Cerebral circulation and metabolism

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Selected papers of particular interest to neurosurgeons and neurologists, which were presented at the June, 1973, International Symposium of Cerebral Circulation and Metabolism in Philadelphia, are summarized and discussed.

KEY WORDS cerebral blood flow · brain metabolism · ischemia · intracranial pressure · autoregulation · chemical control · neurogenic control

A n International Symposium on Cerebral Circulation and Metabolism was held in Philadelphia in June, 1973, organized by the Departments of Neurology and Anesthesiology and the Division of Neurosurgery of the University of Pennsylvania.* It was the sixth in a series of symposia on cerebral blood flow (CBF) since 1965, and the first to be held in the United States. Studies of brain metabolism were emphasized because of continuing evidence that measurements of CBF alone are limited in assessing brain function and especially brain damage in experimental animals and man. The reason is that flow and metabolism are often dissociated. CBF may be normal in patients with severe depression of brain metabolism and neurological function produced by various types of insult; on the other hand, the brain may be capable of normal function when CBF is markedly reduced if the decrease in metabolism is proportional to the decrease in flow, as occurs in the hypothermic state, for example; reduction in temperature reduces metabolism, and CBF falls proportionally due to metabolic autoregulation.

This summary includes symposium topics thought to be of most interest to neurosurgeons and neurologists.

Autoregulation

Autoregulation is ordinarily defined as a change in the diameter of blood vessels in an organ or tissue so as to maintain a constant blood flow during a change in perfusion pressure. Cerebral perfusion pressure is elevated by raising the systemic

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*The complete proceedings of the symposium will be published by Springer-Verlag early in 1974. Material presented at the symposium is referred to in this paper by authors' names unaccompanied by reference numbers, and will be found in the Proceedings.
arterial pressure (SAP) and lowered by either decreasing SAP, increasing intracranial pressure (ICP), or increasing cerebral venous pressure. The upper and lower limits of autoregulation to a change in SAP were defined in papers presented at the symposium.

In normal baboons with a resting mean SAP of 80 to 100 mm Hg, Strandgaard found that the CBF remained constant to a mean SAP of 125 to 140 mm Hg and then increased rapidly with any further rise in SAP. The rise in CBF marks the upper limit of autoregulation. The lower limit in normal animals is determined primarily by lowering SAP. In a study by Fitch, et al., in anesthetized baboons, the CBF began to fall when the mean SAP was lowered to 65 mm Hg by hemorrhagic shock. This lower limit of autoregulation is somewhat higher than the values of 45 to 60 mm Hg reported in previous studies using essentially the same methodology. When SAP was lowered pharmacologically with Halothane, autoregulation persisted to a mean SAP of approximately 35 mm Hg. The authors concluded that under conditions of hemorrhagic hypotension sympathetic stimulation results in constriction of large intracranial arteries that counteracts the dilatation of cerebral arterioles which is the physiological basis of autoregulation.

Strandgaard also studied the upper and lower limits of autoregulation in patients with essential hypertension. In nearly every case the limits were shifted upward so that the CBF began to increase at a mean SAP of 145 to 175 mm Hg compared to 100 to 130 mm Hg in normal subjects. Of particular interest was the demonstration that the limits of autoregulation returned to the normal range after effective pharmacological treatment of the hypertension. These observations are important in selecting techniques and establishing the limits of hypotension in neurosurgical anesthesia. Agents that either impair the capacity of cerebral arterioles to dilate or produce constriction of large cerebral arteries by sympathetic stimulation raise the limit of hypotension that the brain will tolerate; this limit may be considerably elevated in hypertensive patients.

A breakthrough of the upper limit of autoregulation manifested by an increase in CBF during rising SAP should be of no concern as long as the arterial hypertension does not result in some type of brain damage. In fact, Ekstrom-Jodal, et al., reported a breakdown of the blood-brain barrier in normal dogs, manifested by extravasation of a vital dye into the brain parenchyma, when the upper limit of autoregulation was exceeded. The parieto-occipital region of the brain was most vulnerable. The extravasation of dye through tight capillary junctions that constitute the anatomical blood-brain barrier presumably was produced by increased pressure in the capillary bed that occurred as autoregulation failed. Extravasation of a vital dye which is always attached to serum protein should produce brain edema with its pathological consequences, but the water content of the brain was not measured in this study.

In most experimental studies of autoregulation in response to decreased cerebral perfusion pressure, perfusion pressure has been changed by either lowering SAP or elevating ICP. There have been few studies of the response of CBF to increased cerebral venous pressure. One of the most commonly accepted theories to explain the mechanism of autoregulation is a change in transmural pressure across the walls of the autoregulatory vessels; for example, when the transmural pressure is increased by increasing SAP the arterioles constrict. It should follow then that if increased cerebral venous pressure is transmitted upstream through the capillary bed to the arterioles the transmural pressure should increase and the arterioles constrict. This would be an undesirable effect, a perversion of the autoregulatory response resulting in a further decrease in CBF beyond that produced by the increased venous pressure and decreased perfusion pressure. Emerson and Parker reported active vasoconstriction during a progressive rise in cerebral venous pressure, thus supporting the myogenic theory of autoregulation and demonstrating that in this particular circumstance the autoregulatory mechanism fails in its purpose.
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Chemical Control

The definition of autoregulation given in the previous section is sometimes reserved for “pressure” autoregulation as distinct from “metabolic” autoregulation which is defined as a change in flow to meet the metabolic demands of the tissue. Here the primary event is a change in metabolism, as by an epileptic discharge, that produces a compensatory change in blood flow to provide sufficient oxygen to meet the changed metabolic needs of the tissue. There is general agreement that in metabolic autoregulation the diameter of the resistance vessels is determined by the H⁺ ion concentration in the extracellular space. As metabolism increases, for example, more H⁺ ions are produced in the cells; the H⁺ ions diffuse from the cells through the extracellular space to the vasoactive vessels which then dilate, increasing CBF.

Hypercapnia also increases CBF by decreasing extracellular pH (acidosis), and hypocapnia (alkalosis) has the opposite effect. However, at the severe levels of hypocapnia (PaCO₂ 20 to 25 mm Hg) sometimes seen in neurosurgical patients either spontaneously or induced for therapeutic purposes, the CBF might be reduced by means of intense vasoconstriction to the point of cerebral ischemic hypoxia. The hypoxia in turn would produce brain acidosis tending to counteract the alkalosis caused by the hypocapnia. This complex situation was investigated in normal volunteers by Harp, et al. During respiratory alkalosis produced by lowering PaCO₂ to between 20 and 30 mm Hg, they superimposed metabolic alkalosis by intravenous infusion of sodium bicarbonate. The additional alkalosis should have caused a further decrease in CBF, but in fact CBF increased. The authors explained the results by a degree of hypoxic vasodilatation of the cerebral vessels that more than counterbalanced the vasoconstrictive effect of the combined respiratory and metabolic alkalosis. The hypoxia in turn was caused by a shift in the oxygen dissociation curve (Bohr effect) produced by the superimposed metabolic alkalosis and resulted in less available O₂ to the tissue. The important conclusions from this study were that severe hypocapnia and systemic alkalosis could reduce CBF to the point that ischemic hypoxia of the brain occurred; however, a further reduction in PaCO₂ did not produce more hypoxia because the hypoxic stimulus to vasodilatation at least equaled the hypocapnic stimulus to vasoconstriction, and CBF either increased or remained the same as the PaCO₂ continued to fall. These results probably explain the clinical observation that some patients tolerate PaCO₂ levels below 20 mm Hg without functional brain damage.

Measurements of regional CBF (rCBF) in both animals and man have demonstrated consistent regional differences among cortical areas and subcortical gray structures. In general, gray matter flow is four to five times higher than white matter flow. Inhomogeneity of flow in the microcirculation has been described but not to the degree reported by Leniger-Follert and Lubbers; they have developed a method for measuring flow in the brain capillary bed from the rate of hydrogen clearance using a microrecording system with tip diameters as small as 1 μ. With this technique it is possible to measure quantitatively the flow in a single capillary. They described variability in flow through microregions of the brain from 0 to more than 500 ml/100 gm/min. The results demonstrate that inhomogeneity of flow is the rule in the microcirculation, and suggest that chemical control of the cerebral circulation is exerted primarily at the capillary or immediate precapillary level. If the control point were the arterioles (about 40 μ in diameter), flows in capillaries supplied by a single arteriole should vary in concert.

In another study, Stromberg and Fox also demonstrated the remarkable resolution of current microtechniques. Blood pressure was measured in pial vessels ranging in diameter from 260 to 10 μ, the latter slightly larger than a capillary, using micropipettes with a tip diameter as small as 0.1 μ. During changes in SAP and PaCO₂ that were induced to study the loci of autoregulation and chemical control within the resistance vessels, the resultant changes in pressures demonstrated that the vasoactive segments were the smallest vessels, 20 μ.
and less in diameter. Thus, these micropressure observations are in accord with the results obtained with microflow measurements. However, somewhat different results were obtained by Gotoh, et al., who observed vessels with a dissecting microscope during changes in SAP and PaCO₂. Autoregulation occurred primarily in vessels larger than 50 μ whereas vessels smaller than 50 μ in diameter responded to changes in PaCO₂. It is well known from single unit studies in neurophysiology that one neuron may be very active at times when an adjacent one is silent. The present studies suggest that the availability of metabolites for cell function is exquisitely controlled at the microcirculatory level, probably by extracellular pH.

Neurogenic Control

The evidence for and against neurogenic control has been obtained by a large variety of techniques used to study the autonomic nervous system in general. These might be better described as neurogenic influences on the cerebral circulation. This variety of approaches plus species differences account for the fact that this remains one of the most controversial areas of research on the cerebral circulation. The anatomical evidence for innervation of cerebral arteries by both adrenergic and cholinergic fibers is undisputed,12,37 The adrenergic nerve endings disappear following surgical sympathectomy. The origin of the cholinergic fibers is less clear, but at least some of them emerge from the brain stem through the facial nerve to join the intracranial internal carotid artery.12 For some time it was thought that the distribution of autonomic fibers was confined entirely to large and medium size arteries, but recent investigations using more refined techniques have demonstrated a plentiful supply on small arteries and on arterioles as small as 10 and 20 μ in diameter. Licata, et al., reported that they found cholinergic fibers in all segments of the cerebral arterial circulation.

The principal techniques that have been used to study the physiological significance of the vascular nerves are stimulation and ablation of the cervical sympathetics and the use of alpha and beta adrenergic and cholinergic stimulating and blocking agents. In the material presented at the symposium the species studied included the mouse, rat, hamster, guinea pig, rabbit, cat, dog, rhesus monkey, baboon, and man. The techniques used to measure CBF ranged from the xenon33 method in animals and man to measurements of microflow in deep nuclei such as the hypothalamus. Some subjects were awake, and the type and depth of anesthesia varied in the others. This large variability in methodology must be taken into consideration in evaluating discrepancies in the results presented.

Cervical Sympathectomy

The effects of cervical sympathetic block and surgical ablation have been studied frequently in stroke patients.32,33,47 The results have varied, but in general the effects of both stimulation and ablation have been minimal or absent. For this reason cervical sympathectomy has been largely abandoned in the treatment of atherosclerotic disease, vasospasm, migraine, and other cerebrovascular disorders.

Skinhoj reported that in a study on the vascular response to stellate ganglion block in man the upper limit of autoregulation was unchanged. However, Stone, et al., found that chronic sympathectomy in rhesus monkeys produced a significant decrease in the sensitivity of cerebral vessels to hypercapnia. Some of the most interesting results reported were in patients with autonomic dysfunction. In the Shy-Drager syndrome the autonomic nervous system is defective, and in previous studies cerebral autoregulation was found to be impaired in these patients.38 In a series of 10 patients with orthostatic hypotension studied by Shinozawa and Goto, there was dysautonomia of a lesser degree; cerebral autoregulation was defective in all. CBF was also measured by Eidelman, et al., in a series of patients who were quadriplegic as a result of cervical spinal cord injury; in these patients with cervical sympathetic nerves theoretically disconnected from central neurons, the cerebrovascular response to hypocapnia was greatly reduced by comparison to a group of control patients. Thus,
there is evidence that chronic sympatheticotomy impairs both autoregulation and the responsiveness of cerebral vessels to changes in PaCO₂.

Cervical Sympathetic Stimulation

Lluch, et al., reported that supramaximal stimulation of the cervical sympathetic nerve in unanesthetized goats produced a frequency-dependent reduction in CBF of as much as 55% when measured with an electromagnetic flow meter around the internal maxillary artery. In a similar study in anesthetized dogs by Traystman, common carotid blood flow was reduced by as much as 40% of control during sympathetic stimulation, but CBF measured from the confluence of sinuses showed no change. Presumably the sympathetic stimulation caused constriction of the carotid artery while CBF was maintained by collateral circulation. These studies emphasize that caution must be exercised in interpreting results in terms of the methodology used to measure CBF.

There is general agreement that the microsphere technique is one of the best methods available for quantitative measurements of CBF. Radioactive microspheres approximately 15 μ in diameter and therefore too large to pass through the capillary bed are injected intraarterially; the concentration of radioactivity in each region of the brain examined when compared to the arterial concentration, permits calculation of regional CBF (rCBF). Since this method does appear to be so accurate, it is of interest that stimulation of the cervical sympathetic nerve in the dog had no effect on the ipsilateral hemisphere CBF when measured by Meyer and Klassen using this technique.

Pharmacological Sympathetic Stimulation

Pharmacological stimulation of alpha adrenergic terminals causes vasoconstriction in the distribution of the extracranial sympathetic system, while beta adrenergic stimulation produces vasodilation. Several investigations reported at the symposium were designed to determine if the same mechanisms exist in brain arteries. In a study by Ekstrom-Jodal, et al., intravenous norepinephrine produced a significant reduction in CBF in the dog; in two other studies in unanesthetized goats (Lluch, et al.), and in rabbits (Rosendorff, et al.), tyramine which releases norepinephrine from vascular terminals also caused a reduction in CBF. In the experiments of Rosendorff, et al., microflow was measured in the hypothalamus of rabbits, and minute amounts of drugs were injected into the tissue from which rCBF measurements were made. Norepinephrine in very small concentrations increased rCBF, and the effect was blocked by propanolol, a beta blocker. Larger doses of norepinephrine decreased the rCBF, and the effect was blocked by phenoxybenzamine, an alpha blocker. The results provide clear pharmacological evidence for both alpha and Beta adrenergic receptors on resistance vessels in the hypothalamus.

These observations were supported by the results of Seylaz, et al., who measured rCBF in the lateral geniculate body and the caudate nucleus in the rabbit. These structures were selected, because histofluorescence studies showed abundant adrenergic terminals on vessels in the caudate nucleus and relatively few in the lateral geniculate. Beta adrenergic stimulation with intra-arterial isoprenaline had no effect on rCBF in the lateral geniculate but caused an increase in rCBF in the caudate that was twice that produced by 5% CO₂. The isoprenaline-induced vasodilation was blocked by propanolol. Thus, not only were there significant alpha and beta adrenergic effects on the cerebral vessels; these effects were regional and in at least one study correlated well with the anatomic distribution of catecholamine terminals.

Pharmacological Sympathetic Blockade

In five papers presented at the symposium (Hoff; Lluch, et al.; Ekstrom-Jodal, et al.; Hernandez-Perez and Erickson; and Mathew, et al.), phenoxybenzamine alone produced only a slight increase in CBF and did not influence the autoregulatory response to a change in perfusion pressure whereas both phenoxybenzamine and phentolamine, another alpha blocker, consistently blocked the cerebral vasoconstric-
tion produced by systemic norepinephrine and tyramine as well as sympathetic stimulation. However, neither phenoxybenzamine nor thymoxamine, a third alpha adrenergic blocker, altered the vasoconstrictor response to hypocapnia.

Other Vasoactive Agents

There were few studies of the cholinergic system, and the results reported indicated a minimal effect compared to adrenergic mechanisms. Local application of carbamoylcholine, a parasympathomimetic agent, caused dilatation of the pial arteries but only in large concentrations, and the maximum increase in diameter was 20%, reported by Kuschinsky and Wahl. Intravenous atropine had no effect on CBF (Hernandez-Perez and Erickson) nor was there any change in the diameter of pial vessels following local application of atropine (Kuschinsky and Wahl). In dogs, Ekstrom-Jodal, et al., found that serotonin decreased CBF, and the effect was not influenced by adrenergic blockers. Small doses of dopamine decreased CBF while larger doses increased it; the decrease with small doses was eliminated by alpha-adrenergic blockade.

The results of these many investigations provide compelling evidence for significant neurogenic influences on the cerebral circulation. However, considerable negative data were presented, and several studies demonstrated methodological pitfalls in the interpretation of positive data. Since it is well known that the autonomic nervous system operates as a defense mechanism in the face of stress, the next step would appear to be investigation of the significance of neurogenic influences in pathological states affecting the cerebral vessels.

Diffuse Ischemia

Diffuse brain ischemia (cerebral circulatory arrest) occurs clinically during cardiac arrest and when intracranial pressure (ICP) equals systemic arterial pressure (SAP) in patients with severe brain swelling. Virtual cessation of CBF is seen occasionally in patients with extensive extracranial vascular disease, but the occlusive process occurs slowly, and nearly all patients die from focal infarctions before vascular occlusion is complete. This is of some significance if one is attempting to correlate animal investigations of diffuse ischemia with clinical states, since one of the commonest methods used to produce experimental arrest of the cerebral circulation involves cross clamping of the aorta or its cephalic branches, a condition that does not occur in clinical pathology, at least not acutely.

In this section of the symposium, attention was directed primarily to the length of time the brain can be made ischemic before irreversible damage occurs and the biochemical and pathological substrates of irreversible injury. In previous studies, large portions of the brain failed to reperfuse with blood when the arterial clamps were removed following transient total occlusion of the arterial inflow to the brain.1-6 This was termed the "no-reflow phenomenon" and was discussed by Ames and Brierley in this symposium. After 15 minutes of cerebral circulatory arrest, approximately 50% of the brain was not reperfused; the cause could not be certainly determined. The principal explanations proposed were intravascular sludging and collapse of the capillary bed by endothelial or perivascular glial cell swelling. If it could be demonstrated that neurons and glial cells would survive prolonged ischemic anoxia if recirculation of the brain were adequate when perfusion pressure was restored, the no-reflow phenomenon could be used to explain the fact that most patients suffer irreversible brain damage following cardiac arrest for only a few minutes; and this would have important therapeutic implications. According to this explanation, the brain fails to survive not because of 5 minutes of cardiac arrest but because of much more prolonged periods of cerebral ischemia produced by the no-reflow phenomenon after cardiac function has been restored. On the other hand, if the special vulnerability of the brain to ischemic anoxia is due to pathological changes in brain cells that become irreversible within a few minutes of cerebral circulatory arrest,6 the no-reflow phenomenon which is minimal within the first 10 minutes of complete ischemia could be considered an epiphe-
nomenon of the ischemia of little clinical significance.

The no-reflow phenomenon was evaluated in three studies presented at the symposium by Matakas, et al.; Kobayashi, et al., and Hossman and Zimmerman. These findings can be summarized as follows. The volume of brain that is not reperfused following periods of complete ischemia ranging from 15 to 60 minutes is in large part dependent on the level of SAP maintained during postischemic restitution. When postischemic SAP is 80 to 90 mm Hg there is little or no recovery of brain electrical activity; the CBF is then decreased and continues to fall during the postischemic period. The fall in CBF correlates with the formation of brain edema, and in one study endothelial cell edema caused obstruction of the capillary lumina that appeared to account for the failed reperfusion. These observations probably explain prior studies in which the existence of the no-reflow phenomenon was questioned. The level of SAP in the postischemic period determines the volume of brain reperfused; the failure at relatively hypotensive levels is caused by brain edema and increased ICP.

There remains a discrepancy in the measurements of the period of time the brain will tolerate complete ischemia. Criteria for irreversible brain damage include neurological status, brain electrical activity, the morphological state of the cells, and the energy state of the brain. High energy phosphates, particularly adenosine triphosphate (ATP), are formed by oxidative phosphorylation in mitochondria, and ATP supplies the energy for the metabolic functions of the cells. In man and other species, including studies in the rat reported by Ljunggren and Siesjo, irreversible brain damage occurs after cerebral circulatory arrest for 5 minutes. However, Hossman and Zimmerman reported that after 60 minutes of complete ischemia in cats followed by several hours of effective recirculation of the brain, there was steady improvement in brain electrical activity. Moreover, brain ATP which had virtually disappeared during the first few minutes of ischemia returned to approximately 60% of control values. These observations provide some encouragement in the management of patients with cardiac arrest. After arrest SAP should be maintained at normal or above normal values (the optimal level has not been determined), and anti-edema therapy should be given. However, these results in experimental animals must be qualified by previous observations in patients in whom ICP, rCBF, and brain metabolism were measured after cardiac arrest. In two patients the CBF was markedly increased, not decreased; the ICP was minimally elevated at a time when cerebral metabolism had virtually ceased and the patients exhibited most of the clinical criteria of brain death. Brierley, et al., presented an additional note of caution regarding the tolerance of the brain to hypoxia; a combination of hypoxemia and relative ischemia in rats for 30 minutes produced progressive ischemic morphological changes during the period of restitution.

Two reports dealt with the effect of a progressive decrease in CBF on the cerebral metabolism of O₂ and glucose (Hamer, et al.; Bruce, et al.). The levels of perfusion pressure, CBF, and O₂ availability necessary for tissue integrity are critical only in terms of the metabolic demands of the tissue. If metabolism remains normal throughout a steady decrease in the availability of metabolites, these levels can be established for each species investigated. However, if metabolism decreases with decreasing CBF, the CBF can be reduced to lower levels before ischemic hypoxic brain damage occurs. Both studies demonstrated that when CBF is decreased by either decreased SAP or increased ICP, cerebral metabolism of O₂ and glucose also decreases. The cause of the decreased metabolism is unknown, and the interpretation of the results is difficult. Teleologically it could represent a mechanism to protect the brain during a decreased O₂ supply or, on the other hand, the decrease in metabolism could be considered a form of brain damage at levels of CBF that had been considered more than adequate to maintain brain function. Harbig and Reivich found a shift in the oxidation-reduction state of the pyridine nucleotide enzyme system (NADH/NAD⁺) toward the reduced side.
during a minimal decrease in brain perfusion pressure produced by lowering the SAP. The pyridine nucleotide system is essential in numerous metabolic steps within the cell, again demonstrating an alteration in metabolism with remarkably little change in perfusion pressure.

**Focal Lesions**

In recent years there have been numerous investigations of the pathophysiology and biochemical changes produced by unilateral carotid or middle cerebral artery occlusion in experimental animals. The purpose has been to establish models of acute thrombotic and embolic stroke. In previous CBF symposia there have been reports on changes in rCBF and vascular reactivity in and adjacent to ischemic brain accompanied by much discussion and disagreement on the incidence and significance of the intracerebral steal phenomenon; this concept assumes that hypercapnia decreases rCBF in ischemic brain because of dilatation of resistance vessels in normal brain resulting in a "steal" of blood from the damaged brain. The explanation is that the vessels in ischemic brain are already maximally dilated and cannot dilate further with increased PaCO₂. There is general agreement that the intracerebral steal phenomenon exists, but it appears to be uncommon in stroke patients.

Sengupta, et al., reported at this symposium that there was no change in cerebral hemisphere CBF following common carotid ligation in baboons. However, the expected increase in hemisphere CBF with systemic hypoxia was markedly reduced, and CBF fell passively with a decrease in SAP. These observations support the basic concept of the steal phenomenon, namely that resistance vessels distal to an arterial occlusion are maximally dilated.

Most of the studies presented at the symposium were designed to investigate the length of time the middle cerebral artery can be occluded before irreversible brain damage occurs, the time course and extent of biochemical changes in ischemic brain, and the contribution of brain swelling to the pathophysiology of ischemia. Two principal models were used, namely, occlusion of the carotid or middle cerebral artery, and a lesion of the cortex and underlying white matter produced by application of intense cold to the overlying dura. The latter lesion is well known to produce spreading edema in the white matter and appears to simulate a mechanical contusion.

Evidence was presented for progressive brain infarction in the distribution of the occluded middle cerebral artery in rhesus monkeys, but Crowell and Olsson found little or no clinical deficit or histological evidence of infarction in animals in which the clip was removed after up to 8 hours of occlusion. If the results can be applied to patients they suggest that revascularization procedures within that time limit should be beneficial. Following carotid ligation in the gerbil, which lacks posterior communicating arteries (Harrison and Ross Russell), middle cerebral artery occlusion in cats (O’Brien and Waltz), and carotid emboli in dogs (Held, et al.), swelling of ischemic brain occurs. The blood-brain barrier becomes permeable to large molecules, and the swelling is due to edema proven by measurements of water content. The concentration of ATP decreases rapidly in ischemic brain, then increases toward normal despite progressive infarction (Kogure, et al.; Held, et al.).

Two papers in this session dealt with the possible contribution of abnormal catecholamine metabolism to the biochemistry of infarction. Kogure, et al., reported that the concentration of norepinephrine decreased in involved brain at 5 minutes after carotid embolization in rats then increased to normal during continued infarction of the tissue. These results argue against the hypothesis that increased release of norepinephrine might lead to vasoconstriction and aggravation of the ischemia as has been suggested in acute spinal cord injury. However, in a study of middle cerebral artery occlusion in squirrel monkeys by Zervas and Hori, treatment of the animals with alpha-methyl-para-tyrosine, a drug that blocks synthesis of norepinephrine, improved neurological function and survival when the animals were compared to untreated controls.

The purpose of the cold lesion investiga-
tions was to study the effect of the lesion and its consequent edema on rCBF and the energy state in brain adjacent to and remote from the lesion. Brain cells are severely damaged or destroyed within a contusion, but the remote effects, spreading edema and increased ICP, may be more significant in terms of neurological dysfunction and mortality than the lesion itself. Wallenfang, et al., reported that in cats 24 hours after creation of the lesion, rCBF was decreased throughout the ipsilateral hemisphere, most markedly adjacent to the lesion; the ATP content was decreased and lactate content increased adjacent to the lesion, indicating that the decrease in rCBF was sufficient to produce ischemic brain damage. Moderate hypocapnia improved rCBF and increased ATP content throughout the hemisphere, but severe hypocapnia (PaCO₂, 11.5 mm Hg) caused a marked further decrease in both rCBF and ATP content. The reason for this is not clear, but the results demonstrate the potential danger of severe hypocapnia in brain damaged subjects. The observations on rCBF in the report by Wallenfang, et al., were confirmed by the results of Dick, et al., in which rCBF decreased throughout the white matter of the hemisphere ipsilateral to a cold lesion, and the decrease in rCBF correlated well with tissue water content. Miller, et al., in a study of cold lesion edema in baboons, found that when SAP was increased, rCBF in the damaged hemisphere did not increase, suggesting intact autoregulation. However, the ICP increased concomitant with the rise in SAP, indicating “false” autoregulation in which increased tissue pressure prevents dilatation of non-autoregulating vessels giving the impression that autoregulation is intact.

Severe edema caused by a brain contusion is observed commonly in head-injured patients. Perhaps the best example is the “burst temporal lobe.” However, the effect of edema on cell function beyond the confines of the lesion has not been clearly defined. The studies reported suggest that rCBF is reduced, even in brain remote from the lesion, and that this decrease is sufficient to produce brain damage. The effects of infarction produced by vascular occlusion are similar. The lesion is progressive, and the progression appears to correlate well with the formation of edema which causes a decrease in rCBF adjacent to infarcted brain. Perhaps this is due to collapse of the microcirculation from endothelial cell or perivascular glial cell swelling as described in some models of diffuse ischemia. However, the animal studies do not explain the clinical observation that some patients with carotid or middle cerebral artery occlusions rapidly develop a hemiplegia that is complete and irreversible even though the patients do not develop signs of brain swelling or intracranial hypertension. In contrast, other patients with the same apparent vascular pathology follow a course similar to that described in experimental animals.4

These observations have an important impact on the selection of patients for surgical therapy. If progressive brain swelling is due to ischemic edema, early revascularization following the occlusion should improve CBF, and the edema should subside. However, the high mortality rate in patients with extracranial carotid occlusion, hemiplegia, and evidence of brain swelling following successful re-establishment of carotid artery flow is attributed to hemorrhagic infarction. For these reasons, animal studies of focal ischemia must be interpreted cautiously.

Relation of Experimental ICP to CBF

During progressive intracranial hypertension, CBF is maintained by autoregulation. In most experimental studies ICP has been increased diffusely and rather acutely by infusion of fluid into the subarachnoid spaces. This does not simulate a pathological condition in man. The situation might be quite different during expansion of an intracranial mass lesion, particularly if pressure gradients develop across the supratentorial space; if this occurs the problem becomes more complex, because then it is necessary to measure local tissue pressures rather than pressure from a CSF space in order to establish the relationships between pressure and flow.

In two studies in baboons rCBF and bilateral extradural or subdural pressures were recorded during gradual expansion of
an extracerebral balloon. Symon, et al., reported that extradural pressure on the side of the balloon was 16 to 30 mm Hg higher than on the opposite side, whereas Johnston and Rowan found the maximum difference in pressure was 7 mm Hg, and this difference was not statistically significant. In neither study did rCBF decrease in the compressed hemisphere compared to the opposite hemisphere. Whether the differences in the results obtained in the two series of experiments are due to rates of balloon expansion, the locations of the recording transducers, or the positions of the balloons is uncertain.

Clinical Studies

Methodology

Clinical methods of measuring CBF, which is expressed as average blood flow per unit weight of the brain (ml/100 gm/min), are based on the Fick principle. Kety and Schmidt applied the Fick principle to the clearance of nitrous oxide from the brain in order to make the first quantitative measurements of CBF in man. The next major step was the introduction of radioactive tracers to measure CBF in multiple regions of the brain using scintillation detectors. In recent years xenon has been used most frequently in clinical studies. Techniques of measuring CBF have been discussed in detail in two recent reviews. Only those aspects of the methodology that are pertinent to papers presented at the symposium will be discussed here.

In most rCBF studies, xenon is injected as a bolus through a catheter inserted into the internal carotid artery under x-ray control; rCBF is recorded from brain clearance curves using multiple scintillation detectors mounted in a collimator block placed alongside the patient's head. The clearance curve consists of an abrupt rise in counts from baseline to a sharp peak that represents the height of the curve as the bolus enters the brain, followed by a gradual fall in counts as the isotope is washed out from each region under observation; the steeper the slope of the washout curve the higher the flow rate. Each curve can be analyzed by three methods in order to obtain a quantitative rCBF value. The stochastic or height/area method gives a mean flow value. Bicompartmental analysis of the curve is based on evidence that the isotope is cleared from two major compartments, a fast flow compartment which is gray matter and a slow flow compartment which is white matter. Calculation of flow is also based on the relative weights of the two compartments which are determined from the clearance curve. Normally the volume of brain “seen” by each detector consists of approximately 60% gray matter and 40% white matter. From the flows and weights of each compartment another flow (mean compartmental flow) is calculated which can be compared to the mean flow for the same region obtained by the stochastic method. A third method of analyzing the clearance curves consists of measurement of the slope of the first 2 minutes of the curve which is termed the 2-minute index or initial slope index. This gives a mean flow value that is higher than mean stochastic flow but appears to vary proportionally to stochastic flow during physiological tests and in pathological conditions. It has the advantage that rCBF is measured within 2 minutes of injection of the isotope, an important consideration in acutely ill patients in whom it may be difficult to maintain a steady state during the 10 to 15 minutes required for compartmental and stochastic analyses.

Despite the fact that rCBF studies have been performed in many clinics in the past 10 years there is relatively little information on normal values, the reproducibility of regional values in the same patient under presumed steady state conditions, and interregional differences. In a study presented, Herrschaft, et al., reported that mean flow as determined by bicompartmental analysis was consistently higher than mean flow obtained by the stochastic method in the same region, 63.1 and 56.5 ml/100 gm/min, respectively. There was considerable variation among 22 healthy volunteers studied under nitrous oxide-Halothane analgesia, whereas in serial studies changes in flow within a region in the same individual were minimal, rarely exceeding 5%. Gray matter flow was consistently higher in the precentral and
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central regions and in the basal ganglia and lowest in the anterior frontal and occipital regions.

In a similar study in anesthetized ventilated patients by Miller, et al., flows recorded from the same regions in successive tests again showed little variation. The clearance curves were analyzed by all three methods described above. Of particular interest was a comparison of regional flow values obtained with common carotid and internal carotid injections of the xenon\textsuperscript{133}. Common carotid injections have been avoided in the past because clearance of isotope from extracerebral tissue in the distribution of the external carotid artery creates a third compartment that is mixed with the two brain compartments. However, the mean difference in rCBF using the two routes of injection was 3 ml/100 g/min, and this difference was not statistically significant. It is known that flow through the extracerebral compartment is considerably slower than white matter flow, and the present results suggest that it can be largely ignored. Since rCBF measurements are often performed at the time of carotid angiography, another issue has been whether the contrast medium used for angiography changes rCBF. In the report of Miller, et al., rCBF measured 20 and 40 minutes following routine angiography was unchanged from control values.

The results described above justify considerable confidence in the techniques of analysis when CBF is normal or nearly so. However, doubts have been expressed concerning the usefulness of bicompartamental analysis in patients with severe brain pathology and marked derangement of the cerebral circulation. In these circumstances large relative changes in both the flows and weights of gray and white matter have been recorded. If the changes in weight can be accepted the data would be of considerable value in identifying gray matter and white matter edema, for example. Two papers presented at the symposium were addressed to this problem. One was a series of patients studied under normocapnia and hypocapnia by Iliff, et al. The fall in rCBF produced by hypocapnia was consistently accompanied by a relative decrease in gray weight, but the authors concluded that this was an artifact of the method of analysis, not a real change in the relative weight of gray matter. The second study was done by Bruce, et al. In patients with severe head injuries, mean rCBF values, calculated by the stochastic and bicompartamental methods, were compared during changes in rCBF produced by mannitol and by raising SAP in order to test autoregulation. The stochastic method was found to be more accurate than measurements of gray flow by bicompartamental analysis, particularly in low flow states where the clearance curve approached a monoeXponential function. Thus, when CBF is markedly deranged and especially in low flow states, stochastic analysis is preferable to bicompartamental analysis of the clearance curve and apparent changes in the weights or volumes of gray and white matter are probably artifactual.

These observations are also important in the analysis of cerebral clearance curves obtained with "non-invasive" techniques of introducing the isotope. The major limitation of the wider application of the carotid injection technique concerns the justification for puncture of the carotid artery in order to do the study. There have been differences of opinions about the safety of the procedure, and in a formal discussion on invasive and non-invasive techniques, Ingvar presented convincing evidence for the safety of the procedure in experienced hands. Nevertheless, there is general agreement that rCBF measurements will be useful in clinical management to the extent that they can be repeated at frequent intervals with little or no risk and discomfort for the patient. Thus, there is great interest in the non-invasive methods that have been described in the past several years.

Measurement of rCBF by inhalation of xenon\textsuperscript{133} was first described by Mallett and Veall.\textsuperscript{29} Subsequently, Obrist, et al.\textsuperscript{34} described another method of analyzing the inhalation clearance curves. In a paper presented at the symposium by Corbett and Eidelman, the two methods of analyzing the inhalation clearance curves were compared with mean CBF estimated from cerebral arteriovenous O\textsubscript{2} content differences in volunteer subjects. Studies were carried out at rest, during hyperventilation,
and during infusion of an alpha blocking agent, thymoxamine. The correlation between CBF determined by arteriovenous O₂ differences and the Obrist xenon¹³³ inhalation method was excellent, considerably better than with the Veall method.

In Obrist's original description of the method of analysis of the inhalation clearance curves it was necessary to record the isotope clearance for 50 to 60 minutes in order to separate the extracerebral from the brain compartments. In a report presented at the symposium, Obrist, et al., described the results of a different method of mathematical analysis of 10-minute clearance curves obtained after 2 minutes of inhalation of xenon¹³³. The study included volunteers and patients undergoing endarterectomy. In the normal patients rCBF values were very close to those obtained in normals using the intracarotid injection technique. Another advantage of the inhalation method is the ability to record rCBF from both hemispheres simultaneously, and in this study there was excellent correlation in rCBF values obtained from homologous regions of the two hemispheres, a difference of 8% or more occurring less than 5% of the time. However, there was a large day-to-day variability within the same regions, probably due to variations in levels of alertness in these unanesthetized patients.

Xenon¹³³ can also be injected intravenously, and the analysis of the data is essentially the same as with the inhalation technique except that in a paper presented at the symposium, Austin, et al., reported using an analog rather than a digital computer for analysis. The rCBF values in normal patients reported by Austin, et al., are virtually identical to the values obtained with both the intracarotid and inhalation methods.

Thus, the non-invasive methods provide reliable results in patients with normal CBF. It is now necessary to test their reliability in patients with severe brain insults by comparing the intracarotid and inhalation or intravenous methods serially in the same patient at rest and during changes in CBF produced by hyper- or hypocapnia and by changes in SAP when autoregulation is defective. This is particularly necessary in low flow states where the clearance curve tends to become monoexponential. The disadvantage of these techniques is that the stochastic method of analysis, which is generally considered to be the most accurate, cannot be used. Also, the analysis of the cerebral clearance curve is dependent on simultaneous recording of the pulmonary expiratory curve for xenon¹³³ using a separate detector. In turn this analysis depends on the assumption that the expiratory curve is a close approximation of arterial clearance of the isotope and this may not be the case in patients with significant pulmonary pathology.

Head Injuries

There is still uncertainty concerning the relationship between ICP, CBF, and the neurological status in patients with severe head injuries. Both good¹³²,¹⁶ and poor⁸,¹⁶,²¹ correlations between ICP and survival have been reported. CBF is generally reduced in these patients, but normal CBF has been observed even in patients with intracranial hypertension,⁸ and in some patients CBF is supernormal even when the patients are deeply comatose.¹⁶,²⁰,⁴¹ These observations were confirmed by Cold, et al., who observed very high regional flow values in comatose head injured patients. The rCBF values tended to become normal in patients who improved clinically. Thus, previous studies have shown a rather poor correlation between CBF and ICP and between CBF and survival, and the relationship between ICP and survival remains problematical.

Two additional studies in severely head injured patients were reported at the symposium in which ICP was measured continuously from the intracranial space and CBF was measured with the Kr⁵⁵ or xenon¹³³ methods. Kelly, et al., reported a good correlation between ICP, CBF, and survival; all patients with normal CBF at the time of the initial study recovered satisfactorily, reduced CBF carried a poor prognosis, and the outcome was worst in patients with both low CBF and high ICP. However, vigorous treatment of the intracranial hypertension with hypertonic mannitol reduced mortality in the latter group. In the second patient study, Tweed and
Overgaard emphasized the importance of impaired autoregulation that was found in one or more regions in all patients investigated. When SAP was increased in the presence of impaired autoregulation, ICP also increased, sometimes to very high values, while rCBF rose little if at all. This is another example of the “false” autoregulation described in the section on Focal Lesions. In previous studies, the phenomenon was observed rarely, even when there was global loss of autoregulation throughout the hemisphere studied. Nevertheless, this catastrophic complication of induced arterial hypertension can occur, resulting in brain herniation and brain stem compression. It has also been seen in patients with subarachnoid hemorrhage and vasospasm in whom SAP was increased in an attempt to improve rCBF in brain distal to the vasospasm.

Stroke

Alterations in rCBF and cerebrovascular responses to changes in SAP and PaCO₂ have been described in many large series of patients with thromboembolic cerebrovascular occlusion and intracerebral hemorrhage. A summary of these investigations has been reported recently. In previous symposia there were numerous clinical reports on the incidence and significance of the intracerebral steal phenomenon, and the principal purpose of these studies was an attempt to determine optimal levels of SAP and PaCO₂ for brain oxygenation in acute stroke patients.

The reports presented at this symposium represented extensions of various aspects of these studies. In half of a group of 16 patients, most of whom had had an acute stroke, autoregulation was found to be defective in the involved hemisphere (McHenry, et al.). The response to hypercapnia was better preserved in the group with intact autoregulation, but in previous studies considerable discrepancy has been noted between the cerebrovascular response to changes in SAP and PaCO₂. This has been termed “dissociated vasoparalysis” in which the autoregulatory mechanism may be preserved at a time when CO₂ responsiveness is lost and vice versa.

Blood-brain barrier permeability increases in ischemic regions of the brain and is associated with edema (see Focal Lesions). Heiss, et al., demonstrated a good correlation between the brain scan and rCBF values in acute stroke patients. In 11 patients with a negative scan, mean hemisphere flow and focal flow in the region of involved brain were significantly higher than mean hemisphere flow and regional flow in 17 patients with a large increase in the uptake of the isotope in the ischemic region.

Since autoregulation is often defective throughout the involved hemisphere in stroke patients, and brain swelling and increased ICP are common in these patients, an increase in SAP might produce a marked increase in ICP and the picture of false autoregulation, as in the occasional head-injured patient. Although an increase in ICP was described in patients with defective autoregulation by Fieschi, et al., in none of the cases was the increase in ICP sufficient to prevent the increase in CBF. Thus, false autoregulation was not observed. However, since the phenomenon does occur in head-injured patients especially when there is severe brain swelling, it might well occur in stroke patients in whom there is marked edema and about a large ischemic lesion. Thus, a marked rise in SAP, either spontaneous or induced in an attempt to increase CBF, is a potentially dangerous procedure, and it is especially so in patients with clinical evidence of brain swelling and intracranial hypertension irrespective of the etiology.

Carotid Stenosis and Occlusion

Measurements of rCBF, carotid stump pressure, and continuous registration of the EEG have been used to test the safety of temporary carotid occlusion during surgery for stenosis of the extracranial internal carotid artery and for carotid ligation in the treatment of intracranial aneurysms. A review of a series of patients in whom the three methods of evaluation were compared has been published recently. Measurement of jugular venous O₂, another method of evaluating the adequacy of cerebral circulation during carotid occlu-
tion, was not investigated in this particular study, but there is evidence that this procedure provides little useful information in these patients.\textsuperscript{48} Boysen\textsuperscript{4} found that clamping of the common carotid artery in patients with extracranial internal carotid stenosis reduced CBF in nearly all patients, and the flow reduction was homogeneous over the hemisphere studied even in patients with focal rCBF alterations caused by their stroke. Since hypercapnia has been advocated during endarterectomy his observation that the average reduction of rCBF was 47% in hypercapnic patients but only 17% in hypocapnic patients is particularly important. The critical level of hemisphere CBF reduction, determined by the EEG, was 18 to 23 ml/100 gm/min. Carotid stump pressure gave reliable information on collateral function, and the critical value in terms of EEG activity was 50 to 55 mm Hg. The internal carotid artery stump pressure varied directly with rCBF changes. Therefore, he concluded that measurements of stump pressure may be adequate to assess the adequacy of collateral circulation during carotid occlusion.

Herrschaf, et al., reported that hemisphere CBF on the side of carotid stenoses occluding 70% or more of the vessel lumen was reduced by a mean of 30%, but there was great variability in rCBF among patients with the same apparent degree of stenosis. In postoperative studies, following endarterectomy, mean hemisphere CBF increased to values approaching normal. The responses of rCBF to changes in PaCO\textsubscript{2} were investigated in a series of patients by Pistolese, et al., who found that when CBF was reduced to approximately 30 ml/100 gm/min, the hypercapnic response was lost, and the hypocapnic response was considerably diminished. Jennett, et al., measured rCBF in an attempt to establish criteria for carotid ligation in patients with intracranial aneurysms; they found the method to be quite accurate in selecting those patients in whom the ligation should not be done for fear of postoperative ischemic complications. This group used the criterion that ligation should be abandoned when ipsilateral hemisphere CBF is reduced by 25% or more below control values during temporary clamping of the carotid artery; under these circumstances the incidence of ischemic complications which has been reported to be as high as 40% was reduced to less than 10% in this series.

Finally, a new application of rCBF techniques was reported by Schmiedek, et al. They used rCBF as a criterion for selection of patients for superficial temporal artery-middle cerebral artery anastomoses and to determine the patency of the bypass shunts following operation. They reported their postoperative results as follows: The shunt was intact in 11 patients and occluded in two; six of the patients with an intact shunt had marked improvement in rCBF in a previously ischemic region.

Conclusions

The scope of the investigations reported at the symposium indicates a continued high level of interest in CBF and brain metabolism. In part this is due to the continuing development of new experimental designs and techniques of analysis. For example, the application of fluorescent histochemical techniques to studies of the innervation of cerebral vessels has been mainly responsible for reopening the issue of neurogenic control of the cerebral circulation, and the number of papers on neurogenic control presented at this symposium exceeded the total number presented at all previous CBF symposia. However, the functional significance of cerebrovascular nerves is far from resolved. The other area of research that attracted particular attention was ischemic brain damage. This is important for clinicians, because brain ischemia appears to be the final common denominator of neurological dysfunction and death in most neurosurgical patients whether the initial insult is head injury, subarachnoid hemorrhage, thrombotic stroke, or postoperative complications of intracranial surgery. Another important contribution of the symposium is the evidence that measurements of CBF alone provide insufficient information on brain function, prognosis, and response to therapy. Brain metabolism of O\textsubscript{2} and glucose must also be determined. Finally, clinical measurements of CBF and brain...
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metabolism are still research tools for the most part. However, non-invasive techniques for introducing the isotope are promising, and if they can be proven to be reliable in pathological states affecting the cerebral circulation, frequent rCBF measurements in the same patient may be applied widely in diagnosis and assessing responses to therapy.

The next CBF symposium in this series will be held at the Aviemore Conference Centre, Inverness-shire, Scotland, in June, 1975, and will be organized by Dr. A. Murray Harper and Mr. Bryan Jennett of the University of Glasgow.

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