Cerebral Blood Flow Studies in Stroke*

JOHN STIRLING MEYER, M.D.

Professor and Chairman, Department of Neurology, Baylor College of Medicine, Houston, Texas

I will discuss here some work we are doing in our laboratory on the measurement of cerebral blood flow (CBF). We are using the gamma camera, which is connected to a computer, to measure regional CBF. We inject ^{133}Xe into the carotid artery and, by using multiple probes, measure the clearance from multiple regions of the head. The advantage of the gamma camera is that it has excellent resolution and has common probe characteristics. It may be thought of in terms of multiple probes, although it has a single crystal, and it achieves the desirability of multiple regional CBF recordings confined essentially to one hemisphere because of the depth characteristics of the collimation.

The formula for height-over-area analysis in the clearance for fast and slow flow (or the first and second slopes of the curve, F1 and F2) is handled by the computer which gives an automatic write-out. In addition, having injected the xenon, which washes out fairly rapidly over an interval of 12 minutes, we then inject with a nondiffusable isotope, technetium. By use of a different formula, this gives us the regional cerebral blood volume, so that in the same patient, we have both the regional cerebral blood flow and the regional cerebral blood volume on the computer write-out. Table 1 is a typical record that comes out of the automatic print-out; it has the advantage of being rapid, taking place while the patient is being examined. It comes out objectively with a minimum amount of error, the program being highly reliable, and gives you both the regional cerebral blood flow (ROI) and the mean hemispheric flow (RCBF "H/A"), which is in good agreement with hydrogen clearance using an entirely different methodology, as well as the standard deviation. It gives you the fast or so-called gray flow (FG), the white flow (FW), the so-called weight of gray matter (WG), the weight of white matter (WW), a regional flow calculated by another method (RCBF "LOG"), and the regional cerebral blood volume (RCBF), which is of considerable use because, knowing blood flow, blood volume, and cerebrospinal fluid pressure, you can say a great deal about the amount of blood and parenchyma present in the region under study and about the various pressure-tissue-flow relationships.

For our metabolic studies, we feel that it is less traumatic and highly reliable to pass the catheter up into the lateral sinus via the brachial vein; this is done under visualization of the fluoroscope in the cardiac catheterization laboratory. I say it is highly reliable, because one can inject a little dye at the time of placement of the catheter, from which much can be learned. About 20% of patients have abnormalities of the venous system, and there is no question that, with the blind puncture or modifications of it, the needle often finishes up sampling blood that was certainly not coming from the brain, which accounts for some of the errors in methods.

To summarize some of the data—it will be found that the earlier the patient is studied after a stroke, the greater is the reduction of CBF. I would like to point out that CBF is reduced not only on the diseased side but also on the healthy side (Table 2). We called it diaschisis and supposed that it was due to the release, following stroke, bilaterally or perhaps from the brain stem, of some neurotransmitter, and it was suggested that it might be serotonin or some related substance. Judging from our current studies, it now appears that indeed there are neurotransmitter releases in a unilateral stroke and that these neurotransmitters, bilaterally, include norepincphrine, serotonin, and C-AMP; these reduce cerebral blood flow and decrease me-

* This is an edited transcription of a lecture presented by Dr. Meyer, February 7, 1974, at the Medical College of Virginia, Richmond.

TABLE 1

REGIONAL CEREBRAL BLOOD FLOW MEASUREMENTS USING GAMMA CAMERA AND INTERTECHNIQUE COMPUTER SYSTEM

		Typical Print-Out of RCBF Data					
ROI	RCBF "H/A"	FG	WG	FW	WW	RCBF "LOG"	RCBV
1,4	42.2	41.57	65.1	14.81	34.9	32.2	9.62
2,3	35.2	48.93	38.2	28.27	61.8	36.2	8.95
2,4	33.7	43.88	46.3	19.70	53.7	30.9	7.58
2,5	32.5	37.52	49.1	18.96	50.9	28.1	6.29
2,6	32.0	33.69	61.0	16.27	39.0	26.9	6.09
3,3	32.2	46.13	47.8	19.62	52.2	32.3	8.30
3,4	32.5	41.98	49.5	17.73	50.5	29.7	6.49
3,5	27.6	38.04	34.3	19.81	65.7	26.1	5.59
3,6	26.8	50.74	35.5	25.35	64.5	34.3	5.21
4,3	35.4	53.48	30.3	30.26	69.7	37.3	7.36
4,4	35.4	52.30	44.3	25.99	55.7	37.6	6.37
4,5	37.1	51.31	33.0	19.81	67.0	30.2	4.90
4,6	23.9	31.24	29.9	25.84	70.1	27.5	4.77
5,4	26.9	49.68	29.0	23.76	71.0	31.3	5.59
5,5	24.6	59.84	10.7	28.68	89.3	32.0	4.50
6,4	19.4	30.68	25.1	17.24	74.9	20.6	4.05
6,5	22.1	33.82	43.5	40.35	56.5	23.2	4.15
MEAN	30.0	41.87	39.5	23.08	60.5	30.4	6.22
S.D.	5.7	13.04	13.0	6.27	13.0	4.6	1.61

Radioisotope: ^{133}Xe

Diagnosis: Acute subarachnoid hemorrhage due to rupture of basilar artery aneurysm, diffuse vasospasm, and acute hydrocephalus

TABLE 2

HEMISPHERIC BLOOD FLOW AND METABOLIC INDEXES IN A SERIES OF PATIENTS WITH ACUTE UNILATERAL CEREBRAL ISCHEMIA

	Healthy Side	Diseased Side
HBF (ml/100 gm brain/min)	34.6 ± 3.4 (N = 30)	32.4 ± 3.3 (N = 32)
	0.01 < P < 0.02	
HMI_{O_2} (ml/100 gm brain/min)	2.28 ± 0.42 (N = 25)	2.07 ± 0.45 (N = 31)
HMI_{CO_2} (ml/100 gm brain/min)	1.84 ± 0.52 (N = 24)	1.88 ± 0.48 (N = 31)
HMI_{GI} (ml/100 gm brain/min)	3.54 ± 1.17 (N = 25)	2.87 ± 1.02 (N = 30)
	0.02 < P < 0.05	
HG:O (ml/100 gm brain/min)	1.58 ± 0.54 (N = 25)	1.46 ± 0.63 (N = 30)
HRQ	0.80 ± 0.17 (N = 24)	0.92 ± 0.23 (N = 31)
	0.02 < P < 0.05	

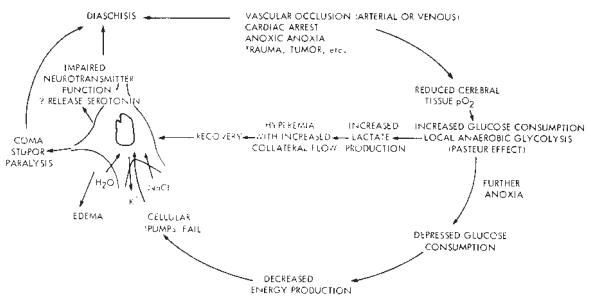
Values = mean ± standard deviation
N = number of cases
P = t test values
HBF = hemispheric blood flow
HMI_{O_2} = hemispheric oxygen consumption
HMI_{CO_2} = hemispheric carbon dioxide production
HMI_{GI} = hemispheric consumption of glucose
HG:O = hemispheric glucose:oxygen utilization ratio
HRQ = hemispheric respiratory quotient

tabolism bilaterally, despite the fact that one has only a unilateral stroke (Fig. 1).

One notices that with the passage of time, CBF improves and after about three weeks, the flow in the nonischemic hemisphere returns to normal. The quantitative reduction inflow also correlates with the size of the infarct, as assessed clinically, as well as with the degree of EEG change, particularly if it is a cortical infarct; the correlation is a little more difficult if it is a subcortical infarct. There are correlations, to some extent, with other assessments of the degree of involvement such as of the brain stem. Bilateral reduction of oxygen and glucose consumption and CO_2 production are noted, as well as blood flow reduction, although there is a greater reduction on the diseased side than on the healthy side, the respiratory quotient (RQ) is normal.

It should be noted that a hemisphere having a major infarct with hemiplegia still consumes appreciable oxygen—more than one would think, considering the neurological deficit. Also, abnormal metabolism was occurring on both sides (Table 3). There was a release of free fatty acids and inorganic phosphate, as well as serotonin and norepinephrine, from the infarcted brain; this has now been confirmed from cerebrospinal fluid. Inorganic phosphate from the infarcted brain appears only in the first 14 days of stroke and tends, with the recovery process, to revert to no essential A-V difference.

I want to mention a little about studies with



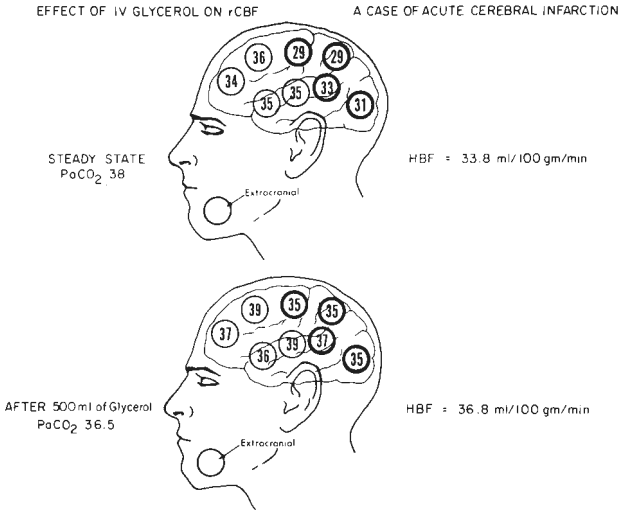
the use of intravenous glycerol and its effects on CBF and metabolism. We are interested in glycerol because not only did it bring about a significant reduction in intracranial pressure in our stroke patients, after intravenous treatment, but the patients also showed a significant clinical improvement. We were unable to show this with mannitol and, for this reason, think that perhaps glycerol had some metabolic benefits along with its hyperosmolar effect. It is a very nice investigative tool for manipulating the cerebral metabolism as well. An infusion of glycerol increases cerebral blood flow, but (and this was a big surprise to us) it decreases the oxygen consumption. We have 30 more patients now and this has become highly significant. The CO_2 production also goes down, and the glucose consumption (in a mixed group of patients) has a tendency to increase, which was

TABLE 3

HEMISPHERIC METABOLISM IN ACUTE UNILATERAL CEREBRAL ISCHEMIA

	Arterial Concentration	Arteriocerebral Venous Difference		Concentration in CSF
		Healthy Side	Diseased Side	
β-Hydroxybutyrate (mg/dl)	4.36 ± 4.47 (N = 13)	+1.04 ± 0.73* (N = 6)	+0.27 ± 0.32* (N = 13)	N.E.
		0.001 < P < 0.005		
Glutamate (mg/dl)	3.98 ± 2.21 (N = 9)	+0.25 ± 0.25* (N = 7)	+0.21 ± 0.15 (N = 8)	N.E.
Triglyceride (mg/dl)	87.5 ± 38.5 (N = 13)	+1.3 ± 10.6 (N = 9)	+1.5 ± 7.0 (N = 13)	N.E.
Free Fatty Acid (mM/L)	1.153 ± 1.765 (N = 8)	+0.121 ± 0.237 (N = 5)	−0.208 ± 0.217* (N = 8)	N.E.
Inorganic Phosphate (mg/dl)	2.34 ± 0.49 (N = 14)	−0.13 ± 0.23 (N = 6)	−0.15 ± 0.12* (N = 14)	N.E.
Serotonin (μg/dl)	12.48 ± 4.35 (N = 18)	1.92 ± 3.19 (N = 12)	−0.23 ± 1.92 (N = 18)	6.10 ± 4.86* (N = 18)
		0.02 < P < 0.05*		

* = statistically significant difference from normal
Values = mean ± standard deviation
N = number of cases
N.E. = not examined



significant in diabetics and insignificant in nondiabetics. We have postulated that we were improving metabolism other than the usual oxidative metabolism; possibly, we were recoupling uncoupled oxidative metabolism. We also considered that glycerol may provide another source of energy, which may tend to improve cerebral energy production as well as the membrane integrity and function. The EEG improves regularly and the improvement appears within two hours during continuous recording. There is an increase in central venous pressure, as might be anticipated, due to the hyperosmolar effect of an infusion of 500 cc of a substance that is drawing fluid into the circulating blood volume. Since the intracranial venous pressure is a mean between the central venous pressure and the cerebrospinal fluid (CSF) pressure, then essentially, there is an increase followed by a decrease in the intracranial venous pressure. The mean arterial pressure is increased also by a substance that increases a circulating blood volume. Regional CBF and blood volume studies of the effects of glycerol on the ischemic area of the middle cerebral artery occlusion show redistribution of blood with an increase in blood flow and blood volume in the infarcted zone (Fig. 2). Often, if there is a marked hyperemia on the border zone, there is a redistribution of blood in the infarcted zone, with reduction on the bordering zone. The mean hemispheric flow goes up regularly. Our data show a significant reduction, after the use of glycerol, in the release of free fatty acids and/or inorganic phosphates from the infarcted brain. We believe that glycerol is combining with free fatty acids to form triglycerides. Inorganic phosphate may be taken up by ADP to form ATP. It could also be that the phospholipids are being resynthesized.

Norepinephrine and serotonin in the CSF of patients with acute stroke are elevated; it seemed likely that, in cerebral ischemia, the reduced tissue P_{O2} might be interfering with the synthesis of neurotransmitters, such as norepinephrine and serotonin and that the release of these might interfere with neuronal function. We measured C-AMP in the cerebrospinal fluid of these patients and found that it was significantly increased, actually much more significantly than serotonin and norepinephrine. If these neurotransmitters were disordered in the brain and were causing trouble, we wondered whether, with the use of adrenergic blockades such as propranolol or phenoxybenzamine, one could show an effect similar to that of glycerol, and indeed, this is what happened. The introduction of propranolol shows the same reduction of oxygen consumption, CO_2 production, and glucose utilization. This reaction makes sense because norepinephrine is known to stimulate glycolysis and oxidative consumption and has been shown to be released in infarcted brain and to stimulate the release of free fatty acid. This finding supported our view that the release of these neurotransmitters is very important in cerebral infarction and may enhance the symptoms. We found also that the release of fatty acids was improved by the infusion of propranolol, which makes sense because norepinephrine stimulates the release of free fatty acids from fat stores and lipids. Inorganic phosphate, likewise, tended to be reduced and the consumption of triglyceride, increased. Phenoxybenzamine, which is another α-adrenergic blocker and blocks serotonin as well as norepinephrine without having any effect whatsoever on hemispheric blood flow, reduced oxygen consumption and CO_2 production in the same pattern that we found with both propranolol and glycerol. The use of phenoxybenzamine tended to reduce the release of free fatty acids and enhance the uptake of inorganic phosphate and triglycerides by the brain.

After about the 14th day, the serotonin disappears, as does the C-AMP, from the cerebrospinal fluid in patients with acute cerebral infarction; the serotonin change can be correlated with the cerebral blood flow. As the serotonin disappears, CBF increases, which supports the view that serotonin is important in diaschisis and the bilateral reduction

of CBF. Other vasoconstrictive substances, such as epinephrine or norepinephrine, angiotensin, or prostaglandins may exist, which we have not measured yet.

C-AMP is the second messenger for virtually all the neurotransmitters of the central nervous system, certainly for serotonin and norepinephrine. We found that there was similar elevation of C-AMP in cerebral venous blood when compared to the arterial blood in the steady state before glycerol. After giving glycerol, there was a reduction in the cerebral venous C-AMP, an inhibition of the release of C-AMP from the infarcted brain. An elevation of C-AMP in the steady state was noted in the cerebrospinal fluid of patients with cerebral infarction as well. When glycerol is given intravenously, there is a reduction of the C-AMP in the cerebrospinal fluid.

This consideration of the relationship of neurotransmitters not only to cerebral infarction but also to subarachnoid hemorrhage is, to my mind, the most promising area of investigation over the next decade. There is also a quantity of evidence that neurotransmitters play a large part in spasm following subarachnoid hemorrhage and in the disturbance of neurological function in that situation. Following subarachnoid hemorrhage, some remediable medical problems arise. Apart from clipping of the aneurysm, which the neurosurgeons are able to do, there is the problem of communicating hydrocephalus, which is extremely common in about 40% of patients. It can be discerned by the method of determining regional CBF and doing a spinal tap. If you note an increase in cerebral blood flow with removal of 25 cc of spinal fluid, you know you have a problem with communicating hydrocephalus. This is because autoregulation is disturbed. This increase will not occur when a spinal tap is done on a normal person who does not have communicating hydrocephalus. Finally, one can give glycerol and reduce the brain edema in patients with subarachnoid hemorrhage and brain swelling.