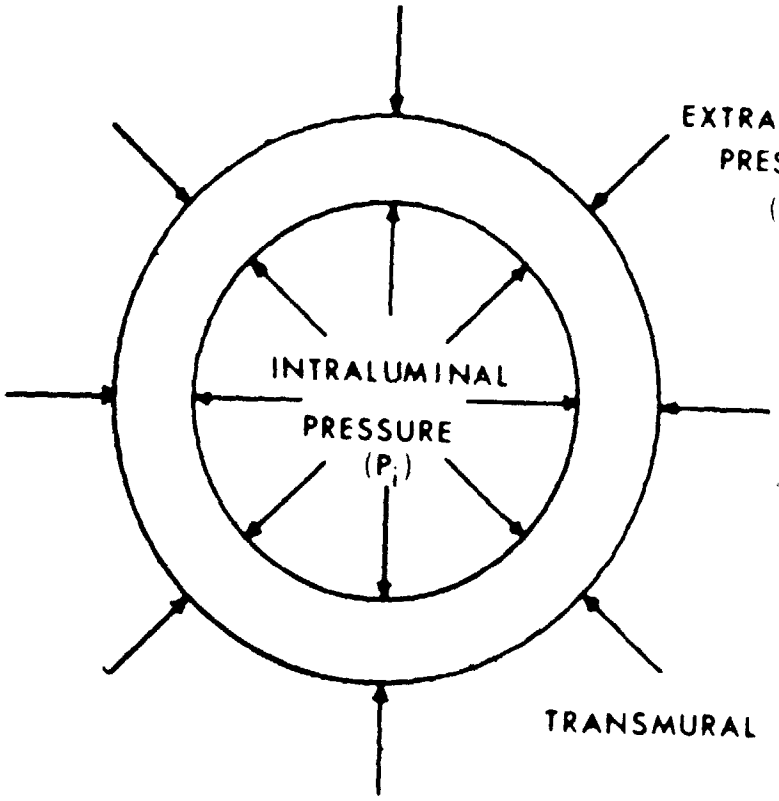
difference between the intraluminal and extraluminal pressures and is called the transmural* pressure. (Figure 2). In the cerebral circulation, the transmural pressure is the arterial blood pressure minus the intracranial or cerebrospinal fluid pressure. Clearly then, a fall in blood pressure, or an increase in intracranial pressure, will tend to passively narrow the cerebral arteries. It is important to note here, that it is the difference between these two forces, and not the magnitude of either one, which determines the vessel caliber.

Passive resistance to this stretching is provided by the elastic components of the arterial wall, elastin and collagen (Roach and Burton, 1959; Wolinsky and Glagov, 1964). This phenomenon is termed elastance and is the tendency of the wall to resist increases in diameter. An increase in elastance represents a decrease in the distensibility of the wall. The elastance of arteries changes with transmural pressure, increasing as pressure is raised (Roach and Burton, 1957). That is, as the transmural pressure is increased, the wall becomes "stiffer". Two other factors known to affect the stiffness of the wall are age (Roach and Burton, 1959; Busby and Burton, 1965; Crawford, 1966; Roach, 1970), and degree of atherosclerosis (Lansing, Alex and Rosenthal, 1950; Nichol, 1955; Yu and Blumenthal, 1963; Crawford, 1966). Each of these tends to increase the elastance. Therefore, the diameter of an artery will depend on its age and degree of atherosclerosis as well as on the transmural pressure. When considering passive reductions in radius and blood flow of a particular

* Literally, the pressure across the wall.

FIGURE 2

This illustrates that the force acting to distend the walls of an artery is the transmural pressure (intraluminal (P_i) - extraluminal (P_e) pressure).


EXTRALUMINAL
PRESSURE
(P_e)
INTRALUMINAL
PRESSURE
(P_i)
TRANSMURAL PRESSURE = $P_i - P_e$

artery, age and development of atherosclerosis are constant. Transmural pressure is the factor which determines the extent of radius and flow reductions.

4) RATIONALE AND OBJECTIVES

(i) If autoregulation is lost, transmural pressure and perfusion pressure determine arterial radius and flow in a passive manner.

(ii) Transmural pressure has been shown to affect the radius of intracranial arteries and is the basis of the myogenic theory of autoregulation.

(iii) When an artery is in spasm, a reduction in transmural pressure (i.e., by increasing external pressure) will decrease the force opposing the constriction. This will decrease the radius of the vessel and increase resistance to flow.

The objective of this thesis is to investigate the relationship between flow, perfusion pressure, and transmural pressure in major cerebral arteries under these three conditions:

(i) An absence of smooth muscle tone;

(ii) Normal smooth muscle tone; and

(iii) Active vasoconstriction.

In this manner, the relative importance of active versus passive narrowing of large intracranial arteries can be determined.

III. PASSIVE PRESSURE-FLOW RELATIONSHIPS IN MAJOR HUMAN CEREBRAL ARTERIES

1) INTRODUCTION

Passive pressure-flow relationships have been observed following loss of autoregulation and during high intracranial pressure (Iwabuchi et al, 1973; Miller et al, 1973; Johnston et al, 1973). In many of these investigations, transmural pressure and cerebral perfusion pressure have been used as synonyms. This assumption will be discussed. The possibility that passive flow reductions may originate in the major cerebral arteries has not been investigated previously.

2) MATERIALS AND METHODS

(a) ARTERIAL SPECIMENS -

The 26 arteries used in these experiments were human cerebral arteries from the circle of Willis and its branches. These were obtained at autopsies and immediately stored in 0.9 percent saline at approximately 3°C for at least 24 hours. This was done to ensure that active smooth muscle contraction was eliminated, and that only passive changes in radius could occur during the course of an experiment. This process was proved to be effective when repeated attempts to stimulate the arteries with noradrenaline (10^{-6}M) and serotonin (10^{-4}M) failed to elicit any response. All arteries selected for study were straight segments cut to a length of 2 ± 0.1 cm. Side branches were ligated with fine silk thread. Any artery which leaked, or in which ligation of a side branch produced a noticeable distortion of the arterial wall, was discarded.

The arteries were then studied in two groups: one group (10 arteries) in which single arteries were perfused, and the other group (16 arteries) in which two arteries were cannulated in parallel and perfused simultaneously.

(b) PERFUSION OF SINGLE ARTERIES -

The apparatus (Figure 3(a)) consisted primarily of a pressure-tight plexiglass box or housing, to simulate the skull, and inflow and outflow cannulas to mount the artery. The artery and cannulas were placed in a metal "cradle" (Figure 3(b)) to ensure that the length of the arterial segment would remain constant during the course of the experiment. The artery was then placed in the housing and perfused from a constant pressure reservoir of isotonic* saline (10 litre capacity). The housing was filled with saline and coupled to a brass cylinder with a micrometer-driven piston. Saline could then be injected or withdrawn from the housing. The resultant changes in housing pressure were monitored visually with a mercury manometer and electronically by a pressure transducer** (Statham, Model P34Db). Flow through the artery was measured with an electromagnetic flowmeter** (Carolina Medical, Model 322), and pressure on both sides of the artery monitored with pressure transducers. All pressure and flow measurements were recorded on an 8-channel chart recorder (Beckman Type R Dynograph). Screw clamps allowed the resistance at either end of the artery to be varied.

* Isotonic saline is a solution of 0.9 percent sodium chloride in distilled water. This solution has an osmotic pressure identical with that of human blood.

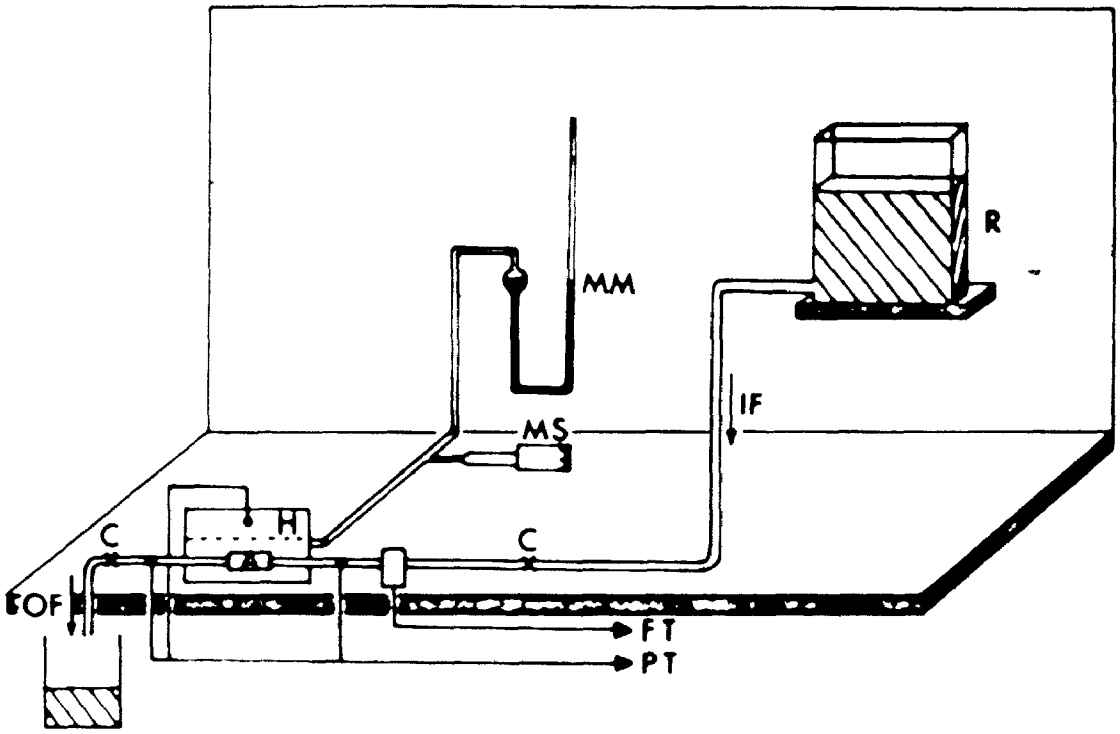
** See Appendix 3

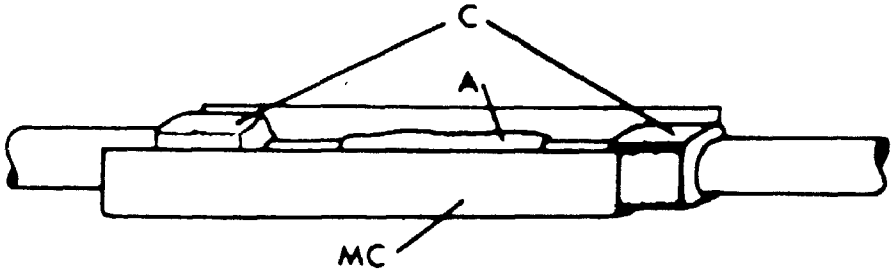
FIGURE 3(a)

Schematic diagram of the apparatus used showing the cannulated artery (A), plexiglass housing (H), reservoir (R), adjustable clamps (C), mercury manometer (MM), micrometer syringe (MS), flow transducer (FT), pressure transducers (PT), inflow (IF), and outflow (OF).

FIGURE 3(b)

Schematic diagram of the metal "cradle" (MC) which was used to secure the cannulas (C) and artery (A) at a fixed length.


R
MM
IF
MS
H
C
C
FOF
FT
PT


C
A
MC

Inflow pressure was increased or decreased by raising or lowering the pressure reservoir. In all experiments, the housing pressure and perfusion pressure were varied from 0 to 100 mm Hg and each set of measurements was repeated at least twice.

(c) PERFUSION OF TWO ARTERIES IN PARALLEL -

The apparatus employed was essentially the same as that described in section (b) except that the housing was increased in size to accommodate two arteries cannulated in parallel. Proximal* to the arteries in the housing, a glass Y-tube was introduced providing a symmetrical bifurcation** (outside the housing). Flow and pressure for each artery were measured and recorded as described previously.

(d) PROTOCOL -

In each experiment, two sets of pressure conditions were imposed on the artery (or arteries).

(i) Perfusion Pressure -

To assess the relationship between flow and perfusion pressure, the housing pressure was maintained at 0 mm Hg and the inflow pressure was varied between 0 and 100 mm Hg.

(ii) Transmural Pressure -

The perfusion pressure was maintained at a constant

* Proximal refers to positions 'upstream' from the artery and distal refers to positions 'downstream'.

** A bifurcation is a fork or branching where a single structure divides into two.

value and the housing pressure was varied between -50 and +120 mm Hg. This was repeated for several different perfusion pressures and in the presence or absence of an external resistance (provided by the screw clamps).

3) INITIAL CONSIDERATIONS AND ASSUMPTIONS

(a) LAMINAR FLOW -

As an indication of whether flow in the proximal cannula was streamlined or turbulent, the Reynolds number (Vennard, 1962, pg. 224) was calculated using the formula:

$$Re = \frac{\rho}{\eta} \cdot \bar{V} \cdot D$$

where ρ is the density, η is the viscosity, $\bar{V}$ is the average velocity, and D is the diameter of the tube. This calculation was done for all cannulas at the corresponding maximum flow velocities. The maximum Reynolds number calculated for these experiments was 1,700. Because laminar flow normally occurs in a long straight tube when Re 2,000, it has been assumed that the flow remains laminar in the inflow cannula. This may not be so for the outflow cannula in all cases owing to the non-uniform diameter of the arterial segment*.

(b) INFLOW PRESSURE -

The measurement of inflow pressure was made proximal to the housing and artery. The actual inflow pressure at the artery can be estimated by calculating the pressure losses between the point of measurement and the artery. Laminar flow pressure losses will occur in

* See section c (ii)

the connecting tubing (i.d. = 0.35 cm, length = 8 cm) and in the bore of the cannula (length = 1.5 cm, variable diameter). These losses may be calculated by the relation:

$$\Delta P = \frac{8 F \eta L}{\pi r^4} \qquad \text{(Poiseuille's Law)}$$

where ΔP is the pressure loss, F is the volume rate of flow, L is the length, and r the radius of the tube. The pressure loss (in cm of water) due to the sudden decrease in diameter between the connecting tubing and the cannula can be estimated using the expression:

$$\Delta P = K_L \frac{V_c^2}{2g}$$

where $g = 980\ cm/sec^2$, V_c is the velocity of flow in the cannula, and K_L is the loss coefficient which depends on the ratio of the cross-sectional area of the cannula to that of the tubing (Vennard, 1962, pg. 314).

These pressure losses were calculated and subtracted from the measured inflow pressure by computer and the resultant will be referred to as the inflow pressure.

(c) PERFUSION PRESSURE -

The perfusion pressure, as previously defined, is the difference in pressure between two ends of a tube or collection of tubes. In the following experiments, perfusion pressure could be defined as:

(i) the pressure drop along the arterial segment, or

(ii) the difference between the inflow pressure and the measured outflow pressure distal to the artery.

The assumptions and restrictions of each are presented below.

(1) Pressure Drop Along the Arterial Segment -

It will be shown that the lumen of the artery closes if the transmural pressure is approximately 0 mm Hg. This indicates that the internal pressure of the artery must be slightly greater than the external (housing) pressure to maintain an open channel along the entire length of the artery. In other words, whenever flow through the artery exists, the internal pressure at the distal end of the artery must be greater than the housing pressure. When the housing pressure is increased, the artery becomes narrower due to reduced transmural pressure, and flow decreases. As the housing pressure approaches the inflow pressure, the situation depicted in Figure 4 arises. The pressure at point A will approximately equal the inflow pressure (IP), since flow rate is small. The pressure at point B is less than at point A (since flow exists), but must be greater than the housing pressure (since the artery is open). As the housing pressure increases, the pressure at B must increase and the pressure drop from A to B must decrease. If this pressure drop is used to define perfusion pressure, then as the housing pressure approaches the inflow pressure, the perfusion pressure approaches zero. When the artery is closed, however, the pressure at A equals the inflow pressure, and the pressure at B equals the outflow pressure (0 mm Hg), and the perfusion pressure becomes equal to the inflow pressure. The reason for this discrepancy is that the major pressure drop in Figure 4 occurs between points B (artery) and C (cannula). The transition between the narrowed artery and the cannula represents a sudden expansion which results in a large pressure loss. This pressure loss is a result of the arterial narrowing and as such, should be included in the calculation of perfusion

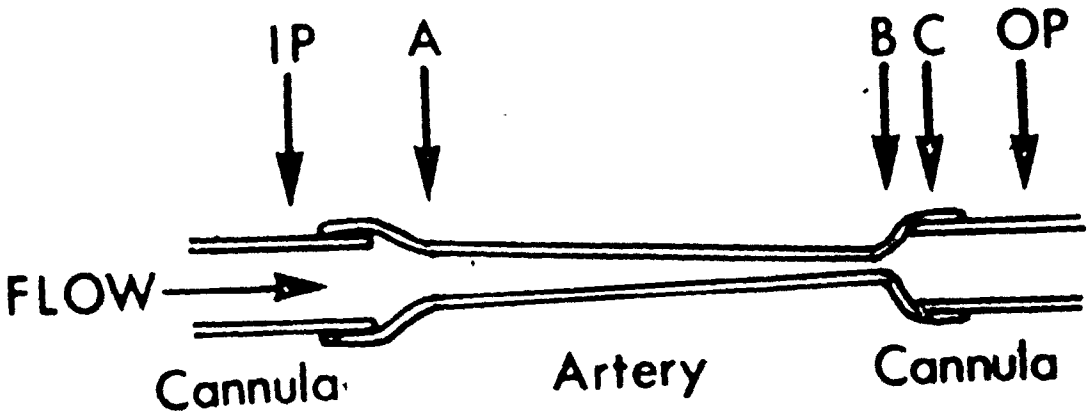
FIGURE 4

Illustration representing a cannulated artery which has been narrowed by increased extra-luminal pressure.

IP - inflow pressure

OP - outflow pressure

A, B and C - points of reference - see text


IP
A
B
C
OP
FLOW
Cannula
Artery
Cannula

pressure. If this is not done, a false relationship develops between flow and "perfusion pressure".* As the housing pressure increases, flow and "perfusion pressure" decrease. If this relationship is linear, or nearly linear, the resistance of the artery will appear to be constant (recall that flow = perfusion pressure/resistance). The reduction of flow, however, is due to the narrowing of the artery which is usually associated with an increased resistance.

Another disadvantage of this definition of "perfusion pressure" is that the pressure at point B is not easily obtainable and therefore must be estimated.

For these reasons, this definition of "perfusion pressure" will not be used.

(ii) The Inflow-Outflow Pressure Difference -

Perfusion pressure will be defined as the difference between the inflow pressure and the measured outflow pressure distal to the artery. The disadvantage of this definition is that the pressure drop across the distal cannula will be included in the measurement of perfusion pressure. This pressure drop could not be accurately measured or calculated since the assumption of laminar flow could not be made in the region distal to the artery. When the arterial diameter is smaller than that of the cannula, eddy formation and local turbulence may occur within the cannula and an assumption of laminar flow would be invalid. The cannula, therefore, introduced

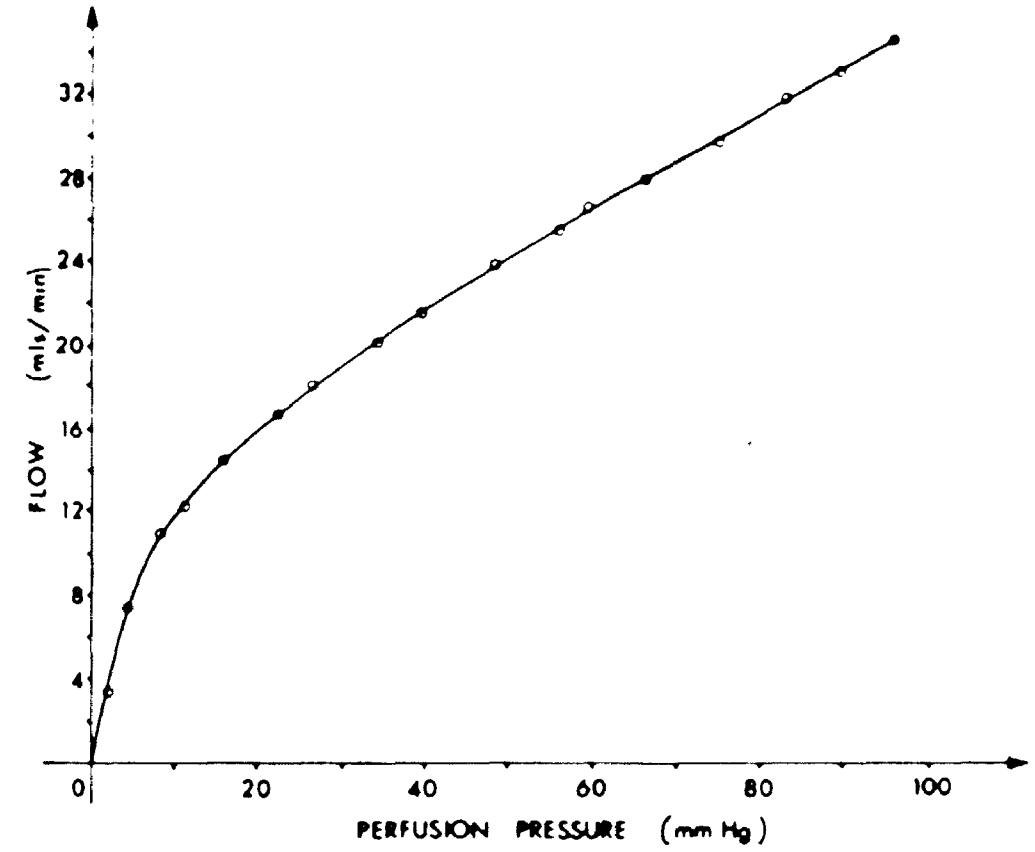
* "Perfusion pressure", when in quotes, will refer to the pressure drop between points A and B in Figure 4.

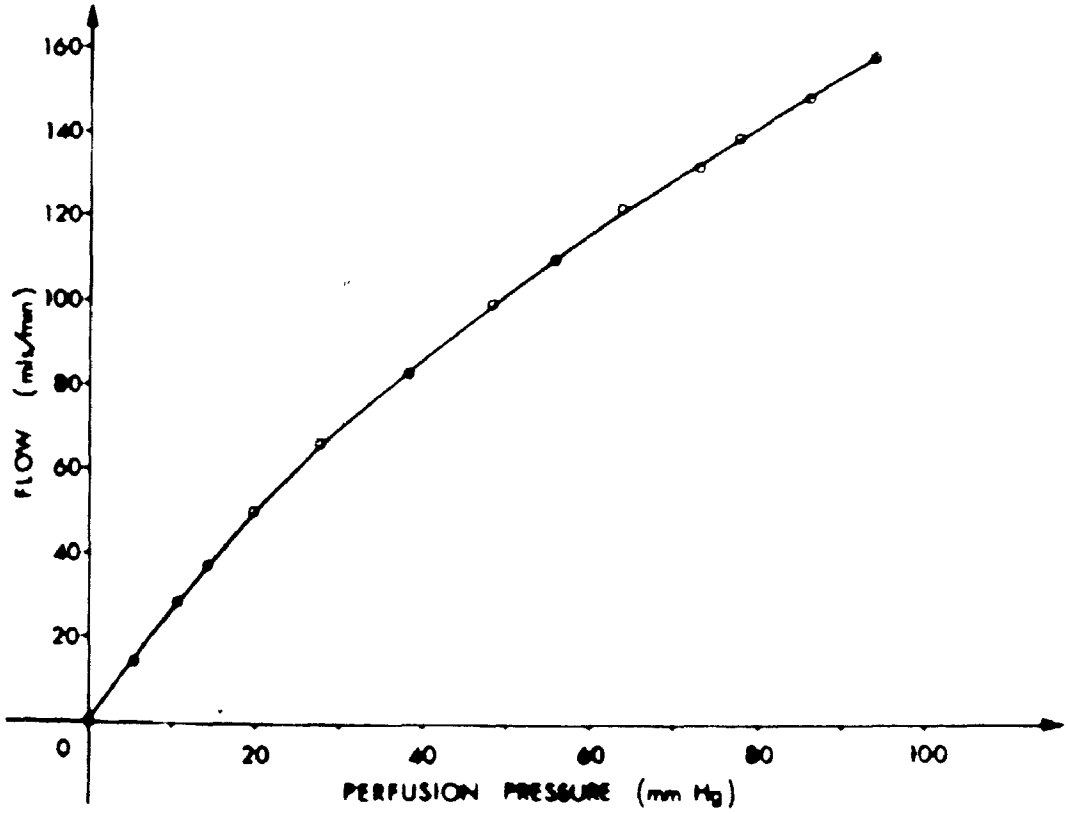
FIGURE 5(a)

Diagram showing the variation of flow with perfusion pressure for a small cerebral artery (diameter = 0.08 cm at 100 mm Hg). Flow increases with increasing perfusion pressure and the graph is concave towards the pressure axis.

FIGURE 5(b)

Comparable diagram for a large cerebral artery (diameter = 0.198 cm at 100 mm Hg)". The tendency to curve towards the pressure is less marked than in Figure 5(a). In both cases, flow ceases at a perfusion pressure of zero mm Hg.


FLOW (mls/min)
32
28
24
20
16
12
8
4
0
20
40
60
80
100
PERFUSION PRESSURE (mm Hg)


FLOW (mls/min)
160
140
120
100
80
60
40
20
0
20
40
60
80
100
PERFUSION PRESSURE (mm Hg)

a resistance to flow distal to the artery.

(d) TRANSMURAL PRESSURE -

Since the pressure at point B (Figure 4) cannot be measured or estimated, the change in transmural pressure along the arterial segment could not be measured. The transmural pressure will therefore be defined as the difference between the inflow and the housing pressures. This is a measure of the maximum pressure available to distend the walls of the artery.

4) RESULTS

(a) THE PERFUSION OF SINGLE ARTERIES -

(i) Perfusion Pressure -

The variation of flow with perfusion pressure is shown in Figures 5(a) and 5 (b). In all cases, flow increased with increasing perfusion pressure and the flow-perfusion pressure curve was concave towards the pressure axis. This effect was more pronounced for small arteries (Figure 5(a)) than for large arteries (Figure 5(b)). Flow ceased when the perfusion pressure was 0 mm Hg. All results were reproducible to within $\pm$ 1 percent.

(ii) Transmural Pressure -

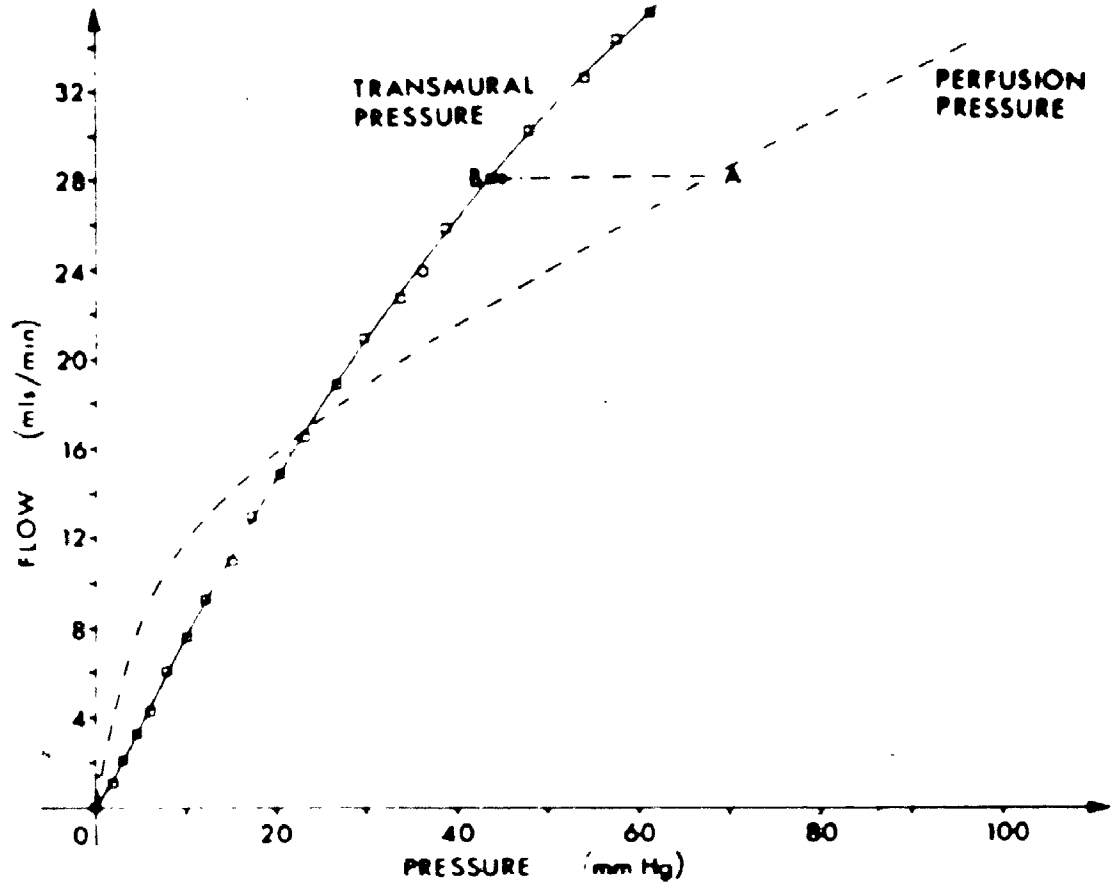
The flow-transmural pressure and the flow-perfusion pressure relationships are shown for a superior cerebellar artery (diameter at 100 mm Hg = 0.081 cm) and a larger anterior cerebral artery (diameter at 100 mm Hg = 0.198 cm) in Figures 6(a) and 6(b),

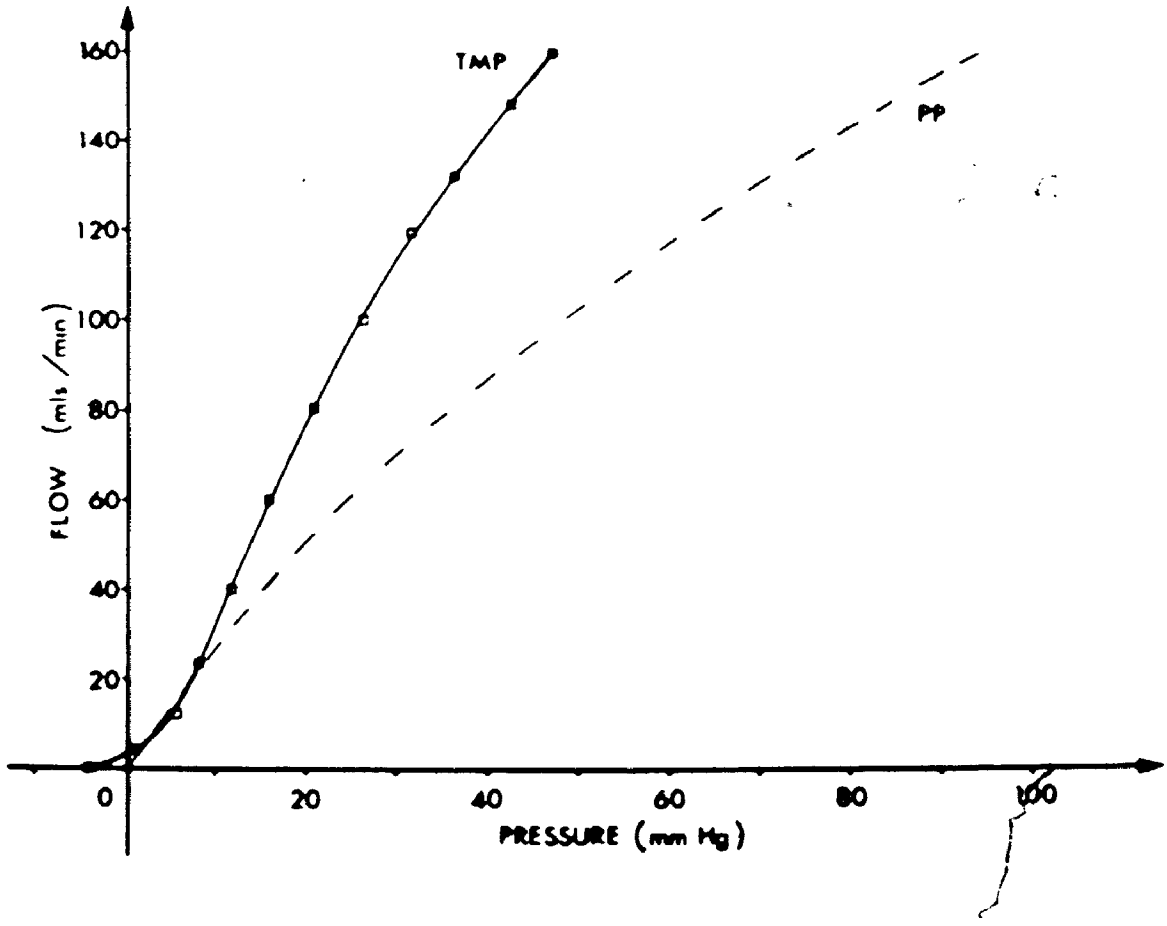
FIGURE 6(a)

Diagram showing the variation of flow with transmural pressure (solid line) and the flow-perfusion pressure curve of Figure 5(a) (broken line). In going from point A to point B, the transmural pressure is reduced but no change in flow occurs. The area between the curves above the point where the two lines cross is the linear region, and that below is the collapsible region.

FIGURE 6(b)

Comparable diagram for the larger artery of Figure 5(b). The collapsible region is noticeably smaller and begins at lower pressures than that in Figure 6(a).


TRANSMURAL PRESSURE
PERFUSION PRESSURE
B
A
FLOW (mls/min)
32
28
24
20
16
12
8
4
0
20
40
60
80
100
PRESSURE (mm Hg)


TMP
PP
FLOW (mls/min)
160
140
120
100
80
60
40
20
0
20
40
60
80
100
PRESSURE (mm Hg)

respectively. The area between the curves will be divided into two regions. The area above the point where the two lines cross will be called the linear region, and that below, the collapsible region.

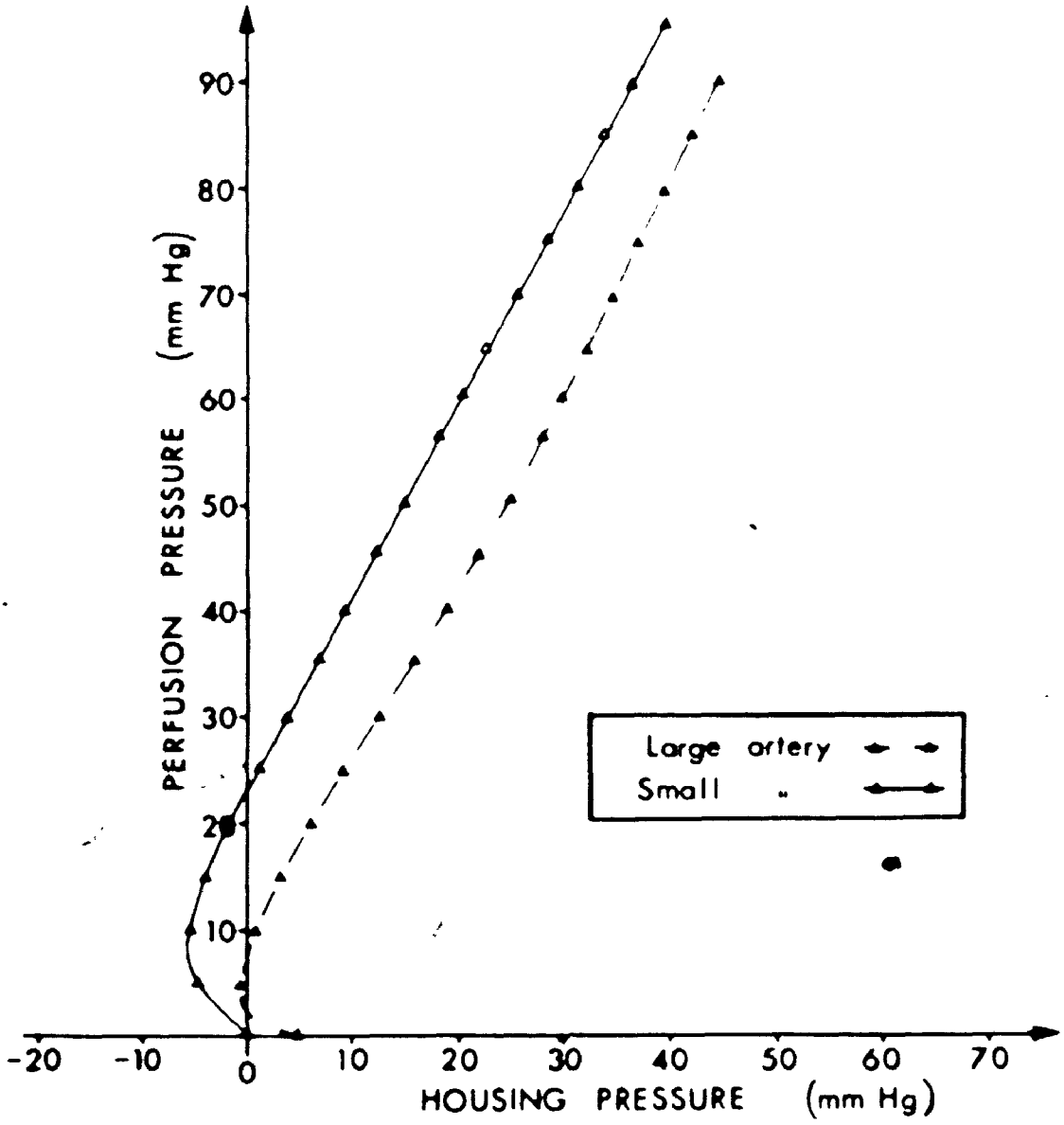
In the linear region, the maximum flow rate through the artery was determined by the perfusion pressure. If the transmural pressure was increased, by decreasing the housing pressure, no change in flow occurred. At any given perfusion pressure in this region, the transmural pressure could be lowered by increasing the housing pressure. No change in flow occurred until a critical transmural pressure was reached. For example, in going from point A to point B on graph 6(a), the transmural pressure is lowered but no change in flow occurs. The critical transmural pressure increased with increasing flow and perfusion pressure, and was dependent on the size of the artery and the presence or absence of atherosclerosis. This dependence will be shown for all arteries in section (c) of this chapter. If the transmural pressure was decreased beyond this critical value, flow decreased along the flow-transmural pressure curve until flow ceased (at -0.5 mm Hg in Figure 6(a) and -4.0 mm Hg in Figure 6(b)).

In the collapsible region, the critical transmural pressure was greater than the perfusion pressure. Flow could be increased by increasing the transmural pressure. As the transmural pressure was reduced, flow decreased to zero. This region was smaller and occurred at lower pressures for large arteries (Figure 6(b)).

The minimum increase in housing pressure required to cause a reduction of flow through the artery is the perfusion pressure minus the critical transmural pressure. The relationship between the perfusion pressure and this housing pressure increase is shown in Figure 7.

FIGURE 7

Diagram of the minimum housing pressure which caused a reduction in flow (as seen in Figure 6), plotted against the perfusion pressure for the large (broken line) and small (solid line) arteries shown previously. Larger increases in external (housing) pressure are required to reduce flow in the larger artery at all perfusion pressures.


PERFUSION PRESSURE (mm Hg)
90
80
70
60
50
40
30
20
10
-20
-10
0
10
20
30
40
50
60
70
HOUSING PRESSURE (mm Hg)
Large artery
Small "

The housing pressure required to reduce flow was higher for large arteries (compared to smaller arteries) at all perfusion pressures.

(iii) External Resistance -

Figure 8 shows the effects of proximal and distal resistance on the flow-transmural pressure curve. The resistances were provided by screw clamps placed proximal and distal to the housing. The screw clamps were situated at least 10 cm from the pressure transducer connections so that changes in flow velocity distal to the clamps (or "jetting") would not affect pressure measurements. Curve A is the variation of flow with transmural pressure when no additional resistance was present. The flow has a maximum value determined by the perfusion pressure and the resistance of the artery and distal cannula. Curve B represents the relationship obtained when a resistance was introduced proximal to the cannulated artery. Curve B is identical to Curve A except for the lower maximum flow rate.

A larger resistance distal to the artery yields a similar result. Curves B and C could be interchanged by varying the resistance used. In all cases, however, once the transmural pressure had been reduced to a critical value, the same curve resulted and flow decreased to zero. These observations were identical in all experiments.

(iv) Vessel Diameter -

The variations of flow with transmural pressure for six arteries are shown in Figure 9. The perfusion pressure in all cases was 90 mm Hg. The diameters were measured at 100 mm Hg,

FIGURE 8

Diagram showing the effects of distal and proximal resistance on the flow-transmural pressure relationship of an artery with an internal diameter of 0.121 cm (at 100 mm Hg). Curve A is the curve obtained without external resistance. Curves B and C show the flow-limiting effect of a proximal and distal resistance (respectively). The maximum flow rate depends on the magnitude of the resistance applied.

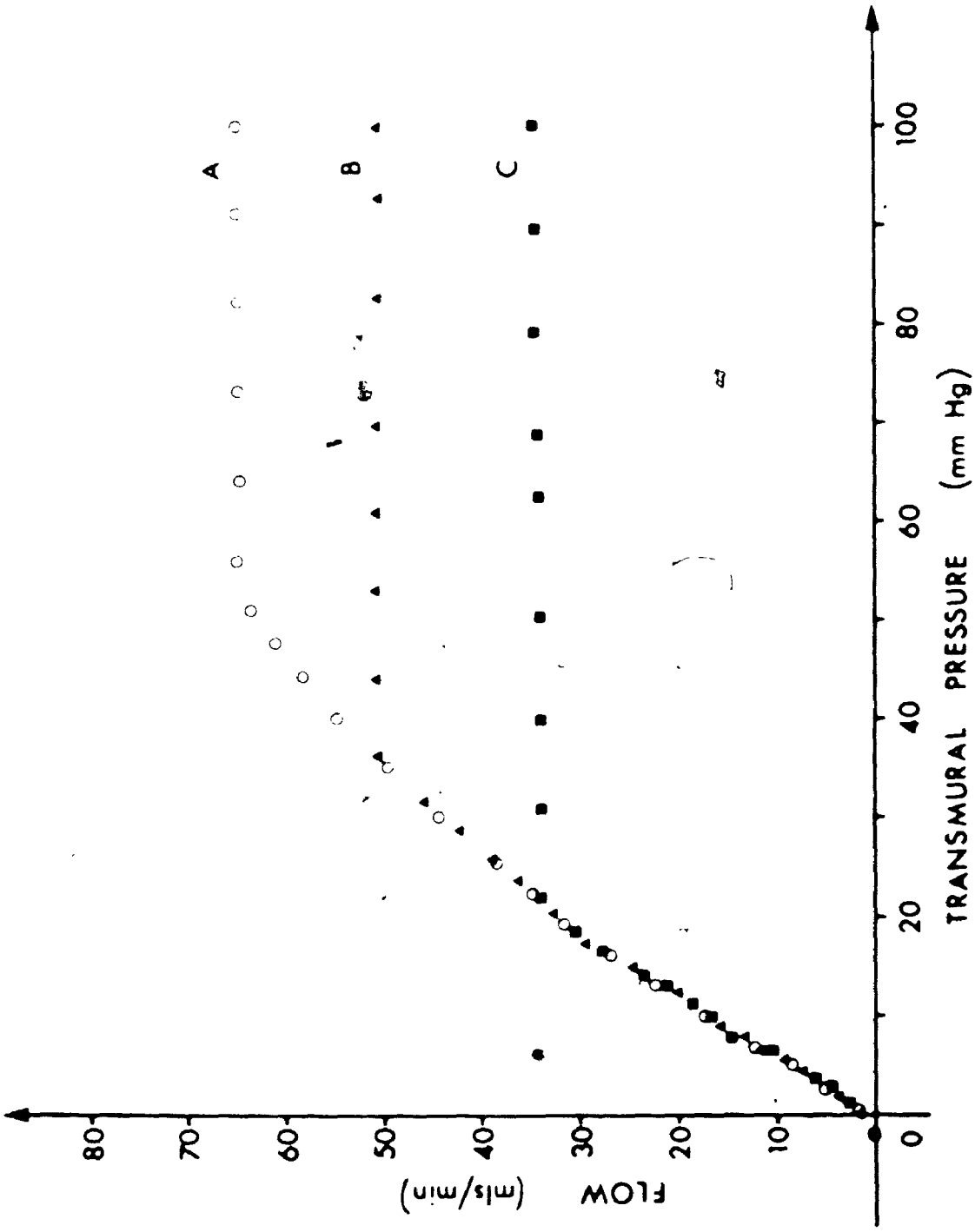
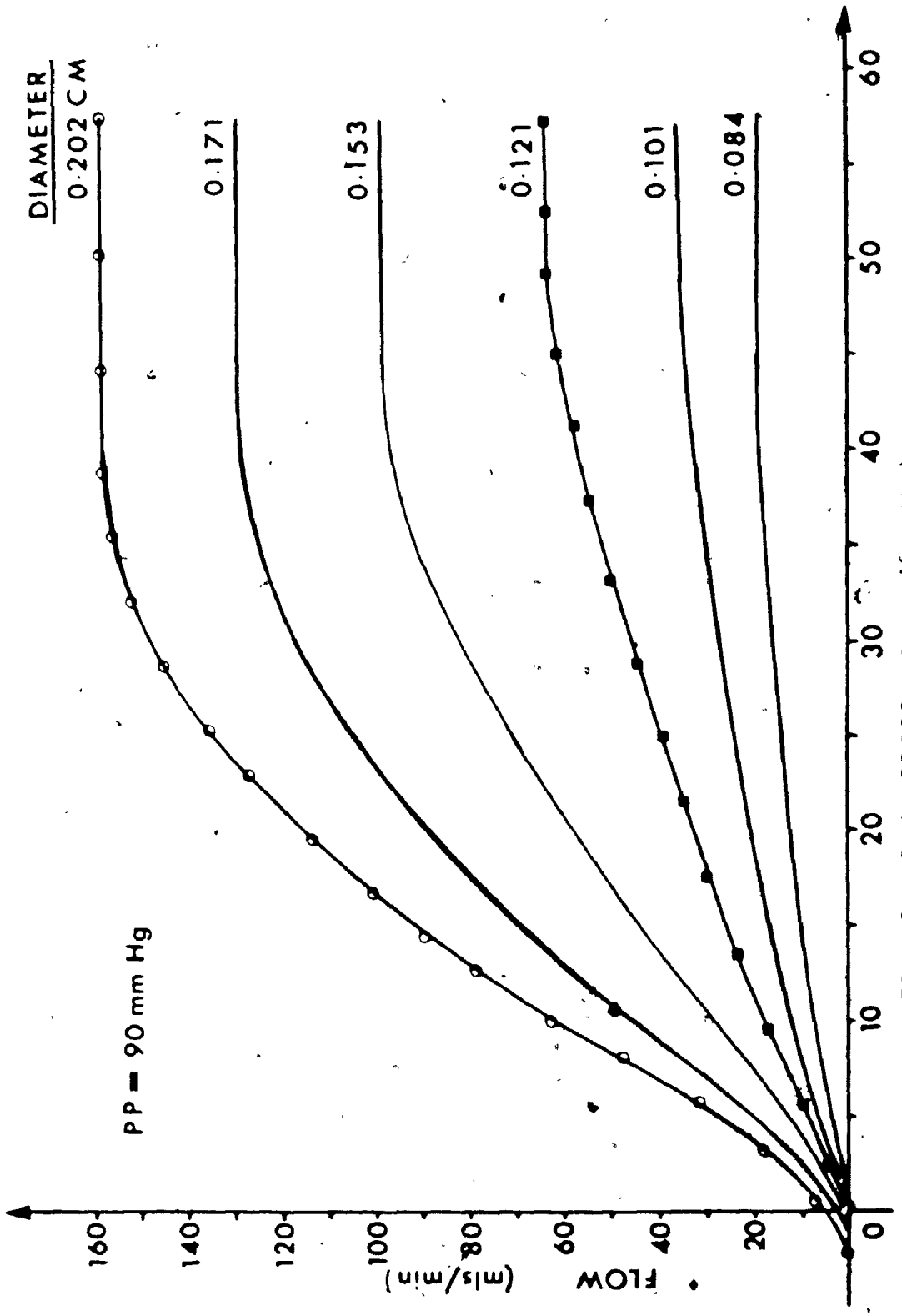

A
B
C
FLOW (mls/min)
80
70
60
50
40
30
20
10
0
TRANSMURAL PRESSURE (mm Hg)
0
20
40
60
80
100

FIGURE 9

Diagram showing the effects of lumen diameter (measured at 100 mm Hg) on the flow-transmural pressure relationship. Perfusion pressure (PP) was 90 mm Hg. The maximum flow rate increases with increasing diameter and larger arteries close at a lower transmural pressure.


DIAMETER
0·202 CM
0·171
0·153
0·121
0·101
0·084
PP = 90 mm Hg
FLOW (mls/min)
TRANSMURAL PRESSURE (mm Hg)
0
20
40
60
80
100
120
140
160
10
30
50

and represent maximum internal diameters. These curves are representative of all non-atherosclerotic arteries. The maximum flow rate increased with increasing diameter. This flow was maintained to lower transmural pressures (higher housing pressures) by the large arteries compared to the smaller ones. The transmural pressure at which flow ceased, varied from +2 mm Hg for the smallest artery to -5 mm Hg for the largest. For grossly atherosclerotic arteries, this closing pressure was as low as -15 mm Hg.

(b) THE PERFUSION OF TWO ARTERIES IN PARALLEL -

(i) Perfusion Pressure -

The variation of flow with perfusion pressure for arteries perfused in parallel showed no significant difference from that observed when they were perfused singly. The results obtained were similar in all respects to those presented in section (a) of this chapter.

(ii) Vessel Diameter (No Atherosclerosis) -

When the arteries in parallel were of approximately equal diameter, the flow in both arteries decreased simultaneously as the transmural pressure was decreased (Figure 10). There was no significant difference in their critical transmural pressure or closing pressure. This effect was observed in three different experiments in which the arterial diameters were approximately equal.

When the perfused arteries were of different diameters, the variation of flow with transmural pressure was quite

FIGURE 10

Diagram showing the variation of flow with transmural pressure for two non-atherosclerotic arteries of approximately equal diameter, cannulated and perfused in parallel. There is no significant difference in their behavior. Perfusion pressure (PP) was 90 mm Hg.

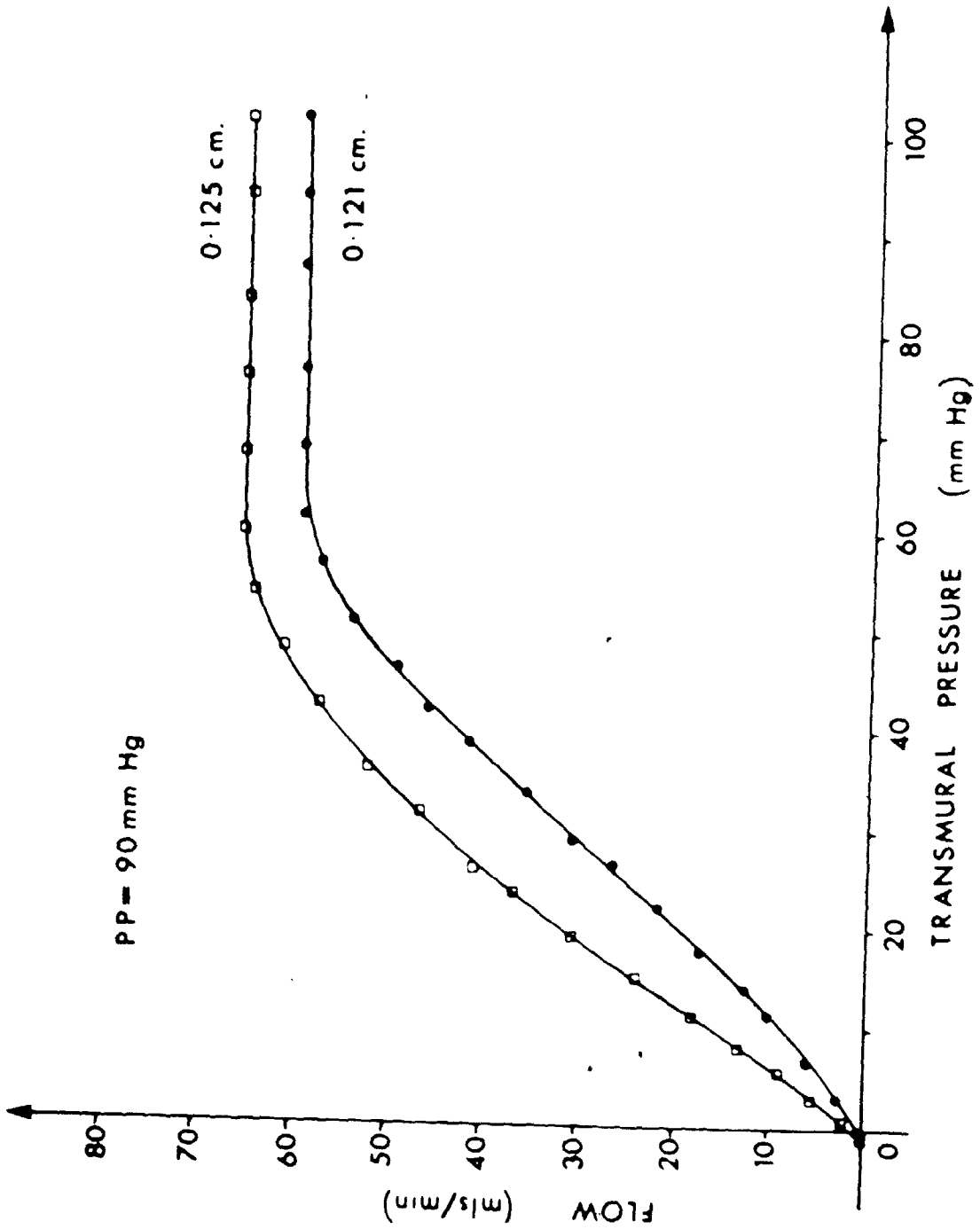
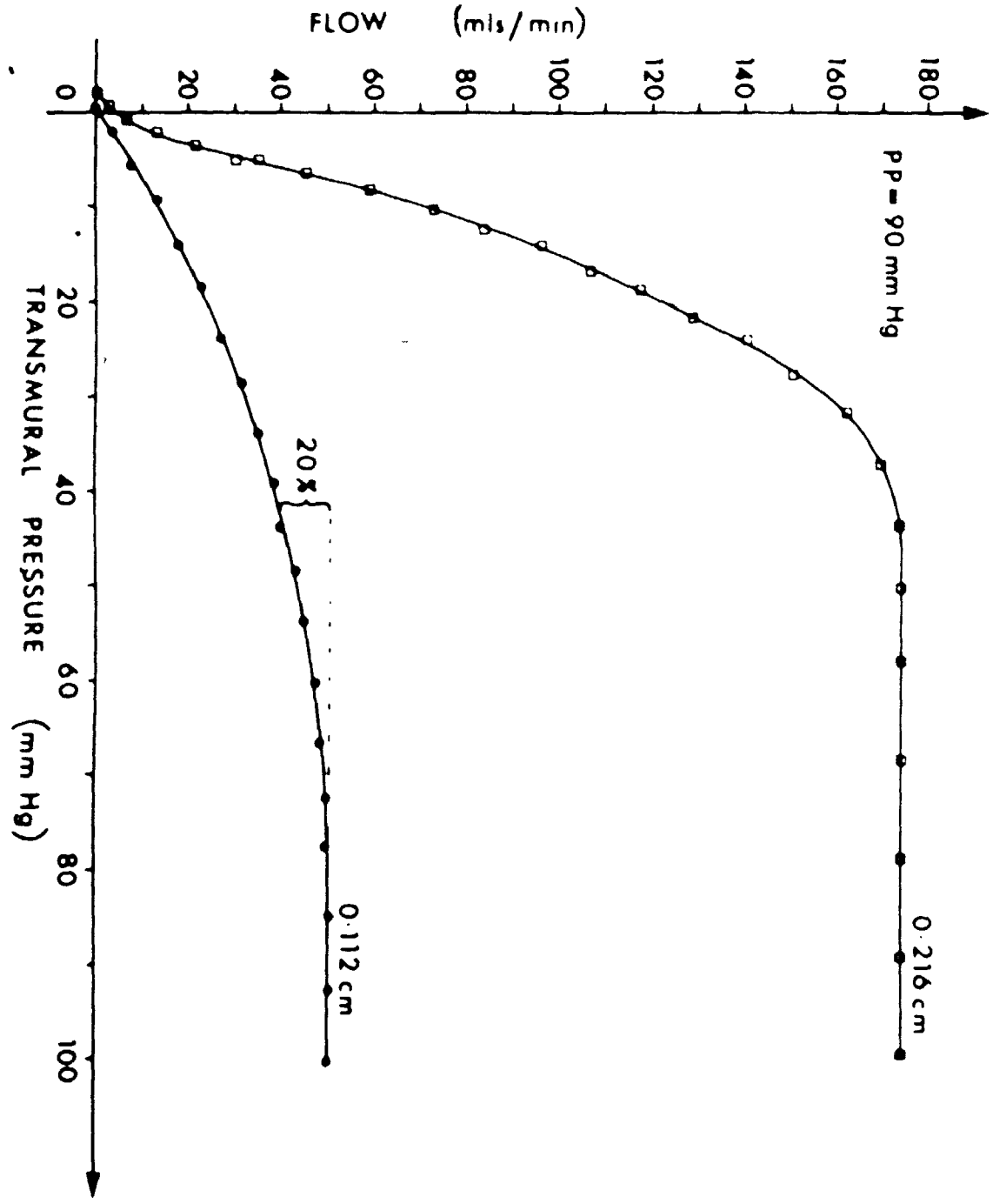

0·125 cm.
0·121 cm.
PP = 90 mm Hg
FLOW (mls/min)
TRANSMURAL PRESSURE (mm Hg)
0
10
20
30
40
50
60
70
80
20
40
60
80
100

FIGURE 11

Diagram demonstrating a 20 percent decrease in flow through the small artery prior to any reduction in flow through the larger artery. The arteries were perfused in parallel at the same perfusion pressure. Neither artery was atherosclerotic.


FLOW (mls/min)
0
20
40
60
80
100
120
140
160
180
PP = 90 mm Hg
0·216 cm
0·112 cm
20 %
TRANSMURAL PRESSURE (mm Hg)
0
20
40
60
80
100

different. Figure 11 shows this relationship for an anterior cerebral artery (0.216 cm) and its first generation branch (0.112 cm). The flow through the smaller artery began to decrease at a transmural pressure of 60-70 mm Hg, whereas the flow in the larger artery remained constant until the transmural pressure fell below 40-45 mm Hg. There was a 20 percent decrease in the flow through the smaller artery before there was any noticeable decrease in that of the larger artery. This effect was observed in three pairs of arteries in which the diameter differed by more than 0.05 cm. The average decrease in flow through the smaller artery was 16 percent.

(iii) Atherosclerosis -

In two sets of paired arteries, one of the two cannulated arteries was visibly atherosclerotic. Figure 12 shows the results obtained for two middle cerebral arteries, from the same circle of Willis, with approximately equal diameters. The flow through the atherosclerotic artery remained constant until the transmural pressure fell below 30-35 mm Hg. The flow through the normal artery was reduced by 47 percent at this transmural pressure. The closing pressure of the normal artery was +1 mm Hg, and that of the atherosclerotic artery was -7 mm Hg.

A similar result was obtained for arteries of unequal diameters when the larger artery was visibly sclerosed (Figure 13). An atherosclerotic posterior cerebral artery (0.206 cm) was perfused in parallel with a normal superior cerebellar artery (0.098 cm). At a transmural pressure of 20-25 mm Hg, the flow through the sclerosed

FIGURE 12

Diagram showing the flow-transmural pressure curves of two middle cerebral arteries with approximately equal diameters (0.165 cm). The arteries were perfused in parallel and one was visibly atherosclerotic. Flow through the normal artery was decreased by 47 percent at a transmural pressure of 33 mm Hg, while that through the atherosclerotic artery was unchanged.

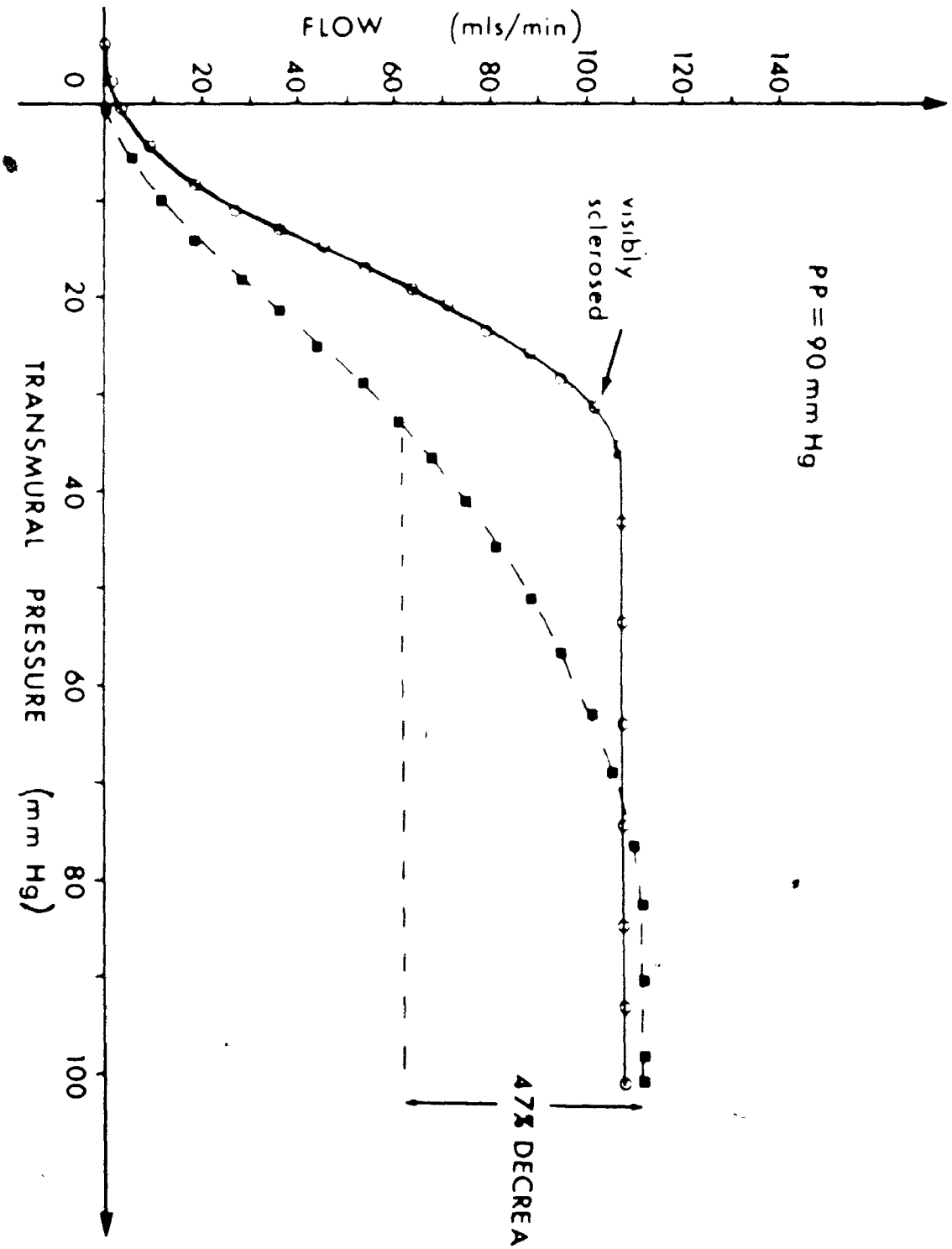
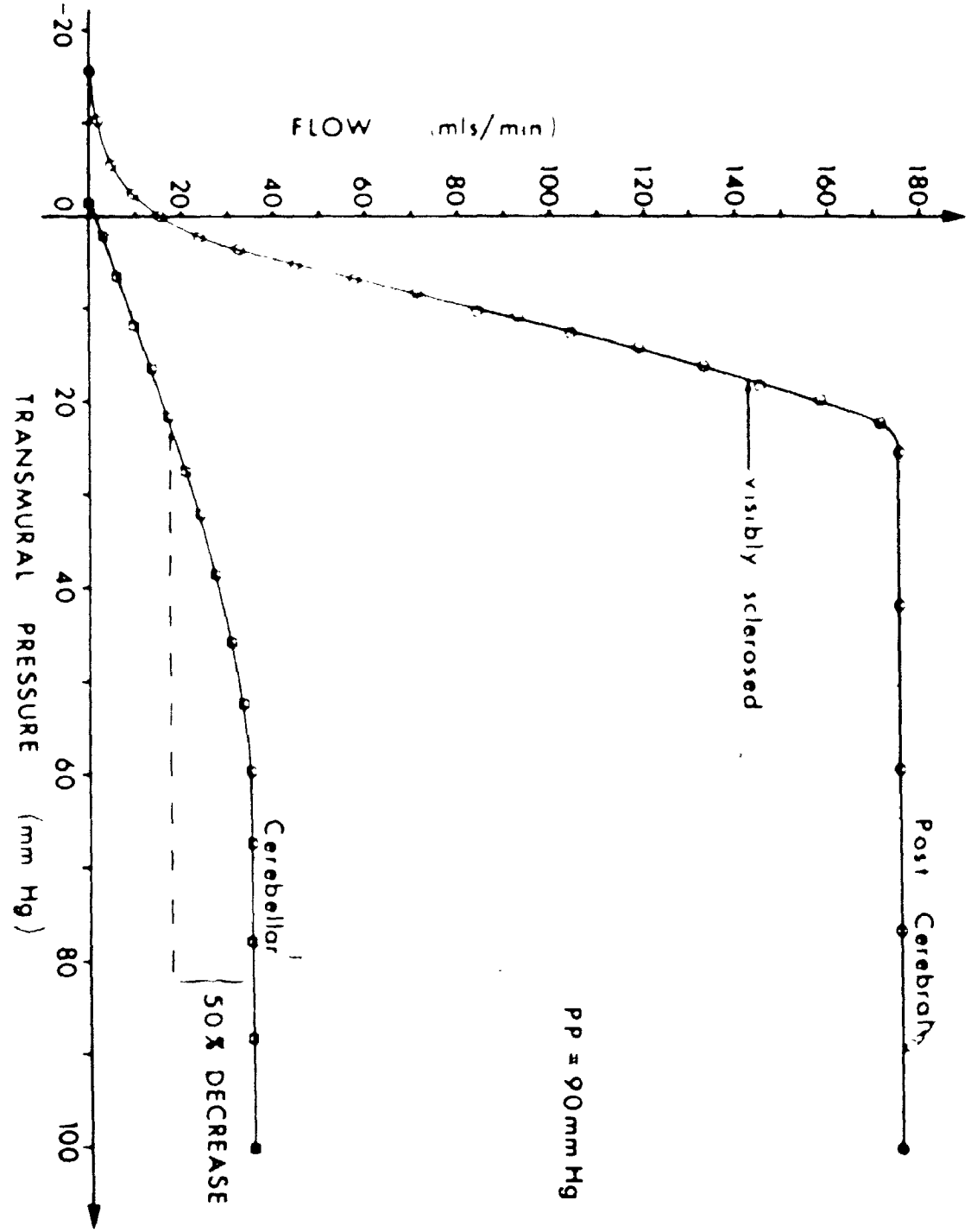

FLOW (mls/min)
0
20
40
60
80
100
120
140
visibly sclerosed
PP = 90 mm Hg
TRANSMURAL PRESSURE (mm Hg)
0
20
40
60
80
100
47% DECREASE

FIGURE 13

Diagram showing a 50 percent reduction in flow through a normal (small) artery before any decrease in flow occurs in the atherosclerotic (large) artery. The arteries were cannulated in parallel with a perfusion pressure (PP) of 90 mm Hg.


FLOW (mls/min)
-20
0
20
40
60
80
100
120
140
160
180
TRANSMURAL PRESSURE (mm Hg)
20
40
60
80
100
visibly sclerosed
Post Cerebral
Cerebellar
50% DECREASE
PP = 90mm Hg

artery was unchanged, but a 50 percent flow decrease had occurred in the normal artery. The normal artery closed at a higher transmural pressure (0 mm Hg) than the atherosclerotic artery (-15 mm Hg).

(c) ATHEROSCLEROSIS AND ARTERIAL DIAMETER IN PASSIVE NARROWING -

Lumen diameter and the presence of atherosclerosis were found to affect the variation of flow with transmural pressure. All 26 arteries used in this experiment were compared to one another on the basis of large versus small lumen diameter and sclerotic versus normal arterial walls. An artery was termed atherosclerotic if atherosclerotic lesions appeared in three or more histological sections from three different areas of the arterial specimen. In some arteries, gross atherosclerosis could be seen visually. The arteries were grouped according to lumen diameter using 0.130 cm as the dividing point.

Table 1 shows the critical transmural pressure of all arteries, measured at a perfusion pressure of 90 mm Hg. (This value was chosen as an estimation of diastolic blood pressure). P-values* were calculated using the paired t-test. The critical transmural pressures of large and small atherosclerotic arteries were not significantly different ($P<0.2$). Small normal arteries showed a higher critical transmural pressure than large normal arteries ($P<0.05$ showing 95 percent confidence). The critical transmural pressure of all

* The P-value gives the probability that the difference between two mean values is due to chance alone.

TABLE 1

Critical Transmural Pressure of 26 Human Cerebral Arteries

Lumen Diameter at 100 mm Hg (cm)	Number of arteries	Condition AS or N*	Critical TMP ± SEM† mm Hg	
Greater than 0 130	7	AS	38 ± 4	P < 0 05
Less than 0 130	3	AS	44 ± 2	
P < 0 2				
Greater than 0 130	5	N	54 ± 4	P < 0 001
Less than 0 130	11	N	63 ± 2	
P < 0 05				
Greater than 0 130	12	ALL	45 ± 4	
Less than 0 130	14	ALL	59 ± 3	
P < 0 005				
All arteries	10	AS	40 ± 3	
	16	N	60 ± 2	
P < 0 001				

* AS — Atherosclerotic N — Normal

† Transmural Pressure ± Standard Error of the Mean

large arteries (45 mm Hg) was significantly lower than that of all small arteries (59 mm Hg), ($P<0.005$). The critical transmural pressure of atherosclerotic arteries was consistently lower than that of the normal arteries (an average of 40 mm Hg for atherosclerotic arteries as compared to an average of 60 mm Hg for normal arteries ($P<0.001$).

The transmural pressure at which flow through the artery was decreased from its maximum value by 50 percent was also measured from the graphs and tabulated (Table 2). The half-flow transmural pressure shows an identical dependence on atherosclerosis and vessel diameter as that shown for the critical transmural pressure. Small arteries narrowed more easily than large arteries and normal arteries narrowed more easily than atherosclerotic arteries when subjected to increased external pressure.

5) DISCUSSION

(a) PERFUSION PRESSURE

Many investigators examining the relationship between increased intracranial pressure and cerebral blood flow, have used the term "perfusion pressure" to describe the difference between mean arterial blood pressure and intracranial pressure (Zwetnow, 1968; Johnston et al, 1973; Miller et al, 1973; Iwabuchi et al, 1973). When this definition is used, the pressure drop between the intracranial and extracranial venous systems is neglected. The resistance of the intracranial vasculature is defined in terms of cerebral perfusion pressure (resistance = (perfusion pressure)/flow). When autoregulation is lost, cerebral blood flow has been found to be a linear

TABLE 2

Half-flow Transmural Pressure of 26 Human Cerebral Arteries

Lumen Diameter at 100 mm Hg (cm)	Number of arteries	Condition AS or N*	Half-flow TMP ± SEM (mm Hg)	
Greater than 0·130	7	AS	12 ± 2	
Less than 0·130	3	AS	14 ± 1	P < 0·05
P > 0·30	No significant difference			
Greater than 0·130	5	N	16 ± 2	P < 0·001
Less than 0·130	11	N	21 ± 1	
P < 0·01				
Greater than 0·130	12	ALL	14 ± 1	
Less than 0·130	14	ALL	20 ± 1	
P < 0·001				
All arteries	10	AS	12 ± 1	
	16	N	20 ± 1	
P < 0·001				

* AS — Atherosclerotic.
N — Normal

function of the "perfusion pressure" described above. This implies that the resistance of the arterio-venous system is constant. This, in turn, implies that the radius of the cerebral blood vessels is constant. It is well known, however, that arteries and veins decrease in radius when transmural pressure is reduced in the absence of autoregulation. (Busby and Burton, 1965; Scott et al, 1972). This contradiction can be resolved by defining perfusion pressure as the difference between mean arterial blood pressure and the venous outflow pressure. The difference between mean arterial pressure and intracranial pressure is the transmural pressure.

In the present study, the variation of flow with perfusion pressure was non-linear. The flow-perfusion pressure curve was concave towards the pressure axis. This was due to an increasing pressure drop occurring at the outflow cannula. An expansion occurs when the diameter of the cannula changes to that of the distal connecting tubing. The pressure loss, in cm of water, due to a sudden expansion is approximated by the expression:

$$\Delta P = \left[1 - \left[\frac{D_s}{D_L}\right]^2\right]^2 \frac{V_s^2}{2g}$$

where ΔP is the pressure loss, D_s and D_L are the diameters of the small and large tubes respectively, and V_s is the flow velocity in the small tube, and $g = 980$ cm/sec^2 (Vennard, 1962, pg. 310).

Since the diameter of the outflow tubing was constant, the diameter of the cannula determined the pressure loss at a given flow velocity. For this reason the largest cannula on which the artery could be mounted, was always chosen. The outflow cannula provided a

resistance to flow distal to the artery. This situation is similar to the normal case in which the arterioles of the brain provide a large resistance distal to the major cerebral arteries. The brain receives approximately one-fifth of the cardiac output, or about 1000 mls/min. Of this total, two-thirds is carried by the carotid arteries and one-third by the basilar artery (Brain, 1957). The basilar artery divides to form the two posterior cerebral arteries. Therefore each posterior cerebral artery would normally have a blood flow of approximately 160 mls/min at a mean arterial blood pressure of 90-100 mm Hg. A similar flow rate was attained in the present study, indicating that the resistance provided by the distal cannula is not very different from that normally occurring in the cerebral circulation.

(b) TRANSMURAL PRESSURE -

As the external pressure in the housing was increased, no change in flow occurred until a critical transmural pressure was reached (at high perfusion pressures). This would suggest that the radius of the cannulated artery was in excess of that required to maintain the observed flow rate and that the distal resistance was limiting the flow. As the transmural pressure was decreased below this level, the radius of the artery decreased and flow was reduced due to increased resistance provided by the narrowed artery. The radius of an artery depends only on the transmural pressure if there is no smooth muscle contraction (Roach and Burton, 1957). Therefore, at any transmural pressure below the critical value, the radius of the artery will be determined by the transmural pressure. The flow-transmural pressure curve is therefore independent of external

resistance at any flow rate below the maximum value. The addition of distal or proximal resistances, shown in Figure 8, lowered the maximum flow rate, but did not affect the flow-transmural pressure relationship. This confirms the fact that external resistance serves only to limit the maximum flow rate through the artery.

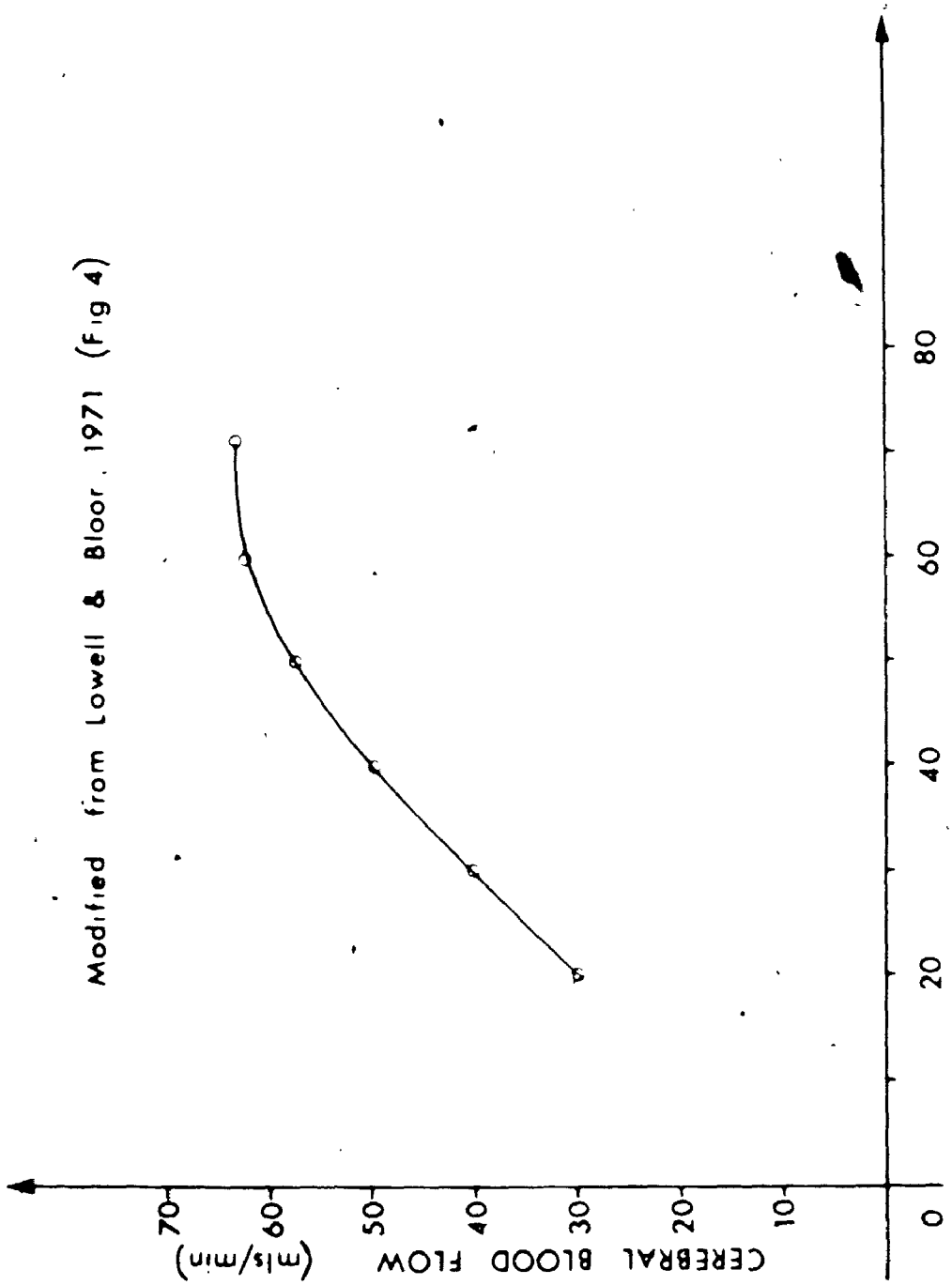
In the collapsible region in Figure 6(a), the critical transmural pressure was greater than the perfusion pressure. At any perfusion pressure in this region, the resistance provided by the artery was the flow-limiting factor. Both the radius of the artery and the flow rate could be increased by increasing the transmural pressure. Therefore, whenever the resistance of the artery was comparable to that of the distal resistance, changes in transmural pressure determined changes in flow through the artery.

The flow rates obtained in this experiment suggest that the resistance of the distal cannula is comparable to that occurring distal to the major arteries in the normal cerebral circulation. In both cases, the maximum flow is determined by the distal resistances. The average critical transmural pressure was 52 ± 3 mm Hg, suggesting that decreases in transmural pressure below this value will narrow the major cerebral arteries sufficiently to reduce the normal cerebral blood flow. Previous investigations have found this value to be 40-60 mm Hg in normal autoregulating systems (Kety et al, 1948; Langfitt et al, 1965; Miller et al, 1973; Johnston et al, 1973; Iwabuchi et al, 1973). A similar variance of cerebral blood flow with transmural pressure may be obtained from the data on graph 4 of Lowell and Bloor's work (1971) with Rhesus monkeys (Figure 14). Many investigators have also observed that the cerebral blood flow ceased when transmural

FIGURE 14

Diagram showing the variation of total cerebral blood flow with transmural pressure for a Rhesus monkey. This data was calculated from Lowell and Bloor (1971), Figure 4.

* The transmural pressure was calculated as the mean arterial blood pressure (MABP) minus the sagittal sinus wedge pressure (SSWP).


Modified from Lowell & Bloor, 1971 (Fig 4)
CEREBRAL BLOOD FLOW (mls/min)
70
60
50
40
30
20
10
0
20
40
60
80
TRANSMURAL PRESSURE (mm Hg)
[MABP – SSVP]*

pressure was approximately zero (Cushing, 1901, 1902, 1903; Langfitt et al, 1965; Iwabuchi et al, 1973; Johnston et al, 1973). In all aspects, these results from normal autoregulating systems are similar to those obtained for the major arteries of the circle of Willis. In the present study, the distal resistance was constant and the resistance of the cannulated vessel was increased (by narrowing) until the radius of the vessel became the flow-limiting resistance of the system. In the experiments by others on autoregulating systems, the distal resistance of the arterioles decreased as intracranial pressure increased. In both instances, however, the "limit of autoregulation", or the onset of a passive relationship between transmural pressure and flow, occurred when the transmural pressure was 40-60 mm Hg. It is concluded therefore, that when the resistance of the major cerebral vessels approaches that previously supplied by a distal resistance, a passive flow-transmural pressure relationship will develop and "autoregulation" will be lost.

Autoregulation can be lost due to a maximal dilatation of the arterioles in severe hypercapnia (Häggendal and Johansson, 1965; Iwabuchi et al, 1973). In these experiments, a passive flow-transmural pressure dependence persisted to high levels of cerebral blood flow and arterial blood pressure. It would appear from this that, whenever the resistance of the distal arterioles is largely reduced, a passive pressure-flow relationship will exist. This type of dependence was found in the collapsible region of Figure 6, but could not be confirmed at higher flow rates since the resistance of the distal cannula could not be decreased. It is speculated that whenever a passive flow-pressure

relationship develops, the major arteries of the circle of Willis may play an important role in determining the extent or onset of flow reductions due to reduced transmural pressure. This phenomenon appears to be caused by a shift of the flow-limiting resistance from the arterioles to the larger cerebral vessels.

(c) WALL "STIFFNESS" AND PREFERENTIAL NARROWING -

Two factors were found that determined the transmural pressure at which onset of flow reduction, half-flow, and vessel closure occurred. Atherosclerotic arteries and those with large diameters appeared to be "stiffer" and more resistant to increased external pressure. The critical and half-flow transmural pressures of atherosclerotic arteries (40 $\pm$ 3 mm Hg and 12 $\pm$ 1 mm Hg, respectively) were consistently and significantly lower than those of non-atherosclerotic arteries (60 $\pm$ 2 mm Hg and 20 $\pm$ 1 mm Hg, respectively). Atherosclerotic arteries closed at transmural pressures as low as -15 mm Hg, whereas the range of closing pressures for normal arteries was found to be -5 to +2 mm Hg. Large arteries were also found to be "stiffer" than small arteries in a similar comparison (Tables 1 and 2, Figures 7 and 9). Higher housing pressures were required to reduce flow at all perfusion pressures and flow levels for large or atherosclerotic arteries compared to smaller or non-atherosclerotic arteries. These differences in vessel "stiffness" were shown to be capable of producing preferential narrowing of one artery compared to another at the same perfusion pressure and reduced transmural pressure (Figures 11, 12, and 13).

When the arteries perfused in parallel were of unequal diameter, flow reductions ranging from 12 to 20 percent were observed in the smaller artery with no change in flow through the larger. Preferential flow reductions of 47 and 50 percent were seen in non-atherosclerotic arteries when perfused in parallel with visibly atherosclerotic arteries. The average transmural pressure that resulted in a 50 percent decrease in flow was found to be 12 $\pm$ 1 mm Hg for atherosclerotic arteries and 20 $\pm$ 1 mm Hg for normal arteries. Therefore, decreased transmural pressure has been shown to produce both diffuse (50 percent flow reduction) and preferential narrowing of the major cerebral arteries.

It would not be possible to distinguish between this type of narrowing and that caused by active contraction in an angiographical examination. The criteria used in diagnosis of arterial "spasm" are narrowed arteries and/or slowed blood flow. The passive narrowing described above would produce both these effects without the aid of smooth muscle contraction. These findings suggest that the role of passive narrowing due to increased intracranial pressure should be assessed in conjunction with active narrowing to determine the relative importance of each in producing "spasm" of the major cerebral arteries as seen clinically.

6) SUMMARY

(1) The term "perfusion pressure" was defined to indicate the total pressure drop across the entire system under consideration. The term "transmural pressure" referred to the difference between the

inflow pressure and the extraluminal pressure.

(2) The relationship between flow and transmural pressure was examined at various perfusion pressures for 26 major human cerebral arteries without smooth muscle intervention. A passive variation of flow with transmural pressure was established when the resistance provided by the artery was comparable to the distal resistance of the system.

(3) The maximum flow rate was determined by the magnitude of the distal resistance when this resistance was greater than that of the artery. If the resistance of the artery was comparable to the distal resistance, the transmural pressure determined the radius of the artery and, therefore, the maximum flow rate.

(4) The addition of external resistance lowered the maximum flow rate, but did not alter the flow-transmural pressure curve of the artery at flow rates lower than this maximum value. It is concluded therefore, that the flow-transmural pressure relationship is independent of external resistance at sub-maximal flow rates and depends only on the resistance of the artery.

(5) The evidence here suggested that the loss of "autoregulation" could be produced by a shift of the flow-limiting resistance from a distal location, in the arterioles, to the larger arteries of the brain. This shift occurred when the distal resistance was

lowered, in comparison to that provided by the large arteries, or when the resistance of the large arteries was increased in comparison to the distal resistance (i.e., by decreasing the transmural pressure).

(6) At physiological flow rates, the average transmural pressure at which flow began to decrease was 52 ± 3 mm Hg. This was in good agreement with published data for normal, autoregulating systems. This critical transmural pressure ranged from 40 ± 3 mm Hg for atherosclerotic arteries to 60 ± 2 mm Hg for non-atherosclerotic arteries.

(7) Higher external pressures were required to reduce flow in atherosclerotic arteries and large arteries as compared to non-atherosclerotic arteries and small arteries respectively. This was true at all perfusion pressures and flow levels. This was attributed to the relative "stiffness" of the vessel walls.

(8) Preferential flow reductions ranging from 12 to 50 percent were observed in normal or non-atherosclerotic arteries when they were perfused in parallel with large or atherosclerotic arteries. These preferential flow reductions occurred when both arteries were at the same perfusion pressure and the same reduced transmural pressure.

(9) The transmural pressure at which flow ceased, varied from +2 mm Hg for small, non-atherosclerotic arteries to -15 mm Hg for large, atherosclerotic arteries.

(10) Angiographically, passive flow and arterial diameter reductions due to increased intracranial pressure could be similar to those produced by active narrowing due to smooth muscle contraction.

IV. WALL TO LUMEN RATIOS - THE POSSIBILITY OF ACTIVE CLOSURE

1) INTRODUCTION

Severe narrowing or closure of a major cerebral artery is often observed angiographically following subarachnoid hemorrhage. Many investigators have assumed that this phenomenon was the result of arterial smooth muscle contraction. Roach (1970) has shown theoretically that the ratio of wall thickness to lumen diameter will affect the ability of an artery to close in this manner. An accurate measurement of these parameters for the major cerebral arteries was not found in the literature. The ability of these vessels to close by muscle contraction alone, based on the wall to lumen ratio, has not been previously investigated.

2) MATERIALS AND METHODS

Twenty-six human cerebral arteries were fixed in 10 percent formalin at a transmural pressure of 100 mm Hg for 24 hours. The arteries were then sectioned and stained with Gomori-Trichrome. At least four measurements of wall thickness and lumen diameter were made on each section using a travelling microscope. The results obtained for three such sections were combined to arrive at the average luminal diameter and wall thickness of the artery.

FIGURE 15(a)

Photograph of an abnormal circle of Willis obtained immediately after autopsy. One small scale division equals one millimeter. The left posterior cerebral artery (LPCA) is much narrower than that on the right (RPCA). The left posterior communicating artery (LPCoA) is much larger than normal. Other abnormalities are also present. Arrows indicate the normal direction of flow in the posterior cerebral arteries.

FIGURE 15(b)

Photograph showing a closer view of the posterior cerebral (LPCA) - posterior communicating (LPCoA) arterial junction. Normally, the caliber of these two vessels is reversed.

V. COMBINED ACTIVE AND PASSIVE CLOSURE OF LARGE ARTERIES

1) INTRODUCTION

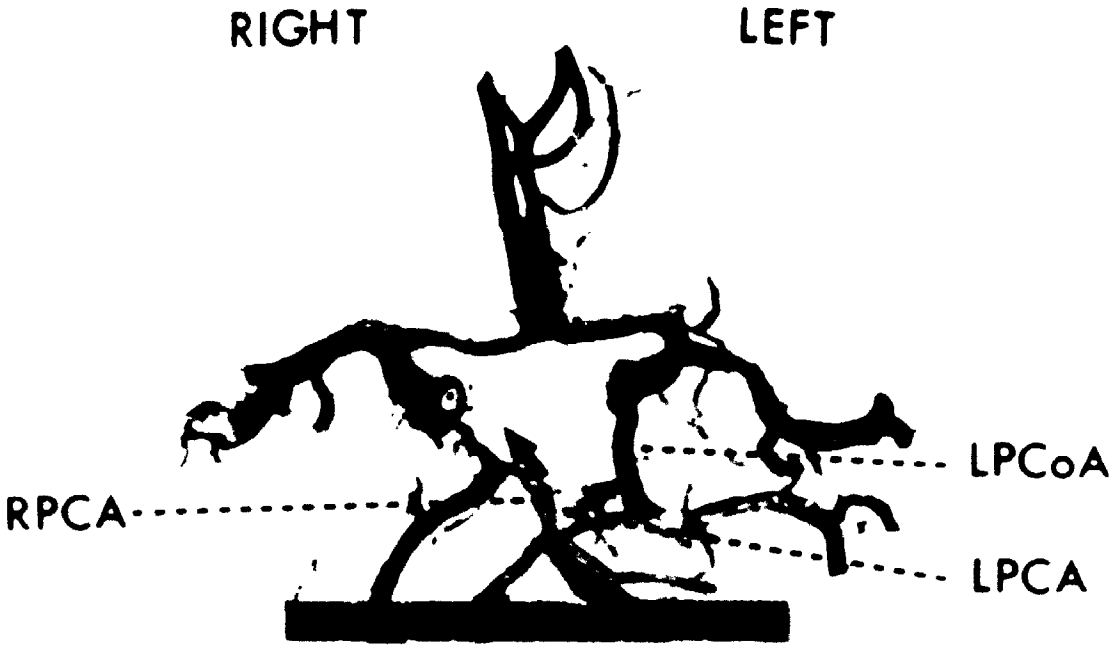
Cerebral arterial spasm and increased intracranial pressure have both been shown to occur following subarachnoid hemorrhage, and both are known to cause reductions in cerebral blood flow. Spasm is currently thought to be the result of active vasoconstriction, and has been shown to last for up to three weeks. Phenoxybenzamine* is currently being investigated as a possible aid in controlling spasm of cerebral arteries (Cummins and Griffith, 1971; Flamm, Yasargil and Ransohoff, 1972). The narrowing of large cerebral arteries is known to cause reductions of cerebral blood flow, but the importance of active narrowing due to arterial smooth muscle contractions, and passive narrowing due to a reduction of transmural pressure, has not been established.

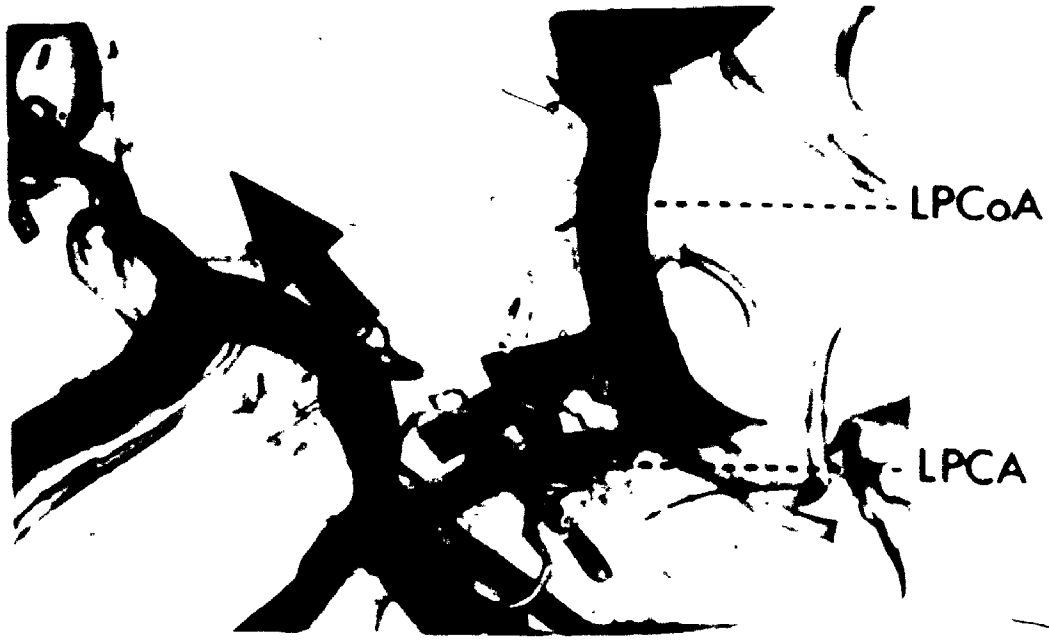
2) MATERIALS AND METHODS

(a) ARTERIES AND APPARATUS -

Human cerebral arteries were not used in these experiments since fresh specimens could not be obtained. An attempt was made to dissect and cannulate cerebral arteries from cats and rabbits

* See Appendix I


RIGHT
LEFT
RPCA
LPCoA
LPCA


LPCoA
LPCA

3) RESULTS

The average lumen diameter and wall thickness are shown in Table 3, along with the calculated average wall/lumen ratios. The measurements obtained for the posterior and anterior communicating arteries are not necessarily representative of average values. These arteries varied considerably in size from one circle of Willis to the next. In one instance, the posterior communicating artery on the left side was completely absent and that on the right was thread-like in appearance. In another specimen (Figures 15(a) and (b)), the left posterior cerebral artery was very narrow proximal to the posterior communicating artery. The posterior communicating artery, on the other hand, appeared nearly as large as the anterior cerebral artery. Distal to the posterior communicating artery, the posterior cerebral artery was of normal caliber. The variations in the anterior communicating artery were not as severe, but were sufficient to make the calculation of an "average" diameter questionable.

4) DISCUSSION AND CONCLUSIONS

The absolute values obtained for diameter and wall thickness are probably about 10 percent too small due to formalin fixation shrinkage artifacts (Stigol, Nebesar and Gold, 1969). The high pressure at which fixation occurred (100 mm Hg) may have decreased this shrinkage, but this was not assessed. Assuming this shrinkage affects both wall thickness and lumen diameter, the ratios obtained are felt to be realistic. The minimum wall thickness to lumen diameter ratio required to completely close an artery by smooth muscle contraction can be calculated if both longitudinal and circumferential limits of

TABLE 3

Wall and Lumen Measurements

ARTERY (NUMBER)	LUMEN DIAMETER (cm)	WALL THICKNESS (cm)	WALL/LUMEN RATIO
Cerebellar (8)	0·098 ± 0·001 *	0·0059 ± 0·0003	0·061 ± 0·005
Posterior Communicating (2)	0·123 ± 0·002	0·0112 ± 0·0015	0·091 ± 0·011
Middle Cerebral (4)	0·133 ± 0·009	0·0116 ± 0·0007	0·088 ± 0·002
Anterior Communicating (1)	0·137 ——	0·0157 ——	0·115 ——
Vertebral (2)	0·170 ± 0·007	0·0098 ± 0·0015	0·058 ± 0·009
Anterior Cerebral (4)	0·177 ± 0·018	0·0103 ± 0·0012	0·059 ± 0·009
Posterior Cerebral (5)	0·185 ± 0·009	0·0098 ± 0·0009	0·054 ± 0·007

* ± SEM

contraction are known (Roach, 1970). Since cerebral arteries are tethered (held in place) by connective tissue and by their side branches, I have estimated that they cannot shorten in length by more than 10 percent. It was assumed that the circumferential muscle fibers cannot shorten in length by more than 50 percent. This is probably a high estimate (Dobrin, 1973(a), (b)). Based on these assumptions, the minimum wall thickness to lumen diameter ratio required to completely obstruct the arterial lumen is 0.43 (Roach, 1970). The measured wall to lumen ratios for the major cerebral arteries were four to eight times smaller than this value.

It was concluded, therefore, that unless there is a plaque, intimal cushion, or thrombus present to partially obstruct the lumen, complete closure of a major human cerebral vessel by arterial smooth muscle alone, is not possible.

V. COMBINED ACTIVE AND PASSIVE CLOSURE OF LARGE ARTERIES

1) INTRODUCTION

Cerebral arterial spasm and increased intracranial pressure have both been shown to occur following subarachnoid hemorrhage, and both are known to cause reductions in cerebral blood flow. Spasm is currently thought to be the result of active vasoconstriction, and has been shown to last for up to three weeks. Phenoxybenzamine* is currently being investigated as a possible aid in controlling spasm of cerebral arteries (Cummins and Griffith, 1971; Flamm, Yasargil and Ransohoff, 1972). The narrowing of large cerebral arteries is known to cause reductions of cerebral blood flow, but the importance of active narrowing due to arterial smooth muscle contractions, and passive narrowing due to a reduction of transmural pressure, has not been established.

2) MATERIALS AND METHODS

(a) ARTERIES AND APPARATUS -

Human cerebral arteries were not used in these experiments since fresh specimens could not be obtained. An attempt was made to dissect and cannulate cerebral arteries from cats and rabbits

* See Appendix I

but in both instances, the arteries were found to be too small. The low flow rates expected and high pressure drops in the appropriate cannulas, would make measurements extremely inaccurate. For these reasons, extracranial rabbit arteries were used. Femoral and common carotid arteries were chosen because of their similarity in diameter to the human cerebral arteries studied previously. Twelve unselected rabbits (2.5 - 3.5 Kg) were anesthetized with 20 percent Urethane (10 g/Kg intraperitoneally) and a 2 cm segment of the right common carotid artery (six rabbits), or the right femoral artery (six rabbits), was marked, gently dissected free from its connective tissue, and then removed. The artery was immediately placed in physiological Ringer's solution.* The cannulas were part of a platform (Figure 16(a)), which could be removed from the housing insert (Figure 16(b)). The distance between the cannulas was adjustable so that the artery could be mounted and then restored to its original length without excessive handling. Once the artery was restored to its original length the cannulas were secured in place so that no further movement occurred. The artery and platform were then joined to the housing insert. The inflow and outflow tubes were connected and the insert was placed in the housing containing Ringer's solution at 37°C (Figure 17). The insert was bolted to the housing and a pressure-tight seal was obtained. The only time the artery was not in Ringer's solution, was when the platform was placed on the insert and the inflow and outflow connections were made (approximately 10 seconds). The housing was equipped with an external reservoir that could be raised or lowered to vary

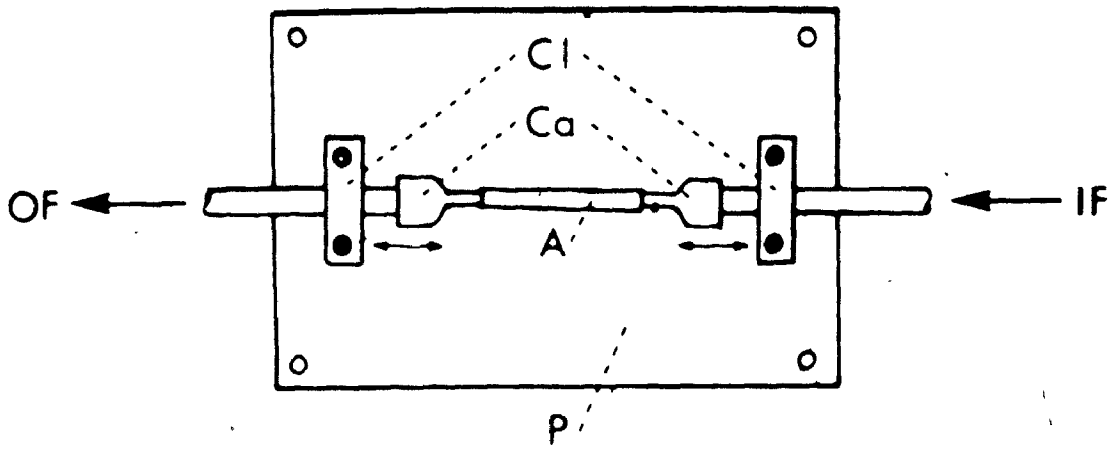
* See Appendix II for composition

FIGURE 16(a)

Schematic diagram of the platform (P) used to support the artery (A) and cannulas (Ca). The cannulas could be moved in the directions indicated by the arrows. After the artery was cannulated and restored to its original length, the clamps (Cl) were tightened to prevent further movement of the cannulas. Also shown are the inflow (IF) and outflow (OF).

FIGURE 16(b)

Schematic diagram of the housing insert showing the platform (P), inflow (IF), outflow (OF), and the connections used to monitor inflow (IP), outflow (OP) and housing (HP) pressures. All pressure measurements were adjusted to read zero at the level of the cannulated artery.


Cl
Ca
OF
IF
A
P

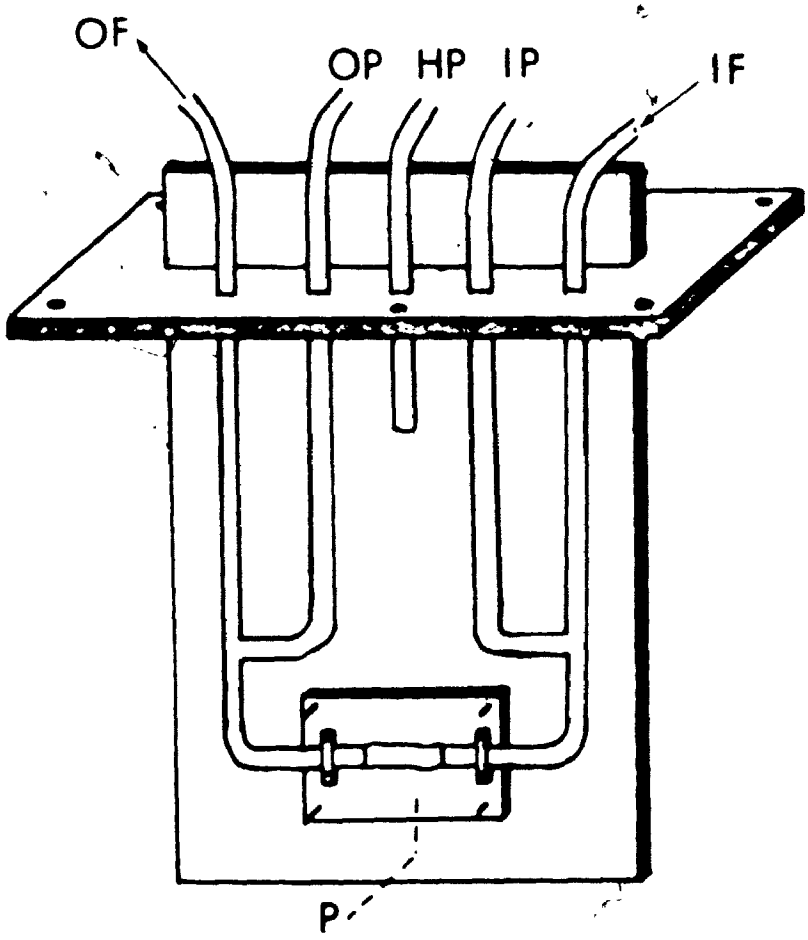
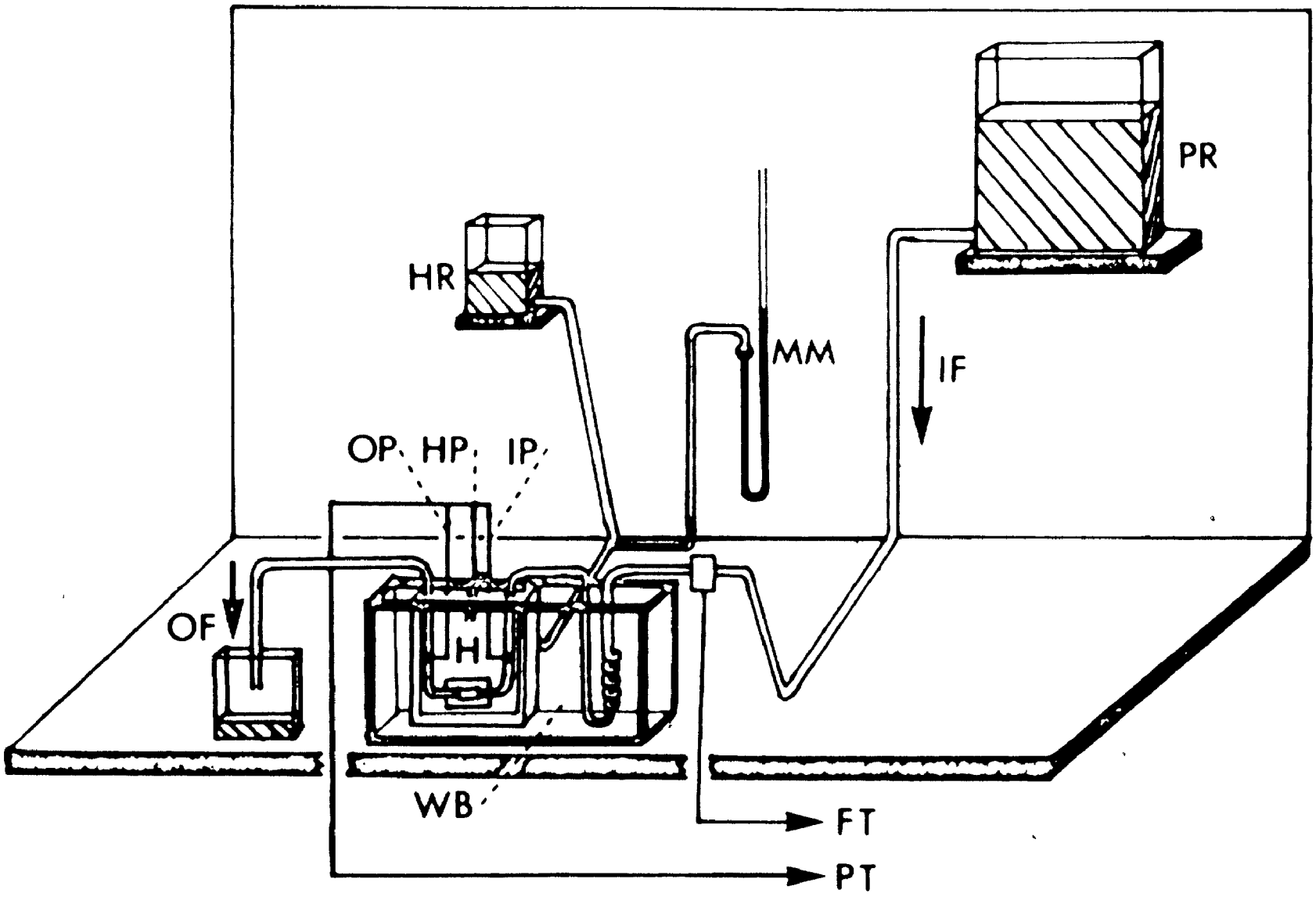

OF
OP
HP
IP
IF
P

FIGURE 17

Schematic diagram of the entire apparatus showing the perfusion reservoir (PR), complete housing (H), housing reservoir (HR), water bath (WB), mercury manometer (MM), flow transducer (FT), pressure transducers (PT), inflow (IF), outflow (OF) and the inflow (IP), outflow (OP) and housing (HP) pressure connections. The water bath warmed the fluid in the housing and the inflow to 37°C.


PR
HR
MM
IF
OP
HP
IP
OF
H
WB
FT
PT

the housing pressure. The perfusate, from a constant pressure reservoir, was warmed to 37°C prior to its entry into the housing (in the water bath surrounding the housing). Inflow, outflow, and housing pressures and flow were measured and recorded as previously described. All pressure measurements were adjusted to zero at the level of the artery in the housing.

(b) PROTOCOL -

At the beginning of each experiment, the artery was perfused with Ringer's solution at a constant pressure for at least one hour to allow the vessel to recover from the excision and cannulation. Variations of flow with prefusion and transmural pressure were examined separately as described previously. A 10-15 minute stabilization period was allowed between runs. Four experimental conditions were imposed on the artery and the flow-transmural pressure and flow-perfusion pressure relationships were determined under each condition.

(1) Control -

Each artery served as its own control. The artery was perfused with Ringer's solution and the variations of flow with perfusion pressure and transmural pressure were determined. This was the 'control' run and deviations from the flow rates observed here, at a given perfusion or transmural pressure, were considered to be due to the experimental conditions. At the end of each experiment, another control run was performed to ensure that no changes had occurred.

(11) Stimulation -

The artery was then stimulated to contract by the continuous infusion of serotonin* (10 mg/l or 1 mg/l) or norepinephrine** (1 mg/l or 0.1 mg/l) in Ringer's solution. These concentrations, 10^{-5} to 10^{-6} M for serotonin, and 5×10^{-6} to 5×10^{-7} M for noradrenalin, are comparable to those used by others in the stimulation of cerebral arteries (Fraser et al, 1970; Toda and Fujita, 1973). Both drugs were found to produce a sustained contraction resulting in a flow decrease through the artery. After the onset of contraction, 10-15 minutes were allowed for the flow rate to become constant. This was considered to be the 'baseline' flow rate under the conditions being tested. Changes of flow in response to perfusion pressure and transmural pressure variations were then recorded. If the initial 'baseline' conditions were re-established but flow failed to return to 'baseline' levels, a new 'baseline' was set and the experiment was repeated. Pressure changes were carried out slowly since preliminary experiments had shown that fast increases in transmural pressure could cause permanent damage to the muscle in the arterial wall. The artery was then returned to control conditions by perfusion with Ringer's solution. These conditions were maintained for 10-20 minutes. At the end of this "rest" period, the same drug in a different concentration, or a different drug was infused and the procedure repeated. The artery

* Serotonin creatinine sulfate complex. Sigma Chemical Company, St. Louis, Mo.

** Levophed bitartrate. Winthrop Laboratories, Aurora, Ontario.

was always returned to control levels after stimulation.

(iii) Relaxation -

The artery was stimulated with serotonin (10 mg/l) or norepinephrine (1 mg/l) and allowed to attain a stable baseline flow rate as above. Sufficient phenoxybenzamine was then added to the stimulant perfusate to produce a concentration of 10 mg/l, and the effects resulting from this procedure were recorded. The flow-perfusion pressure and flow-transmural pressure responses were measured and a Ringer's perfusate was substituted. Another control run was then performed.

(iv) Without Smooth Muscle -

Following the relaxation experiment and subsequent control run, the platform with artery and cannulas attached, was removed from the housing. The entire assembly was stored in 0.9 percent saline for 24 to 48 hours at 3°C. This procedure has been shown previously to inactivate the arterial smooth muscle (see Chapter III, section 2(a)). The procedure was the same as that outlined for the control experiment except that 0.9 percent saline (37°C) was used as the bathing solution and perfusate.

(c) FIXATION -

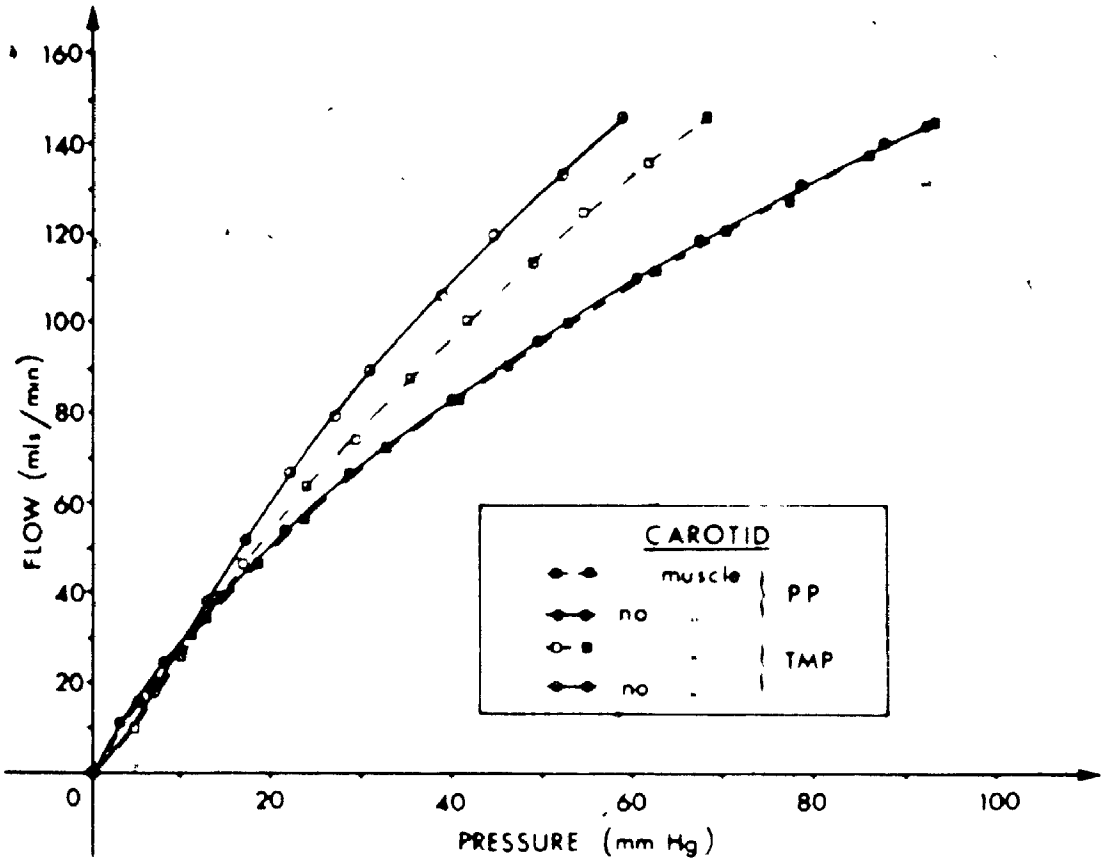
Following each experiment, the arteries were fixed in 10 percent formalin at 100 mm Hg for 24 hours. They were then sectioned and stained with Gomori-Trichrome. The wall thickness and

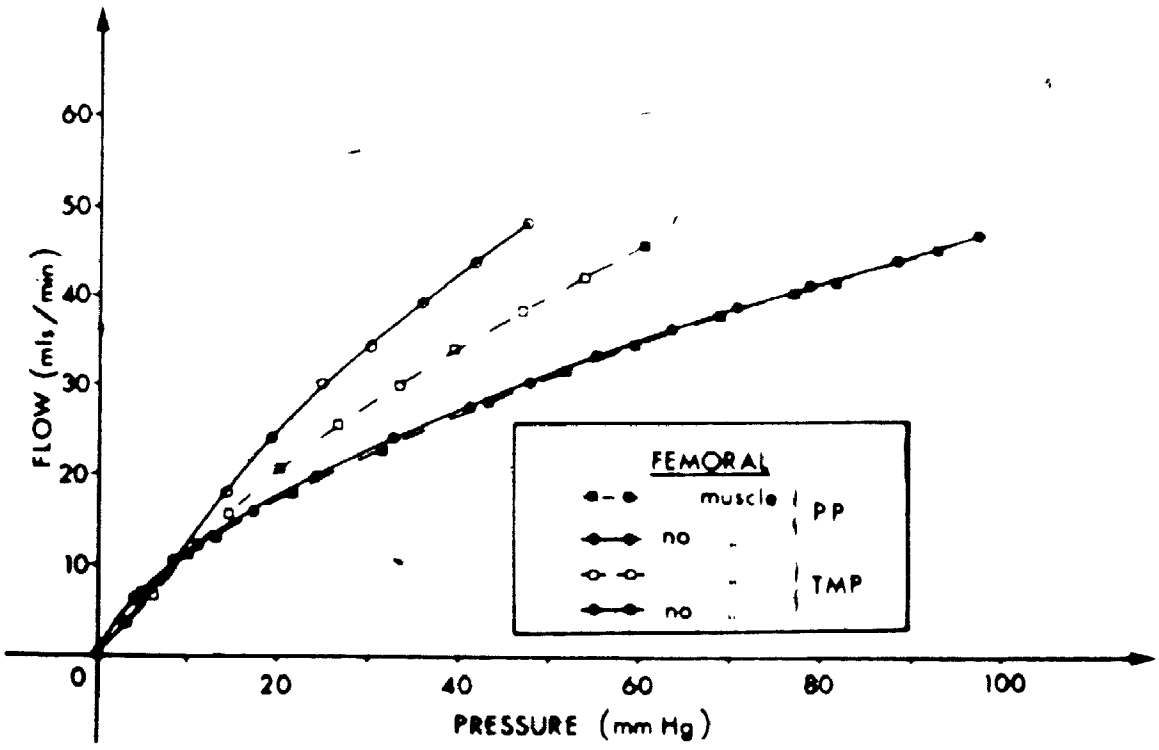
FIGURE 18(a)

Diagram showing the flow-perfusion pressure (PP) and flow-transmural pressure (TMP) relationships of a carotid artery in the presence and absence of smooth muscle tone. The flow-PP curves are not significantly different. The flow-TMP curve obtained in the presence of smooth muscle tone, is shifted to higher pressures.

FIGURE 18(b)

Comparable diagram for a femoral artery. Higher transmural pressures are required to obtain a given flow rate in the presence of smooth muscle tone.


160
140
120
100
80
60
40
20
0
FLOW (mls/mn)
20
40
60
80
100
PRESSURE (mm Hg)
CAROTID
muscle
no
PP
TMP
no


60
50
40
30
20
10
0
FLOW (mls/min)
20
40
60
80
100
PRESSURE (mm Hg)
FEMORAL
muscle
no
PP
TMP
no

lumen diameters were measured using a travelling microscope, and average values were calculated as described in Chapter IV.

3) RESULTS

(a) NORMAL VASOMOTOR TONE -

The effects of normal vasomotor tone on the flow-perfusion pressure and flow-transmural pressure relationships could be seen by comparing the curves obtained for fresh arteries, perfused with Ringer's solution, to those obtained for the same artery with no smooth muscle tone. This comparison is shown in Figures 18(a) and 18(b). In both arteries, the variations of flow with perfusion pressure were not significantly different with smooth muscle tone or without. The curves were similar to those obtained for human cerebral arteries.

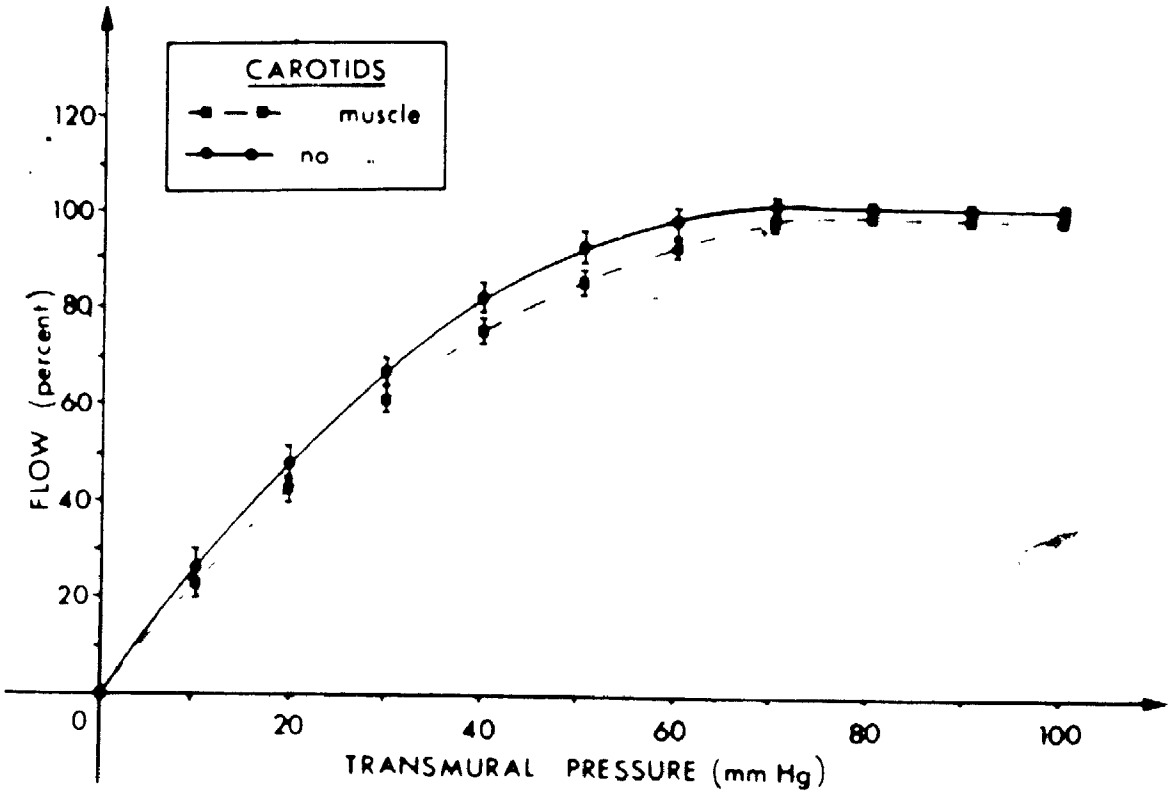
The flow-transmural pressure relationships were found to be different for the two conditions of muscle tone. The critical transmural pressure of the artery was greater when smooth muscle tone was present than when it was absent. This was true for both types of arteries at all perfusion pressures. The average flow-transmural pressure curves for all carotid and all femoral arteries are shown in Figures 19(a) and 19(b) respectively. These curves were obtained at a perfusion pressure of 90 mm Hg. Changes in flow of each artery studied were calculated as a percentage of the maximum flow obtained when normal smooth muscle tone was present. Percentage flows obtained for a given transmural pressure were then averaged and the standard error of the mean was calculated and shown as an error bar on the

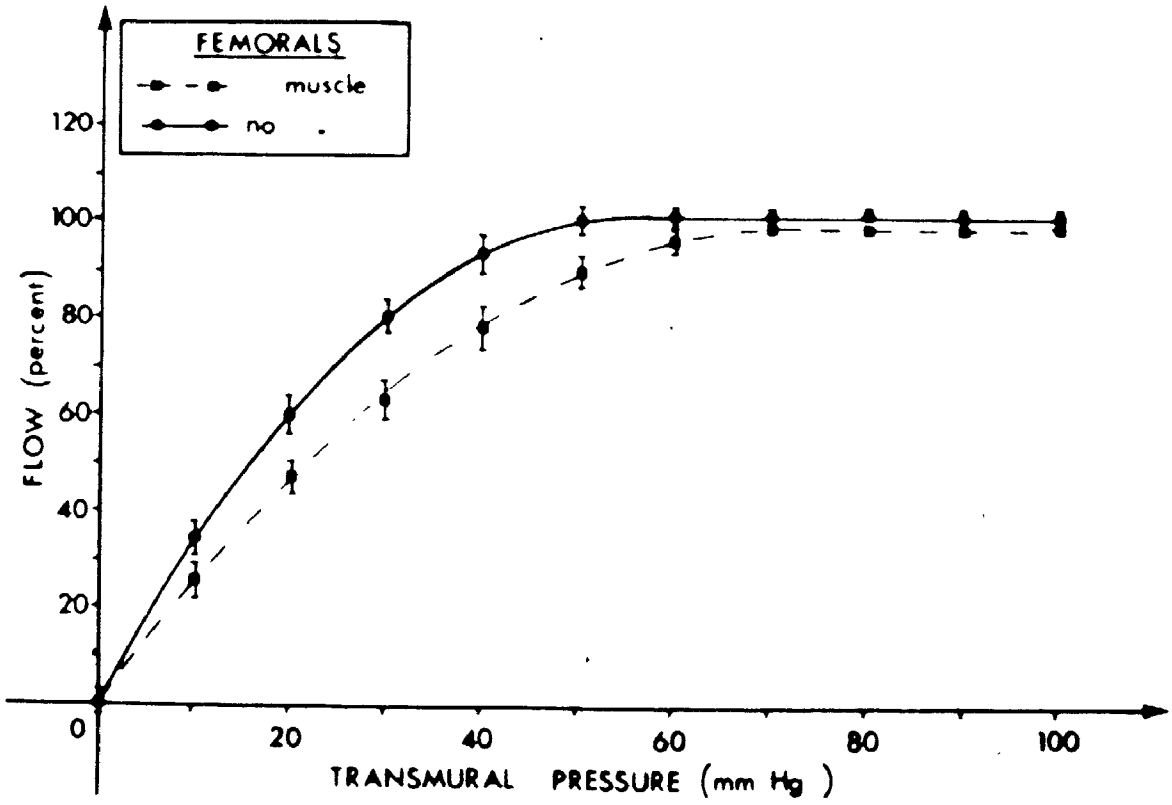
FIGURE 19(a)

Average variation of flow (in percent) with transmural pressure for all carotid arteries tested in the presence and absence of smooth muscle tone. See text for description.

FIGURE 19(b)

Comparable diagram for all femoral arteries. Flow reductions, due to the presence of smooth muscle tone, were greater for femoral arteries than for carotid arteries.


CAROTIDS
muscle
no
FLOW (percent)
120
100
80
60
40
20
0
20
40
60
80
100
TRANSMURAL PRESSURE (mm Hg)


FEMORALS
muscle
no
FLOW (percent)
120
100
80
60
40
20
0
20
40
60
80
100
TRANSMURAL PRESSURE (mm Hg)

graph. The effects of smooth muscle tone on the critical and half-flow transmural pressure are shown in Table 4. Without smooth muscle tone, the critical transmural pressure and half-flow transmural pressure were higher for carotid arteries (56 ± 3 mm Hg and 20 ± 3 mm Hg) than for femoral arteries (43 ± 3 mm Hg and 16 ± 2 mm Hg). In the presence of smooth muscle tone, these values were increased to 66 ± 3 mm Hg and 23 ± 3 mm Hg for carotid arteries, and to 57 ± 4 mm Hg and 21 ± 3 mm Hg for femoral arteries. A higher transmural pressure was required to produce a given flow rate in the presence of smooth muscle tone than in its absence. This was true for both sets of arteries. Flow reductions caused by the presence of normal smooth muscle tone were greater for femoral arteries than for carotid arteries. Flow reductions caused by a given decrease in transmural pressure, however, were larger in carotid arteries than in femoral arteries in both the presence and absence of normal muscle tone.

(b) ACTIVE CONSTRICTION -

In general, a given concentration of either vasoconstrictor tested produced a larger percentage flow decrease in femoral arteries than in carotid arteries. In both arteries, the higher concentration of vasoconstrictor produced a larger flow decrease than did the lower concentration. In an individual artery, the percent constriction caused by serotonin (10 mg/l) was approximately the same as that produced by norepinephrine (1 mg/l). The same relationship was found to exist between serotonin (1 mg/l) and norepinephrine (0.1 mg/l). These responses will therefore be called "strong" contractions,

TABLE 4

Transmural Pressure and Smooth Muscle Tone

ARTERY	MEASUREMENT	SMOOTH MUSCLE TONE	
		ABSENT	PRESENT
CAROTID	Critical TMP	56 ± 3 *	66 ± 3 **
	Half-flow TMP	22 ± 3	23 ± 3
FEMORAL	Critical TMP	43 ± 3	57 ± 4 **
	Half-flow TMP	16 ± 2	21 ± 3

* mm Hg ± SEM

** $P < 0.01$

referring to those resulting from the higher concentrations, and "weak" contractions, referring to those of the lower concentrations.

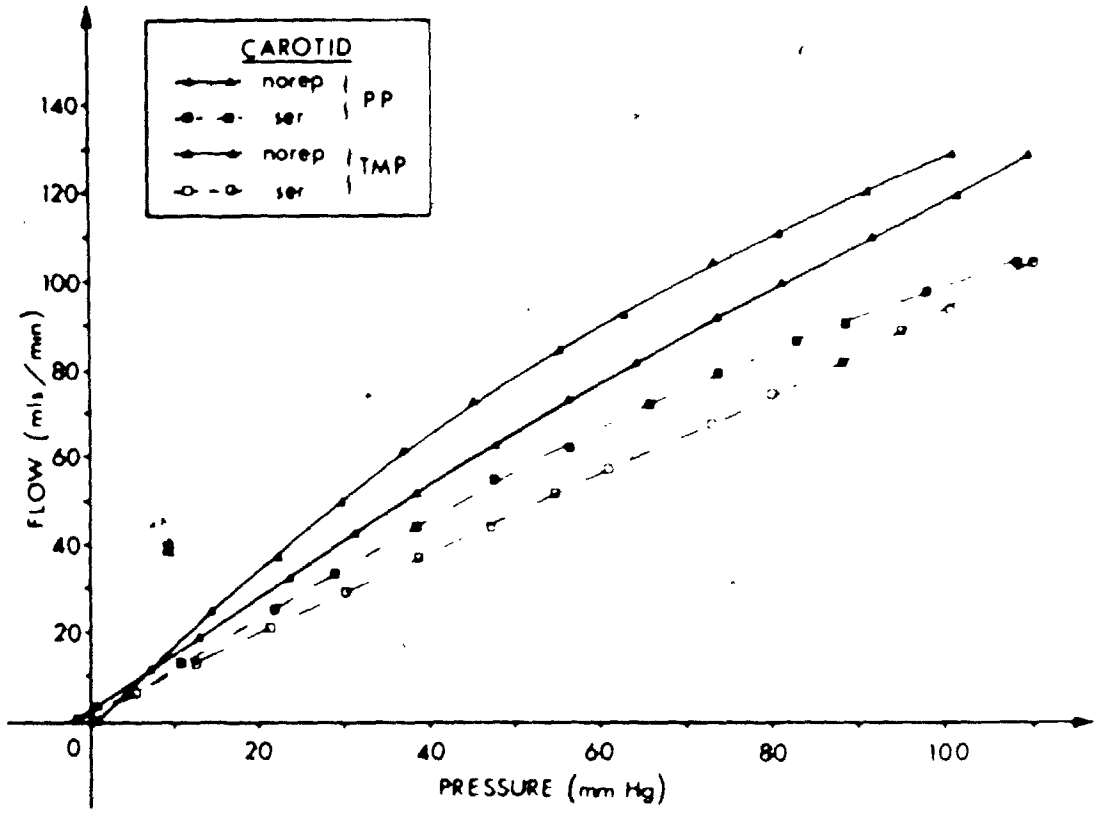
Figures 20(a) and 20(b) show the flow-perfusion pressure and flow-transmural pressure graphs for a carotid and a femoral artery during "weak" and "strong" contractions. The flow-perfusion pressure curves were shifted compared to those seen previously in the presence or absence of normal smooth muscle tone. The perfusion pressure required to produce a given flow rate increased with increasing "strength" of contraction. In other words, the flow rate at a given perfusion pressure decreased as contraction increased. The major change occurred in the flow-transmural pressure curve. For both arteries, the critical transmural pressure was greater than the perfusion pressure irrespective of the degree of constriction. During active vasoconstriction, <u>any</u> increase in housing pressure resulted in a decrease in flow through the artery. The minimum increase in housing or external pressure which caused a reduction in flow through the artery was plotted as a function of perfusion pressure and is shown in Figures 21(a) and 21(b). These values were also calculated from the graphs obtained in the presence of normal smooth muscle tone (Ringer's) and in the absence of vasomotor control (0.9 percent saline), and are shown for comparison. With increasing smooth muscle activity, the housing pressure required to reduce flow decreased. With no smooth muscle interaction, the housing pressure could be increased to 32-36 mm Hg for carotid arteries, or 44-50 mm Hg for femoral arteries, without reducing the flow rate obtained at a perfusion pressure of 90 mm Hg. With normal vasomotor tone, these values decreased slightly to 21-27 mm Hg for carotids, and

FIGURE 20(a)

Diagram showing the flow-transmural pressure (TMP) and flow-perfusion pressure (PP) relationships for a carotid artery during "weak" (norepinephrine : 0.1 mg/l) and "strong" (serotonin : 10 mg/l) contractions. See text for description.

FIGURE 20(b)

Comparable flow-pressure relationships for a femoral artery during "weak" (serotonin : 1 mg/l) and "strong" (Norepinephrine : 1 mg/l) contractions. Flow decreases with increasing "strength" of contraction at any given perfusion pressure or transmural pressure.


CAROTID
norep
ser
PP
norep
ser
TMP
FLOW (mls/min)
PRESSURE (mm Hg)
0
20
40
60
80
100
120
140

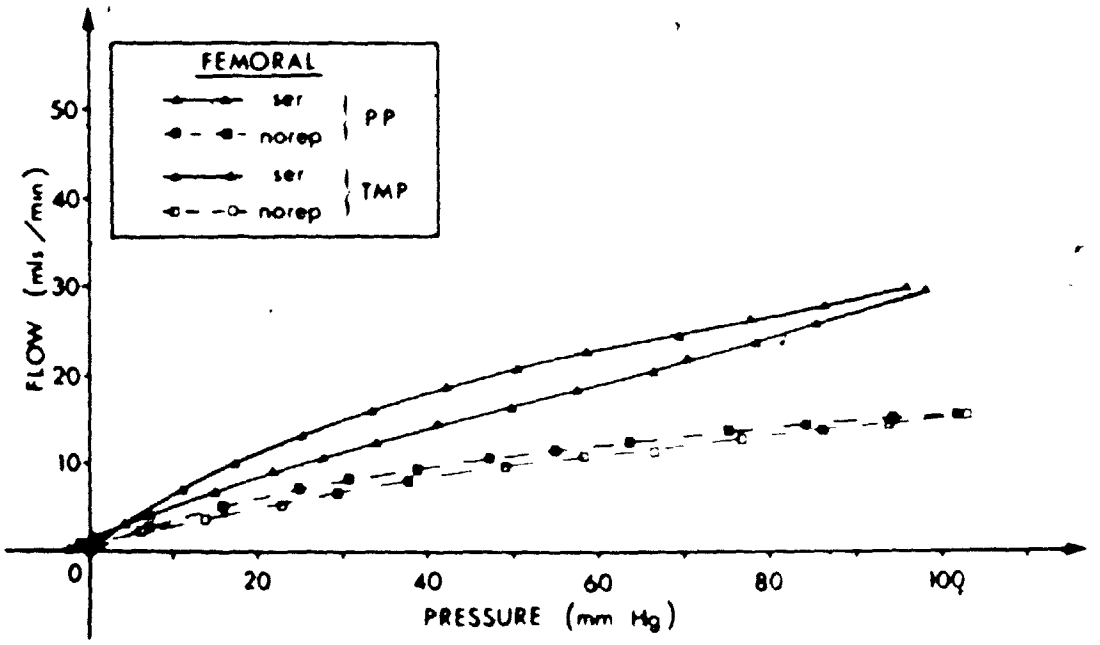
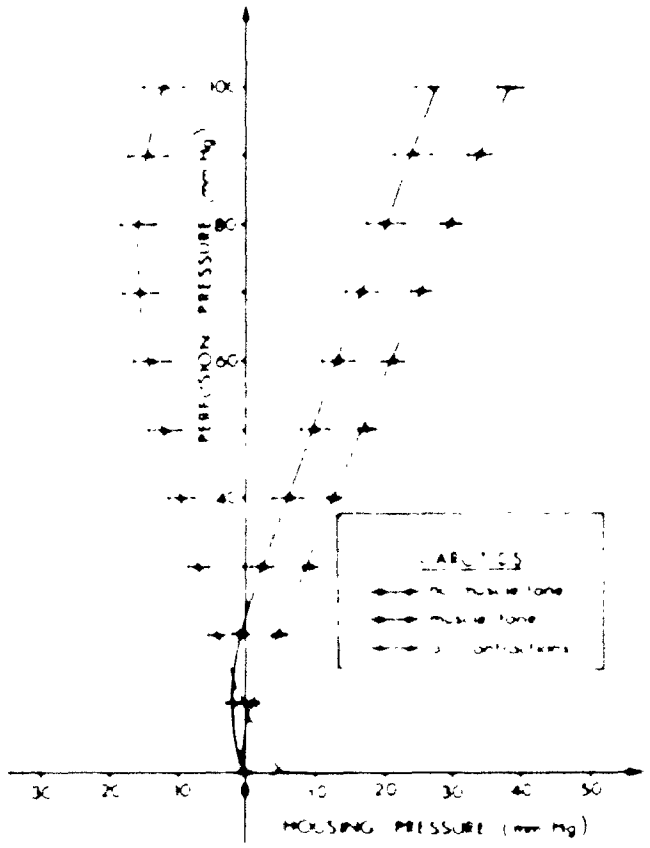

FEMORAL
ser
norep
PP
ser
norep
TMP
FLOW (mls/min)
PRESSURE (mm Hg)
0
10
20
30
40
50
60
80
100

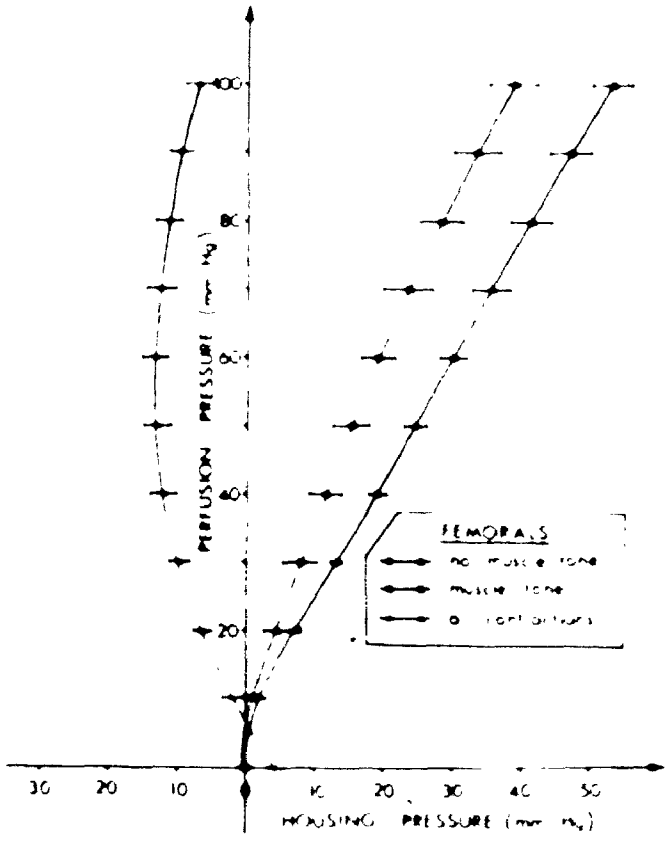
FIGURE 21(a)

Diagram showing the minimum increase in housing (external) pressure which will cause a reduction in flow at a given perfusion pressure. This is shown for all carotid arteries (average) in the absence of muscle tone, the presence of normal smooth muscle tone and in the presence of active contraction. As smooth muscle tone increases, the external pressure required to reduce flow decreases.

FIGURE 21(b)

Comparable diagram for femoral arteries. In both the presence and absence of normal smooth muscle tone, a higher external pressure was required to reduce flow in femoral arteries than in carotids.


PERFUSION PRESSURE (mm Hg)
100
80
60
40
HOUSING PRESSURE (mm Hg)
30
20
10
10
20
30
40
50


PERFUSION PRESSURE (mm Hg)
100
80
60
40
20
FEMORALS
HOUSING PRESSURE (mm Hg)
30
20
10
10
20
30
40
50

to 30-37 mm Hg for femorals, but there was no decrease in flow until the housing pressure exceeded these limits. During active contractions, however, any increase in housing pressure above 0 mm Hg resulted in a decrease in the flow rate. If the housing pressure was decreased (below 0 mm Hg), flow through the artery could be increased. This is indicated by the negative housing pressures obtained during active contractions.

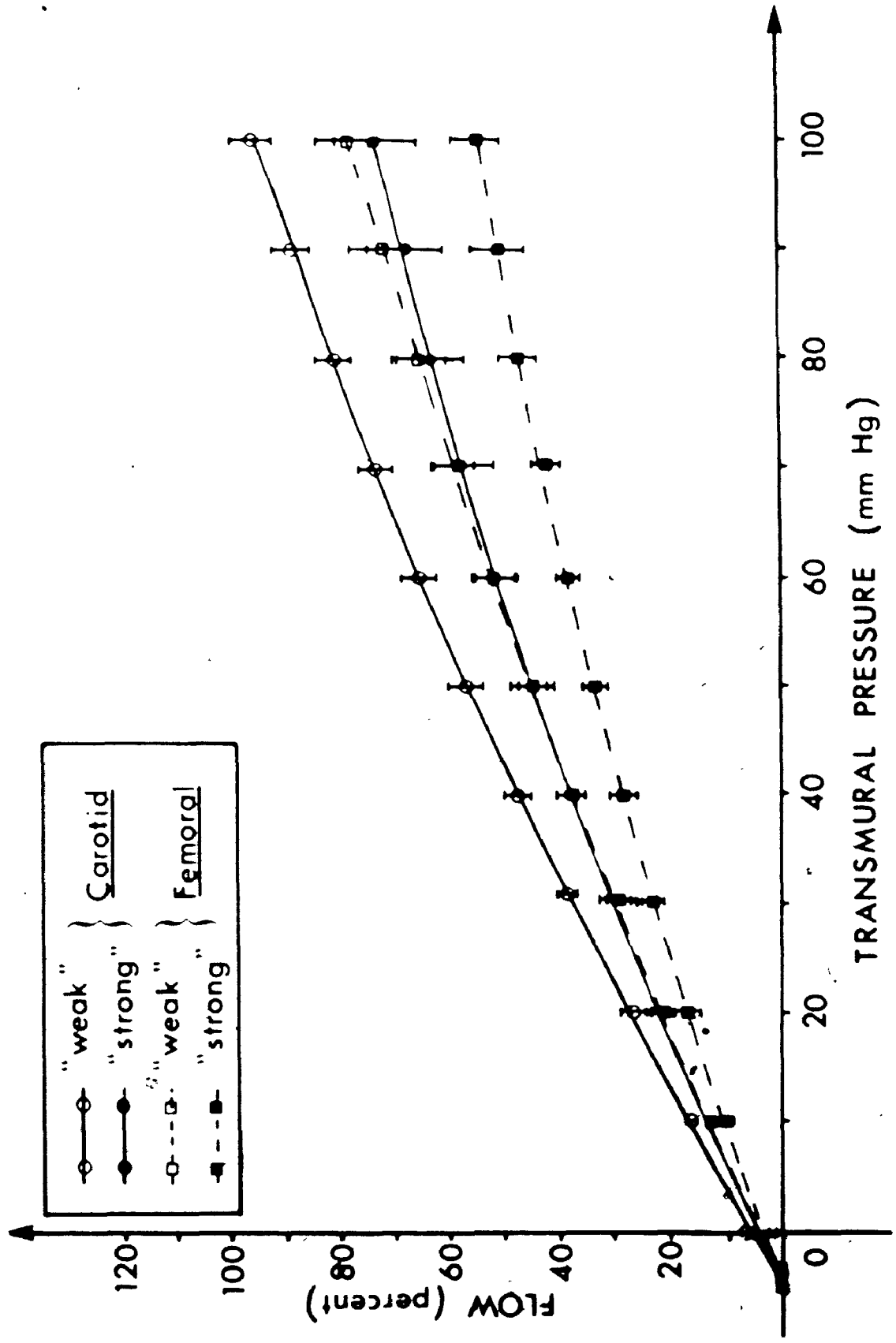
The percent decrease in flow for both sets of arteries was plotted as a function of transmural pressure (Figure 22). (Recall that percent flow is the observed flow rate compared to the maximum flow obtained in the presence of normal smooth muscle tone (Ringer's perfusate) at a perfusion pressure of 90 mm Hg). All curves shown were obtained at a perfusion pressure of 90 mm Hg. At a transmural pressure of 90 mm Hg, there were essentially three degrees of constriction produced, resulting in three ranges of flow reduction: 0-20 percent (carotid "weak" contractions); 20-40 percent (carotid "strong" and femoral "weak" contractions); and 40-60 percent (femoral "strong" contractions). The extent of flow reduction was found to be dependent on the initial degree of constriction and on the transmural pressure. For any given degree of constriction, the percent flow rate depended only on the extent of the reduction in transmural pressure. The flow-transmural pressure lines tended to curve slightly towards the pressure axis as transmural pressure was increased.

(c) REVERSAL OF VASOCONSTRICTION BY PHENOXYBENZAMINE -

In these experiments, sufficient phenoxybenzamine was added to the vasoconstrictor perfusate to produce a final concentration

FIGURE 22

Diagram showing the average percent decrease in flow versus transmural pressure for all carotid (solid line) and all femoral (broken line) arteries. The perfusion pressure was 90 mm Hg. Three ranges of flow reductions were produced at a transmural pressure of 90 mm Hg: 0-20 percent (carotid "weak" contractions); 20-40 percent (carotid "strong" and femoral "weak" contractions); and 40-60 percent (femoral "strong" contractions). The flow-transmural pressure curves depended only on this initial degree of constriction.


"weak"
"strong"
Carotid
"weak"
"strong"
Femoral
FLOW (percent)
120
100
80
60
40
20
0
0
20
40
60
80
100
TRANSMURAL PRESSURE (mm Hg)

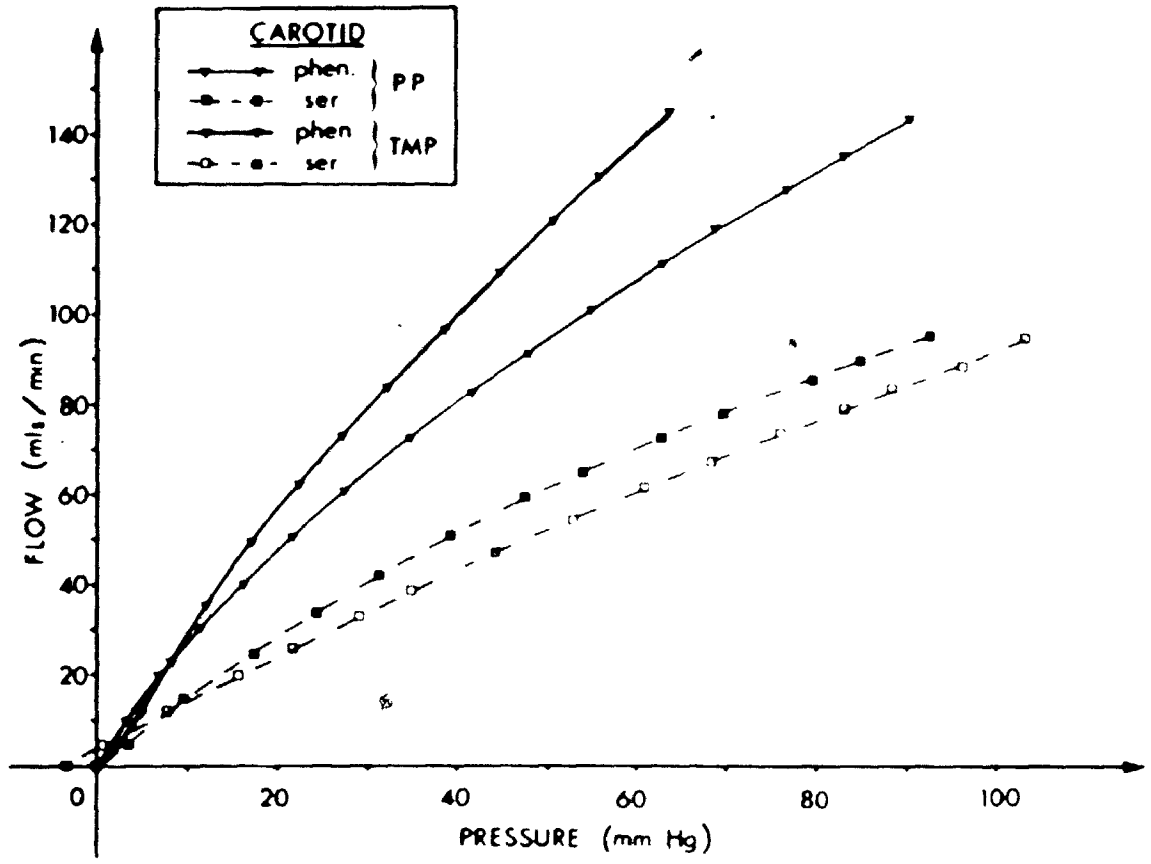
of 10 mg/l. This was done after a maximum constriction had been produced by the vasoconstrictor. Within three minutes, the artery dilated and flow increased. The maximum flow rate produced in this manner was not significantly different from that found during normal vasomotor tone experiments. The effect of the dilatation on the pressure-flow relationships of the artery are shown in Figures 23(a) and 23(b). Phenoxybenzamine reversed the constrictions caused by all concentrations of serotonin and noradrenalin, completely. The flow-perfusion pressure curve was not significantly different from that obtained during normal vasomotor tone. The average flow obtained at a given transmural pressure was slightly lower at low transmural pressures, and slightly higher at high transmural pressures, than previous normal muscle tone values. These differences were not significant. Phenoxybenzamine, therefore, appeared to return the artery to its "pre-constriction" state. Figures 24(a) and 24(b) show the variations of flow (in percent) with transmural pressure during "weak" and "strong" contractions and the improvements in flow caused by phenoxybenzamine. At transmural pressures greater than 60 mm Hg, flow was increased to between 95 and 100 percent of its normal value regardless of the degree of constriction occurring prior to the introduction of phenoxybenzamine. The half-flow transmural pressure during phenoxybenzamine perfusion was approximately 25 mm Hg in both sets of arteries. In seven arteries, an attempt was made to constrict the artery with serotonin (10 mg/l) and noradrenalin (1 mg/l) after perfusion with phenoxybenzamine. In no instance was a constriction produced. No attempt was made to establish the "endpoint" of this protection although it was

FIGURE 23(a)

Diagram showing the effectiveness of phenoxybenzamine (solid line) in relieving a "strong" contraction (broken line), produced by serotonin (10 mg/l), in a carotid artery. When phenoxybenzamine was added to the vasoconstrictor perfusate, the flow-perfusion pressure (PP) and flow-transmural pressure (TMP) relationships return to "pre-contraction" values.

FIGURE 23(b)

Diagram showing the comparable reversal of constriction (norepinephrine: 1 mg/l) by phenoxybenzamine in a femoral artery.


CAROTID
phen.
ser
PP
phen
ser
TMP
FLOW (mls/min)
0
20
40
60
80
100
120
140
PRESSURE (mm Hg)

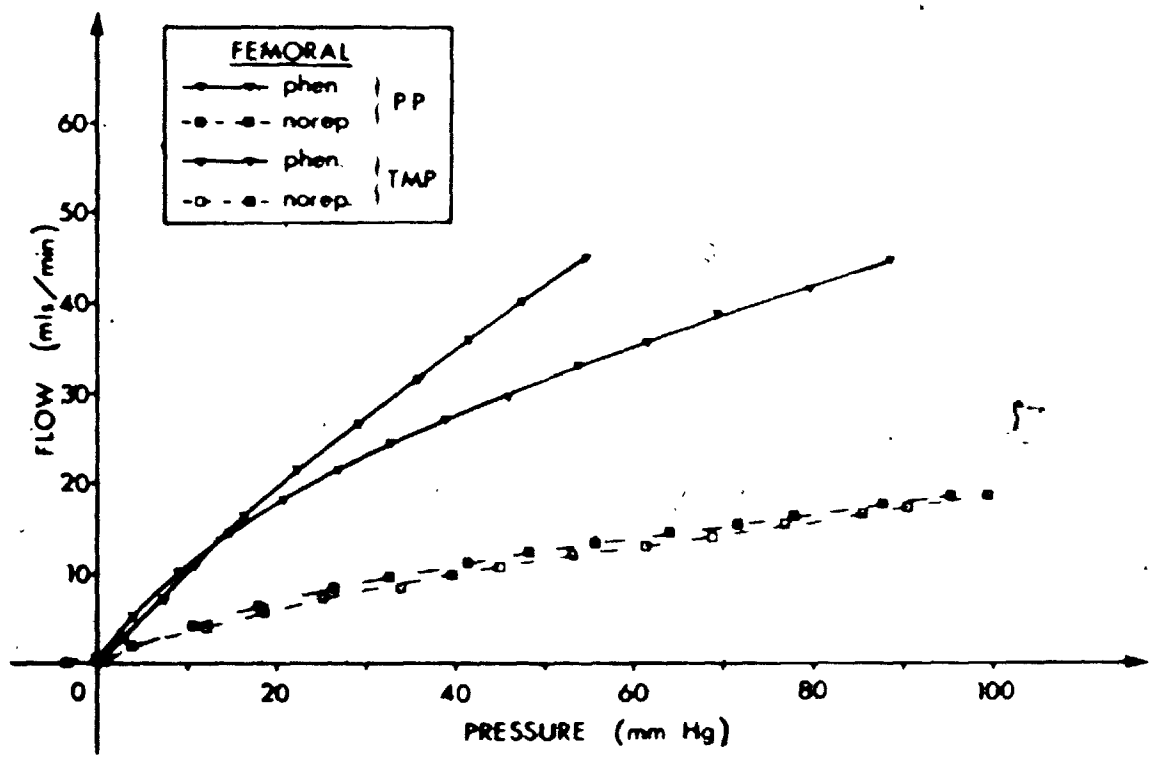
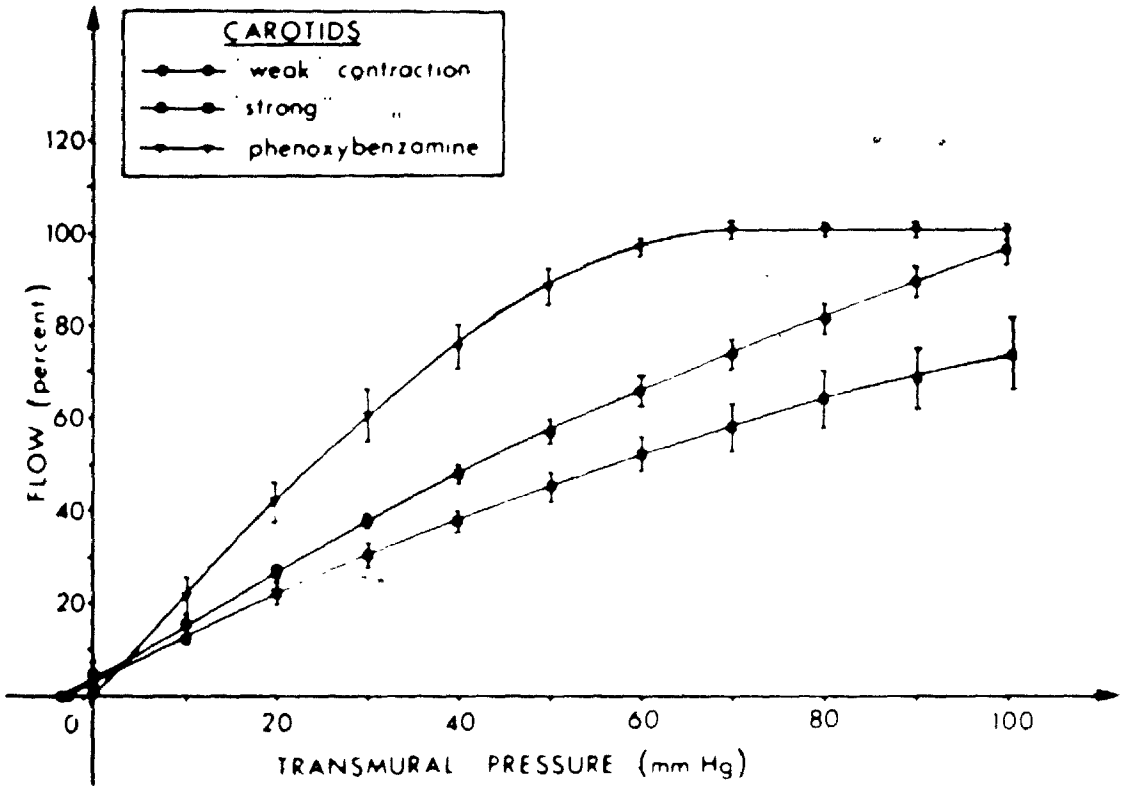

FEMORAL
phen
norep
PP
phen.
norep.
TMP
FLOW (mls/min)
0
10
20
30
40
50
60
PRESSURE (mm Hg)

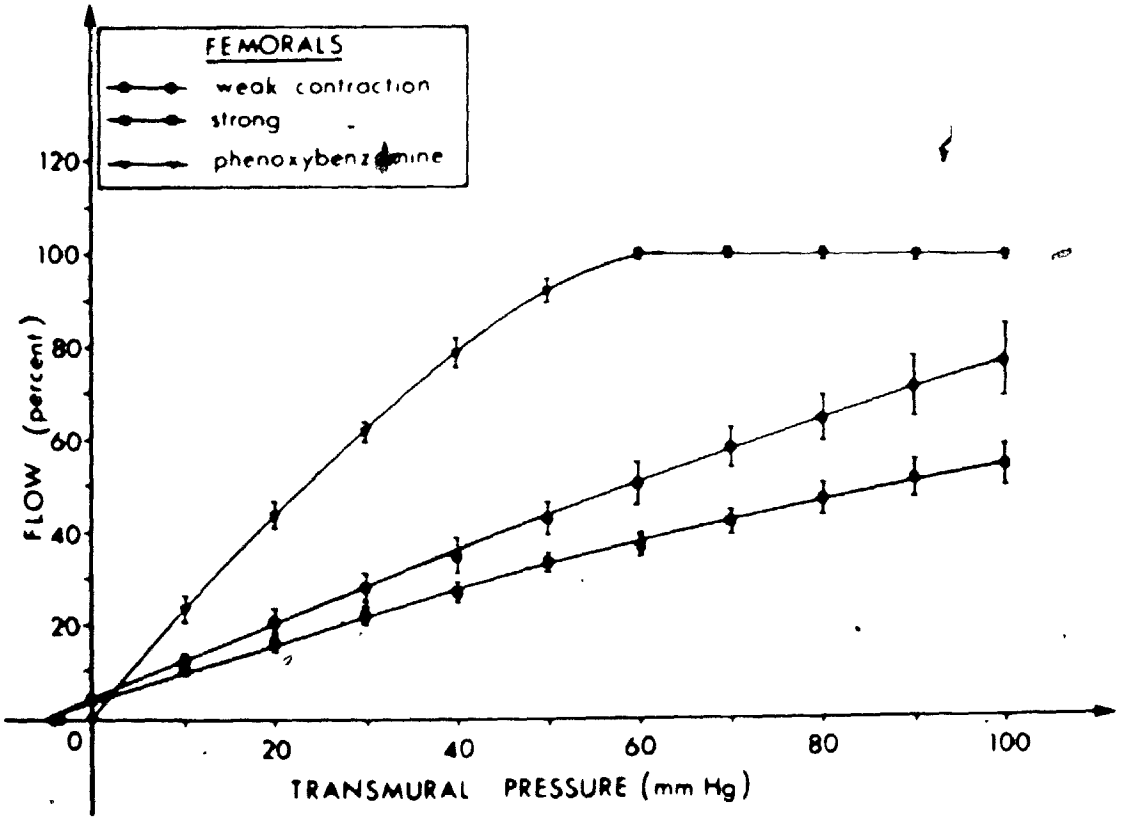
FIGURE 24(a)

Diagram showing the flow increases produced by phenoxybenzamine compared to flows occurring in "weak" and "strong" contractions in carotid arteries. As the transmural pressure decreases, this improvement in flow decreases.

FIGURE 24(b)

Diagram showing the comparable flow increases produced by phenoxybenzamine in femoral arteries. In both graphs, flow is increased to 100 percent at high transmural pressures, regardless of the "strength" of constriction.


CAROTIDS
weak contraction
strong "
phenoxybenzamine
FLOW (percent)
120
100
80
60
40
20
0
20
40
60
80
100
TRANSMURAL PRESSURE (mm Hg)


FEMORALS
weak contraction
strong
phenoxybenzamine
FLOW (percent)
120
100
80
60
40
20
0
20
40
60
80
100
TRANSMURAL PRESSURE (mm Hg)

observed to last at least 30 minutes.

(d) WALL TO LUMEN RATIOS -

The average diameter of the carotid arteries used in this experiment was 0.169 $\pm$ 0.014 cm with an average wall thickness of 0.0094 $\pm$ 0.0004 cm. The femoral arteries had a smaller lumen diameter (0.117 $\pm$ 0.008 cm), but had thicker walls (0.0120 $\pm$ 0.0004 cm) than the carotid arteries. The wall to lumen ratio was 0.056 $\pm$ 0.009 for carotid arteries, and 0.103 $\pm$ 0.006 for femoral arteries, measured at a transmural pressure of 100 mm Hg.

4) DISCUSSION

(a) LITERATURE REVIEW -

Cerebral arterial spasm or narrowing is known to occur following subarachnoid hemorrhage, and is especially common following the rupture of an intracranial aneurysm (Ecker and Reimenschneider, 1951; Schneck and Kricheff, 1964; Fields and Saks, 1965). This narrowing of the major cerebral arteries is known to cause severe and prolonged reductions in blood flow and is often a major cause of morbidity and death (Ecker and Reimenschneider, 1951, 1953; Allcock and Drake, 1965). The exact cause of this narrowing is undecided, but the one common element in almost every instance of clinically observed spasm is the presence of blood in the subarachnoid space (Fields and Saks, 1965). The direct application of blood (Echlin, 1965; Flamm, Yasargil and Ransohoff, 1972), or a single injection of blood, into the subarachnoid space (Landau and Ransohoff, 1968; Echlin, 1971) have been

shown to produce a short-term, 20-60 percent constriction of the major cerebral vessels typical of the "acute" phase of clinical spasm. This constriction is thought to be caused by serotonin which is released by blood platelets during clotting (Raynor, McMurtry and Pool, 1961; Brawley, Strandness and Kelly, 1968). Serotonin-induced spasm is a short-term constriction and does not produce the long-lasting or "chronic" phase of spasm (Brawley, Strandness and Kelly, 1968). In fact, the presence of blood in the cerebrospinal fluid produces spasm in only 40 percent of patients, studied angiographically, during the time when chronic spasm generally occurs (Stornelli and French, 1964; Allcock, 1966; Griffith, Cummins and Thomson, 1972). This would indicate that other factors must influence the production of long-term spasm.

Stornelli and French (1964) observed that all of their patients with spasm had an elevated intracranial pressure and that diffuse spasm was present only in association with increased intracranial pressure. Yamaguchi and Waltz (1971) reported only slight decreases in cerebral blood flow following puncture of the middle cerebral artery of cats, when intracranial pressure was maintained at normal levels. The most successful attempts at producing chronic spasm experimentally have occurred when care was taken to repair any incisions made in the arachnoid and dural membranes, or when only small puncture holes were made to introduce blood into the subarachnoid space. In these instances, chronic (Wilkins and Levitt, 1970), and even biphasic (Brawley et al, 1968; Echlin, 1971) spasm could be produced, although intracranial pressures were not reported during the chronic stage.

Repeated injections of blood were found to be more effective than single injections (Landau and Ransohoff, 1968), and vessel puncture was most effective in producing consistent, chronic spasm (Landau and Ransohoff, 1968; Brawley et al, 1968). Intracranial pressures were not reported. McQueen and Jelsma (1967) found that the intracisternal injection of 8 mls of whole blood resulted in a sustained intracranial hypertension of 30 cm of water, and that the injection of 8 mls of plasma containing red blood cell ghosts resulted in an intracranial pressure increase to 100 cm of water in seven hours. These increases began about five hours after injection and reached maximum levels in seven to ten hours. A similar injection of serotonin had no effect. Bradford and Sharkey (1962) suggested that red blood cells block the uptake of cerebrospinal fluid. Red blood cells accumulate and degenerate in the arachnoid villi (Alksne and Lovings, 1972), and disappear in about two weeks. Nornes and Magnaes (1972) and Nornes (1973) have shown repeated hemorrhages resulting in progressively higher levels of increased intracranial pressure. They found that immediately after a hemorrhage, intracranial pressure often reached a level between the systolic and diastolic blood pressure. In some cases, this pressure declined to between 40 and 80 cm of water, and remained there for up to two weeks (Nornes' "Type 1" hemorrhage). In other cases, intracranial pressure remained between systolic and diastolic blood pressures, and the patient usually died within hours (Nornes' "Type 2" hemorrhage).

Therefore, subarachnoid blood is known to cause and maintain high intracranial pressures and these pressures have been shown to exist clinically following subarachnoid hemorrhage for up to two weeks.

The possibility that increased intracranial pressure, in conjunction with active smooth muscle contraction, might produce long-term spasm has not been investigated prior to this study.

(b) EXPERIMENTAL RESULTS -

(i) Choice of Arterial Models -

Since fresh human cerebral arteries were unavailable and since rabbit and cat cerebral arteries were found to be too small, femoral and common carotid arteries from rabbits were chosen as experimental models.

The constriction produced in these arteries by a given concentration of serotonin or noradrenalin may not cause the same degree of constriction in a human cerebral artery. Reductions in flow due to increased external pressure were assumed to depend only on the severity of constriction produced initially and not on the response of an individual artery to a particular drug. This assumption was later found to be justified. These arteries were also chosen because their diameters were approximately equal to those of the human cerebral arteries studied previously.

(ii) Passive Behavior -

The flow-perfusion pressure and flow-transmural pressure curves obtained in the absence of normal smooth muscle tone could be compared to those of the human cerebral arteries described in Chapter III (Table 5). For carotid arteries at a perfusion pressure of 90 mm Hg, the critical transmural pressure (transmural

TABLE 5

Comparison of Intracranial and Extracranial Arteries

ARTERY	ORIGIN	CONDITION (AS or N*)	CRITICAL TMP (mm Hg ± SEM)	HALF-FLOW TMP (mm Hg ± SEM)
CAROTID	RABBIT	N	56 ± 3	20 ± 3
LARGE CEREBRAL	HUMAN**	N	54 ± 4	16 ± 2
SMALL CEREBRAL	HUMAN	N	63 ± 2 £	21 ± 1 £
FEMORAL	RABBIT	N	43 ± 3	16 ± 2
SMALL CEREBRAL	HUMAN	AS	44 ± 2	14 ± 1

* AS — Atherosclerotic . N — Normal

** From Tables 1 and 2

£ $P < 0.01$

pressure at which flow begins to decrease), was 56 ± 3 mm Hg and the half-flow transmural pressure was 20 ± 3 mm Hg. These values were not significantly different than those obtained for large, normal human cerebral arteries (54 ± 4 mm Hg, and 16 ± 2 mm Hg, respectively). The femoral arteries, however, had a critical transmural pressure of 43 ± 3 mm Hg, and a half-flow transmural pressure of 16 ± 2 mm Hg. The comparative values for small, normal human cerebral arteries were 63 ± 2 mm Hg, and 21 ± 1 mm Hg. Both values were significantly different ($P<0.01$) in femoral arteries as compared to normal human cerebral arteries of a comparable lumen diameter. If the femoral arteries were compared to small atherosclerotic human arteries, there was no significant difference (critical transmural pressure of 44 ± 2 mm Hg, and half-flow transmural pressure of 14 ± 1 mm Hg). Therefore, femoral arteries appear to be "stiffer" than normal human cerebral arteries of a similar caliber.

A possible explanation for this difference is that small human (cerebellar) arteries have an average wall thickness of 0.0059 cm, whereas that for the femoral arteries was found to be 0.0120 cm. The thicker wall of the femoral arteries would be harder to deform and would therefore appear "stiffer". The wall thickness of the carotid arteries was not significantly different from the wall thicknesses of large human cerebral arteries. In all other aspects, the flow-transmural pressure and flow-perfusion pressure curves were the same as those obtained for human cerebral arteries. This would suggest that the passive behavior of all large arteries, in response to decreased transmural pressure, is determined only by the lumen

diameter, thickness of the arterial wall, and the presence or absence of atherosclerosis. This has been shown to be true for femoral and common carotid arteries of rabbits and major human cerebral arteries.

(iii) The Influence of Normal Vasomotor Tone -

The flow-perfusion pressure curves obtained during normal smooth muscle tone were not significantly different from those obtained in the absence of vasomotor tone. This indicates that the distal cannula is providing the major resistance to flow in both instances. Therefore, normal smooth muscle tone did not decrease the radius of the artery sufficiently to significantly influence the maximum flow rate obtained at a given perfusion pressure.

Normal smooth muscle tone did, however, cause a shift in the flow-transmural pressure curves. In the femoral arteries the critical transmural pressure increased from 43 $\pm$ 3 mm Hg to 57 $\pm$ 4 mm Hg, and the half-flow transmural pressure increased from 16 $\pm$ 2 mm Hg to 21 $\pm$ 3 mm Hg. A similar, but somewhat smaller, shift was seen in the carotid arteries where the critical transmural pressure increased from 56 $\pm$ 3 mm Hg to 66 $\pm$ 3 mm Hg, and the half-flow transmural pressure changed from 20 $\pm$ 3 mm Hg to 23 $\pm$ 3 mm Hg. This shows that smaller increases in external pressure were required to reduce flow to any given level when normal smooth muscle tone was present.

Arterial smooth muscle is known to constrict in response to stretch (Dobrin, 1973 (a), (b)). As the transmural pressure is increased from zero, the radius or circumference of the artery increases and therefore the muscle fibers in the wall are stretched. The smooth muscle constricts, in response to this stretch, which tends

to oppose an increase in radius. At any given transmural pressure, therefore, the radius of the artery will be smaller than when this muscle tone was absent, and flow through the artery will be reduced. As transmural pressure is increased, this muscle tone becomes greater and the transmural pressure required to produce a given flow rate will increase. This would explain the observed shift in the flow-transmural pressure curves obtained in the presence of normal smooth muscle tone.

This shift was larger for femoral arteries than for carotid arteries. This was presumably due to the larger wall thickness (thicker muscle layer) of the femoral arteries since the walls were primarily smooth muscle. A similar shift would be expected to occur for human cerebral arteries. The magnitude of this increase in critical transmural pressure is not certain and would depend on the amount of smooth muscle in the wall and the "stiffness" of the wall itself (i.e., due to atherosclerosis). The wall thickness of the femoral and carotid arteries used in this experiment are comparable to those of large cerebral arteries indicating that, in the absence of atherosclerosis, increases of 10-15 mm Hg in critical transmural pressure could occur in major human cerebral arteries. If this is true, then reductions in flow due to decreased transmural pressure would be greater for arteries with normal smooth muscle tone than in those in which this tone has been abolished (by maximal dilatation for example). That is, the critical transmural pressure, or "limit of autoregulation" would increase with increasing smooth muscle tone.

(iv) Active Vasoconstriction (spasm) -

In the presence of active vasoconstriction, the flow-perfusion pressure curves were also found to be shifted. The flow rate at any given perfusion pressure was decreased from that obtained during normal vasomotor tone. This indicates that the distal resistance of the cannula is no longer the flow-limiting resistance. The maximum flow rate was determined by the radius of the artery and therefore by the transmural pressure. At all perfusion pressures, the critical transmural pressure was greater than the perfusion pressure, and flow could be increased by increasing the transmural pressure. There was a passive flow-transmural pressure relationship over the entire range of transmural pressures studied (i.e., "autoregulation" was lost), and any increase in housing pressure resulted in a decrease in flow through the artery. This occurred regardless of the initial degree of constriction produced when the housing pressure was zero mm Hg.

The initial flow decrease was dependent on the concentration of vasoconstrictor used, and on the reactivity of the artery being tested. Femoral arteries were more reactive than carotid arteries, and larger initial flow reductions were produced in response to a given vasoconstrictor. The higher concentrations of serotonin and noradrenalin produced the largest initial flow reductions in both arteries. Once the initial contraction was established, further reductions in flow could be produced by decreasing the transmural pressure.

The flow-transmural pressure curve of carotid

arteries with "strong" contractions was the same as that of femoral arteries with "weak" contractions. In addition, the flow-transmural pressure curves (for a given artery) obtained using serotonin (10 mg/l) were identical to those obtained using noradrenalin (1 mg/l). The same relationship was true for the smaller concentrations of both drugs. Therefore, the flow-transmural pressure relationship was independent of the drug used or the artery being tested, and depended only on the initial flow decrease. This observation leads to the conclusion that the curves obtained for these arteries are comparable to the curves that would be produced by human cerebral arteries with the same initial degree of constriction.

The constrictions produced in these experiments resulted in three ranges of initial flow reduction (0-20 percent, 20-40 percent, and 40-60 percent). These will be referred to as mild, moderate, and severe constrictions. The half-flow transmural pressure increased with increasing severity of constriction, ranging from 43 $\pm$ 3 mm Hg for mild constrictions, to 89 $\pm$ 10 mm Hg for severe constrictions. Clearly, flow through a major cerebral artery will be severely compromised if even a mild constriction is accompanied by an increase in intracranial pressure.

To assess the severity of these flow reductions produced by increases of intracranial pressure, the initial degree of constriction produced by a subarachnoid hemorrhage must be determined. There have been very few studies done on the reactivity of human cerebral arteries. Angiographic studies demonstrated that 60 percent of patients with blood in the subarachnoid space, show no significant decrease in major cerebral arterial diameter; yet it is known

that serotonin is released by human blood platelets during clotting (Hardisty and Stacey, 1955). Spasm has been produced in almost 100 percent of monkeys in which a major cerebral artery has been ruptured experimentally, if the membranes surrounding the brain were carefully repaired. In similar experiments, however, flow decreases were slight in the absence of increased intracranial pressure. Toda and Fujita (1973) found that cerebral arteries produced weaker constrictions than extracranial vessels in response to serotonin and norepinephrine, and no response at all to electrical stimulation. It would appear, therefore, that human cerebral arteries are less reactive than those of experimental animals, and care must be taken in applying experimental results to human arteries. Based on these observations, it appears that human cerebral arteries are capable of only mild to moderate constrictions in the absence of increased intracranial pressure.

Intracranial pressures of 40-80 cm of water (30-60 mm Hg) are common following subarachnoid hemorrhage (Nornes, 1973). Assuming only a mild constriction exists, flow will be reduced by 20-50 percent with an intracranial pressure of 45 mm Hg, depending on the mean arterial blood pressure (120-90 mm Hg respectively). It is possible, therefore, to produce large flow decreases with relatively low intracranial pressures when a mild constriction is present. This would suggest that increased intracranial pressure is an important factor in determining decreases in cerebral blood flow following subarachnoid hemorrhage. Increased intracranial pressure has been shown to follow the same time-course as clinically observed spasm. There is

an initial, "acute" phase immediately following hemorrhage, and a long-lasting, "chronic" phase (Nornes and Magnaes, 1972; Nornes, 1973). This similarity, coupled with the results found in the present study, suggest that increased intracranial pressure combined with a mild constriction could be responsible for the narrowing of major cerebral arteries, and may be the determining factor in the development of "chronic" spasm. The effectiveness of increased intracranial pressure in reducing flow through large arteries is reduced greatly when active contractions are not present.

(v) Effects of Phenoxybenzamine -

When phenoxybenzamine was added to the vasoconstrictive perfusate, the flow-perfusion pressure curve returned to pre-constricted levels, and the distal cannula again became the flow-limiting resistance. The flow-transmural pressure curve returned to the values obtained under normal smooth muscle tone. The vasoconstrictor effects of serotonin and noradrenalin were reversed completely. At high transmural pressures (below the critical transmural pressure), flow was increased slightly compared to the normal muscle tone values. This reversal of constriction persisted after the perfusion with phenoxybenzamine was stopped, and repeated attempts to constrict the arteries with noradrenalin and serotonin failed to elicit any response.

Fraser et al, (1970), found that phenoxybenzamine was capable of reversing spasm (in the basilar arteries of monkeys) produced by blood, serotonin and noradrenalin. They also found that

no further constrictions were possible after the application of phenoxybenzamine and that the arteries dilated to a larger than normal diameter. Flamm et al, (1972) found similar results, but stated that mechanical manipulation could still produce a constriction of the basilar artery of the cat. Cummins and Griffith (1971) found that intra-arterial phenoxybenzamine was capable of relieving spasm in humans. The present results would support these observations. As the transmural pressure is decreased, however, the improvement in flow produced by phenoxybenzamine decreases. In cases of diffuse spasm, when high intracranial pressures are present, phenoxybenzamine would increase flow only minimally. Both active muscle constriction and increased intracranial pressure would have to be relieved to restore flow to its original, pre-spasm level.

5) SUMMARY

Twelve rabbit, common carotid and femoral arteries were used to examine the pressure-flow relationships through large arteries during active vasoconstriction, normal smooth muscle tone, and in the absence of vasomotor tone. The results obtained in these arteries led to general conclusions which could be applied to major human cerebral arteries.

(1) Carotid and femoral arteries from rabbits, in the absence of smooth muscle tone, exhibit passive flow-pressure relationships similar to those obtained previously for human cerebral arteries. The decrease in flow produced by a given reduction of transmural

pressure, depended on the lumen diameter and the "stiffness" of the arterial wall. Wall thickness was found to affect the wall "stiffness".

(2) Normal smooth muscle tone was shown to decrease the level of external pressure which would cause a flow reduction through carotid and femoral arteries by 10 to 15 mm Hg at a perfusion pressure of 90 mm Hg. In other words, the resistance provided by carotid and femoral arteries caused reductions in flow at transmural pressures 10 to 15 mm Hg higher when normal muscle tone was present, than when it was absent. Similar increases in resistance were predicted for major human cerebral arteries on the basis of lumen diameters and wall thicknesses. Therefore, the predicted "limit of autoregulation" would occur at higher transmural pressures (lower intracranial pressures) when normal smooth muscle tone is present. This indicates that reductions in cerebral blood flow to below normal values could occur at lower intracranial pressures during normal vasomotor tone than if the vessel were maximally dilated and were without vasomotor control. This distinction as to the transmural pressure at which flow falls below normal levels in the two different situations, has not been mentioned previously.

(3) When the arteries were constricted, a passive flow-transmural pressure relationship was observed over the entire range of pressures and flow rates examined. The flow-limiting effect of the distal resistance was lost and the resistance of the constricted artery controlled the flow rate. Flow reductions were determined by

the transmural pressure and the degree of constriction.

(4) The degree of constriction was dependent on the concentration of vasoconstrictor in the perfusate and on the reactivity of the artery being tested. Femoral arteries were found to be more reactive than carotid arteries, and the higher concentration of both vasoconstrictors resulted in a "stronger" contraction than the lower concentration. There was no significant difference in the contraction produced by serotonin (10 mg/l) and that produced by noradrenalin (1 mg/l) in a given artery. This was also true for the lower concentrations.

(5) The flow-transmural pressure curve obtained for carotid arteries perfused with a high concentration of either vasoconstrictor was not significantly different from that obtained for femoral arteries perfused with the lower concentration of vasoconstrictor (Figure 22). Therefore, the flow-transmural pressure relationship depended only on the degree of constriction and was independent of the vasoconstrictor used to achieve this constriction or the artery in which the constriction was produced. The initial degree of constriction was judged by the resultant decrease in flow produced at a transmural and perfusion pressure of 90 mm Hg. There were three initial degrees of constriction produced in these experiments. These were termed mild (resulting in a 0-20 percent flow decrease), moderate (20-40 percent), and severe (40-60 percent). A major cerebral artery exhibiting one of these three degrees of constriction would be expected to have a flow-transmural pressure relationship

typical of that degree of constriction. This similarity in the behavior of constricted arteries to reduced transmural pressure has not been demonstrated previously.

(6) A review of the literature suggested that human cerebral arteries were capable of only mild to moderate constrictions in response to vasoconstrictors known to be present following subarachnoid hemorrhage. I have shown experimentally, that, in the presence of a mild constriction, flow reductions of 20 to 50 percent could be produced by intracranial pressures known to exist following subarachnoid hemorrhage. This would indicate that intracranial pressure may be an important factor in determining the flow through major cerebral arteries following subarachnoid hemorrhage.

(7) Increased intracranial pressure has been shown to follow a similar time-course to that observed for cerebral arterial spasm. This similarity of time-course, coupled with the experimental results of this investigation, suggest that increased intracranial pressure could be a major factor in the production of angiographically observed spasm of the large cerebral arteries. These two phenomena have been linked only by their coincidence of occurrence in previous experimental and clinical observations.

(8) Phenoxybenzamine was shown to reverse the contractions produced by serotonin and noradrenalin in femoral and common carotid arteries of rabbits. Phenoxybenzamine was observed to prevent subsequent contractions due to these vasoactive drugs for at least thirty

minutes following its administration to the arteries. These results are similar to those obtained by others for cerebral arteries. In the present study, however, increases in flow due to this reversal of constriction, decreased with decreasing transmural pressure. Therefore, in patients with high intracranial pressure, reversal of arterial spasm may not result in an increase in cerebral blood flow sufficient to improve the clinical status of the patient.

VI. GENERAL DISCUSSION

1) AUTOREGULATION

(a) CURRENT CONCEPTS -

A survey of the literature showed that there are two major theories describing the nature of autoregulatory control of the cerebral circulation. The myogenic theory suggests that changes in smooth muscle tone, in response to variations in transmural pressure, are responsible for regulating the diameter of the arterioles, and hence, their resistance to flow (Folkow, 1964). The matabolic theory suggests that this control of arteriolar resistance is accomplished by variations in the local concentrations of metabolites (Berne, 1964).

In spite of this difference of opinion, there are several points of general agreement (Lassen, 1964; Harper and Häggendal, 1968). One of these, is that this control of the cerebral circulation is provided by diameter changes in the arterioles of the brain and is probably the result of a combination of the above mechanisms. Another point of agreement is that once the perfusion pressure or the transmural pressure falls below 40-60 mm Hg, autoregulation fails and cerebral blood flow decreases (Heilbrun et al, 1972; Johnston et al, 1973; Miller et al, 1973). This is known as the "limit of autoregulation". At perfusion or transmural pressures

below this level, flow decreases passively with decreasing pressure. The literature suggests that the limit of autoregulation occurs when the arterioles have dilated to their maximum diameter. Subsequent decreases of pressure are thought to decrease this maximum diameter, increase arteriolar resistance, and cause a passive reduction of flow. The results of the present study, however, suggest that there may be an alternate explanation for this observed loss of autoregulation.

(b) RESULTS OF THE PRESENT STUDY -

I demonstrated that a passive pressure-flow relationship occurred in isolated major human cerebral arteries, whenever the resistance of the artery became comparable to that of the distal resistance. The distal resistance used in these experiments was shown to be approximately equal to that normally produced by the cerebral arterioles during autoregulation. The cerebral arteries tested were without smooth muscle tone. The transmural pressure was reduced to the level reported to be the limit of autoregulation (40-60 mm Hg). At these transmural pressures, the resistance of the major cerebral arteries was increased to a value comparable to that normally occurring in the cerebral arterioles. This increase in arterial resistance resulted in a passive pressure-flow relationship and "autoregulation" was lost. The limit of autoregulation, therefore appears to occur when the flow-limiting resistance is shifted from the arterioles to the large cerebral arteries. This definition of the limit of autoregulation indicates that any situation which causes an increase in the resistance of the large cerebral arteries, or a

decrease in that of the arterioles, will alter the value of transmural pressure at which autoregulation is lost, and a passive pressure-flow relationship is developed.

In subsequent experiments, using extracranial arteries, I showed that the presence of smooth muscle tone caused an increase in the experimental limit of autoregulation. When these arteries were stimulated to contract (high vasomotor tone), the "limit of autoregulation" became greater than 100 mm Hg, and a passive pressure-flow relationship was present over the entire range of transmural pressures tested. Similar results were predicted for human cerebral arteries. Therefore, as the vasomotor tone of the large cerebral arteries is increased, the minimum transmural pressure required to maintain a normal cerebral blood flow is increased. The range of transmural pressures in which autoregulatory responses can maintain a normal cerebral blood flow is expected to decrease with increasing arterial vasomotor tone, and increase with decreasing vasomotor tone. This dependence of the cerebral circulation on the vasomotor tone of the major cerebral arteries has not been suggested previously in the literature. (It has been noted, however, that large cerebral arteries in spasm are capable of reducing cerebral blood flow.)

2) INCREASED INTRACRANIAL PRESSURE AND CEREBRAL BLOOD FLOW

(a) INTRACRANIAL TUMORS -

(i) Clinical Observations -

Increased intracranial pressure is known to occur in patients with intracranial tumors. If the transmural pressure was

below 40-60 mm Hg, in these cases, autoregulation was lost and cerebral blood flow was reduced (Ketv, Shenkin and Schmidt, 1948; Heilbrun, Jorgensen and Boysen, 1972). Cerebral blood flow was improved if the intracranial pressure was decreased by the removal of cerebrospinal fluid (Heilbrun et al, 1972).

(ii) Experimental Evidence -

The slow expansion of an intracranial balloon is often used to simulate tumor growth experimentally. This increases the intracranial pressure which causes a reduction in transmural pressure. When the transmural pressure falls to 40-60 mm Hg, cerebral blood flow decreases (Langfitt, Kassel and Weinstein, 1965; Lowell and Bloor, 1971; Johnston, Rowen, Harper and Jennett, 1973; Miller, Stanek and Langfitt, 1973). The increase in intracranial pressure produced by an intracranial tumor, however, may not be transmitted equally to both sides of the brain. Pressure differences of up to 30-50 mm Hg have been demonstrated in monkeys and cats with a unilateral mass expansion in the intracranial cavity (Langfitt, Shavaluk, Mahoney, Stein and Hedges, 1964; Brock, Beck, Markakis and Dietz, 1972).

(iii) Results of the Present Study -

Flow was decreased in major cerebral arteries, with no smooth muscle tone, when the transmural pressure was reduced to below 40-60 mm Hg. Experiments on extracranial arteries suggested that this value would increase in the presence of normal smooth muscle

tone. These results agree well with those found previously in clinical and experimental investigations.

I have also shown that preferential flow reductions of up to 50 percent could occur in human cerebral arteries, perfused in parallel, when both arteries were subjected to the same transmural and perfusion pressures. This tendency towards preferential narrowing, coupled with the possibility of local differences in intracranial pressures, strongly suggests that focal flow deficiencies may occur in patients with intracranial tumors. These flow reductions occurred in the major cerebral arteries in the absence of active contraction.

It seems reasonable to conclude, that flow reductions observed in the presence of increased intracranial pressure caused by a tumor, could originate in the major cerebral arteries. These flow reductions may be focal in nature. This would indicate that flow could be improved by decreasing the intracranial pressure as suggested by Heilbrun et al (1972).

(b) SUBARACHNOID HEMORRHAGE AND CEREBRAL ARTERIAL SPASM

(i) Clinical Occurrence -

Cerebral arterial spasm is known to occur in approximately 40 percent of patients following subarachnoid hemorrhage (Allcock, 1966). This type of arterial narrowing has been shown to be capable of causing almost complete closure of the large cerebral arteries resulting in severe reductions of cerebral blood flow. (Ecker, 1945). Most surgeons will agree that spasm is often the major factor causing death or the development of severe neurological deficiencies following subarachnoid hemorrhage. Marshall (1973) has

shown that spasm is most severe 5 to 13 days after hemorrhage.

Increased intracranial pressure has also been observed following subarachnoid hemorrhage. For example, Kaufmann and Clark (1970) found intracranial pressures between 25 and 65 mm Hg. Similar pressures were reported to occur by Nornes and Magnaes (1972) following their "Type 1" hemorrhage (30-60 mm Hg). Their "Type 2" hemorrhage was associated with even higher intracranial pressures (90-160 mm Hg). Most clinical measurements of intracranial pressure have been obtained by lumbar puncture.* Langfitt, Weinstein, Kassel and Simeone (1964) and Kaufmann and Clark (1970) have shown both experimentally and clinically, that a blockage can occur in the connections between the subarachnoid space of the spinal cord, and that of the brain, following subarachnoid hemorrhage. They reported that intracranial pressure could be as much as 50-70 mm Hg higher than that demonstrated at lumbar puncture. Therefore, pressures measured by lumbar puncture are not necessarily representative of those actually present in the intracranial space following subarachnoid hemorrhage.

Intracranial pressure has been shown to follow a time-course similar to that observed for spasm. There is an initial "acute" phase immediately following hemorrhage, which lasts for less than an hour, and a longer lasting "chronic" phase which lasts for days ("Type 1" hemorrhage of Nornes (1973)). Ng and Nimmannitya (1970) have suggested that increased intracranial pressure reaches a

* Lumbar puncture is the puncture of the subarachnoid space of the spinal cord in the lumbar region. The pressure of the cerebrospinal fluid, measured in this manner, is used as an indication of the intracranial pressure.

maximum level three to five days after massive cerebral infarction* following subarachnoid hemorrhage. Stornelli and French (1964) stated that all of their patients who exhibited spasm, also had increased intracranial pressure. In an angiographic study, Pribram (1961) was unable to perfuse the cerebral arteries with contrast medium. He attributed this blockage to increased intracranial pressure although few measurements were given.

(ii) Experimental Investigations -

Brawley, Strandness and Kelly (1968) found that spasm, following subarachnoid hemorrhage, was a biphasic phenomenon with an "acute" phase and a longer-lasting "chronic" phase. This was later confirmed by Echlin (1971) and Kuwayama et al, (1972). Unfortunately, these experiments did not include careful measurement of intracranial pressure. Many mechanisms have been proposed as the cause of cerebral arterial spasm. These include mechanical stimulation, stimulation of the cerebral arterial nerve supply, and stimulation produced by vasoactive substances released from blood in the subarachnoid space. These mechanisms were discussed in more detail in Chapter II. All of these factors were found to produce short-term spasm in the cerebral arteries of experimental animals but were unable to produce long-term "chronic" spasm.

* A cerebral infarction is defined in Dorland's Medical Dictionary as "an ischemic condition of the brain, producing a persistent focal neurological deficit in the area of distribution of one of the major cerebral arteries".

Cerebral arterial spasm is observed almost exclusively in the presence of blood in the subarachnoid space. Yamaguchi and Waltz (1971), however, found that spasm due to subarachnoid hemorrhage in cats was slight if intracranial pressure was maintained at normal levels. It has also been shown, as mentioned previously, that spasm occurs in only 40 percent of cases with subarachnoid hemorrhage in humans. In spite of the obvious clinical significance of arterial spasm, the exact cause of this phenomenon has not been established.

Increased intracranial pressure and cerebral arterial spasm have been shown to be present following subarachnoid hemorrhage. Both of these phenomena are known to be capable of causing reductions of cerebral blood flow. The flow-reducing effects of increased intracranial pressure during active vasoconstriction, however, have not been investigated.

(iii) Results of the Present Study -

Femoral and common carotid arteries of rabbits were used as an experimental model of a contracting cerebral artery. These arteries were chosen because of their similarity in diameter to the major cerebral arteries studied previously. There were three initial degrees of constriction produced in these experiments - mild, moderate, and severe. The flow-transmural pressure relationship was shown to depend only on the degree of constriction and was independent of the vasoconstrictor used to achieve this constriction or the artery in which the constriction was produced. This led to the conclusion that a major (cerebral) artery with a given degree of constriction would exhibit a flow-transmural pressure curve typical of that

constriction.

Experimental evidence, obtained in the absence of increased intracranial pressure, suggested that cerebral arteries are capable of only mild to moderate sustained constrictions in response to the external application of blood. The fact that 60 percent of all patients with subarachnoid hemorrhage show no signs of spasm, serves to confirm this opinion that the cerebral vessels are relatively unreactive.

I showed that a mild constriction, in the absence of increased external pressure, produced an average flow reduction of only 10 percent. An increase in intracranial pressure to a level known to exist in the "chronic" phase of subarachnoid hemorrhage (45 mm Hg), did not alter the flow rate by more than 10 percent in the absence of an active constriction. However, if the external pressure was increased to 45 mm Hg in the presence of a mild constriction, flow reductions of up to 50 percent resulted.

I propose, therefore, that the occurrence of "acute" cerebral arterial spasm is caused by a combination of a mild arterial constriction amplified by the presence of increased intracranial pressure. The presence of either of these phenomena, in the absence of the other, produces only small reductions in flow which may not be angiographically detectable. This may be the cause of the "hit and miss" occurrence of spasm following subarachnoid hemorrhage. When both of these factors are present, increased intracranial pressure is the cause of major reductions in flow and arterial diameter.

I have also shown that, based on measurements of wall thickness and lumen diameter, the complete closure of major

cerebral arteries by smooth muscle contraction alone, is not possible. Increased intracranial pressure, however, is capable of causing the complete closure of cerebral arteries. Therefore, whenever a cerebral artery is completely occluded, with no prior evidence of an obstruction to flow in the artery, this closure must be due, in part, to increased intracranial pressure.

Phenoxybenzamine was shown to be effective in reversing the contractions produced by serotonin and noradrenalin in femoral and common carotid arteries of rabbits. Similar results have been obtained by others for human cerebral arteries. In the present study, it was stressed that in patients with high intracranial pressure, reversal of arterial contraction may not produce an increase in cerebral blood flow sufficient to improve the clinical status of the patient. Both active muscle contraction and increased intracranial pressure would have to be relieved to restore flow to its original, pre-spasm level.

VII. SUMMARY AND CONCLUSIONS

The purpose of this thesis has been to investigate the relationships between flow, perfusion pressure and transmural pressure in major cerebral arteries under various degrees of vasomotor tone. This investigation was carried out primarily to establish the relative importance of passive and active narrowing of the large cerebral arteries on the cerebral circulation. The results of the study are presented below:

(1) The term "cerebral perfusion pressure" has been used in the literature to describe the difference between the mean arterial blood pressure and the intracranial pressure. This was found to be inconsistent with the current concepts of vascular resistance. The term "transmural pressure" was therefore adopted to indicate this difference between the mean arterial pressure and the intracranial pressure. The term "perfusion pressure" was defined to indicate the total pressure drop across the entire system under consideration.

(2) At high transmural pressures and in the absence of smooth muscle tone, the maximum flow rate in the large cerebral arteries was determined by the perfusion pressure and the magnitude of the distal resistance. As the transmural pressure was lowered,

the radius of the cerebral arteries decreased and their resistance increased. When the resistance of the artery became comparable to the distal resistance, a passive pressure-flow relationship developed and flow decreased with decreasing transmural pressure. The onset of this passive pressure-flow relationship was found to depend on the lumenal diameter of the artery and the "stiffness" of the arterial wall. The transmural pressure at which this relationship developed ranged from 60 mm Hg, for small, non-atherosclerotic arteries, to 40 mm Hg for large, atherosclerotic arteries. It was argued that since the distal resistance was comparable to that normally occurring in the cerebral arterioles, the onset of this passive pressure-flow relationship was similar to the loss of cerebral autoregulation. The literature suggests that the limit of autoregulation occurs at transmural pressures between 40 and 60 mm Hg. On the basis of these similarities, I propose that the loss of autoregulation occurs when the flow-limiting resistance is shifted from the cerebral arterioles to the large cerebral arteries.

(3) In subsequent experiments, using extracranial arteries, I demonstrated that the experimental "limit of autoregulation" increased with increasing vasomotor tone in the large arteries. Similar increases were predicted for human cerebral arteries. From this, it was concluded that the range of transmural pressures in which autoregulatory responses can maintain a normal cerebral blood flow, will decrease with increasing arterial vasomotor tone, and increase with decreasing tone.

(4) I showed that flow through major human cerebral arteries was decreased at transmural pressures known to occur in the presence of intracranial tumors. The transmural pressures at which these flow reductions began, agreed well with those reported to cause the onset of cerebral blood flow reductions in patients with intracranial tumors. Preferential flow reductions of up to 50 percent were shown to occur in human cerebral arteries, perfused in parallel, when both arteries were under the same perfusion and transmural pressures. I propose, therefore, that flow reductions, possibly focal in nature, could originate in the major cerebral arteries of patients with increased intracranial pressure resulting from an intracranial tumor. It is suggested that, angiographically, these passive flow and arterial diameter reductions caused by increased intracranial pressure, could appear similar to those resulting from active smooth muscle contraction.

(5) Based on measurements of wall thickness and lumen diameter, I showed that the complete closure of major human cerebral arteries by smooth muscle contraction alone, is not possible. Increased intracranial pressure, however, can completely close the arterial lumen when the transmural pressure is approximately zero.

(6) I demonstrated that the flow-transmural pressure relationship of constricting arteries depends only on the degree of constriction and is independent of the vasoconstrictor used to achieve this constriction, or the artery in which the constriction

is produced.

I conclude that a major human cerebral artery with a given degree of constriction, will exhibit a flow-transmural pressure curve typical of that constriction irrespective of its cause.

(7) Phenoxybenzamine is effective in reversing the contractions produced by serotonin and noradrenalin in isolated femoral and common carotid arteries of rabbits. Similar results have been reported by other investigators for human cerebral arteries. I showed, however, that the reversal of arterial contraction produces only minimal flow increases in the presence of high external (intracranial) pressure.

(8) Clinical and experimental observations found in the literature, suggest that human cerebral arteries are capable of only mild constrictions in the absence of increased intracranial pressure.

I showed that increases in intracranial pressure to levels reported to occur in the "chronic" phase of subarachnoid hemorrhage (45 mm Hg), do not alter the flow rate in human cerebral arteries by more than 10 percent in the absence of an active constriction. Similarly, a mild constriction, in the absence of increased intracranial pressure, results in an average decrease in flow of only 10 percent. However, when the external pressure is increased to 45 mm Hg in the presence of a mild constriction, flow reductions of up to 50 percent occur. The presence of either of these

phenomena, in the absence of the other, may not be angiographically detectable.

I suggest that this dual requirement for the production of severe narrowing, may be the cause of the "hit and miss" occurrence of cerebral arterial spasm as seen clinically.

(9) I propose that acute cerebral arterial spasm is the result of a mild arterial constriction which is amplified by the simultaneous occurrence of increased intracranial pressure. When both of these are present, increased intracranial pressure is the major cause of reductions in arterial blood flow and diameter.

In summary, autoregulation of the cerebral circulation is lost when the flow-limiting resistance is shifted from the arterioles to the large cerebral arteries. The range of transmural pressures over which autoregulatory responses can maintain a normal cerebral blood flow, will decrease with increasing arterial vasomotor tone, and increase with decreasing tone. A passive narrowing of the major cerebral arteries could be the cause of general and focal flow reductions in patients with increased intracranial pressure resulting from an intracranial tumor. Major human cerebral arteries cannot close by active contraction, and it appears that they are capable of only mild constrictions resulting in minor reductions of cerebral blood flow. Increased intracranial pressure, in conjunction with these mild constrictions, results in severe flow reductions. In the presence of high intracranial pressure, reversal of arterial

contraction produces only minimal increases in flow. Increased intracranial pressure, therefore, is the major cause of reductions in cerebral blood flow and cerebral arterial diameters. Acute cerebral arterial spasm is the result of a mild arterial constriction which is amplified by the simultaneous occurrence of increased intracranial pressure.

VIII. SUGGESTIONS FOR FUTURE RESEARCH

Additional questions arise from this study which suggest possible areas for future investigations.

(1) What is the relationship between the volume of a tumor or hemorrhage and the resulting increase in intracranial pressure?

(2) What is the maximum volume increase that can be compensated for by increased absorption or displacement of cerebrospinal fluid, without causing a large increase in intracranial pressure?

(3) Are increases in intracranial pressure due to subarachnoid hemorrhage transmitted equally to both sides of the brain?

(4) Can small areas of increased pressure develop within the clotted blood in the subarachnoid space?

(5) What role does brain swelling due to edema play in the production and maintenance of increased intracranial pressure?

(6) What level of increased intracranial pressure is associated with diffuse spasm? localized spasm?

(7) What is the time-course of the vasoactive nature of bloody cerebrospinal fluid?

(8) How much can human cerebral arteries contract in response to bloody cerebrospinal fluid?

(9) Do all human cerebral arteries exhibit the same degree of reactivity?

(10) Does vasomotor tone increase in the chronic phase of spasm?

(11) Why does spasm appear in some areas but not in others equally distant from the site of hemorrhage?

(12) How much can spasm, as seen angiographically, be relieved by the reduction of intracranial pressure?

(13) Can diffuse arterial spasm be reduced significantly by relieving the active contraction?

(14) How soon after hemorrhage, and to what extent, can intracranial pressure be reduced without excessive risk of rebleeding?

(15) What is the relationship between the size of the arterial rupture and the resulting increased intracranial pressure, volume of hemorrhage, and spasm?

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APPENDIX 1

'DIBENZYLINE'

(PHENOXYBENZAMINE HYDROCHLORIDE)*

Phenoxybenzamine is an investigational drug currently being tested as a possible method of controlling cerebral arterial spasm following subarachnoid hemorrhage. The mechanism of action of 'Dibenzyline' is not well defined, but it is known to act directly and specifically on alpha-adrenergic cells. It selectively blocks the excitatory response of smooth muscle to norepinephrine, epinephrine and 5-hydroxytryptamine. It does not, however, alter the ability of the smooth muscle to contract in response to mechanical stimulation.

Phenoxybenzamine can be administered to humans in dosages up to 1 mg/Kg.

* The phenoxybenzamine used in this investigation was supplied by Smith, Kline and French Laboratories, Montreal, Quebec. The author wishes to express his appreciation.

APPENDIX 2

PREPARATION OF RINGER SOLUTION

Distilled water was used to make the solution. The other constituents in percent (by weight) were:

Sodium Chloride	0.9	percent
Potassium Chloride	0.042	percent
Calcium Chloride	0.024	percent
Sodium Bicarbonate	0.02	percent

This solution was prepared the day before each experiment and stored in a refrigerator at 3°C overnight. On the day of an experiment, sufficient glucose was added to make a final concentration of 0.1 percent. Phosphoric acid (1 M) was then added until the pH fell to 7.35 ± 0.02. The pH was measured using a glass electrode pH meter (Beckman). If a vasoactive solution was being prepared, the stimulant was added prior to making any pH adjustments.

Aeration of the solution was found to be unnecessary as sufficient oxygen was already present to satisfy the low oxygen requirements of the cannulated arterial segment.

All solutions were warmed to 37°C prior to contact with the arterial specimen.

APPENDIX 3

CALIBRATION OF PRESSURE AND FLOW TRANSDUCERS

(a) Pressure transducers (Statham, Model P23Db):

A mercury manometer was used to calibrate the pressure transducers during each experiment. The linearity and reproducibility of pressure measurements obtained in this manner were checked by varying the pressure repeatedly from 0 to 100 mm Hg. The corresponding output from the transducers following 13 such runs was found to be reproducible ($\pm$ 0.5 mm Hg) and linear ($\pm$ 1 percent) within this pressure range. It is thought that these limits of accuracy are due primarily to difficulty in obtaining exact pressure readings visually from the mercury manometer. There was no measurable baseline drift during the course of an experiment (2-4 hours).

(b) Flow transducers (Carolina Medical, Model EP300-1/8):

The flow transducers used were of the "flow-through" type with an internal diameter of 1/8 inch. This type of transducer did not exhibit the zero instability and calibration inaccuracy observed frequently when using the "cuff" type transducer. There was no detectable baseline drift during a pressure-flow experiment (10-20 minutes). The zero-flow baseline was checked prior and subsequent to each experimental run. The flow versus flowmeter output calibration curves obtained for these transducers were both linear and reproducable

($\pm$ 1 percent). A contributing factor to this stability was the non-structured nature of the perfusate solutions used (saline and Ringer) as opposed to that of a cellular suspension such as blood.