Interrelationship between blood pressure and regional cerebral blood flow in experimental intracranial hypertension

M. N. Shalit, M.D., and S. Cotev, M.D.
Departments of Neurosurgery and Anesthesiology and Laboratory of Experimental Surgery, Hadassah University Hospital, Jerusalem, Israel

The interrelationship between systemic blood pressure (BP), regional cerebral blood flow (rCBF), and intracranial pressure (ICP) was investigated in two experimental models of intracranial hypertension in cats. In one group, ICP was raised by the inflation of an extradural balloon; in the other, brain swelling was produced. The effects of raised blood pressure on rCBF and ICP in the two groups differed considerably. In the "brain-swelling" group, elevated BP had no beneficial effects on rCBF. When ICP approached diastolic BP, an increase in BP was followed by a marked increase in ICP and a decrease in rCBF. Therefore, the elevated BP often observed in extreme intracranial hypertension (Cushing response) cannot be regarded as a beneficial, compensatory defense mechanism, but rather as a deleterious phenomenon.

KEY WORDS: cerebral blood flow · intracranial pressure · increased blood pressure · brain swelling

The significance of the increase in systemic blood pressure that often coincides with marked intracranial hypertension, and its effects on cerebral blood flow (CBF), have been studied by many investigators.2-4,7-14,16,17,19,22,23 Cushing2-4 postulated that this increase in blood pressure was a meaningful phenomenon and regarded it as a compensatory mechanism intended to keep blood pressure (BP) above intracranial pressure (ICP), thereby maintaining perfusion of the vital centers in the brain.

Cushing's experiments were carried out on animals in which ICP was increased either by an expanding intracranial balloon or by perfusion of the subarachnoid space with saline. Many of the investigators who subsequently studied the Cushing reflex used the same methods of increasing ICP and generally confirmed Cushing's original hypothesis. These experimental models, however, do not simulate most of the circumstances under which the Cushing response is manifest clinically. Severe brain swelling, which is a major factor in generating the ICP increase in patients suffering from head injury or acute expanding intracranial mass, is absent in the "balloon" experiments where brain tissue water content is not increased.21 Furthermore, an increase in ICP produced by perfusion of the subarachnoid space does not simulate any known clinical pathological condition. Cerebral blood flow and metabo-
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Activity as well as the physical properties of cerebral tissue, including its compressibility, must obviously be different under these circumstances. Recent evidence points to the fact that CBF control is indeed different under these diversified situations.

The present series of experiments were designed to explore the interrelationship between ICP, BP, and regional cerebral blood flow (rCBF) in two different experimental models of increased ICP, namely, one that uses brain swelling and another that uses an expanding intracranial balloon. In addition, it was our intention to find out whether the beneficial effects of the Cushing phenomenon on cerebral perfusion and metabolism could also be demonstrated in experimental brain swelling.

Materials and Methods

The experiments were carried out on adult cats under pentobarbital anesthesia. Blood pressure (BP) was measured directly from one of the femoral arteries by a pressure transducer. A femoral vein was cannulated for the administration of fluids and drugs. The trachea was cannulated and the animals paralyzed by gallamine and artificially ventilated with a volume respirator* while the arterial pCO2 (PaCO2) was maintained between 30 and 35 mm Hg. Arterial oxygen tension (PaO2) was maintained above 80 mm Hg by adding oxygen to the inspired air when required.

A small craniectomy was then performed in the right frontal region and an area of dura about 5 mm in diameter exposed. After the animals had been hyperventilated for a period of 10 minutes, the dura was gently elevated from the brain surface and cauterized using a low current, to eliminate dural blood flow in that region. The rCBF of the underlying cortex was repeatedly determined by the Kr 85 washout technique; the radioactive substance was injected into the brachiocephalic artery.

The EEG was recorded continuously by means of six brass electrodes screwed into the skull at the frontal, parietal, and occipital regions of each hemisphere.

Intracranial pressure was continuously monitored by the use of an epidural transducer applied over the right parietal region. The transducer was sealed into the bone by the use of acrylic cement.

A small balloon made of latex connected to a fine polyethylene tube was then applied to the epidural space in the parietal region of the left hemisphere. The small craniectomy which was required for this procedure was sealed hermetically by acrylic cement. The polyethylene tube was connected to a syringe filled with saline and attached to a Harvard perfusion pump for gradual inflation of the balloon. To maintain ICP at a certain level, continuous inflation of the balloon was required. When inflation was stopped, ICP tended to decrease gradually.

Arterial pO2, pCO2, and pH were checked intermittently using an electrode system.* End-tidal CO2 was continuously monitored by the use of a Beckman infrared CO2 analyzer.† Body temperature was maintained at about 39°C by means of an electric heating pad.

At this stage, the presence of an effective autoregulation mechanism was tested in each animal by increasing the BP about 50 mm Hg by use of a noradrenaline drip; animals showing an increase in rCBF by more than 25% of control values were excluded.

The animals were divided into two groups representing the two methods used to produce the increase in ICP.

Group 1: Balloon Inflation

In this group, consisting of 18 cats, the ICP was raised stepwise (about 20 mm Hg each step) by gradual inflation of the extradural balloon. At each level of ICP, the rCBF was determined. In six of these animals the BP was intermittently raised (noradrenaline drip) by 40 to 80 mm Hg for 10 to 15 minutes. This procedure was carried out at each level of ICP. The rCBF was determined both at the control and increased BP. In five animals the BP was arti-

†Infrared CO2 analyzer manufactured by Beckman Instruments, Inc., 2500 Harbor Boulevard, Fullerton, California.
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ficially raised only when the ICP reached diastolic BP; in the rest (seven animals) the BP was not artificially altered.

**Group 2: Progressive Brain Swelling**

In this group, ICP was increased gradually by the effect of progressive brain swelling. Brain swelling was produced in the following fashion: A gradual inflation of the balloon was first carried out until ICP reached the level of diastolic BP. At that point, both carotid arteries were occluded temporarily by loose ligatures. After a period of 5 to 10 minutes, when a severe depression of EEG activity had been observed, the balloon was rapidly deflated and the ligatures around the carotid arteries were released. This procedure had to be repeated as many as two to three times in some cats before brain swelling became evident. Thirteen of the 32 animals in which this procedure was attempted developed brain swelling; these comprise the “brain swelling” group. In most of these animals ICP reached diastolic BP in about 2 to 4 hours. In four animals the BP was intermittently raised at different ICP levels similar to the procedure used in Group 1. In four other animals the BP was artificially raised only when the ICP reached diastolic BP. In the rest (five animals) the BP was not artificially altered.

**Results**

An increase in ICP was followed in both groups of animals by a decrease in rCBF and perfusion pressure (PP); PP is the mean BP minus the ICP. Figure 1 demonstrates the effect of a decrease in PP obtained by increasing ICP only, without any alterations in BP; therefore, no autoregulatory effect is demonstrable. Although the total results demonstrate a linear relationship between PP and rCBF, it should be noted that in Group 1 the fall in rCBF in the individual experiments began only when the ICP had increased above approximately 60 mm Hg (12 animals). This particular behavior of rCBF is not indicated in Fig. 1 because of the spread of the data, mostly due to a different initial PP in each individual experiment. No such threshold phenomenon could be observed in most of the experiments in Group 2. In five animals of Group 1, the rCBF rose spontaneously by some 20% to 40% above the control levels as the ICP began to increase. The rCBF then fell gradually when the ICP was increased above 50 to 60 mm Hg.

An increase in BP obtained either spontaneously (the Cushing response) or by noradrenaline infusion resulted in different effects on the PP and rCBF in the two groups of animals.

**Intermittent Increase in BP**

In Group 1, an intermittent increase in BP produced by the administration of noradrenaline did not significantly affect ICP as long as the initial ICP was below 70 to 80 mm Hg. The increase in PP was generally associated with a parallel increase in rCBF.

In Group 2, similarly induced changes in BP at ICP's below 70 mm Hg resulted in an intermittent increase in PP although to a much lesser extent than in Group 1, since in most cases some increase in ICP accompanied the rise in BP. The rCBF, however, was increased only in five animals of this group; in another five it was unaltered and in five, decreased.
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When the ICP was above 70 to 80 mm Hg, an induced rise in BP caused a remarkably different response of both the PP and rCBF in the two groups. In most Group 1 animals, an increase in BP caused an elevation in PP (Fig. 2). This rise in PP was not as significant as when the ICP was lower than 70 mm Hg, because each rise in BP was followed by a partial increase in ICP that tended to inhibit the rise in PP. The rise in ICP that followed the rise in BP was most marked at higher initial ICP's. Similarly, the increase in rCBF that accompanied each rise in BP was not as consistent as when initial ICP's were below 70 mm Hg. In Group 2, at initial ICP's higher than 70 mm Hg, an increase in BP brought about an increase in ICP that usually exceeded the increase in BP, thereby decreasing PP. The rCBF was markedly decreased under these circumstances (Fig. 3).

Figure 3 illustrates typical individual experimental results in Groups 1 and 2. In the experiment from Group 1, at a normal ICP an increase in the BP did not significantly affect either the ICP or rCBF, indicating effective autoregulation. When the ICP was increased by inflation of the balloon, the rCBF was markedly increased with each rise in BP. However, at a very high ICP, an increase in BP produced a marked rise in ICP, while the increase in rCBF was smaller or absent. An EEG depression appeared at an ICP of about 50 mm Hg, while the rCBF was still remarkably high. The EEG activity was not improved when the rCBF was increased. In the experiment from Group 2, at a relatively low ICP, the rCBF was not affected despite an increase in PP. At ICP's higher than 70 mm Hg, an increase in BP resulted in a marked increase in ICP and a decrease in rCBF. The EEG depression was noted throughout the experiment, beginning during the initial production of brain swelling.

Prolonged Elevation of BP

Prolonged induced elevations of BP (40 to 80 mm Hg for up to 60 minutes) were carried out in four animals of each group at different ICP's. This produced different...
effects on ICP and rCBF in the two groups.

In Group 1, a prolonged increase in BP carried out at a relatively low initial ICP did not affect the ICP. The rCBF was significantly increased above control levels during the period of hypertension. At a higher ICP (Fig. 4 upper graph), a prolonged increase in BP was accompanied initially by
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A marked rise in ICP. Within a few minutes, however, the ICP tended to decrease gradually with a consequent increase in the PP and rCBF.

In Group 2, a prolonged increase in BP caused an increase in ICP at initially high as well as at lower ICP's. The increase in ICP was not a transitory phenomenon as observed in the previous group, but persisted and always progressed gradually with a consequent decrease in PP and rCBF (Fig. 4 lower graphs). This effect of increased BP on ICP in brain swelling progressed rapidly when the ICP was initially high.

**Induced and Spontaneous Increase in BP as ICP Reaches Diastolic BP**

When the BP rose spontaneously or was raised by noradrenaline at ICP's approaching diastolic BP, different results were obtained in the two groups.

In Group 1, a spontaneous increase in BP (of about 40 to 80 mm Hg) occurred at that high ICP in six animals. In another five animals a similar rise in BP was drug-induced. Basically there were no significant differences in the behavior of ICP and rCBF between animals with spontaneous and induced arterial hypertension. Initially, ICP rose markedly and then tended to regress gradually. The rCBF tended to fall initially and then increased gradually with the fall in ICP.

In Group 2, the ICP never exceeded diastolic BP. When it reached diastolic pressure, however, the rCBF was decreased to very low values that could not be improved by artificially induced arterial hypertension (four animals). Under those circumstances the ICP was completely dependent on BP and changed in parallel with BP changes, leaving the PP unchanged. In three experiments an increase in BP at this stage produced a complete arrest of rCBF.

In five animals a spontaneous Cushing response was evident. The PP was never increased as a result of the rising BP, and the rCBF was either unchanged or decreased. In two animals, this phenomenon was followed by pupillary dilation, complete arrest of rCBF, and a gradual decrease in BP; the fact that animals could not be re-

![Graph showing the relationship between BP, ICP, and rCBF during a prolonged increase of BP.](image)

**Fig. 4.** Graphs showing the relationship between BP, ICP, and rCBF during a prolonged increase of BP. **Upper Graph:** Animal in the Balloon Group. Note that the rCBF, measured prior to this recording, was 0.5 ml/gm/min. When the BP was raised, the PP decreased and rCBF fell to 0.3 ml/gm/min. Afterward, a gradual decrease in ICP was evident. PP was therefore increased and rCBF was 0.8 ml/gm/min. **Lower Two Graphs:** Animal in the Brain Swelling Group. Initially, there was a brief increase in rCBF; thereafter, PP diminished progressively with a fall in rCBF. The fall in BP at the end of this period did not establish either PP or rCBF although the ICP was markedly reduced.
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Fig. 5. Graph showing the spontaneous increase in BP following an increase in the ICP (Cushing response) in an experiment of the Brain Swelling Group. There was no increase in PP, and the rCBF was reduced at the peak of this phenomenon. A few minutes later the BP began to fall with a diminution of ICP. The BP was reduced to zero, and the EEG became iso-electric.

suscitated at that point suggested that brain death had occurred (Fig. 5).

Effects on the Electroencephalogram

In Group 1, a marked general depression of EEG activity was observed whenever the ICP reached 50 to 60 mm Hg, even in experiments where sufficient perfusion pressure (more than 60 to 70 mm Hg) was still evident. Similarly, EEG depression was observed in spite of the presence of adequate rCBF (above 0.8 ml/gm/min). In Group 2, EEG depression had already appeared during the initial stages of brain swelling and deteriorated markedly when extreme ICP levels were reached.

Discussion

Increased ICP presents various clinical signs including vasomotor and respiratory manifestations known as "Cushing response," which includes arterial hypertension, bradycardia, and respiratory disturbances. It is not yet clear whether this reflex is evoked only when the ICP reaches the level of diastolic blood pressure or may appear also at lower ICP's. In our present studies, when the ICP was raised consequent to brain swelling, the Cushing response was observed, but only when the ICP was increased to the level of the diastolic BP.

Of all the various signs of increased ICP, only arterial hypertension has been considered to be a beneficial compensatory mechanism. It should be remembered that Cushing's original postulation was made at the beginning of this century, when the CBF was considered to be passively dependent on arterial BP. Other important factors known today to affect CBF were unrecognized at that time. Consequently, an increase in BP in intracranial hypertension was regarded as advantageous to the brain, since it was believed to increase CBF. It was further believed that a high CBF could benefit the patient with increased ICP. This concept was proven incorrect in many cases. Modern treatment of brain swelling and increased ICP includes the use of hyperventilation, which generally tends to reduce CBF.
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Thus, the brain tissue would be protected from further damage and ICP would be reduced. It should be emphasized that the increase in CBF does not by itself serve a purpose; it is simply one means of meeting the metabolic needs of the brain. The effects of BP elevations in increased ICP due to brain swelling, on both CBF and brain metabolic activity should, therefore, be re-evaluated.

The results of the present series of experiments indicate that the relationships between ICP, BP, CBF, and brain metabolic activity as reflected in the EEG are different in the two experimental models used. Although the balloon inflation model may simulate some clinical states of increased ICP such as chronic subdural hematoma, the Cushing response is observed less frequently under these circumstances. The most striking clinical conclusion to be drawn from the observations made in the balloon group is that the metabolic activity of the brain was often depressed before any decrease in CBF was evident. It is conceivable, therefore, that the critical factor for brain metabolic activity in this situation is not lack of blood flow and oxygen but the increased ICP per se. An increase in CBF at that point would not be of any advantage to a brain unable to utilize the increased availability of oxygen.

The “brain swelling” group seems to represent the clinical condition better than the “balloon” group. It is clear that an increase in BP, induced either artificially by drugs or appearing spontaneously at ICP levels approaching diastolic BP, is of no advantage to cerebral PP, blood flow, and EEG activity. Under these conditions, brain tissue compressibility reaches its maximum limits, and any further increase in the intracranial blood volume would result in an additional increase in ICP. Therefore, unlike Group 1, where brain compressibility is greater, the effect of increased BP on the intravascular blood volume in Group 2 animals is to produce a dangerous persistent increase in ICP. This would result in a further increase in BP and a vicious circle would develop, so that ICP may increase more than 100 mm Hg (Fig. 5). This fact alone may invalidate the idea that the Cushing response is a compensatory mechanism, since the experiment actually expands the basic pathological condition to its extreme manifestations.

The idea that in the presence of high ICP an increase in BP above the control level might be dangerous to the brain has already been mentioned. As in our present experiments, MsDowall, et al., observed that by the time the Cushing response appeared, the ICP had risen in parallel with BP, and the PP was little improved by the systemic hypertension while the CBF was not improved to any extent. In addition, Miller, et al., noted that in brain swelling, the CBF fell progressively and failed to increase despite increases in arterial blood pressure; at that stage, an increase in BP caused a pronounced rise in ICP.

In our studies of the effect of a prolonged increase in BP on ICP and rCBF in animals with brain swelling, there was a progressive increase in the ICP and a decrease in rCBF. The higher the initial ICP, the more rapid the subsequent increase in ICP. This phenomenon is probably the consequence of the progressive increase in the water content of the white matter associated with the duration of the hypertension. Therefore, although transitory increases of BP at relatively low ICP's may sometimes be followed by a partial but parallel increase in CBF, a prolonged increase of BP endangers the brain regardless of the initial ICP. On the other hand, after prolonged arterial hypertension, a fall in BP to its control levels might reduce the cerebral blood supply even further (Fig. 4 lower).

Therefore, it seems that either high or low blood pressures are dangerous in the presence of brain swelling. The optimum BP must lie between these extremes and is probably determined by a complexity of factors related to the biochemical and physical properties of brain tissue.

Our experience in this series of experiments designed to simulate the common clinical pathological conditions of intracranial hypertension suggests that an increase in BP in intracranial hypertension is not a favorable compensatory mechanism designed to maintain brain function as Cushing postulated. More likely, it is a sign of breakdown of brain mechanisms and should be regarded in the same perspective as the other two components of the Cushing triad.
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Address reprint requests to: M. N. Shalit, M.D., Department of Neurosurgery, Hadassah University Hospital, P.O.B. 499, Jerusalem, Israel.