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DYNAMIC PRESSURE-FLOW RELATIONSHIPS OF
BRAIN BLOOD FLOW IN THE MONKEY.

The Ohio State University, Ph.D., 1967
Physiology

University Microfilms, Inc., Ann Arbor, Michigan

DYNAMIC PRESSURE-FLOW RELATIONSHIPS
OF BRAIN BLOOD FLOW
IN THE MONKEY

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

Calvin Buddy Early, B.S., B.A., M.D.

* * * * *

The Ohio State University
1967

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ACKNOWLEDGMENTS

I am deeply indebted, both literally and figuratively, to the United States Navy under whose auspices I was permitted to return to The Ohio State University for residency training in neurosurgery, and to work toward the Ph.D. degree.

To Dr. Heinz P. Pieper, I express sincere gratitude for his patience, suggestions, and advice from the conception to the conclusion of the research reported in this dissertation. In addition, I am indebted to Dr. Pieper for the example he has provided, as physiologist, bio-engineer, and gadgeteer.

I am profoundly indebted to Dr. William E. Hunt for his training and guidance in my development as a neurosurgeon, for his encouragement in the present research, and for his provision of sufficient time unhindered by clinical commitments to allow the research to culminate in this dissertation.

I wish to express sincere appreciation to my colleague, Dr. Robert Hess, for his assistance and encouragement during this research, and particularly for his "carrying the ball" on several occasions when clinical commitments precluded my presence.

I would like to express grateful thanks to Mr. Henry Penner for his technical assistance throughout the project. Thanks are due Mr. Donald McDaniel for his aid in the calculations and photography required for the dissertation. To Professor Paul Barton I owe a great debt of thanks for

his untiring and invaluable efforts to transform my rough writing into more palatable prose. I am most appreciative of the able anesthesia, surgical assistance and other support provided by Mrs. Anna Early, C.R.N.A.

Financial support from the Central Ohio Heart Association and the National Institutes of Health is gratefully acknowledged.

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CHAPTER I

INTRODUCTION AND REVIEW

A. Historical Background

The doctrine of A. Monro (1) and G. Kellie (2) regarding brain blood flow originated in 1783, and persisted well into the fourth decade of the present century. The Monro-Kellie doctrine was based on the idea that, since the brain is housed in a rigid, bony box, neither it nor its vascular system could either expand or contract. The calibre of the vasculature being thus fixed, it followed that any variation of blood flow through the brain could only result from a change in perfusing pressure. As late as 1929 Weed (3), and in 1932 Flexner (4), upheld the doctrine.

In 1902 Bayliss (5) described a constrictive reaction of blood vessels to an increase in transmural pressure, thus becoming the father of what is known today as the myogenic theory of auto-regulation. His observations, however, dealt only with extracranial vessels. He firmly espoused the Monro-Kellie doctrine and specifically rejected any suggestion that intracranial vessels might participate in a myogenic response (6).

Though the Monro-Kellie doctrine precluded any local auto-regulation of brain blood supply, it did not imply that the brain was the passive recipient of whatever quantity of blood the cardiovascular system chanced to deliver to it. On the contrary, the brain

was thought to assure itself of a proper perfusion pressure of blood by active control of the extracranial cardiovascular system. Certain principles of this control mechanism, such as the carotid sinus reflex (7) and the Cushing ischemic reflex (8), have only been strengthened by further investigation.

Roy and Sherrington (9) in 1890 were the first to affirm that autoregulatory control of brain blood flow existed. Little credit is generally accorded them. Johnson (10) credits Bayliss with the earliest experiments giving evidence of autoregulatory behavior of blood vessels, but twelve years before Bayliss' work, Roy and Sherrington stated:

We conclude then, that the chemical products of cerebral metabolism contained in the lymph that bathes the walls of the arteries of the brain can cause variations in the calibre of the cerebral vessels: that in this reaction the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity.

The conclusions were based on observations of the brains of dogs through open skull windows. They noted marked dilatation of the brain vasculature after injecting into the internal carotid artery a filtrate prepared from the brains of recently asphyxiated dogs.

Yet another forty years passed before serious consideration was given to local autoregulation of brain blood supply. From 1928 to 1943 many studies provided definite evidence of such control. Observation through a tightly closed skull window was a common method of study, best exemplified by the work of Forbes and Wolff (11), and Fog (12,13). It was clearly shown that the brain in situ in its

rigid case did not pulsate as it does when viewed through the open skull by the neurosurgeon. Further, only the larger vessels appeared to pulsate, and then only minimally as compared to other vascular beds. These findings were not incongruous with the Monro-Kellie doctrine. But over longer periods of time the pial blood vessels were seen to constrict or dilate over wide ranges in response to various conditions. Thus, finally, the Monro-Kellie doctrine fell asunder.

During this same period some crude estimations of intracranial blood perfusion were made. Methods included the placement of thermocouples in the internal jugular vein (14) and in the brain substance itself (15), and the measurement of the outflow from the cerebral veins (16) and the inflow into the internal carotid artery (17). Unfortunately, most of the work of this era so violently disrupted the normal physiology of the brain or so poorly estimated the sought-after quantities, that little definitive information was obtained. This can be well exemplified by the work of Finesinger (17); who concluded that of all the various conditions to which his experimental monkeys were subjected, including hypercapnia, hypocapnia, hypoxia, acidosis and alkalosis, the most marked variations in brain blood flow occurred with variations in perfusion pressures, even when these pressures were kept well within physiological limits. The important contributions of the era are reviewed in detail by Wolff (15). Certainly the two most significant in the light of present-day knowledge were:

- a. The finding that there is local autoregulation, by whatever mechanisms, of brain blood supply.

b. The finding that the innervation of the brain vasculature exercises little and certainly no significant vasomotor control. Both of these points have been repeatedly confirmed by later and more refined research.

In 1943 Dumpke and Schmidt (18) reported their findings on brain blood flow as measured in the internal carotid arteries of the rhesus monkey by the bubble flowmeter. Their method did not, apparently, too drastically alter normal physiology, because their findings have been confirmed in large part by many other workers.

Kety and Schmidt (19) in 1945 introduced the nitrous oxide method of determining brain blood flow, based on the indirect Fick (20) principle. This method, easily applied to man, has subsequently been found to be reasonably accurate and reliable, with a few minor limitations (21,22). There have been many modifications of the technique; the blood sampling has been made less tedious, the blood specimens have been reduced in amount, and radioisotopic materials have been substituted for nitrous oxide. Further modifications have allowed estimation of regional as well as total blood flow.

These methods and their results have been summarized by McHenry (23) and Lassen (24). More specifically pharmacological aspects have been reviewed by Sokoloff (25).

Although the methods of the previous paragraph confirmed the presence of autoregulation of brain blood flow, all of them are quite indirect. More importantly, however, they permit only intermittent estimation of flow, usually requiring several minutes for each single

determination. Further, there are serious limitations in the number of serial determinations that can be made using most of the methods. Obviously, conditions cannot be changed during the period required for a determination. Such techniques can not be used for evaluating rapidly changing conditions or transient events. These factors pose serious disadvantages in the use of these methods to evaluate the mechanisms of blood flow regulation. This fact becomes more evident when one considers the nature of the pressure-flow relationships in vascular beds.

B. Pressure-Flow Relationships in Vascular Beds

In all studies performed to date relating blood flow, F , to perfusion pressure, P , under conditions precluding autoregulation, resistance to flow, defined as P/F , decreases with increasing pressure (26-34). The exact relationship of pressure to flow is in some question, and specifically has not been determined for the vascular bed of the brain. The factors causing resistance to decrease with increasing pressure include: (a) passive dilatation of the resistive bed, (b) the beginning or cessation of flow not at zero but at some positive perfusion pressure--the critical closing pressure of Burton (35), and (c) a slight decrease in viscosity with increasing flow rates, though this latter factor appears to be of minor importance (36,37).

Figure 1 shows a typical hypothetical relationship of flow versus pressure at constant vasomotor tone. Computations of peripheral

Fig. 1.--Hypothetical flow vs. pressure curve. This shows a decrease in calculated peripheral vascular resistance, P.V.R., with an increase in blood pressure from P_1 to P_2 , with constant vasomotor tone.

$$P.V.R. = \frac{P}{F}$$

$$P.V.R._1 = \frac{80}{2} = 40$$

$$P.V.R._2 = \frac{120}{5} = 24$$

Figure 1

vascular resistance, P.V.R., at pressures P_2 and P_1 indicate a marked reduction at P_2 .

A change in vasomotor tone will cause a shift of the flow versus pressure curve, as seen in Figure 2. Although vasomotor tone has changed, equal values of P.V.R. are computed at pressures indicated by points P_1 and P_2 .

Figure 3 illustrates how a change of vasomotor tone can be clearly demonstrated if the flow versus pressure relationships are known for two different vasomotor tone conditions. At any given pressure, a decrease of tone is indicated by an increase in flow, and vice versa. Similarly, at any constant rate of flow, an increase of tone is indicated by an increase in pressure, and vice versa.

From Figures 1 and 2 it is evident that single values of resistance are inadequate for a meaningful description of the vascular bed unless either (a) the relationship between pressure and flow with vasomotor tone constant is known, or (b) either pressure or flow is held constant during the observation period. The literature contains no reports of investigations of brain blood flow of the type described under (a). Though few in number, some investigations of the type described under (b) have been reported.

Geiger and Magnes (38) perfused cats' brains at controlled pressures while measuring brain blood flow by venous outflow through a stromuhr. Many alterations of the vascular anatomy requiring extensive dissection were required to assure that the venous outflow measured was representative of brain blood flow. These workers

Fig. 2.--Hypothetical flow vs. pressure curves. These show equal values of peripheral vascular resistance at pressures P_1 and P_2 , although there has been a marked change in vasomotor tone as demonstrated by a shift in the flow vs. pressure curve from A to B. The dashed line is a locus of points of equal ratio of P to F, or an iso-resistance line.

Figure 2

Fig. 3.--Hypothetical flow vs. pressure curves. Change in vasomotor tone is clearly shown by the difference in rate of flow at any given pressure. A line of constant pressure (dashed line), arbitrarily chosen at 100 mm. Hg., is drawn upward through curves A and B, which represent two different conditions of vasomotor tone.

Figure 3

reported no significant evidence of autoregulation either to perfusion pressure changes or to arterial carbon dioxide tension.

Guyton and Sagawa (39) in 1961 perfused dogs' brains while measuring arterial inflow with a strohmuhr. Again extensive dissection was necessary to preclude the passage of the measured blood flow to areas other than the brain. Again, no evidence of autoregulation in response to changes in perfusing pressure was reported.

Rittman (40), in 1966, measuring arterial inflow with the electromagnetic flowmeter, showed minimal evidence of autoregulation with perfusion pressure. However, it is evident in his report that a large and indeterminant part of the flow he measured perfused extra-cranial structures.

In contrast to the above three reports, Rapela and Green (41), after reporting that they had achieved good isolation of brain circulation from extra-cerebral circulation, showed excellent autoregulation of brain blood flow with variations in perfusion pressure in the dog. Brain blood flow remained essentially constant with pressures from 50 to 100 mm. Hg. Using the Kr⁸⁵ clearance method (42) for determining brain blood flow in the dog, Haggendal and Johannsson (43) also have shown marked autoregulation of brain blood flow with variation in perfusion pressure. In their study, flow remained nearly constant over a range of pressure from 40 through 160 mm. Hg.

Findings by Haggendal (43) and Harper (44) dispute the lack of autoregulation of brain blood flow with changes in arterial carbon dioxide tension which was reported by Geiger and Magnes (38).

Haggendahl and Harper, both determining brain blood flow by the radioactive Kr^{85} clearance method in dogs, varied arterial carbon dioxide tension while holding perfusion pressure constant. Brain blood flows decreased about 25% with lowering of arterial carbon dioxide tensions to 15 mm. Hg. and increased to from 50% to 100% with elevation of CO_2 tension to 80-90 mm. Hg. Reivich (45) obtained similar results perfusing the monkey brain at constant pressure while measuring internal jugular flow with thermistor flowmeters.

In agreement with previous work by Green (46), Reivich found that arterial oxygen tension had no significant effect on brain blood flow. Haggendahl (43), however, showed up to 100% increase in flow with low arterial oxygen tension and significant reduction in flow with higher than normal oxygen tension.

Using methods already described above, Rapela (47) found that variations of blood pH appear to alter brain blood flow in a manner independent from the effects of CO_2 tension. Again using the Kr^{85} clearance technique, Harper (48) found no effect of pH on brain blood flow in the absence of alterations in CO_2 tension. The latter finding correlates with the findings of Schieve (49) using the nitrous oxide method of flow determination in man.

When one analyzes the results of the research described in this section, it is clearly, if painfully, evident that there are major points in dispute regarding every mechanism commonly held to control brain blood flow. The controlling variables upon which these mechanisms

are based include: (a) blood pressure, (b) carbon dioxide tension, (c) oxygen tension and (d) hydrogen ion concentration.

In the past, some consideration has been given to the innervation of the vasculature of the brain and to adrenergic and cholinergic substances as possible mediators of brain blood flow. Presently there is general agreement that these factors do not exercise any significant control over the vasomotor activity of the brain (50-54).

The small number of these studies, the lack of agreement among them in many cases, and the gross distortion of the circulatory anatomy in others, indicate the need for more investigation, preferably by improved methods, of the mechanisms of control of brain blood flow.

C. The Dynamic Pressure-Flow Relationship--DPFR

In 1953 Wetterer and Pieper (55) employed a positive displacement pump, whose output described a sine wave, to force blood into and draw blood out of the arterial system of experimental animals. This resulted in an oscillation of the arterial blood pressure of the same frequency as the pump cycle, upon which the usual pressure variations with each heartbeat were superimposed. Wetterer and Pieper originally used the method to determine the elasticity of the arterial system, but it also enabled them to calculate diastolic outflow from the arterial system by analysis of the diastolic pressure slopes in conjunction with the pump displacement (56). Thus a relationship between total outflow from the arterial system and pressure could be determined over the range of pressures resulting from the pump action. This

pressure-flow relationship could also be determined for any particular regional vascular bed if the arterial inflow into the bed could be determined by a method whose frequency response was reasonably rapid in comparison to the pump cycle. The pressure-flow relationship was determined for the common carotid artery distribution of the dog by Pieper and Wetterer (30) and for the coronary arterial bed by Pieper and Paul (26).

Pieper has called this relationship the dynamic pressure-flow relationship, or DPFR, to distinguish it from other reported pressure-flow relationships in which vasomotor activity is not precluded during the relationship determination. Vasomotor activity is precluded by operating the sine wave positive displacement pump at a speed too great to allow vasomotor response--usually about one cycle every four seconds. That this speed is too great for such responses in the general circulation has been determined by Guyton (57), Scher and Young (58), and Leverett (27). Further supporting evidence is found in innumerable experiments in which a stepwise change in perfusion pressure has been applied to various vascular beds, including that of the brain (41,54). In these cases, active vasomotor response is not seen in less than about 15 seconds.

Since the DPFR is capable of indicating actual changes in vasomotor tone, it would appear to provide an effective way to evaluate the vasomotor control of brain blood flow. In an effort to obtain information which might help to resolve the discrepancies set forth in Section B above, DPFR's for brain blood flow were determined under

various physiological conditions in the neurosurgical research laboratory of The Ohio State University. These determinations provide the basis for this dissertation.

D. Isolation of Brain Blood Flow

A major obstacle in the assessment of brain blood flow is the problem of isolating the blood perfusion system of the brain from vasculature perfusing non-nervous structures. Specifically, such isolation is necessary if dynamic pressure-flow relationships are to be determined. Intercommunications, both arterial and venous, were described in detail in various species, including dog, cat, monkey and man by Batson (59). Arterial communications, in these and still other species, were considered by Ask-Upmark (60). He described a "rete mirabile," a diffuse arterial intercommunication network over the surface of the brain, which is seen in many species, including the dog and cat, but not in monkey or man. Both of these authors described intercommunications between the external and internal carotid circulations through the ophthalmic area and in the area of the base of the skull in the middle fossa, but on the basis of dye studies, Batson concluded that these communications were not important in monkey or man. His findings in this regard were corroborated by Dumpke and Schmidt (18), and Hedlund (61). Jewell (62) and Green (51) on the other hand, have attested to their major importance in the dog.

The anastomoses of the vertebral arteries with the extracranial circulation in the neck are well known. They exist in all species of

commonly employed laboratory animals and in man, and were described in detail by Batson. Their major functional importance has been strikingly demonstrated by White (63), Schechter (64), and Donald (65). However, there are no known significant communications between the extracranial circulation and the vertebral arteries distal to their passage through the dura. Unfortunately, access to these arteries in this region is technically very difficult and measurement of flow through them in this region has not been reported. Many studies have been reported in which flow is measured through the vertebral arteries proximal to their entry into the transverse foraminal canal, but such measurements are obviously poor estimators of brain blood flow.

In the neurosurgical laboratory of The Ohio State University, several attempts have been made to apply electromagnetic flowmeters to the vertebral arteries just proximal to the point where they pierce the dura. Successful flow measurements were made on two occasions, but the technical procedure required to properly apply the flowmeters was so expensive and time-consuming that these efforts were abandoned in favor of the procedure to be described and justified below.

Descriptions of the venous outflow from the brain have been supplied not only by Batson, but also by Shenkin (66) and in the dog by Sagawa (39) and Green (51). In all common laboratory species as well as in man, it appears that there are multiple intercommunications between the intracranial and extracranial venous systems. While it has been shown that most of the blood passing through the jugular bulbs comes from intracranial structures, it does not appear that all

drainage from intracranial structures follows this route. Instead, a sizeable and apparently variable amount of blood passes from the brain through (a) the base of the skull and the pterygoid plexus, (b) the veins of the orbit, (c) several emissary veins, and (d) the internal and external vertebral plexuses. The capacities of these channels can perhaps best be appreciated when it is considered, as Batson pointed out, that even in man both internal jugular veins are frequently ligated without disaster.

Many of these workers who have described the multifarious intercommunications between the intracranial and extracranial circulations have also offered methods of dealing with them. Unfortunately, such methods require extensive dissection, usually with rather drastic disruption of the normal anatomy, and probably of the corresponding physiology. It is likely that these factors account in large part for the diverse conclusions which have been drawn from research employing these methods (See Section B, above).

Is there a method of measuring the blood flow through a fixed portion of the brain which does not require such disruption of normal conditions? On the basis of Batson's conclusion that communications between the external and internal carotid circulations in man and monkey are insignificant, a test was devised. If the communications are significant, then when the blood supply of the external carotid bed is occluded, blood flow through the ipsilateral internal carotid artery should increase to help supply the external carotid bed through the functionally significant communications. Likewise if the internal

carotid artery is occluded, flow through the external carotid artery should increase. The reasoning behind this test seemed sound, and the work of Green (67) supports its validity.

A review of the literature showed that Symon (68) had performed such a test in the monkey. Applying an electromagnetic flowmeter to the common carotid artery, he measured flow through the artery first with the external carotid artery occluded, then with the internal carotid artery occluded, and then with both branches open. The sum of the flows with one branch occluded did not exceed the flow with both branches open by more than five per cent. Similar findings are shown in tracings of flow measurements obtained by Meyer (69) though no statement to this effect was made in his paper. Finally, these findings were confirmed by similar measurements performed in the neurosurgical laboratory of The Ohio State University. Thus, it is evident that communications between the external and internal carotid arterial beds in the monkey, under normal conditions, are not significant. Further, the test shows that the communications are not significant when the internal carotid flow is measured with the single ipsilateral external carotid artery occluded. It must be stressed, however, that these statements might not hold if additional arteries of supply to the area are occluded. This point is emphasized by Green (67). Indeed, Meyer (69) has shown that the communications do become significant when the contralateral carotid arteries are occluded. Undoubtedly, supply of the occluded external carotid bed by known rich anastomoses with its fellow of the opposite side is important in precluding supply from

the ipsilateral internal carotid artery through its existent but normally functionally insignificant communications.

The knowledge that the communications of the internal carotid artery with the external carotid bed are insignificant, even with the external carotid artery occluded, is important, because it allows one to ligate the latter artery and measure brain blood flow by placing the flowmeter on the common carotid artery. Placement of the flowmeter on the internal carotid artery itself is technically much more difficult, and requires much more extensive dissection, which, as has already been emphasized, is to be avoided if at all possible.

Thus it appears evident that measurement of blood flow through the common carotid artery with the ipsilateral external carotid artery ligated provides an adequate basis for the determination of the dynamic pressure-flow relationships of brain blood flow in the monkey.

CHAPTER II

MATERIALS AND METHODS

A. The Chronic Restraining Chair

Dynamic pressure-flow relationships of brain blood flow were determined in adult male rhesus monkeys, ranging in weight from 8.2 to 11.4 kilograms. Because of the known inhibitory effects of anesthetic agents, especially the barbiturates, on vasomotor activity in general (70-73), and on brain blood flow and metabolism in particular (25,74,75), these dynamic pressure-flow relationships were determined while the animals were awake and alert. To accomplish this, it was necessary to construct a chronic restraining chair which would allow access to the animal while at the same time preventing him from interfering with the experiment. Such a chair is shown in Figure 4.

The supporting frame for the chair is aluminum, while the chair itself is made of Plexiglas (Rohm and Haas Company, Philadelphia, Pennsylvania). The chair may rotate around its lateral axis by means of the swivels labelled A. This allows the animal to be placed in a reclining position, if desired. To preclude pressure necrosis while in the reclining position, a hammock, B, made of a fluffy, wool-like synthetic material (Decubicare Pad, Norwood Mills, Inc., Janesville, Wisconsin) is applied to the back of the chair. When in the upright position, this back may be removed and replaced by a single one-inch-wide nylon strap, covered with the fluffy material, across the mid back region. Thus, one is afforded access to either the front or the

Fig. 4.--Monkey chronic restraining chair. The chair may rotate around its lateral axis by means of the swivels, A. The back hammock, B, is made of a material designed to minimize the possibility of pressure necrosis.

Figure 4

back of the animal, while the animal is prevented from reaching these areas, but has free access to his mouth and head for feeding purposes.

The seat of the chair is constructed of 3/8 inch diameter stainless steel rods, so spaced that the natural ischial callosity covers two rods. This arrangement permits excreta to fall into the collecting pan below. The seat may be raised or lowered through a range of about five inches to accommodate variations in animal size.

Conductive materials in the vicinity of electromagnetic flowmeter leads can cause significant variations in output. Therefore, special attention was given to avoiding the use of metal in the vicinity of the flowmeter or its leads. Nylon nuts, bolts, screws and washers (Weckesser Company, Inc., Chicago, Illinois) were used in place of metal wherever necessary.

Animals have remained in the chair for over three months without harmful effects except gradual weight loss.

B. Chronic Implantations

1. Electromagnetic flow probes and vessel occluders.--To allow DPFR's to be determined with the monkeys awake, it was necessary to make chronic implantations of the electromagnetic flowmeter probes and certain other devices which will be described below. The probes used were of the Series Q type manufactured by Statham Medical Instruments, Los Angeles, California. They were fabricated especially for chronic implantation. The bodies were made of a hyporeactive epoxy resin, while the leads were encased in silicon tubing, and were fitted

on the outer end with miniature five-pin connectors. Originally, these connectors were not properly shielded, and when they were handled while the flowmeter was in operation, large variations in output occurred. As a result, the connector had to be taken apart, the leads had to be separated and shielded with silver paint (G-C Silver Printed-Circuit Print, G-C Electronics, Division of Hydrometals, Inc., Rockford, Illinois) and finally the connector had to be reassembled, coated, and bonded together with the epoxy material of its original manufacture (Casting compound C9-4206, Hardener H2-3490, Hysol Corporation, Olean, New York). Statham Medical Instruments was informed of this condition, and later probes were properly shielded, which was evident upon X-ray examination and was verified by their proper operation.

Probes of either 2.5 or 3.0 mm. lumen diameter, appropriate to the size of the common carotid artery, were used. Probes on arteries for chronic implantations should fit fairly loosely, instead of producing the 10 to 20% reduction in artery diameter advised in acute implantations.

Electromagnetic flowmeters require that a zero baseline be obtained by mechanical occlusion of the artery distal to the probe. It was necessary to devise a means to accomplish this in a chronic animal preparation. A device for this purpose is shown in Figure 5. The bodies of the occluders are made of the same epoxy material as the flow probes. A short section (about 3/16 of an inch) of thin-walled silicone rubber tube, A (Cat. No. 7002-040 Vivosil Medical Grade

Fig. 5.--Remote vessel occlusion device. Fluid forced through the thick-walled silicone tube, B, by a micrometer syringe, expands the thinner-walled tube, A, compressing an artery within the housing of the occluder against the opposite side. The housing is made of hyporeactive epoxy material. A U.S. dime is shown for size comparison.

Figure 5

Silicone Tubing, Becton, Dickinson and Company, Rutherford, New Jersey) is closed off at one end by a 6-0 stainless steel surgical wire ligature. The other end is secured by a similar ligature to one end of a 1/8 inch long section of an 18 gauge needle shaft. A thicker walled silicone tube, B (Cat. No. 7002-040-1), is similarly secured to the other end of the needle shaft.

Epoxy is then fashioned to the shape shown and drilled to receive and enclose the thin-walled silicone tube. Additional epoxy is then used to seal and fuse the parts together.

The occluder is then fused with additional epoxy to the distal end of the robe as shown in Figure 6. Eyelets, A, used to hold the probe in place in the animal, are made from the same epoxy materials.

To operate the occluder, a micrometer syringe filled with water is attached to the open end of the thicker walled tube. Fluid is forced through this tube into the thinner walled tube, expanding it and compressing the artery against the opposite side of the occluder housing. A partially damped tracing of flow recorded from the output of an electromagnetic flowmeter is shown in Figure 7. Vessel occluder operation is clearly indicated. The second tracing seen in Figure 7 is aortic pressure.

Before implantation, the probe-occluder assemblies were treated with Siliclad (Clay-Adams, Inc., New York, N.Y.) to provide a silicone coating of the epoxy parts to minimize tissue reaction. Tests were made in vitro to assure that such a coating would not interfere with probe operation.

Fig. 6.--Remote vessel occlusion device affixed to electromagnetic flow probes. Eyelets, A, also affixed to the probes, are used to hold the probe in position in the experimental animal. A U.S. dime is shown for size comparison.

Figure 6

Fig. 7.--Electromagnetic flowmeter tracing showing zero flow baseline obtained by vessel occlusion produced by the remote vessel occlusion device. The second tracing is a recording of aortic pressure.

The epoxy of the probes and occluders will not withstand either autoclaving or ethylene oxide gas sterilization. For this reason the probe-occluder assemblies were sterilized by soaking for three hours in 2% glutaraldehyde solution (Cidex, The Arbrook Company, Somerville, New Jersey).

Surgery was performed under general Fluothane (Halothane, Ayerst Laboratories, Inc., New York, N.Y.) endotracheal anesthesia. The animal was pre-medicated with about 0.5 mgm./lb. of Sernylan (76) (1-[1-phenylcyclohexyl] piperidine HCl, Parke, Davis and Co., Detroit, Michigan). This provided excellent sedation and analgesia. Under this premedication, the animal was shaved as necessary to provide a clear surgical field, an intravenous infusion was started, and the endotracheal tube passed. With the monkey in the supine position, the head was secured in a pin-vise designed for this purpose. The skin was prepared by thorough scrubbing with hexachlorophene detergent (Hexa-Germ, Huntington Laboratories, Huntington, Indiana) and povidone-iodine surgical scrub (Betadine, Physicians Products Company, Inc., Petersburg, Virginia).

Atropine (Intra-Products, Inc., Dayton, Ohio), 0.2 mgm. was given intravenously, and general anesthesia was then administered.

Under standard sterile surgical conditions, an incision was made from just behind the angle of the mandible downward along the sternomastoid muscle nearly to the clavicle. Bipolar electrocoagulation was used to maintain meticulous hemostasis.

In the monkey it is important to stay laterally in this region, close to the sternomastoid muscle, lest one enter the pharyngeal pouch. Should this pouch be entered, a direct communication is established from the area of implantation to the oral cavity and the outside world, which would be disastrous to any chronic implant.

The carotid sheath was located, opened, and the carotid artery dissected free from a point inferior to the omohyoid muscle to above the bifurcation. The external carotid artery was ligated; the sinus nerve was left intact. The flow probe was applied and tested. Securing the position of the probe to provide accurate alignment and minimal trauma to the artery required resection of a small amount of the longus cervicis muscle. Besides providing space for the probe, this allowed access to the periosteum of the lateral processes of the cervical vertebrae, to which the flow probe could be rigidly affixed by means of its eyelets with 5-0 Tevdek suture (J. A. Deknatel and Son Inc., Queens Village, Long Island, New York). A picture of the probe and vessel occluder fixed in position at surgery is shown in Figure 8. The carotid bulb is indicated by A and the ligature of the external carotid artery is seen at B. The flowmeter probe ground connection is labelled C.

The leads from the probe and the operating tubing from the occluder were brought around the sternomastoid muscle and passed through the subcutaneous space posteriorly to a point just medial and inferior to the clavicle. The wound was closed in four

Fig. 8.--Electromagnetic flowmeter probe and vessel occluder fixed in position on the common carotid artery. The carotid bulb is labelled A. The arrow from B points to the ligature on the external carotid artery. The flow probe ground lead is labelled C.

Figure 8

layers: (a) deep cervical fascia, (b) platysma, (c) subcutaneous tissue and (d) skin. Tevdek 5-0 suture was used throughout, and the skin was closed with a subcuticular stitch to prevent the animal from removing the sutures.

After this procedure and after implantation of femoral catheters as described below in Subsection 2, the animal was returned to his cage for seven to ten days before the flow probe and occluder leads were brought to the exterior posteriorly. This delay was necessary to allow tissue ensheathment of the leads, which prevented infectious agents from passing inward along the tract through which the leads were brought out. In early trials of the procedure, the leads were exteriorized at the same time that the probes were implanted, and infection frequently ensued. No infections were seen after this staging delay was incorporated. Further protection against infection was provided by giving the animals 0.5 c.c. of Combiotic (Chas. Pfizer and Company, Inc., New York, N.Y.) twice daily starting before surgery and continuing until his usefulness as a research animal terminated.

The exteriorization procedure was simple. Under Sernylan sedation and analgesia a small (1.5 cm.) incision was made over the flowmeter connector, which then was brought to the exterior along with the occluder activating tubing. After these parts were cleaned and dried, brain blood flow could be recorded. Flow measurements could be obtained from probes implanted as described above for as long as three months after implantation.

2. Femoral catheters.--Immediately after implantation of the flow probe, catheters were implanted in each femoral artery. Femoral catheters were necessary to connect the animal to the sine wave positive displacement pump and to pass a catheter-tip manometer into the aorta. However, since the catheters to be used for these purposes were too large to be chronically implanted, tiny teflon guide catheters were implanted so that larger catheters could be passed immediately before the determination of DPFR's, by a procedure to be described below in Section D. The implanted catheters had a 0.027 inch inside diameter and a 0.047 inch outside diameter (Cat. No. TTX 027, Becton, Dickinson and Company, Rutherford, New Jersey). One such catheter is indicated by A in Figure 9. Its outer end is fitted with a female luer lock catheter adapter (Cat.No. 3021F).

Surgical prep for catheter implantation was the same as for probe implantation, described in Subsection 1, above. A two centimeter long incision was made along the inguinal ligament over the femoral artery. The artery was dissected free, and punctured just at its exit from under the inguinal ligament with a 19 gauge thin-walled modified Cournand needle (Cat.No. PN-25, U.S. Catheter and Instrument Corp., Glens Falls, New York). A stainless steel spring wire guide of 0.025 inch diameter (Cat.No. SG-25F, U.S. Catheter and Instrument Corp., Glens Falls, New York) was then passed through the needle and up into the artery a few inches. The needle was withdrawn and the catheter passed over the wire into the artery. The wire was then withdrawn. A cap, indicated by B in Figure 9

Fig. 9.--Femoral catheter assembly. The assembly, C, actually consists of catheter D slipped through catheter E. The tip of D is tapered, as shown at F, to dilate the orifice of the artery to receive the larger catheter, E. Fitting G is a Tuohy-Borst adapter, which serves as a packing gland to prevent the egress of blood around the wire. Closing stopcock H precludes blood loss after the wire is withdrawn. The fitting I is another, larger, Tuohy-Borst adapter, preventing blood loss around the inner dilator catheter. Stopcock J prevents blood loss after the inner catheter is removed. Stopcock J is of special type, with the bore enlarged to three millimeters to allow passage of the pressure manometer or to allow fluid flow from the positive displacement pump with minimal resistance.

Figure 9

(Cat.No. 42-0004, Becton, Dickinson Co., Rutherford, New Jersey) was placed over the end of the catheter to prevent blood backflow. A bed to accommodate the adapter and cap was developed in the subcutaneous space. The wound was closed in layers with Tevdek 5-0 suture. Again a subcuticular stitch was used in the skin.

Usually about two to three centimeters of this catheter extended into the artery. Thrombotic problems were infrequent and minor if the entry point of the catheter into the artery was right at the inguinal ligament. However, if the catheter entered farther inferiorly, thrombosis became a problem, and in one case led to necrosis of the extremity, infection, and death of the animal. This probably occurred because the catheter was placed too far distally so as to encroach upon the origin of the deep femoral artery. It is likely that this artery supplies collateral circulation from the gluteal vasculature if the catheter causes occlusion of the femoral artery proximally.

Exteriorization of the outer ends of the catheters was delayed for the same length of time as the exteriorization of the flow probe leads, and for the same reasons. A one-centimeter incision was made over the cap on the catheter adapter, and the outer end of the adapter was brought outside and secured in place with 2-0 Tevdek suture.

3. Indwelling tracheostomy.--Since changes in the DPFR's of brain blood flow were to be observed while the experimental animals were breathing various concentrations of respiratory gases, it was necessary to devise a method of administering these gases with the

animals awake. A device for this purpose is shown in Figure 10. It is made entirely of Teflon (Polypenco T.F.E., Dayton Plastics, Inc., Columbus, Ohio) except for the adapter, A, and the balloon and tubing, B. The adapter allows the device to be connected to standard anesthesia fittings and also allows respiratory gas sampling from a 21 gauge hypodermic needle, C, welded into the side wall.

The adapter is made of stainless steel (AISI type 316, Williams and Company, Inc., Columbus, Ohio). When assembled, the device fits into the trachea as shown at D, with a piece of transparent tubing simulating the trachea. Only the flanges, E, fit inside the trachea. The shaft, F, though split, is threaded to allow the retaining nut, G, to hold the sealing collar, H, in place. A second nut, I, serves to lock the first. It is evident that the device does not occlude the trachea when the balloon is not in place. Under these conditions, if the cap, J, is applied, the animal breathes through the normal respiratory passageways. The balloon is made from the tip of a finger cot, and is placed in position only during an experimental run to keep respiratory flow from passing upward or downward through the larynx. Under these conditions, the animal must breathe through the tracheostomy.

This device was put in place at the same time that the electromagnetic probe leads and femoral catheters were exteriorized, using only Sernylan analgesia and local Xylocaine (Astra Pharmaceutical Products, Inc., Worcester, Massachusetts) anesthesia. A standard tracheostomy approach was made. Placement of the indwelling

Fig. 10.--Indwelling tracheostomy. An adapter, A, allows the device to be connected to standard anesthesia fittings. Respiratory gases may be sampled through the needle, C, welded into the side of the adapter. The device is shown assembled, D, in a transparent tube simulating the trachea. Only the flanges, E, fit inside the trachea. The retaining nut, G, holds the sealing collar, H, down against the tissues of the neck around the threaded shaft, F. A second nut, I, locks the first in place. The cap, J, covers the outlet when the device is not in use so that the animal then breathes through the normal respiratory passages. During an experiment, the cap is removed and the balloon, B, is put in place and inflated, blocking flow upward through the larynx. Under these conditions the animal must breathe through the tracheostomy.

Figure 10

tracheostomy device was made easier by having an endotracheal tube in place to support the flanges against the anterior tracheal wall while the sealing collar and retaining nut were snugged down.

This indwelling tracheostomy caused the animals minimal annoyance. They sometimes developed a mild cough, which was probably necessary to loosen secretions accumulating around the flanges. While the device was in place, no major pulmonary complications could be attributed to it.

In two cases, animals succeeded in removing the device, but only after it had been in place for more than three months. Actually, they did not remove it until it had eroded through the anterior tracheal wall. Removal of the device under these conditions can be disastrous, because, with the tracheal rings eroded away anteriorly, the trachea is without support, and may collapse, suffocating the animal. This occurred in one case.

After exteriorization of the flow probe and occluder leads and the outer ends of the femoral catheters, and placement of the indwelling tracheostomy, the animal was placed in the chronic restraining chair to prevent him from tampering with these devices.

C. Instrumentation

1. Sine wave positive displacement pump.--As discussed in Chapter I, Section C, a sine wave positive displacement pump is required to determine DPFR's. The basic characteristics of the pump used in this research have been described by Leverett (27), Wetterer

and Pieper (30), Pieper (77), and Pratt (78). Therefore, only certain modifications will be described here.

The pump was driven by a variable speed D.C. motor controlled by an electronic speed controller (Motor No. NSH 54RL40, Controller No. CX25, Gerald K. Heller Co., Las Vegas, Nevada). This allowed speed control from five to fifty revolutions per minute. The displacement of the pump was transmitted to the recorder by a linear differential transformer displacement transducer (Model 7DCDT 3000, Sanborn Division, Hewlett-Packard Company, Waltham, Massachusetts). The transducer was driven by a Sanborn Model 350-4 D.C. Strain Gage Plug-In unit, operating in a Sanborn 350-1500 Low Level Preamplifier. The latter unit also amplified the output signal to drive the recorder.

The pump was calibrated simply by noting the volume it pumped into a graduate cylinder with each stroke, and correlating this volume with the recorder deflection.

A volume transmitter to allow isolation of the animal's arterial system from any direct connection to the pump was constructed to prevent blood from entering the pump and to keep the animal's blood sterile while still allowing it to flow in and out of the arterial system. This transmitter is shown in Figure 11. The body is made of Plexiglas. The pump communicates with the hemispherical chamber, A, through the fitting, B. A silicone rubber diaphragm, C (Vivosil Medical Grade Surgical Drainage Tubing Cat.No. 7007-1, Becton, Dickinson and Company, Rutherford, New Jersey), separates the

Fig. 11.--Volume transmitter, used to allow isolation of the animal's arterial system from any direct connection to the sine wave positive displacement pump. The pump communicates with the hemispherical chamber, A, through the fitting, B. A silicone rubber diaphragm, C, separates the hemispherical chamber, A, from the opposing chamber, D. This seal is made complete when the screws, E, are snugged down on the Plexiglas body, as shown in the unit on the left. Any volume change in chamber A must be transmitted precisely by deformation of the elastic diaphragm to chamber D. Chamber D is connected to the animal's arterial system through the special large bore stopcock, F. Stopcocks G and H are for bleeding off gas bubbles. Stopcock H may also be used for making intra-arterial injections.

Figure 11

hemispherical chamber, A, from the opposing similar chamber, D. This seal is made complete when the screws, E, are snugged down as shown in the unit at the left. Any volume change induced in chamber A must be transmitted precisely to chamber D by deformation of the elastic diaphragm. The total volume of the entire sphere--that is, the sum of the volumes of chambers A and D--is about 50 cubic centimeters.

Chamber D is connected to the animal's arterial system through the stopcock, F (Cat.No. MSIO-T1, Becton, Dickinson and Co., Rutherford, New Jersey). This stopcock is of especially large bore (0.098 inch) as it comes from the manufacturer, but its bore is further enlarged by drilling to three millimeters to assure minimal resistance to fluid flow. The other two stopcocks, G and H, are of standard type and are for bleeding off gas bubbles. Stopcock H can also be used to make intra-arterial injections.

Since Plexiglas cannot withstand autoclaving, the transmitter unit was sterilized by the ethylene oxide gas technique, a service supplied by the surgical facility of The Ohio State University Hospitals.

2. Electromagnetic flowmeter.--The flowmeter used in this research was the Medicon M-4000 with M-4001 flow modules (Statham Medical Instruments, Los Angeles, California). As received from the factory, this equipment was unsatisfactory in several respects.

First, the main power transformer, listed in the manufacturer's wiring diagram as TR1, was of insufficient voltage rating to provide

voltage regulation of the B+ and B- power supplies. The power supply was sent back to the manufacturer in exchange for a supposedly corrected unit, but it was found that the design of this unit required overloading of the B- OB2 voltage regulator tube, V2. This was corrected by increasing the value of the dropping resistors in this circuit from 3750 ohms to 10,000 ohms.

The vacuum tube heater power supply voltage was low and poorly regulated. This occurred because the resistance of R8 was too great and there was too little power dissipation in the V4 zener diode. The resistance of R8 was changed from 150 ohms to 10 ohms, and the V4 zener was changed from a 1N3022A to a 1N2976B, resulting in well regulated heater voltage of proper magnitude.

In the M-4001 flow module, the manufacturer had used a polarized electrolytic capacitor, C8, in the mean output circuit. Since this circuit frequently reverses in polarity, the capacitors soon broke down, and were replaced by non-polarized capacitors of equal rating (2000 microfarads, 12 volts) without further difficulty in this area.

As the flowmeter warmed up over a period of several hours, its output became non-linear--in some cases resulting in errors of up to 60% in flow readings. The precise origin of this fault was never objectively determined, but on theoretical grounds the malfunction probably resulted from overheating of transistors V5 and V6. Regardless of origin, increased ventilation of the equipment corrected the faulty operation. To increase ventilation, additional louvers were

cut in the bottom of the cabinet, and an exhaust blower (Whisper Fan, Rotron Manufacturing Co., Woodstock, New Jersey) was installed in the top of the cabinet.

After these modifications, the flowmeter operated satisfactorily. The manufacturer was advised of the above faults and corrective changes.

Electromagnetic flow probes were calibrated with saline and with blood of various hematocrits. Blood which was too old to be used for patient transfusion was obtained from The Ohio State University Hospital Blood Bank. The flow probes were fitted to excised arteries of appropriate size from either dogs or monkeys. No differences in calibration characteristics were noted between dog and monkey arteries. Raising the bottle in which the blood or saline was contained to appropriate heights provided sufficient pressure head to induce flow through the artery at any desired rate. Appropriate sizes of Tygon (Tygon Flexible Plastic Tubing, The U.S. Stoneware Co., Akron, Ohio) and polyethylene (Intramedic Polyethylene Tubing, Clay-Adams, Inc., New York, N.Y.) tubing was used to carry fluid from the elevated bottle to the artery, and from the artery to a graduate cylinder. Fluid was collected over a measured period of time in the cylinder, and flow rate was determined as the ratio of measured volume to measured time.

The output from the flowmeter was fed into a Sanborn Model 350-1500 Low Level Preamplifier through a Model 350-2 or 350-2A D.C. Plug-in (Hewlett-Packard Company, Waltham, Massachusetts). Three

different types of Sanborn recorders were used at various times during the research, all of which received equally well the flowmeter output from the Low Level Preamplifier. These were: a Model 296TC two-channel direct-writing recorder, a Model 558M eight-channel photographic recorder, and a Model 4500-AT eight-channel ultra-violet direct-writing recorder. Most calibrations were carried out with the Model 296TC unit.

Linearity of the flow probes was usually within one per cent, and always within two per cent, using any given artery and fluid. Since probe sensitivities usually decrease slightly with increase in hematocrit (79,80), calibration curves were prepared using saline, blood of low hematocrit (about 25%, prepared by drawing off packed cells), blood of essentially normal hematocrit (about 40%), and blood of high hematocrit (over 50%, prepared by drawing off plasma). Some variation in calibration occurred when different bottles of blood were used, even when they had the same hematocrit. This apparently was due to electrolyte composition, but was not investigated further. Accuracy with a given hematocrit was found to be within five per cent even when arteries and bottles of blood were changed and the calibrations were performed several days apart.

On three occasions, calibrations were performed in vitro on the arteries of the experimental animals after they had been used in the determinations of DPFR's. To do this, the flowmeter, artery, and surrounding tissue were excised en bloc, and the calibration tubing

was inserted into the cut ends of the artery. In each case there was a slight decrease in sensitivity, but this was less than five per cent in two cases and about seven per cent in the third. These post-experiment calibrations were discontinued for the following reasons: the changes in calibration were small, and such calibrations were time-consuming and expensive, but more pointedly, they were not essential to the primary research effort, since we compared only relative changes in DPFR's occurring during an experimental procedure.

From the evaluation of the flowmeter system described above, it appeared adequate to measure brain blood flow for the determination of DPFR's, except that frequency response had not been considered. Gessner and Bergel (81) had found less than a five per cent decrease in sensitivity up to fifteen cycles per second in a flowmeter of similar type to the Medicon 4000 instrument. Also noted was a 2.2° /cycle/second phase lag. After this research was in progress, Phillips (82) reported a 3.6° /cycle/second phase lag in the M-4000 equipment, with a two per cent loss of sensitivity at five cycles per second and a six per cent loss of sensitivity at ten cycles per second. Though this performance is less than what might be expected, the frequency response is still very rapid as compared to the sine wave positive displacement pump speed. Therefore, such a frequency response offers no contraindications to the use of the M-4000 Medicon flowmeter in the determination of DPFR's.

3. Pressure measurements.--Aortic pressure was measured with a catheter tip manometer fed up through a catheter in the femoral artery

as described in Section 5 below. This manometer was of the type described by Weterer and Pieper (83). The natural frequency of the device is 450 to 500 cycles per second. According to Fry (84), this should result in a frequency response which is essentially flat up to about 80 to 100 cycles per second.

An impedance matching adapter was made to allow this manometer to be driven by a standard Sanborn Model 350-1100B Carrier Preamplifier. A circuit diagram of this adapter is shown in Figure 12, which is self-explanatory.

With this adapter and preamplifier, maximum sensitivity with the Sanborn recorders was 2.5 mm. deflection per mm. Hg. with the Model 296TC unit or 5 mm. deflection per mm. Hg. with the Model 4508 AT unit.

Venous pressure was measured through a 24 inch Deseret Intracath (C.R. Bard, Inc., Murray Hill, New Jersey) passed up the cephalic or brachial vein and well into the thorax. This catheter was connected through sterile tubing to a sterile venous manometer (Cat.No. 930, Pharmaseal Laboratories, Glendale, California) equipped with appropriate stopcocks to allow flushing and filling of the system with 5% dextrose and 0.2% saline intravenous infusion solution. The reference point on the animal, in the upright position, was taken at the angle of Louis. Since the measurement of venous pressure was always within plus three and minus two centimeters of water, it was not considered necessary to subtract it from aortic pressure to arrive at a reasonable measurement of brain perfusion pressure.

Fig. 12.--Circuit diagram of adapter to allow use of the Wetterer-Pieper manometer with Sanborn Model 350-1100B Carrier Pre-amplifier. Transformer identification figures are the Type Numbers of the manufacturer, The United Transformer Corporation, New York, N.Y.

Figure 12

4. Respiratory gas administration and analysis.--Gases were obtained from The Ohio Chemical and Surgical Equipment Co., Cleveland, Ohio through The Ohio State University Laboratory Supply Store. These were mixed to specifications, and the mixture checked by analysis at the Cardiopulmonary Laboratories of the Ohio Tuberculosis Hospital, using the Scholander technique (85).

Gases were administered through the indwelling tracheostomy with an expandable breathing bag and a non-rebreathing Fink valve (Stock No. 2078141800, Ohio Chemical and Surgical Equipment Co., Madison, Wisconsin). Continuous gas sampling was performed by drawing gas out of the sampling needle of the tracheostomy adapter (See above, Section B, Subsection 3) through an infra-red carbon dioxide analyzer (Model LB-1, Beckman Instruments, Inc., Palo Alto, California). Through a side arm from the sampling tubing, gas was drawn into a nitrogen analyzer (Model A-5, The Waters Corporation, Electro-Medical Instrument Division, Rochester, Minnesota, or Model 305AR, Med-Science Electronics, St. Louis, Missouri).

By continuous expired gas sampling, estimates of arterial blood gases could be obtained. With regard to carbon dioxide, the accuracy of such estimates has been discussed by Suskind (86) and Saxton (87). Accuracy appeared quite good--Suskind was unable to obtain statistically significant differences between end-tidal sample analyses and blood analyses in dogs. In man, Saxton reported that alveolar CO_2 tensions usually averaged about 0.8 mm. Hg greater than blood CO_2 tensions, with a standard deviation of three mm. Hg.

Alveolar oxygen tension estimates were obtained by subtracting measured gas partial pressures from barometric pressure, as shown in the following equation:

$$PO_2 = Ba.P. - 47 - \%N_2 \times Ba.P. - \%CO_2 \times Ba.P.$$

Ba.P. is barometric pressure. The figure 47 represents the partial pressure of water vapor at 37°C. The values for %N₂ and %CO₂ were obtained from the gas analyzers. Such a method is admittedly only approximate, since other inert gases are not taken into account. Suskind (86) and Williams (88) have discussed the accuracy of alveolar oxygen tension as an estimator of arterial oxygen tension. At low oxygen tensions, with animals breathing about ten per cent oxygen, the alveolar-arterial oxygen gradient is only about three to five mm. Hg. However, at normal respiratory oxygen levels, this gradient increases to about twelve to fourteen mm. Hg, and does not change appreciably at higher oxygen tensions. This gradient is due primarily to arterio-venous mixing after blood passes through the pulmonary capillary bed, but is also due in part to variations in ventilation-perfusion ratios throughout the lungs.

In spite of the inaccuracies of the method, it served well in providing indications of relative changes in and general estimates of arterial oxygen tension.

Use of the continuous gas analyzers also provided a good indication of when the experimental animals had reached a steady state after being given a particular mixture of gases to breathe. That is, when there was no longer any change seen in the breath-by-breath

analyses, it was assumed that the animal had equilibrated with the particular gas mixture being administered. This rarely took more than five to ten minutes.

Output from the carbon dioxide analyzer was fed into the recorder through a Sanborn 350-2700 High Gain Preamplifier. A Sanborn 350-1000 D.C. Preamplifier was used to transfer the output from the nitrogen analyzer to the recorder galvanometer.

The Med-Science Electronics Model 350AR nitrogen analyzer was not received until late in the project. The Waters Model A-5 analyzer was of ancient vintage and required nearly constant attention to assure its operation. During several experiments, it failed to operate on one or more of the runs, as indicated by the blank spaces in Table 1, Chapter III, Section B.

D. Experimental Procedure

Five to seven days were allowed to pass after the exteriorization procedures described in Section B before an experimental procedure was undertaken. This delay was to permit at least partial healing of the groin catheter exteriorization sites, so that bleeding from these wounds would not occur when the larger catheters were passed as described below. When fewer than five days of healing time were allowed before an experimental run, bleeding of significant volume occurred from these sites after the animal was heparinized. Heparinization was required to prevent blood coagulation in the isolation volume transmitter of the positive displacement pump.

A small dose, about 0.15 mgm./Kg., of Sernylan was given to the animal as he sat in the chronic restraining chair. The duration of action of this drug is markedly dose-dependent. Because this dose was small, all effects of the drug were usually gone within about 1.5 hours. After the Sernylan had rendered the animal tranquil, he was removed to a table, where the venous pressure and infusion catheter was passed as described in Section C, Subsection 3.

The groin areas were prepared in the same way as has been described for the previous surgical procedures. Using sterile technique, a 0.025 inch diameter stainless steel spring wire guide was passed through the tiny catheters previously implanted in the femoral arteries (See Section B, Subsection 2). The wires were fed several inches up into the arteries, and the small catheters were removed. Larger catheter assemblies, as shown in Figure 9, C, were then fed over the wires into the femoral arteries and up into the abdominal aorta.

The catheter assembly, C, was designed to enter the artery with as little trauma as possible. It actually consists of two catheters, D and E, with D just able to slide through the lumen of E. The tip of D is tapered down, as shown at F, to a diameter that will just allow the passage of the guide wire. Thus the tip of D served to smoothly dilate the entry port in the artery to nearly the size of catheter E. All catheters were made of teflon, to provide minimum friction in passage.

Fitting G is a small Tuohy-Borst adapter (Cat. No. 611A, Becton, Dickinson and Co., Rutherford, New Jersey) which has within it a rubber bushing which is compressed down to fit snugly around the wire by turning the knurled nut. When the catheter assembly was in the animal, then, this fitting served as a packing gland to prevent loss of blood through the inner catheter around the wire.

After assembly C was in position, the wire was withdrawn. The stopcock, H, was closed as the wire passed out to prevent egress of blood.

Fitting I is a second, larger Tuohy-Borst adapter (Cat. No. 614A), which served as a packing gland around the inner dilator catheter. After removal of the wire, this inner catheter was withdrawn. As the catheter passed out through the stopcock, J, the stopcock was closed, again preventing blood loss. At this point, only the larger catheter, E, remained in the femoral artery. On the right side, this catheter was 0.076 inch inside diameter (Cat. No. TTX 076, Becton, Dickinson and Co.) for connection to the positive displacement pump. On the left side, the catheter was 0.095 inch inside diameter (Cat. No. UTX095) to allow passage of the pressure manometer.

The stopcock, J, shown in Figure 9 is of the special large bore type described in Section C, Subsection 1.

The large catheters were secured in position, with their tips in the lower abdominal aorta, with sutures of 3-0 Tevdek around the catheter adaptors and through the skin. At this point it was necessary to heparinize the animal, which was accomplished with 3 mgm./Kg. of

The experimental scheme, then, was as shown in Figure 13. The recorder display could be monitored through the oscilloscope shown (Sanborn Model 769, Hewlett-Packard Co., Waltham, Massachusetts). A tracing made during an experimental run is shown in Figure 14. This tracing was made during epinephrine infusion.

Experimental runs were made under the following conditions:

1. Breathing room air (control run).
2. Breathing 100% oxygen.
3. Breathing 11.16% oxygen, 88.84% nitrogen.
4. Breathing 6.08% carbon dioxide, 93.92% air.
5. Hyperventilating.
6. During epinephrine infusion.

Under each of these conditions the animal was allowed to reach a steady state, as shown on the monitor, before a run was started. By this time, all effects of the Sernylan had worn off, and the animal was awake and alert. The recorder and pump were then turned on, and recording continued through several pump cycles.

An A.V.R. resuscitator (Model No. 24935, National Cylinder Gas Division, Chemetron Corporation, Chicago, Illinois) was used to hyperventilate the animals. This provided a maximum positive pressure of 13 mm. Hg. and a maximum negative pressure of 9 mm. Hg. As can be seen in Chapter III, Tables 1 and 2, it was very effective in reducing alveolar carbon dioxide tension.

heparin sodium (Abbott Laboratories, North Chicago, Illinois).

After locally anesthetizing the trachea and larynx just above the indwelling tracheostomy with Xylocaine (Astra Pharmaceutical Products, Inc., Worcester, Massachusetts), the small rubber tubing from the endotracheal occlusion balloon (Figure 10, B) was passed up through the nose. The balloon was inflated with enough water to snugly occlude the trachea just above the tracheostomy.

The animal was then transferred back to the restraining chair. The electromagnetic flowmeter, nitrogen analyzer, and CO₂ analyzer connections were made as described in the sections dealing with each of these pieces of equipment. Leads were taken from each extremity for EKG recording mediated through a Sanborn 350-2700 High Gain Preamplifier. The sine wave positive displacement pump was connected through the isolation volume transmitter to the left femoral artery catheter, and all air bubbles were bled from this system through stopcocks G and H of Figure 11.

The pressure manometer was calibrated against a mercury manometer and passed into the aorta through the catheter in the right femoral artery. The Tuohy-Borst adapter (Figure 9, I) then served as a packing gland around the manometer to preclude blood loss; at the same time it held the manometer in position. The manometer was manipulated upward to obtain a pressure wave trace as free from reflected wave interference as possible. Such a reflection-free trace was usually obtained when the manometer tip was in the aortic arch or proximal thoracic aorta.

Fig. 13.--Schematic diagram of experimental procedure set-up.

Figure 13

Fig. 14.--Recorder display of an experimental run. During this particular run, the animal was receiving 0.4 microgram/Kg./min. of epinephrine.

Figure 14

Epinephrine (Adrenalin Chloride, Parke, Davis and Co., Detroit, Michigan) infusion was at the rate of 0.4 micrograms per kilogram animal weight per minute. This rate was regulated by diluting the epinephrine in normal saline and infusing at the appropriate rate through an IV-OMETER (No. BM20 IV-ometer, Inc., San Marino, California).

The order in which the experimental conditions were imposed upon the animals was varied at random, except for epinephrine infusion, which was always the last condition imposed. Subjecting the animals to further experimental conditions after epinephrine infusion was considered unwise, since one could not be assured that some epinephrine effect would not persist during further observations. No differences in findings under a given experimental condition could be attributed to the order in which the conditions were imposed.

After the necessary data were obtained, a small dose of Sernylan was administered, and the animal was removed from the chair and placed on a table for catheter removal. The catheters and surrounding areas were prepared as described above for sterile surgical procedures. The guide wires were placed back into the femoral arteries through the catheters, again using the packing glands described above to prevent blood loss. The large catheters were then removed. The small 0.027 inch inside diameter catheters were passed into the arteries over the guide wires, after which the guide wires were withdrawn. Pressure was required over the catheter entry sites at this time to prevent blood loss. Protamine sulfate (Eli Lilly and Co.,

Indianapolis, Indiana), 3 mgm./Kg., given slowly intravenously was used to reverse the heparin anticoagulation. Pressure was maintained over the catheter entry sites until blood coagulation prevented further bleeding. This usually required twenty to thirty minutes but occasionally required over an hour. The small catheters were secured in position with 3-0 Tevdek suture. The animal was then returned to the chair, and kept in the reclining position until he became alert and regained good control of his posture.

During the experiments most of the animals gradually lost motor activity of their lower extremities, undoubtedly because the catheters occluded the passage of adequate blood supply. After the experiments, motor ability returned over a period of a few hours, unless other complications developed (See Chapter III).

Dynamic pressure-flow relationships of the brain circulation were plotted as shown in Figures 15 through 25. Points from which the regression lines were derived were determined by plotting the planimeter average of flow versus the planimeter average of pressure for each heartbeat, over at least one complete pump cycle. The number of points used to determine a line varied from nine to fourteen. Regression lines were determined by the standard method of least squares. Statistical tests of significance will be discussed further in Chapter III.

CHAPTER III

RESULTS

A. General Results

Ten animals were subjected to the implantations as described above. Before this particular protocol began, however, experience in the implantation technique was gained through efforts in additional animals to implant flow probes on the vertebral arteries high in the neck as they enter the dura. These efforts and the reasons for their abandonment were discussed in Chapter I, Section D.

Dynamic pressure flow relationships were determined for eight monkeys. In the other two animals brain blood flow could not be determined, due to instability of the zero base line in one, and rupture of the carotid artery in the other. The animal in which the rupture occurred was an unusually ferocious beast, and it is believed that his extreme unruliness led to erosion of the artery by the flow probe.

In three animals, it was possible to obtain a second determination of DPFR's about one week after the first. Since no significant differences were noted in these second determinations, the data from them were treated in the same way as for the rest of the experiments.

In five animals, only one determination of DPFR's could be made. In one case this was because the probe became unstable. In

another, the femoral catheters became dislodged, and efforts to regain access to the femoral arteries were unsuccessful. The remaining three animals expired as a result of complications of the first experimental procedure. Two of the three animals from which a second determination of DPFR's was obtained expired as a result of complications of the second procedure.

Causes of death were varied. One animal developed a lower nephron nephrosis, confirmed by histopathological examination, probably due to blood hemolysis. Hemolysis most likely resulted from the pump action. This occurred while the isolation volume transmitter design was still being evolved; a less efficient volume transmitter was being used which was apparently more traumatic to the blood.

One animal died of a thrombotic ischemic necrosis of the lower extremity which became infected. One death was attributable to renal thrombosis and infarction. The remaining two deaths were due to pulmonary thromboemboli.

All animals underwent post-mortem examination. In addition to the findings cited above, conditions of the carotid arteries, on which the probes had been implanted, and of the femoral arteries in which the catheters had been implanted, were of interest. Usually the carotid arteries were slightly thickened in the area of the probes, but the lumens remained smooth. The leads were closely ensheathed by connective tissue in their entire intra-corporeal course. The femoral arteries were patent in four animals, and definitely not patent in two. In the

remainder, the arteries were contracted; it was impossible to judge whether they were functionally patent around the catheters.

The reaction of the monkeys to blood pressure changes induced by the pump was of interest, since the use of this method on awake subjects has not been reported. When the pump was first turned on, the animals were obviously aware that something was going on; they would look up and around as if trying to find out what it was. However, after a few pump cycles they appeared to relax again--at least to the same degree that they had been relaxed before the pump was started.

B. Data Analysis; Methods of Presentation

Regression lines of DPFR's were determined as described in Chapter II, Section D.

Figures 15 through 25 display the regression lines of all experimental runs. Figures 15 and 16, in addition, show all the points from which some of these lines were determined (for 11% oxygen, 6% CO₂ and hyperventilation in Figure 15; and for 11% oxygen, epinephrine infusion, and hyperventilation in Figure 16). There was considerable scatter of the points from some runs--Figure 15 shows the worst scatter seen. Most runs, however, provided data points of a much tighter fit, as seen in Figure 16. Because of the obvious confusion which would result from plotting each point from each heart cycle during the period of one sine pump revolution, points determined from individual heart strokes were omitted in Figures 17 through 25. The central operating

Legend for Figures 15 through 25

Dynamic Pressure-Flow Relationship Plots

Condition	Line	Point
Breathing room air	—————	•
Breathing 100% O ₂	- - - - -	◊
Breathing 11% O ₂		*
Breathing 6% CO ₂	· - - - -	◦
Hyperventilating	- - - - -	■
During epinephrine infusion	—————	△
The central operating point is indicated by a circle around any of the points shown above, i.e.		⊙
Iso-resistance line	-----	

Figure 15
(Experiment No. 1)

Figure 16
(Experiment No. 2)

Figure 18
(Experiment No. 4)

Figure 20
(Experiment No. 6)

Figure 21
(Experiment No. 7)

BLOOD FLOW (c.c./min.)

BLOOD PRESSURE (mm. Hg.)

Figure 22
(Experiment No. 8)

Figure 24
(Experiment No. 10)

Figure 25
(Experiment No. 11)

points, however, are shown on all figures, and are denoted by a circle around the specific point indicator symbol for each condition. Each central operating point was determined by plotting the planimeter average for flow, during the complete sine pump cycle from which the regression line was obtained, against a similarly determined value for pressure. A resistance value, R , was then determined as the quotient of central operating point pressure divided by central operating point flow. A line drawn through the origin and the central operating point will obviously be a locus of all points having the same R -value. Such a line for the control condition is plotted on each figure, indicated in the figure legend as the iso-resistance line.

The central operating point values of flow, pressure and resistance are shown in Table 1. Also shown in Table 1 are the heart rates, sine pump periods, and alveolar carbon dioxide and oxygen tensions (PCO_2 and PO_2) for all conditions during each experiment. Values of gas tensions for some conditions of some experiments are not shown, because faulty gas analyzer operation during those runs precluded their determination.

Table 2 lists mean blood pressures, mean brain blood flows, and mean resistances averaged from all experiments under each condition. The average increases or decreases of these values from the control or room air condition to each of the other conditions are also shown as $\Delta B.P.$, ΔF and ΔR . The statistical significance of each of these mean changes, or more specifically, the probability of each of these

Table 1.--Individual experiment observations.

Central operating point perfusion pressure, mm. Hg.	O-B.P.
Central operating point brain blood flow, c.c./min.	O-Flow
Central operating point vascular resistance, O-B.P./O-Flow	R
Heart rate, beats per minute	Ht. Rt.
Period of the sine wave positive displacement pump, seconds	T-pump
Alveolar carbon dioxide tension	PCO ₂
Alveolar oxygen tension	PO ₂

Central operating point is defined in Chapter III, Section B. During some experiments faulty operation of the gas analyzers precluded the obtaining of some data. Such instances are indated by a dash in the table.

TABLE 1

Condition	O-BP	O-Flow	R	Ht. Rt.	T-Pump	PCO ₂	PO ₂
<u>Experiment No. 1</u>							
Rm. Air	87.7	23.5	3.73	228	3.7	28.5	106
100% O ₂	83.7	16.5	5.07	222	3.7	31.1	660
11% O ₂	77.7	28.9	2.69	228	3.7	21.5	41
6% CO ₂	113.5	33.9	3.35	216	3.7	54.8	122
Hyperventilation	65.0	12.9	5.04	228	3.7	10.1	145
Epinephrine	93.5	26.9	3.48	216	3.7	24.4	129
<u>Experiment No. 2</u>							
Rm. Air	100.5	22.0	4.57	198	3.3	33.4	110
100% O ₂	104.7	21.5	4.86	212	3.3	31.2	663
11% O ₂	85.8	24.4	3.52	222	3.3	28.2	46
6% CO ₂	123.8	30.6	4.04	204	3.3	58.0	117
Hyperventilation	76.6	14.2	5.40	228	3.3	12.6	132
Epinephrine	106.0	16.6	6.39	216	3.3	29.8	111
<u>Experiment No. 3</u>							
Rm. Air	95.3	20.0	4.76	162	4.0	38.0	99
100% O ₂	101.6	13.0	7.81	162	3.9	36.1	649
11% O ₂	82.2	22.1	3.72	198	4.0	31.7	41
6% CO ₂	108.3	28.4	3.82	168	4.0	56.0	118
Hyperventilation	72.7	11.1	6.55	210	3.9	10.0	136
Epinephrine	104.3	21.2	4.92	204	3.9	29.8	106
<u>Experiment No. 4</u>							
Rm. Air	97.6	24.8	3.94	192	3.8	39.6	109
100% O ₂	94.9	16.3	5.82	186	3.8	32.1	665
11% O ₂	87.1	31.8	2.74	192	3.8	29.2	55
6% CO ₂	116.9	33.1	3.53	184	4.0	57.0	120
Hyperventilation	73.2	19.7	3.72	198	3.8	12.7	139
Epinephrine	104.4	24.8	4.21	192	3.8	34.0	113
<u>Experiment No. 5</u>							
Rm. Air	75.4	29.3	2.57	162	3.7	27.8	---
100% O ₂	104.2	27.7	3.76	186	3.8	27.9	665
11% O ₂	68.8	33.3	2.07	186	3.8	22.7	37
6% CO ₂	104.2	45.3	2.30	180	3.9	50.0	---
Hyperventilation	60.4	15.4	3.92	168	3.8	11.3	---
Epinephrine	79.2	25.1	3.16	168	3.8	29.7	---

TABLE 1--Continued

Condition	O-BP	O-Flow	R	Ht. Rt.	T-Pump	PCO ₂	PO ₂
<u>Experiment No. 6</u>							
Rm. Air	76.1	18.9	4.03	174	3.7	30.6	115
100% O ₂	74.7	17.2	4.34	186	3.6	30.0	668
11% O ₂	75.5	20.1	3.75	192	3.5	25.8	37
6% CO ₂	86.6	23.9	3.63	174	3.7	52.4	128
Hyperventilation	54.3	11.6	4.67	180	3.6	13.5	133
Epinephrine	93.5	24.6	3.80	186	3.6	31.4	115
<u>Experiment No. 7</u>							
Rm. Air	79.6	21.8	3.66	168	3.7	31.3	116
100% O ₂	76.6	18.6	4.12	186	3.8	29.4	666
11% O ₂	66.3	21.0	3.16	192	3.6	30.6	43
6% CO ₂	95.8	28.8	3.33	168	3.7	51.0	130
Hyperventilation	48.5	14.4	3.37	192	3.7	13.4	134
Epinephrine	99.5	21.8	4.56	186	3.8	29.8	117
<u>Experiment No. 8</u>							
Rm. Air	104.4	28.7	3.64	180	3.9	29.9	114
100% O ₂	101.5	25.6	3.97	186	3.9	33.6	664
11% O ₂	82.9	33.0	2.51	180	3.9	28.4	54
6% CO ₂	116.4	31.2	3.73	168	3.9	53.0	---
Hyperventilation	73.7	18.9	3.90	186	3.9	9.5	139
Epinephrine	117.2	25.0	4.69	168	3.9	30.6	108
<u>Experiment No. 9</u>							
Rm. Air	94.5	22.8	4.15	156	3.6	32.8	108
100% O ₂	76.7	13.0	5.90	162	3.6	---	---
11% O ₂	88.5	22.8	3.88	156	3.5	25.4	55
6% CO ₂	102.0	23.7	4.30	132	3.6	52.1	127
Hyperventilation	59.6	12.1	4.93	174	3.6	14.9	138
Epinephrine	107.2	18.1	5.93	168	3.6	29.2	112
<u>Experiment No. 10</u>							
Rm. Air	78.5	22.6	3.47	174	4.2	27.8	---
100% O ₂	98.7	19.1	5.17	168	4.2	25.8	670
11% O ₂	74.1	27.5	2.69	198	4.2	25.4	58
6% CO ₂	97.5	31.5	3.09	180	4.2	47.5	---
Hyperventilation	44.1	9.6	4.59	192	4.2	9.2	---
Epinephrine	100.2	25.8	3.89	192	4.2	27.3	---

TABLE 1--Continued

Condition	O-BP	O-Flow	R	Ht. Rt.	T-Pump	PCO ₂	PO ₂
<u>Experiment No. 11</u>							
Rm. Air	100.2	27.1	3.70	222	5.1	23.8	122
100% O ₂	94.8	23.3	4.06	210	5.1	20.4	672
11% O ₂	91.5	39.7	2.30	216	5.1	20.8	41
6% CO ₂	128.1	36.5	3.51	174	5.1	49.4	130
Hyperventilation	84.7	20.5	4.13	222	5.1	9.3	137
Epinephrine	---	----	----	----	---	----	----

Table 2.--Averaged observations from all experiments. Most of the symbols are self-explanatory. The Δ -values refer to changes under the indicated condition from the corresponding value of the parameter under the control condition--i.e. naturally breathing room air without influence of epinephrine. Each P-value refers to the statistical probability that a change, or Δ -value, listed immediately to the left of any particular P-value, occurred by chance. N.S. indicates that the change is not statistically significant.

TABLE 2

Condition	Mean B.P.	Δ B.P.	P-value	Mean F	Δ F	P-value	Mean R	Δ R	P-value	Mean PCO ₂	Mean PO ₂
Rm. Air	90.0	----	----	23.8	---	-----	3.83	---	-----	31.2	111
100% O ₂	92.0	↑ 2.0	N.S.	19.3	↓ 4.5	<0.01	4.99	↑ 1.16	<0.01	29.8	664
11% O ₂	80.1	↓ 9.9	<0.01	27.7	↑ 3.9	<0.01	3.00	↓ 0.83	<0.01	26.3	46
6% CO ₂	108.5	↑ 18.5	<0.01	31.6	↑ 7.8	<0.01	3.51	↓ 0.32	<0.01	52.8	124
Hyperventilation	64.8	↓ 25.2	<0.01	14.6	↓ 9.2	<0.01	4.57	↑ 0.74	<0.01	11.5	137
Epinephrine	100.5	↑ 10.5	<0.01	23.0	↓ 0.8	N.S.	4.50	↑ 0.67	<0.05	29.6	114

changes occurring by chance as determined by the standard Student's t-Test, is shown immediately to the right of each of the $\Delta B.P.$, ΔF and ΔR values. Mean values of PCO_2 and PO_2 are also shown. Statistical P-values for PCO_2 and PO_2 were not determined, since these changes were either obviously significant from inspection of the individual run values, or were not important.

The DPFR's of brain blood flow determined in this research definitely appeared to be linear functions. In Chapter IV this linear relationship will be compared with DPFR's of other vascular beds, as determined by other workers. The statistical analysis of straight-line data, particularly in regard to tests of significance, is not simple. Yet it was obviously desirable to test the significance of shifts of the DPFR regression lines, since such shifts represent changes in vaso-motor tone. After consultation with the statistics laboratory of The Ohio State University, it was decided that a test described by Acton (89) was the best way to evaluate the significance of these shifts. Basically this test determines the probability that the data from which two different regression lines were drawn actually derived from a single population, rather than from two populations, as is presumed when two lines are drawn. To do this, the sum total of squared residuals computed from the data for each of the two regression lines is compared with the sum of squared residuals about a single regression line derived from the pooled data of both of the original regression lines. The reduction in these sums of squared residuals which is produced by plotting two lines rather than one is then found. The quotient of this reduction divided

by the original sum total of squared residuals, with both numerator and denominator weighted appropriately for the number of degrees of freedom, is distributed as "F." ("F" is used here not to denote flow, but to denote the standard statistical "F-distribution.") Table 3 shows probabilities, computed from these "F"-numbers, that the data from which particular pairs of regression lines were plotted could derive from one experimental condition, instead of two. Each P-value in this table is based on a comparison of the regression line data for a particular animal under a particular condition with the regression line data for the same animal under the control condition--i.e. naturally breathing room air.

"F"-numbers and P-values were then determined for comparisons of the pooled data for all animals under each condition with the pooled data for all animals under the control condition. The P-values thus determined are not shown in table form, since in all cases the P-value was less than 0.01.

C. Specific Results Induced by Condition Changes

1. 100% oxygen inhalation.--With the animals breathing 100% oxygen, average brain blood flow showed a statistically significant decrease as compared to the control condition breathing room air. Average blood pressure increased, but this change was not significant. Vascular resistance increased significantly, and correlated well with a significant increase in vasomotor tone, shown by a shift of the DPFR plots to the right in nearly all cases. Mean alveolar PO_2 , of course, increased markedly

Table 3.--Comparison of individual DPFR regression lines under specified conditions with the DPFR regression lines for the control condition, for each experiment. Statistical treatment is explained in Chapter III, Section B. N.S. indicates that the shifts of the regression lines so marked were not statistically significant.

TABLE 3

Comparison--100% O ₂ to room air		Comparison--6% CO ₂ to room air	
Exp. No.	P	Exp. No.	P
1.....	<0.01	1.....	<0.01
2.....	N.S.	2.....	N.S.
3.....	<0.01	3.....	N.S.
4.....	<0.01	4.....	<0.01
5.....	<0.01	5.....	<0.01
6.....	<0.05	6.....	N.S.
7.....	<0.05	7.....	<0.05
8.....	<0.01	8.....	<0.01
9.....	<0.01	9.....	<0.05
10.....	<0.01	10.....	N.S.
11.....	N.S.	11.....	<0.01
Comparison--11% O ₂ to room air		Comparison--Hyperventilation to normal breathing, room air	
Exp. No.	P	Exp. No.	P
1.....	<0.01	1.....	<0.05
2.....	<0.01	2.....	<0.01
3.....	<0.01	3.....	<0.01
4.....	<0.01	4.....	<0.01
5.....	<0.01	5.....	N.S.
6.....	N.S.	6.....	<0.05
7.....	<0.01	7.....	<0.01
8.....	<0.01	8.....	N.S.
9.....	<0.01	9.....	<0.01
10.....	<0.01	10.....	N.S.
11.....	<0.01	11.....	N.S.
Comparison--epinephrine infusion to control condition			
Exp. No.	P	Exp. No.	P
1.....	<0.05	6.....	<0.01
2.....	<0.01	7.....	<0.01
3.....	N.S.	8.....	<0.01
4.....	<0.01	9.....	<0.01
5.....	<0.01	10.....	<0.01

N.S. indicates not significant.

to an average of 664 mm. Hg. There was a slight fall in PCO_2 , which might have been due to random variation, or could have been the result of increased voluntary ventilation of the animals while they were being subjected to breathing through the Fink valve and breathing bag. This decrease in PCO_2 was minimal, however (from 31.2 mm. Hg. to 29.8 mm. Hg.), and probably had no significant effect on brain blood flow.

2. 11% oxygen inhalation.--Blood pressures and vascular resistance decreased in all experiments with the animals breathing 11% oxygen. Brain blood flow increased in every experiment but one, in which there was a very slight decrease. Statistical analysis of this data showed that the mean decrease in blood pressure and vascular resistance and the mean increase in brain blood flow were all statistically significant at the $P < 0.01$ level. PO_2 was markedly decreased, as expected. PCO_2 was also decreased, undoubtedly because the animal hyperventilated slightly in an effort to provide himself with more oxygen. This decrease in PCO_2 , of course, makes the increase in brain blood flow all the more significant. DPFR's were generally shifted to the left showing a marked decrease in vasomotor tone.

3. 6% carbon dioxide inhalation.--According to the original work of Kety and Schmidt (90) and a myriad of other workers using similar methods, brain blood flow increases markedly, blood pressure increases moderately, and vascular resistance decreases moderately while breathing gas mixtures containing increased concentrations of carbon dioxide. These findings were again confirmed in this present research. However, vasomotor tone actually increased significantly, which at first glance

appears contradictory to the finding of decreased resistance. This paradox is more apparent than real, and will be discussed further in Chapter IV. Alveolar PCO_2 increased markedly, as expected, and alveolar PO_2 increased moderately, undoubtedly due to hyperventilation induced by the increased PCO_2 . The increase in respiratory effort was quite marked in all animals.

4. Hyperventilation.--The findings of Kety and Schmidt (91), and more recently of Haggendal (43), Harper (44), Reivich (45) and Rapela (47), showing decreases in brain blood flow and increases in brain vascular resistance, were confirmed in this present study at high levels of statistical significance. In previous studies (92), blood pressure responses during hyperventilation have been extremely variable. This variability is to be considered further in Chapter IV. In this present research, profound decreases of blood pressure were seen in all experiments during hyperventilation, and the mean fall in blood pressure was statistically highly significant.

Though brain vascular resistance was increased during hyperventilation, vasomotor tone showed a mean decrease, which was statistically significant at the $P < 0.01$ level. This apparent paradox is similar to the one cited with the animals breathing 6% carbon dioxide, although changes in vasomotor tone and resistance under these two different conditions were opposite in direction.

As expected, PCO_2 decreased markedly and PO_2 increased moderately during hyperventilation. When first subjected to the ventilator, the animals resisted its efforts to breathe for them, but after a short

time, usually less than one minute, they would allow the ventilator to function without interference. However, at intervals, they would again fight its efforts, and in some cases the periods of relaxation were so brief and transient that it was difficult to obtain DPFR data. Although extremely low levels of PCO_2 were obtained, syncope, tetany, or convulsions were never seen.

5. Epinephrine infusion.--Blood pressure and vascular resistance increased significantly, though the increase in resistance was significant only at the $P < 0.05$ level. Mean brain blood flow decreased 0.8 c.c. per min., but the decrease was not significant. These results are in agreement with those of previous investigators (51,93). DPFR's were always shifted to the right, showing a highly significant increase in vasomotor tone, in correlation with the increase in vascular resistance. PCO_2 was decreased and PO_2 was increased, both in only minor degree. These changes in gas tension were probably due to a slight increase in ventilation induced by the epinephrine.

CHAPTER IV

DISCUSSION

A. Dynamic Pressure-Flow Relationships

The relationship of perfusion pressure to brain blood flow during the four-second sine wave positive displacement pump cycles appeared definitely linear. In most cases, the fit of the points to the regression lines was quite tight, and it is unlikely that a more complex relationship was hidden by the scatter of the data points.

Pieper (26), using methods from which the methods of the present research were derived, found a linear relationship of coronary blood flow to perfusion pressure. Previous workers (94,95) did not report such a linear relationship but their methods did not preclude autoregulation. Therefore, changes in vasomotor tone could have altered the shape of the pressure-flow relationship curves. The same comment can be made about non-linear relationships found by other workers in other vascular beds (31-33,96-101).

Leverett (27), however, using methods similar to those of the present research, found the relationship of flow to pressure for the total systemic circulation to be best approximated by the equation $F = ae^{bP} + C$ where a , b , and C are constants, e is the base of natural logarithms, and F and P are used in their usual context of blood flow and perfusing pressure. Guyton (29), determining the pressure-flow relationship for the total circulation, and Levy (34) determining this

relationship for the hind limb of the dog, used methods during the determinations that should have precluded autoregulation reasonably well. They found in both cases a relationship which appeared to fit the equation $F = cP^n$, where c and n are constants. This equation had originally been derived by Green (32) for several different isolated vascular beds, using methods that did not preclude autoregulation during the determination.

Flacke (102) developed a method which appeared to prevent autoregulation from affecting his plots of pressure-flow relationships for the total systemic circulation in dogs. He found too much variation in this relationship to permit derivation of a mathematical equation.

Thus, the pressure-flow relationship, with vasomotor activity precluded during the determination, remains in dispute in some beds, and without definitive determination in others. At present, however, there is no information available to dispute the linear relationship of flow to pressure in brain blood circulation seen in this present research.

Certainly one might have expected the pressure-flow relationship to be non-linear. Even in the simplicity of the Law of Laplace, $P = T/r$, where T is the tension in the wall, P is transmural pressure and r is the radius, the relationship of radius to pressure, at constant tension, is not linear. The elasticity coefficient of arterial wall is not constant, but increases with strain (100). To further complicate matters even the rate of increase of the coefficient is non-linear. This is not surprising, however, when it is considered that the arterial wall consists of at least three different types of tissue--i.e., smooth

muscle, elastin, and collagen. It is believed that the different tissues supply different proportions of the circumferential tension under different degrees of stretch (103).

Poiseuille's law relates flow to the fourth power of the radius, again a grossly non-linear relationship. Remington (104) showed that when arteries are stretched and relaxed the curve of strain versus stress forms a hysteresis loop, due to a phase lag of strain behind stress. This phenomenon results from what is commonly known as stress relaxation of smooth muscle. If this were a major factor in the present research, the flow measured at a given pressure should be less during the part of the pump cycle when arterial pressure is increasing and greater when the pressure is decreasing. Actually, in those cases where there was some loop formation in the DPFR's, an opposite effect occurred--i.e. at a given pressure, flow was increased during the part of the pump cycle when pressure was on the upswing, and vice versa. This will be discussed further below.

Finally, the non-linear variation in blood viscosity with flow might be expected to result in a non-linear DPFR curve.

That these various factors can combine to produce a linear DPFR seems almost miraculous. Nevertheless Pieper (26) did find such relationship in coronary flow and the present research indicates that such a relationship exists for brain blood flow.

Pieper's findings for coronary DPFR's did not include the region near zero flow. However, previous work by Pieper and Wetterer (30) did include this region for common carotid flow in the dog. In this study,

the DPFR's appeared to remain linear down to zero flow and even into the region of small values of negative flow. However, the common carotid DPFR's showed considerable loop formation, presumably due to the "windkessel effect" proposed by Frank (105), which made it difficult to reach definite conclusions regarding the linearity of the DPFR's. In the present research, DPFR's frequently extended almost to zero flow without departure from linearity. Near-zero flows were seen most commonly during hyperventilation. The plots always intercepted the pressure axis at positive pressure values, affirming the critical closing pressure of Burton (35). In one case, seen in the hyperventilation plot of Figure 15, the relationship appeared to become discontinuous at zero flow, sharply bending toward the origin along the pressure axis. Such discontinuity is certainly strong evidence supporting the concept of critical closing pressure. The small departures from precise zero flow are probably due to the electronic "noise" of the flowmeter, but could be due to oscillations of the blood within the artery.

Some loop formation, as seen in Figure 15, was also seen in several other DPFR plots. As has already been mentioned, these loops were caused by flows that were greater at a given pressure during periods of the pump cycle when pressure was increasing, and vice versa. This effectively eliminates stress relaxation as a causative factor for the loops. Two other possible causes present themselves. First, the loops could be due to the "windkessel effect" of Frank. Second, they could be due to auto-regulation, occurring, for brain circulation, in spite of the four-second

pump cycle period. On the basis of several points of evidence it appears that the second factor is more likely.

The windkessel effect results from an increase in the blood volume in the vascular bed distal to the flowmeter, particularly on the arterial side, during passive distention of the vessels due to increased pressure. Then, when pressure decreases the blood volume decreases again. Therefore, as the pressure increases, the flowmeter measures flow through the bed plus flow required to increase the blood volume of the bed. As pressure decreases, the flowmeter measures flow through the bed minus the decrease in blood volume per unit time. The phase of increases and decreases of flow responsible for the loop formation seen in the present research is compatible with their being derived from the windkessel effect.

However, if autoregulation occurred during the four-second cycle of the pump similar loops would be formed. During periods of low pressure, with resultant low flow rates, the autoregulatory mechanism, whatever it may be, would react (if it is capable of reacting during such rapid pressure cycles) to produce vasomotor relaxation. Immediately after this--that is, during the period of increasing pressure--resistance would be decreased, and flow rate increased. By the same reasoning, flow would be decreased at a given pressure during the part of the pump cycle when pressure is decreasing.

The first point in favor of autoregulation as the major cause of the loop formations is that it occurred in some cases, while in others it did not. Surely such variability can be better explained on the basis of a functional, physiological response than on the basis of a physical,

passive, anatomical phenomenon. This variability occurred not only among different animals and under different conditions in the same animal, but even among different pump cycles under a given condition in the same animal. Figure 26 shows plots obtained from one animal. The two plots to the left are from data obtained from two adjacent pump cycles during a hyperventilation run. One of these loops is considerably narrower than the other. It could be argued that the artificial ventilation altered venous pressure to cause such a reduction in loop breadth. However, the loop and the line on the right were obtained from data observed not during hyperventilation, but during epinephrine infusion--again from adjacent pump cycles. The data points indicated by the triangles were so close to a straight line that no loop could be drawn.

Figures 15 and 16 were derived from the same animal, but the pump cycle period for Figure 15 was 3.7 seconds, while for Figure 16 it was 3.3 seconds. The loops seen in Figure 15 are not seen in Figure 16. This suggests that the increased pump speed precluded the autoregulation present at the slower pump speed, resulting in loop closure.

If there is windkessel effect of significant magnitude, the peak of the flow wave should lead that of the pressure wave (106-108). Pieper found such a flow wave phase angle lead in observations of the common carotid artery vascular bed of the dog. One may think of this lead as being due to "filling of the windkessel." A more modern view of the reason for this leading phase angle of flow is that the distensibility of the blood vessels causes a "compliance" of the vascular bed, which may be likened to the capacitance of an electrical circuit. It is well

Fig. 26.--Dynamic pressure-flow relationship plots showing variability of loop formation.

Condition	Line	Point
Hyperventilating (with minimal loop formation).	-----	■
During epinephrine infusion (with minimal loop formation).	-----	△
Hyperventilating (with maximal loop formation).		○
During epinephrine infusion (with maximal loop formation).	-----	●
The central operating point is indicated by a circle around any of the points shown above, i.e.		⊙

Figure 26

known, of course, that current leads voltage in an alternating current capacitive circuit. To test whether such a leading phase angle of flow existed in the present research, recordings were made of brain blood flow in acute preparations in two animals. At the same time pressure was recorded from a manometer fed into the external carotid artery with its tip in the carotid bulb, right at the distal end of the flowmeter. This placement of the manometer was made so that there would be no time lag between measurement of the pressure pulse and its arrival at the flowmeter, as might occur if the manometer were located proximally in the aorta. A strip from one of the recordings is shown in Figure 27.

Phillips (82) reported that the rise-time of the flowmeter used in the present research is 13 milliseconds. Assuming the worst condition for lag of the flowmeter tracing, (which would be when the pressure pulse rose from diastolic to systolic pressure instantaneously, with a completely faithful pressure recording) then if pressure and flow peaks were actually in phase, the trace would show flow to lag pressure by 13 milliseconds. Actually the flow tracing does show a slight lag. Ten milliseconds on this trace is one-tenth of the distance between the narrow vertical lines, or one-half the distance between the narrow horizontal lines. The flow tracing lag, then, cannot be read with more than about three to five millisecond precision. Within this limit of reading accuracy, and within the limits of variation of individual pulses, the actual flow tracing lag appears to be about equal to the known 13 millisecond rise time. At least, there is no significant phase angle lead

Fig. 27.--Flowmeter recording of brain blood flow (lower trace) and pressure with manometer tip in the carotid bulb (upper trace). When the flowmeter trace is corrected for electronic circuitry lag, the two traces are almost exactly in phase. The rise-time of flowmeter is 13 milliseconds. The distance between vertical time lines represents 100 milliseconds.

in the flow trace as compared to pressure. This, then, is one more point of evidence in favor of autoregulation, rather than the windkessel effect, as the cause of the DPFR loop formations.

In Chapter I, the findings of Forbes (11) and Fog (12,13) regarding observations of brain vasculature through closed, transparent skull windows were cited. In summary, they found that these vessels did not distend with pressure pulses--at least not to any significant degree as compared to vessels of other vascular beds. For the windkessel effect to produce DPFR loop formation, it would be necessary for the arterial vasculature of the brain to distend significantly with pump-cycle-induced pressure changes. On the basis of the findings of Forbes and Fog, this seems unlikely.

As discussed in Chapter I, autoregulation has not been seen to occur in other vascular beds over the time period of the pump cycles used in this research. Pieper (26) did not find such autoregulation in the coronary system. Teleologically, such rapid autoregulation is very attractive, in view of the obvious importance of the brain, but more strikingly in view of the inability of the brain to function under conditions requiring anaerobic metabolism.

The changes of slope, in addition to horizontal and vertical shifts of the DPFR's, invite attention. In general, slopes became steeper in those DPFR's of greater average flows and lower average pressures. Or, put another way, DPFR's at greater average pressures and lower average flows generally had less steep slopes. Similar changes in slope were observed by Pieper (26) and Pieper and Wetterer (30).

Probably these general trends in slope change are related to the various factors which could be expected to cause non-linearity of the elasticity coefficients and resistance changes in arteries, as discussed earlier in this section. Data available to date are insufficient to allow any reasonably precise mathematical formulation of the relationship of these slope changes to any particular independent variable. It can be said, however, that the slope of the DPFR's tends to become steeper as vaso-motor tone decreases.

In some cases, slope changes occurred even without horizontal or vertical shifts of the DPFR's. Good examples of this are seen in Figures 17 and 18. The mechanism by which this could occur is difficult to envision. However, similar findings were obtained by Pieper (26) for DPFR's of both coronary flow and total systemic flow, but only after nor-epinephrine had been administered. Changes of slope of this sort suggest that even at a given pressure, flow, and vascular diameter the arterial wall is capable of active changes in elasticity coefficient, presumably as a result of a change in some factor other than pressure, flow, or diameter. In the present research, such changes of slope appear to indicate that under different experimental conditions (i.e., breathing carbon dioxide, oxygen, or hyperventilating, etc.), the arterial wall is capable not only of changing its strength of contraction, but also of changing its coefficient of elasticity at any given strength of contraction.

Another possible explanation for these changes in slope is that under different conditions, different segments of the vascular bed

contribute different proportions of the total resistance. Levy (34) found that a change of slope in the pressure-flow relationship could occur at a given driving pressure and flow, if venous pressure was changed. This suggests that the observations of venous pressure in the present research were too general, and perhaps should have been made with a system of more rapid frequency response, such as the system used for arterial pressure recording. Venous pressures, as described in Chapter II, were observed from a water manometer connected by a catheter to a point in the lumen of an intrathoracic vein. Observations were taken intermittently, and could not reflect changes within a sine pump cycle period.

B. Effects of Condition Changes

1. High and low oxygen concentrations.---The results of this research are in agreement with the findings of Haggendal (43) and dispute the findings of Reivich (45) and Green (46), as cited in Chapter I, Section B. That is, breathing mixtures of gases of greater oxygen tension than in the control condition caused active constriction of the brain vasculature with a resultant increase in vascular resistance and a decrease in brain blood flow. Such findings are also in agreement with those of many other workers (23-25,90) using the method of Kety and Schmidt (19) or its modifications. In their studies, perfusion pressure was not specifically held constant. However, in the case of higher than normal oxygen tensions, the blood pressure does not change appreciably, and so measurements of flow can provide reliable indications of active

vascular regulation of blood flow. When oxygen tensions are lower than normal, blood pressure is usually reduced. Therefore, the increase in brain blood flow that occurs with mixtures low in oxygen tension is all the more strongly indicative of vasomotor activity.

2. Increased carbon dioxide concentration.--Results shown for this condition are in agreement, so far as pressure, flow, and vascular resistance are concerned, with the observations of Haggendal (43) and Harper (44), and refute the findings of Geiger and Magnes (38).

However, as pointed out in Chapter III, an apparent paradox occurred. While vascular resistance decreased, the DPFR's shifted to the right, indicating a vasomotor tone increase. The explanation for this is found in Chapter I, Section B. Blood pressure usually increased considerably while the animals were breathing the 6% carbon dioxide mixture. Resistance then decreased by passive mechanisms, as described in Chapter I, Section B. This decrease in resistance, coupled with the increase in pressure, resulted in a blood supply which met and apparently in most cases exceeded the metabolic needs of the brain. When the blood supply of the brain exceeded its metabolic needs, the autoregulatory mechanisms reacted to increase vasomotor tone, as shown by the shift of the DPFR's to the right. This in no way disputes the findings of Harper (44) in which flow increased with increased CO₂ tensions when perfusing pressure was held constant. The present research merely shows that when perfusion pressure is not held constant, blood pressure increases enough so that no active dilatation of the brain vasculature is required to meet brain metabolic needs; the passive dilatation is more than

sufficient. And, since the passive response of the vasculature is more than sufficient, an active vasomotor tone increase is invoked to bring the blood supply back to the "just right" level.

3. Hyperventilation.--Hyperventilation is a complex condition. Though the principal effect is a lowering of carbon dioxide tension, oxygen tension is also elevated. Changes in arterial carbon dioxide tension invoke pH changes. In addition to these chemical changes, physical alterations take place. During positive pressure inspiration, pressure relationships within the thorax are reversed. The complexities of hyperventilation have been discussed by Brown (92) and more recently by Rowe (109).

Previously reported blood pressure changes during hyperventilation have been extremely variable. This is undoubtedly due in part to the complexities cited above, but probably is also due in part to the variation in methods of producing hyperventilation. As summarized by Brown, some workers have reported profound decreases in blood pressure, others slight decreases, others no changes, and still others slight increases. Some investigators have found that if carbon dioxide was administered in the breathing mixture, so that arterial carbon dioxide tension remained normal, blood pressure did not change. This finding is disputed by other workers.

It has been reported that decreases in blood pressure are due to the inhibition of venous return by positive pressure in the chest. Others report that the blood pressure may decrease even when average intrathoracic pressure is not increased and even when venous return

and cardiac output are increased. The variability of these findings has not been explained by further research to date.

Whatever the cause, the effect of hyperventilation in the present research was a marked decrease in mean blood pressure from 90 mm. Hg. to 64.8 mm. Hg. It does not seem that inhibition of venous return should have been a major factor, since hyperventilation was induced by a positive-negative cycle, at about 30 to 35 cycles per minute, with the duration of the negative portion of the cycles generally being equal to or greater than the positive portion of the cycles. Changes in brain blood flow and vascular resistance agreed with findings commonly reported--flow decreased markedly and resistance increased moderately but significantly. Here again, however, as with carbon dioxide breathing, a paradox was seen, though in an opposite direction, in that DPFR's shifted to the left, indicating a decrease in vasomotor tone. Thus, when carbon dioxide tension was markedly decreased, and oxygen tension was moderately increased--conditions which are generally considered to effect marked vasoconstriction--the DPFR's indicated that active vasomotor tone actually decreased. The explanation for this paradox is based on the same principles as the explanation of the paradox seen with carbon dioxide breathing, cited in Subsection 2 immediately above.

The fall in blood pressure with hyperventilation, then, regardless of the mechanism of its cause, provided an opportunity to observe a striking autoregulation of the brain blood supply in response to a decrease in brain perfusion pressure. The autoregulatory mechanisms

were capable of eliciting a decrease in vasomotor tone to promote an adequate blood supply to the brain, even when the arterial blood gas tensions were such that, in the absence of the blood pressure decrease, a maximal vasoconstrictor response would have been expected.

4. Epinephrine infusion.--The findings in this research were in agreement with those of other workers as cited in Chapter I, Section B. DPFR's shifted to the right, indicating an increase of vasomotor tone, which in turn increased vascular resistance just enough to hold brain blood flow nearly constant, despite a significant increase in blood pressure.

5. Mean blood pressure changes with pump-induced pressure oscillations.--Ead (110) and Scher and Young (58) have reported that when the carotid sinus is subjected to an oscillating pressure, mean arterial blood pressure falls to a lower level than is seen when the sinus is subjected to a steady pressure equal to the mean oscillatory pressure. This finding was confirmed in the present research. Though a complete analysis was not made, mean arterial blood pressures were generally about 15 to 30 mm. Hg. lower during steady state pump operation than when the pump was not operating.

C. General Comments and Critique

1. Pros and cons of working with awake, alert animals and chronic preparations.--In Chapter II, Section A, disadvantages of making determinations of DPFR's with the animals under general anesthesia were cited. However, certain disadvantages also result from having the

animals awake. Access to them is more awkward, and many special devices are required, as described in Chapter II.

It would have been desirable in this research to obtain DPFR's for the total systemic circulation concurrently with the brain blood flow DPFR's. Theoretically, this could have been done without any additional instrumentation or recordings, by the method of Wetterer and Pieper (55,56). When this method is used, however, any motion of the animal, even normal respiration, causes rather wide scattering of the results. Nevertheless, it was attempted in this research, but the values of peripheral run-off were so widely scattered that they provided no meaningful information. With the animal anesthetized, the use of this method, and the determination of systemic circulation DPFR's concurrently with brain DPFR's, probably would have been possible.

The elevated heart rates seen in Table 1, and the decreased mean carbon dioxide tension seen in Table 2, even while the animals were breathing room air (31.2 mm. Hg.), indicate that they were not in a relaxed state during the runs, even though they usually appeared to be. Anxiety does not appear to alter brain blood flow or metabolism (111). Therefore, the findings in this research were probably not significantly affected by this lack of relaxation.

The desirability of having a continuous record of venous pressure, preferably from the jugular bulb, has already been discussed in Section A of this chapter. This would have been difficult, if not impossible, to obtain with the animals awake. It would also have been desirable to obtain jugular bulb venous blood gas analyses, and

actual arterial blood gas analyses, instead of the estimates of arterial blood gases derived from alveolar gas sampling. Such blood gas analyses would have allowed evaluation of changes in brain metabolism during the runs. With the animals awake, and with the facilities available for this research, such analyses were not practicable.

Using a chronic preparation caused many delays and tedious methodology, including sterile technique during surgical procedures, and construction of several special devices. To use other than a chronic preparation, of course, would have required anesthesia. Further, blood loss in an acute preparation, with the animal heparinized as required when the pump is used, would probably have been excessive, requiring transfusion. Acquisition of blood for this purpose would have been a major problem. Also, methods of determining when and how much to transfuse would have had to be developed.

2. Miscellaneous comments.---Under the conditions imposed during this research, there were multiple variables. For example, when 6% carbon dioxide was administered, alveolar and presumably arterial blood oxygen tension also increased, due to hyperventilation. To study the effect of increased carbon dioxide tension alone, either the animal would have to be artificially ventilated or a gas mixture with reduced oxygen tension would have to be administered. Similar arguments can be made for each of the other conditions. The multitude of variables during hyperventilation has already been discussed (see above, Section B, Subsection 3). Control of these variables becomes especially important if

a quantitative relationship is to be derived, say, between flow and carbon dioxide tension or between flow and oxygen tension.

As reported in Chapter III, Section A, several animals were lost due to thromboembolization, despite doses of heparin which should have been sufficient to prevent clotting (3-4 mgm./Kg.). This suggests that the use of the pump and its catheters considerably increased the likelihood of clotting, and larger doses of heparin probably are required to prevent such occurrences.

CHAPTER V

SUMMARY AND CONCLUSIONS

Dynamic pressure-flow relationships (DPFR's) of brain blood flow were determined in adult male rhesus monkeys. The word "dynamic" is used to indicate that the relationship of flow to pressure was determined by methods which precluded any significant autoregulation or response of the baroreceptor mechanisms during the relationship determination. To accomplish this, blood pressure oscillations were produced by pumping blood into and out of the arterial system with a positive displacement pump, the output of which described a sine wave. The period of the pump cycle was about four seconds. Other investigators have shown that significant autoregulation does not occur, and that the baroreceptors do not react, in response to pressure oscillations of this frequency.

A fixed portion of brain blood flow was measured by an electromagnetic flowmeter placed on the common carotid artery after the external carotid artery was ligated. Studies of other investigators showing that this method provides an adequate measurement of brain blood flow are reviewed, and additional investigation in the present research confirms this point.

Because of the known inhibitory effects of anesthetic agents on vasomotor activity in general, and on brain blood flow and metabolism

in particular, the DPFR's were determined on awake, alert animals. To do this, chronic restraining chairs, devices to allow remote occlusion of the carotid artery for flowmeter zero determination, indwelling tracheostomies, and other special devices were required, and are described. Estimates of arterial blood gas tensions were obtained from continuous expiratory gas analysis.

DPFR's were determined under the following conditions: (a) the control condition, breathing air; (b) breathing 100% oxygen; (c) breathing 11% oxygen; (d) breathing 6% carbon dioxide; (e) during hyperventilation; and (f) during epinephrine infusion.

The planimeter average of flow for each heartbeat of at least one complete pump cycle, plotted against a similarly determined value for pressure, described the DPFR. The relationships, including many determinations extending into the region of near-zero flow, were found to be essentially linear. Regression lines of the plots intercepted the pressure axis at positive values, affirming the concept of critical closing pressure.

Passive changes in vascular resistance with changes in transmural pressure, resulting primarily from changes in the degree of distension of the resistive bed, are shown by each DPFR plot. Therefore, a shift of the DPFR regression line represents an active vasomotor response, i.e. a change in vasomotor tone. Statistical tests of significance of such shifts are discussed.

While the animals were breathing 100% oxygen, brain blood flow decreased, and vascular resistance and vasomotor tone increased as compared to the control condition. Changes opposite in direction to those seen with the breathing of 100% oxygen occurred when the animals were breathing 11% oxygen. Also, a moderate decrease in blood pressure was seen under the latter condition. All changes were statistically significant.

While the animals were breathing 6% carbon dioxide, blood pressure increased moderately, brain blood flow increased markedly, and resistance decreased moderately. All changes were statistically significant. However, shifts of the DPFR regression lines indicated a statistically significant increase in vasomotor tone--an apparent paradox. This was interpreted to indicate that the increased blood pressure and the passive decrease in resistance resulted in a more than sufficient increase of brain blood flow, invoking an active autoregulatory increase in vasomotor tone.

With artificial hyperventilation, resulting in a mean carbon dioxide tension of 11.5 mm. Hg., blood pressure fell from a mean value of 90 mm. Hg. to 65 mm. Hg. Brain blood flow decreased markedly, and resistance increased moderately, but significantly. Vasomotor tone showed a statistically significant decrease, however. This dramatically demonstrated the autoregulatory mechanism invoking a decrease in vasomotor tone, in response to the lowered blood pressure, despite the strong vasoconstrictive influences of a markedly lowered carbon dioxide tension and a moderately elevated oxygen tension.

During epinephrine infusion, blood pressure, resistance, and vasomotor tone all showed statistically significant increases. There was no significant change in brain blood flow.

The presence of loop formations in some of the DPFR plots suggested that autoregulation in response to the pressure oscillations induced by the pump occurred in some cases, despite the short period of the pump cycle. Evidence that these loop formations indicated autoregulation rather than windkessel effect is presented.

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