The Interrelationship of Intracranial Pressure, Cerebral Blood Flow, and Brain Metabolism in Experimental Brain Injury*

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This presentation will be concerned with some of the relationships between intracranial pressure, cerebral blood flow, and brain metabolism as defined in animal models (Fig. 1). We will also be concerned with the pathophysiological changes that occur among these numerous variables.

We begin with the idea that our greatest concern is with normal brain function. The brain, as we know, functions through the electrical activity of its neurons, but another way of measuring or defining brain function is in terms of metabolism. For our purposes, the brain metabolizes only two substances—oxygen and glucose. Apparently, the brain does not have a store of oxygen nor does it have a significant store of glucose. It is, therefore, dependent upon a constant supply of these metabolites. It is also known that the brain is selectively vulnerable to ischemia, that the brain will not tolerate more than five minutes of cerebral circulatory arrest without irreversible brain damage—a unique feature of the brain. One can put a tourniquet around the arm, totally occlude the circulation to the arm for a period of an hour or two for purposes of doing surgery, and following the removal of the tourniquet, the arm functions perfectly normally. The arm contains bone and muscle, but it also contains nerve and the neuromuscular junction. What is so unique about the brain that permits it to tolerate only five minutes of ischemia, whereas peripheral nerve and neuromuscular junction can tolerate up to two hours of ischemia? This is one of the major dilemmas in our search for the pathophysiological and metabolic basis of brain injury; as of the moment, we do not really have a decent answer.

The cerebral metabolic rate of oxygen utilization and the cerebral metabolic rate of glucose utilization are dependent upon an adequate delivery of oxygen and glucose. The amount of oxygen that is available to the brain is determined by two major factors: the oxygen content of the blood and the cerebral blood flow. The amount of oxygen in the blood is, in turn, determined by the pulmonary function and by the blood oxygen-carrying capacity. Figure 2 shows the familiar oxygen-hemoglobin dissociation curve. As the three curves at pH 7.6, 7.4, and 7.2 reach asypntote, they do so at a partial pressure of oxygen (P_{aO_2}) in the blood of about 80-100 mm Hg. When the P_{aO_2} drops below this value, the degree of hemoglobin saturation is significantly influenced by the pH. The normal patient may show a P_{aO_2} value from 80 up to 140 or 200 mm Hg and the saturation of hemoglobin does not increase significantly, and therefore, in terms of treatment, it does not make much difference whether the P_{aO_2} is 80 or 200. We must remember, however, that the amount of oxygen available to the brain is a function not only of this value but also of cerebral blood flow. For example, if the cerebral blood flow is at a critical level, and the P_{aO_2} drops by only a small amount (from 100 to 80), this may be quite sufficient to plunge the brain into hypoxia. It follows, therefore, that in our acutely

* This is an edited transcription of a lecture presented by Dr. Langfitt at the 27th Annual Stoneburner Lecture Series, February 7, 1974, at the Medical College of Virginia, Richmond.
that alkalotic pH, the hemoglobin will not give up the oxygen as well as it did when the pH was acidotic.

What are the factors which govern the flow of blood through the brain? The two major ones include the cerebral perfusion pressure—ordinarily defined as the inflow pressure (the carotid artery pressure) minus the outflow pressure (the jugular vein pressure)—and the cerebral vascular resistance (Fig. 1). The cerebral perfusion pressure, in turn, is influenced by the systemic arterial pressure (SAP) and the intracranial pressure (ICP). The cerebral vascular resistance, under normal circumstances, is primarily a function of arterial resistance; they are therefore called the resistance vessels, the arteries, and the arterioles. Also, under pathological conditions, cerebral vascular resistance is tremendously influenced by events that occur within the microcirculation in the capillary bed, in the form of such things as edema of the wall of the capillaries and sludging of the intravascular blood.

Figure 3 shows Poiseuille's equation for the flow of Newtonian fluids through a system of rigid tubes. This is only roughly applicable to a vascular bed but is helpful to us as we proceed through this discussion. Flow “Q” is directly proportional to the perfusion pressure and to the fourth power of the radius, demonstrating that the diameter or the radius of the cerebrovascular bed is extremely important in governing the flow through it. If we substitute “R” resistance for “R” radius, we come up with a rather simple Ohm's law for the cerebral circulation, which says that the blood flow is equal to the inflow pressure minus the outflow pressure divided by the resistance \( I = \frac{E}{R} \). Under normal circumstances, the perfusion pressure is defined as the carotid artery pressure minus the jugular vein pressure. It is very important, how-
ever, that in the presence of increased intracranial pressure, this relationship no longer holds. This is because it has been well demonstrated that as the intracranial pressure rises, the cerebral venous pressure rises in concert, and the two pressures are essentially equal to all levels of elevated intracranial pressure. It has become the convention to say, therefore, that the perfusion pressure across the brain, in the presence of increased intracranial pressure, is equal to the carotid artery pressure minus the intracranial pressure again divided by the resistance.

If the vascular resistance, the denominator R, remained the same during a change in perfusion pressure, cerebral blood flow would passively follow changes in perfusion pressure, whether the perfusion pressure was decreased by decreasing blood pressure or decreased by increasing the intracranial pressure. We know that this is not true because of the phenomenon of autoregulation. Autoregulation is a ubiquitous physiological phenomenon which occurs in the brain, in the pulmonary circulation, the heart, gastrointestinal tract, and in the kidney. The one conspicuous organ which does not autoregulate is the skin. We define "pressure" autoregulation as a change in the diameter of the resistance vessels where blood flow remains constant in the presence of a change in perfusion pressure. According to Ohm's law of the cerebral circulation, if one reduces the perfusion pressure, the cerebral vessels dilate, thereby maintaining blood flow and if one increases the perfusion pressure, the cerebral vessels constrict, thereby maintaining the same blood flow. The origin of this particular type of autoregulation is somewhat uncertain, but our own data, as well as those of many others, would suggest that it is probably myogenic in origin and that it is probably a vascular reflex of the small arteries and the arterioles of the organ.

In man, normal cerebral blood flow is between 50–55 ml/100 gm/min. What one sees in man is a constant blood flow, even as the mean arterial blood pressure is slowly decreased, until the mean arterial pressure reaches a value of approximately 50–55 mm Hg at which point cerebral blood flow falls off abruptly; the reason it does so at this level is that the blood vessels are now maximally dilated, and they cannot dilate any further in response to the continued decrease in perfusion pressure. It is only at this point that blood flow bears a passive relationship to perfusion pressure.

One of the questions which we asked ourselves sometime ago was whether or not the cerebral vessels autoregulate in the same manner to increased intracranial pressure, decreasing perfusion pressure, as they autoregulate to decreased arterial pressure, decreasing perfusion pressure. This seemed extremely important because so many of our patients with a wide variety of brain insults develop intracranial hypertension. In fact, one could probably say that increased intracranial pressure, as a cause of decreased perfusion pressure, is more common in our patients than decreased blood pressure, or at least we can say that the blood pressure is more readily correctable.

Douglas Miller conducted a series of experiments with dogs in our laboratory, in an attempt to demonstrate the relationship between autoregulation and increased ICP. In these experiments, a hollow screw was put into the torcular Herophili of the dog and an extracorporeal shunt run from the torcular Herophili to the jugular vein; the remaining venous outflow from the dog's head was occluded. Either an electromagnetic flow meter or a bubble flow meter can be used to measure blood flow through the shunt. This gives one a continuous measurement of cerebral blood flow (CBF). Further studies have shown that we are measuring total or nearly total CBF from the hemispheres and the diencephalon in this preparation. Some of Miller's data are seen in Figure 4. First, he decreased the arterial pressure by bleeding the animal and measured the CBF over a wide range of perfusion pressures. He was then able to develop an autoregulatory curve, reflected by the open circles. This is a typical curve of autoregulation showing that there is no significant change in CBF until the mean arterial pressure is reduced to about 50 mm Hg. In the same preparation, he then raised the arterial pressure back to normal by reinventing blood. While the arterial pressure was constant, he raised the intracranial pres-

![Fig. 4.](image-url)
sure, thereby reducing the perfusion pressure. That, then, is represented by the upper curve, the autoregulatory curve for increased intracranial pressure. One can see that the cerebral vessels do, in fact, autoregulate just as well to increased ICP as they do to decreased SAP and, for unexplained reasons, they autoregulate somewhat better to increased ICP. These animals were then subjected to a period of brain hypoxia by reducing the PaO₂ to values of about 15–20 mm Hg for a period of ten minutes. In other words, the animals were subjected to brain insult. The exact procedure was repeated. Figure 5 shows a pressure passive system. Following the cerebral insult, autoregulation was destroyed and the blood flow followed the perfusion pressure passively whether the pressure was decreased again by either decreasing blood pressure or by increasing intracranial pressure.

The importance of these kinds of data is that they demonstrate that when autoregulation is intact in a patient, he will tolerate large decreases in blood pressure, shock, or large increases in intracranial pressure without significant cerebral ischemia. If, however, the patient has had a brain injury of some kind and autoregulation is defective, the brain becomes much more vulnerable to either decreased blood pressure or to increased intracranial pressure.

Trauma to the brain in animals abolishes autoregulation just as hypoxia does. In a study at the University of Pennsylvania, regional cerebral blood flow was recorded from the surface of the cat's brain using the ⁸⁵Kr clearance technique, which is very similar to the ¹³³Xe clearance technique. During the control period, the blood flow from the cortex was normal during a drop in mean arterial pressure, showing values as high as 170 down to about 60 mm Hg. The trauma in this case was minimal, consisting of directing a 500 millisecond impact of nitrogen gas through a nozzle at the surface of the brain. It was minimal in the sense that there was no histological damage of the brain; the blood brain barrier was intact, and the EEG alteration was slight and immediately reversible. Autoregulation, however, was impaired, as demonstrated by the fact that following the trauma, when arterial pressure was again varied over a wide range, the characteristic picture of abolished autoregulation, was seen.

There is a second and equally important type of autoregulation which we term "metabolic" autoregulation, to be distinguished from pressure autoregulation. We can define metabolic autoregulation as a change in the diameter of the resistance vessels in order to meet the metabolic demands of the tissue. A good example of this is a change in cerebral blood flow in the region of the brain during an epileptic attack. Before the seizure occurs, blood flow is set for a given metabolic rate of oxygen. During the seizure, the tremendous increase in neuronal activity is accompanied by intense vasodilation, markedly increasing the blood flow to that region of the brain appropriate to the increased metabolic demands of the epileptic tissue. Whereas pressure autoregulation is a physiologic phenomenon, most likely a physiologic vascular reflex, metabolic autoregulation, by contrast, is presumably a chemical phenomenon, probably due to a change in extracellular pH at the level of the resistance vessels, the small arteries and the arterioles. As the neuron increases its activity, it produces more lactate and hydrogen ions. The hydrogen ions rapidly diffuse out of the neuron, through the extracellular space, and into the vasoactive vessel; the focal acidosis causes the vessel to dilate. The linkage in autoregulation, then, is apparently a hydrogen ion linkage. This means that if metabolism changes, a change in blood flow will follow which will be proportional to the change in metabolism as long as metabolic autoregulation is intact.

An excellent example of this rule can be demonstrated by what happens in hypothermia (Fig. 6).
In hypothermia, the primary change is decrease in brain metabolism. Under normothermic conditions of 37°C, CBF is 50 and the cerebral metabolic rate of oxygen utilization (CMR$_{O_2}$) is 3.5 ml/100 gm/min. When one decreases the CMR$_{O_2}$ to half that value, 1.75, by decreasing the temperature to 30°C, CBF falls at the exact same rate—from 50 to 25. If one did not know about the fall in CMR$_{O_2}$, seeing only that the blood flow had decreased by one-half, he would say that the brain was about to become ischemic because the CBF was at a critical level. This is not true because CMR$_{O_2}$ has decreased the same amount. Even though CBF is markedly reduced, it is perfectly adequate for the needs of the hypothermic brain.

We have stated that pressure autoregulation is sensitive to various types of brain injury. The same statement can be made about metabolic autoregulation; thus, with certain kinds of insults, an unlinkage occurs between metabolism and blood flow and they go their separate ways. Figure 7 shows some selective data from our patients to demonstrate this fact. All of these patients were unconscious; most of them had severe head injuries. In all of these patients the CMR$_{O_2}$ is reduced. The normal value of 3.5 is reduced to as low as one-third of that value and even lower in two of the patients. The first patient (BJS) shows a metabolism that is one-third of normal but the mean CBF is 114 ml/100 gm/min, the highest mean hemisphere blood flow we have seen in our series. In this circumstance, the patient has a condition which we defined a number of years ago as “vasomotor paralysis”—in which there is no metabolic or pressure control of the cerebral vessels; the tone of the cerebral vessels has been destroyed. They passively dilate, thereby increasing cerebral blood flow. It is impossible to influence this process because both the pressure and the metabolic control of the blood vessels has been destroyed. We see the same thing in the second patient (ED) with a CBF about 50% above normal, the CMR$_{O_2}$, again about one-third normal. The third patient (JL) has a normal CBF, but it would not be normal if metabolic autoregulation were intact because the CMR$_{O_2}$, is only one-half normal.

Some of the factors we are most interested in are: What constitutes a critical level of Pa$_O_2$, a critical level of mean arterial pressure, and a critical level of CBF for brain function? How much can we reduce the oxygen content of the blood or the cerebral blood flow before hypoxic tissue damage occurs? There is currently an argument as to what criteria should be used in determining hypoxic tissue damage. Two of these criteria are a decrease in high-energy phosphates (ATP and phosphocreatine) and an increase in anaerobic glycolysis. Normally, most of the glucose that is metabolized by the brain is done so aerobically. When the amount of oxygen is insufficient to maintain aerobic metabolism, anaerobic metabolism through the Embden-Meyerhof pathway increases, and there is a marked increase in the utilization of glucose.

Generically, hypoxia means insufficient oxygen to the brain. But hypoxia may be divided into two categories: hypoxic hypoxia, generally due to inadequate pulmonary function, and ischemic hypoxia, due to inadequate blood flow. It is possible experimentally, in the rat, to reduce the arterial Pa$_O_2$, to a value of about 25–30 mm Hg at which point a decrease in

<table>
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<tr>
<th>Patient</th>
<th>CBF</th>
<th>CMR$_{O_2}$</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>BJS</td>
<td>114</td>
<td>1.05</td>
<td>Dead</td>
</tr>
<tr>
<td>ED</td>
<td>77</td>
<td>1.42</td>
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</tr>
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<tr>
<td>EF</td>
<td>34</td>
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<tr>
<td>MF</td>
<td>32</td>
<td>0.87</td>
<td>Alive, well</td>
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Fig. 7.
Fig. 9.

phosphocreatine occurs. ATP does not change because the phosphocreatine is converted to ATP temporarily. This process, which is a derangement in oxidative phosphorylation in the mitochondria, is one criterion of hypoxic damage. Again, in rats, if the arterial Pa_o, is kept constant but the blood pressure is dropped, in order to find out what the critical mean arterial blood pressure is for the maintenance of adequate oxidative phosphorylation, the value is about 30 mm Hg, at which point we see a drop in phosphocreatine and ATP and an increase in AMP and ADP.

There have been a number of studies in recent years, both in man and in experimental animals, which show that the critical value for cerebral blood flow is approximately 45% of normal. According to Dr. Sundt's studies on patients undergoing endarterectomy, when the CBF dropped to a value of 18 or 19, about 45% of normal, there were EEG changes characteristic of brain ischemia.

There is another new concept regarding the linkage between metabolism and cerebral blood flow. We have said that in metabolic autoregulation, the primary change occurs in metabolism and blood flow follows due to hydrogen ion linkage. In some of our patient studies, we found evidence to suggest a reverse mechanism—when blood flow decreased due to increased intracranial pressure, metabolism seemed to decrease with the decrease in blood flow. Teleologically this is extremely important because it means that if one decreases the CBF slowly enough over a period of time, the metabolism will decrease by some unknown mechanism.

Fig. 10.

Studying the autoregulation curve in the dog with the experimental design described previously, where cerebral blood is measured continuously by the torcular outflow technique, we found that when the mean cerebral perfusion pressure was decreased to about 50 mm Hg by elevating the ICP, blood flow remained constant, but below a perfusion pressure of 50, blood flow began to fall. We had been concerned mostly with the horizontal portion of the curve and had not paid much attention to the falling portion. What we did, therefore, was to increase the intracranial pressure very carefully in small increments in order to produce 10% decreases in CBF. At each one of these levels, we measured the cerebral metabolic rate of oxygen and glucose. Figure 8 shows the data regarding the CMRO_2. On the abscissa, we have CBF beginning with the normal value of close to 50; CMRO_2 is on the ordinate. We see that when CBF has been decreased to about 70% of control, CMRO_2 begins to fall and follows CBF down to approximately one-fifth of control. This decrease in CMRO_2 occurs at values of CBF 70% of normal, far above those values required to provide the brain with an adequate amount of oxygen. At this point, therefore, it seems clear to us
that the decrease in cerebral metabolism is not a manifestation of brain damage; rather it appears to be due to some kind of metabolic control mechanism which tends to turn off the brain as the oxygen supply is reduced, a protective mechanism intrinsic to the brain.

Figure 9 shows some of the data for the glucose—not quite so impressive, but again we see a decline in the cerebral metabolic rate of glucose with decreasing CBF. When we look at the area of the curve where CBF is 15 ml/100 gm/min, we see that this is the point where there is an increase in glucose metabolism. This is a manifestation of the onset of the hypoxic tissue damage—anaerobic glycolysis—which occurs at about 45% of control CBF. Figure 10 shows this more clearly in the form of the so-called glucose index. Normally the brain metabolizes about 90–95% of its glucose aerobically. One can see that at a value of 20–22, about 45% of control CBF, there is a marked change in the oxygen glucose index—a marked increase in anaerobic glycolysis.