Circulatory and Metabolic Effects of Glycerol Infusion in Patients with Recent Cerebral Infarction


SUMMARY
The effect of intravenous infusion of 10% glycerol on regional cerebral blood flow (using hydrogen bolus and Xenon-133 [133Xe] clearance methods) and metabolism was investigated in 57 patients with recent cerebral infarction. Hemispheric blood flow (HBF) increased, together with increase in regional cerebral blood flow (rCBF) and cerebral blood volume (rCBV), in foci of brain ischemia. Hemispheric oxygen consumption (HMI02) decreased together with hemispheric respiratory quotient. Systemic blood levels of glucose, lactate, pyruvate, and triglycerides also increased after glycerol while free fatty acids (FFA) and inorganic phosphate (Pi) decreased. Hemispheric glucose consumption was unaltered after glycerol so that hemispheric glucose to oxygen ratio tended to rise. Pyruvate and lactate production by brain was unchanged. Glycerol moved across the blood brain barrier into brain and cerebrospinal fluid (CSF). Release of FFA and Pi from infarcted brain was reversed by glycerol. Total phosphate balance was maintained across brain both before and after glycerol infusion. Triglycerides increased in CSF after glycerol, originating either from cerebral blood or as a result of lipogenesis in cerebral tissue. The EEG recording and neurological status of the patients improved despite decreased brain oxygen consumption. Results of this study suggest that after intravenous infusion of 10% glycerol in patients with recent cerebral infarction, glycerol rapidly enters the CSF and brain compartments and favorably affects the stroke process in two ways: first, by redistribution of cerebral blood flow with increase in rCBF and rCBV in ischemic brain secondary to reduction in focal cerebral edema; and second, glycerol may become an alternative source of energy either by being directly metabolized by the brain, or indirectly, by enhancing lipogenesis, or by both processes. Involvement of glycerol in lipogenesis with esterification to accumulated FFA might lead to improved coupling of oxidative phosphorylation, a hypothesis that fits the finding of improved neuronal function despite further decrease in cerebral hemispheric oxygen consumption.

Additional Indexing Words:
Hydrogen bolus method  Xenon133  Lactate  Energy metabolism
Triglycerides  Redistribution of cerebral blood flow  Pyruvate  Esterification to accumulated free fatty acids
Improved neuronal function  Lipogenesis

Several studies suggest that oral or intravenous administration of hyperosmolar solution of glycerol is effective therapy in patients with brain edema due to cerebral trauma, neoplasia, and dis-}

ordered metabolism. In animals and man, intravenous infusion of 10% glycerol in doses of 1.2 g/kg has also been shown to reduce cerebral edema following acute cerebral infarction. Reduction of brain edema in man is achieved without rebound (delayed increase of intracranial pressure), electrolyte imbalance, or toxic side effects, and double blind studies have shown significant neurological improvement among glycerol treated, but not placebo treated, patients with acute cerebral infarction.

Mechanisms by which glycerol therapy influences the stroke process are not completely understood. Earlier studies indicated that improvement in neurological function and EEG status after glycerol infusion in patients with subacute cerebral infarction was associated with increased cerebral hemispheric
blood flow (HBF), decreased intracranial pressure, and reduction in hemispheric metabolic index of oxygen consumption (HMI0$_2$), hemispheric carbon dioxide production, and hemispheric respiratory quotient.\textsuperscript{5} This reduction in HMI0$_2$ and HMICO$_2$, despite improved HBF, EEG, and presumed relief of cerebral edema, was considered paradoxical and indicative of a specific metabolic effect of glycerol in infarcted brain. The present report deals with a larger series of patients with acute and subacute cerebral infarction than previously reported. This extended study was attempted not only to confirm earlier results but also to substantiate whether the sources of the apparently beneficial effect of glycerol on ischemic brain function are due to hemodynamic factors, metabolic factors, or a combination of the two.

Since previous studies had shown HBF increase in the infarcted hemisphere was less than would be expected considering the degree of EEG and clinical improvement that eventually resulted.\textsuperscript{6, 8} cerebral hemodynamics were again studied with particular emphasis on possible redistribution of flow and alteration of blood volume in focal ischemic areas. This was evaluated for the first time by means of regional cerebral blood flow (rCBF) and regional cerebral blood volume (rCBV) measurements using $^{133}$Xe.

The question as to the direct metabolism of glycerol in infarcted brain has not been directly answered. The previous paradoxical finding that most cases studied showed improvement in neurological deficit and EEG despite decrease in hemispheric metabolic consumption of oxygen has not been fully explained. Recovery of mitochondrial respiratory control with partial or complete reversal of uncoupled oxidative phosphorylation presumed to exist in focal regions of infarcted brain was hypothesized to explain this further decrease in HMICO$_2$ after glycerol. In the present study, measurement of cerebral arteriovenous differences and cerebrospinal fluid (CSF) levels of additional metabolic parameters have been performed in the hope of further establishing that glycerol is directly metabolized in ischemic brain tissue, considering it as a possible substrate for cerebral energy metabolism and also as a participant in lipogenesis.

Previous studies of patients with subacute cerebral infarction also had shown a negative cerebral arteriovenous (AV) difference for inorganic phosphate (Pi) which was thought to indicate increased cerebral Pi pool due to breakdown of organic phosphate compounds such as high energy phosphates and phospholipids, with Pi release in cerebral venous blood facilitated by damage to the blood brain barrier.\textsuperscript{6, 8} The present study incorporates a continuous measurement system of cerebral AV differences for Pi, together with CSF Pi levels to confirm this finding. The method of separate sampling used in earlier studies may not be accurate. Continuous measurements also permitted observations of dynamic changes in Pi exchange across the brain during glycerol infusion.

Total phosphate was also measured across infarcted brain. In the previous studies, the degree of Pi release measured in the acute states after infarction would have been expected to deplete brain Pi pool unless Pi release was balanced by movement of some other organic phosphate compound into brain. Cerebral AV differences for total phosphate were therefore measured in this series to establish if phosphate balance is indeed maintained in infarcted brain.

Finally, alterations in systemic metabolic parameters produced by glycerol were also more closely observed in the present study, and the significance of change in these parameters is discussed in relation to cerebral hemodynamics and metabolism.

**Materials**

- Hemispheric blood flow and metabolism were examined in 57 patients with acute and subacute cerebral ischemia and infarction confirmed by clinical examination, EEG, angiography, brain scan, CSF examinations, and at autopsy some months later in three cases. Age, sex, clinical diagnosis, grade of severity, associated disease, and the interval of time between the ischemic episode and the time of measurement of CBF and metabolism are listed in table 1. Thirty-one males and 26 females were studied, ranging in age from 43 to 83 years with a mean age of 63. Mean duration between onset of cerebral ischemia and the procedure was 11 days. Forty-eight patients had cerebral hemispheric infarction and nine had brain stem ischemia or infarction.

- The clinical course and severity of the stroke were graded into grades I through IV as follows:

  **Grade I — Transient Ischemic Attack (0)**
  The duration of localized neurological deficit did not exceed 24 hours and recovery was complete.

  **Grade II — Reversible Ischemic Neurological Deficit (27)**
  The neurological deficit, consisting of hemiparesis, monoparesis, or dysphasia, persisted longer than 24 hours, but recovery was virtually complete within three weeks.

  **Grade III — Presumed Cerebral Infarction with Moderate Residual Disability (21)**
  Moderate residual disability persisted after three weeks despite steady progressive recovery.

  **Grade IV — Presumed Cerebral Infarction with Severe Neurological Deficit (9)**
  A severe neurological deficit persisted after three weeks with little or no evidence of recovery thereafter.

- Four patients were given oral or intravenous glycerol for several days, but this was discontinued one or two weeks prior to the measurement of CBF and metabolism. Nevertheless, in these patients, residual effects of glycerol therapy on the metabolic parameters were still measurable, i.e., the blood and CSF glycerol levels were above normal. All measurements were made after nine to 14 hours in the fasting state.

* Circulation, Volume 51, April 1975
Procedure for Obtaining Informed Consent

Suitable patients were selected for admission to the study by two or more staff neurologists after review of the patients' records. Patients with contraindications such as severe cardiac or renal disease were excluded from the study. Each patient was then seen in consultation by a cardiologist and was not admitted to the study if there were cardiological or medical contraindications to the procedure.

The procedure was explained to the patient or the responsible relative on two separate occasions, first by the neurology staff and then by a specially trained nurse who later witnessed the signing of a standard consent form. The consent form described the procedure, including information on catheter placement, any possible risks involved, and stated that further explanation or clarification would be provided upon request. The patient was allowed to withdraw from the procedure at any time.*

Methods

Each patient was premedicated with meperidine hydrochloride (Demerol) 50 mg i.m. and atropine sulfate 0.4 mg i.m. Local anesthesia was induced at all puncture sites by infiltration with 1% procaine hydrochloride.

A catheter was inserted under fluoroscopic control via the basilic vein into the ipsilateral cranial transverse sinus for sampling of cerebral venous blood and measurement of intracranial venous pressure.9 A second catheter was placed into the superior vena cava to measure central venous pressure. A third catheter was inserted into the internal carotid artery ipsilateral to the side of the infarction to record arterial blood pressure and to inject a bolus of hydrogen saturated saline and radioisotopes for CBF measurement. A final catheter was inserted into the brachial artery to sample arterial blood. Lumbar puncture was performed and a catheter was placed in the subarachnoid space in a cephalad direction to monitor intracranial pressure and to sample CSF. All pressures were continuously monitored at heart level with Statham pressure transducers.

Arterial and cerebral venous oxygen tension, carbon dioxide tension, and pH were recorded by electrodes mounted in flow-through cuvettes, and oxygen saturation was monitored with reflection oximeters.10 An infrared absorption CO₂ gas analyzer was used to measure arterial and cerebral venous total CO₂ content after lysis of red cells with lactic acid.11

Hemispheric blood flow was calculated after injection of a bolus of 8-12 ml hydrogen-saturated saline into the carotid artery. The clearance curves of hydrogen were measured by a hydrogen electrode recording of the transverse sinus blood.15

Regional cerebral blood flow and rCBV were measured by the gamma camera, applied to the lateral aspect of the head, following the intracarotid injection of 4 mCi Xenon-133 (2 ml) and 2.5 mCi Technetium-99m (2 ml).18 Ten minute clearance curves were stored on magnetic tape and analyzed automatically by a computer programmed for providing printouts of 15-20 regions of interest throughout the infarcted hemisphere. Regional cerebral blood flow and rCBV values were calculated by stochastic analysis (rCBF₁₅), while flow gray and flow white were calculated by two-compartmental analysis. Regional cerebral blood volume was calculated according to the formula of Fieschi et al.,14 using the mean transit time of ⁹⁹mTc activity curves.

Metabolic parameters were analyzed in blood samples drawn simultaneously from carotid artery and cerebral transverse sinus before and after glycerol. Glucose in arterial and cerebral venous blood was analyzed continuously and in separate samples.13 Lactate and pyruvate were measured by the enzymatic method of Rosenberg and Rush.16

Pi was measured in all patients by an automated colorimetric method adapted for the Technicon Auto-Analyzer.17 Continuous measurements of arterial and cerebral venous Pi were also made in 23 patients by analyzing arterial and cerebral venous blood through the Technicon Auto-Analyzer, and the results were expressed as mg/dl of whole blood. Careful adjustment of the equipment reduced the methodological error to 1% within two hours (0.018 mg/dl by replicate sampling).

Serum phospholipid phosphorus was measured by a semiautomated method using the Technicon Auto-Analyzer.18 Total phosphate was determined colorimetrically.19

Triglycerides and glycerol were measured using a semiautomated fluorometric method.20 Glycerol was used in the blank as a background for the determination of triglycerides. Estimations of plasma total FFA concentrations were made by a colorimetric method based on the formation of FFA copper complexes.21 More detailed analysis of the FFA components was carried out by gas-liquid chromatography, using a modification of the Dole technique,22 plus mass spectrometry. Total FFA levels determined by the two methods were in good agreement.

Glycerol, triglycerides, and Pi were also analyzed in CSF samples taken before and after glycerol infusion.

Results

Cerebral Hemodynamics Before and After Glycerol

Values for HBF measured by the hydrogen bolus technique before and after intravenous infusion of 10% glycerol are shown in table 2. Steady-state HBF of the infarcted hemisphere was reduced by about one-third when compared to normal quoted values.23 HBF values increased significantly in all 57 cases studied immediately after glycerol, although the increase was small. HBF was also measured 50 min after infusion was completed in 23 out of 57 cases. Values increased from a mean of 27.8 ± 2.47 in the steady-state to 28.5 ± 2.5 after glycerol. This latter group suffered more severe infarction with greater neurological deficit, therefore, HBF prior to glycerol infusion was reduced to a greater extent in these patients than in the group as a whole. Furthermore, increases in flow after glycerol were understandably less when measured one hour after the glycerol infusion had been discontinued.

Regional cerebral blood flow (rCBF) and rCBV were measured by the ¹³³Xe technique concurrently with the hydrogen bolus method in 31 patients. Steady-state mean hemispheric rCBV values were obtained by the hydrogen bolus technique correlated closely with those obtained by intracarotid injection of metabolic parameters.

*The method for obtaining informed consent was reviewed and approved by the committee for research involving human beings of Baylor College of Medicine and The Methodist Hospital. These committees were composed of physicians, scientists, and suitably qualified nonmedical persons including a priest.
### Table 1

**Case Material with Clinical Summaries**

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<th>Case No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Interval (days) after onset</th>
<th>Neurological and arteriographic diagnosis</th>
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*Source: Circulation, Volume 51, April 1975*
EFFECTS OF GLYCEROL INFUSION DURING SHOCK

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Mean ± SD 63 ± 8 12 ± 5

Abbreviations: R = right; L = left; MCA = middle cerebral artery.

$^{133}$Xe ($r = 0.832$), except in eight cases with internal carotid artery occlusion in which the $^{133}$Xe curves were heavily contaminated with extracranial circulation. Strong correlation was also observed after glycerol ($r = 0.885$). Mean hemispheric rCBF increased after glycerol infusion from 29.3 ± 6.4 to 33.3 ± 7.6, confirming the findings of flow increase measured by the hydrogen bolus technique, although the degree of increase is apparently somewhat greater than that measured by the latter technique.

Redistribution of blood flow in infarcted brain was studied according to the procedure recommended by Prosenz et al. A region was designated ischemic or hyperemic if its average regional flow was at least 20% below or above the mean hemispheric flow. All regions showing deviation from mean HBF of less than 20% were designated nonischemic.

The largest increase in blood flow and blood volume after glycerol infusion was measured in ischemic gray matter (table 3). Similar but smaller increases were measured in ischemic white matter. Flow and volume also increased in nonischemic areas, but both were decreased in the hyperemic zones. The significant differences observed between rCBF and rCBV values in different areas of the ischemic hemisphere before glycerol were often no longer evident after the infusion.

EEG

Continuous EEG recordings were performed concurrently with rCBF and rCBV measurements in 23 patients. Improvement in focal slow-wave abnormality in the infarcted brain area was seen after the infusion of glycerol in the majority of cases. In 21% of patients, focal slow-wave activity was abolished; 47% of patients showed improvement, but in the remaining 32% no change in EEG activity was observed.

Metabolic Effects of Glycerol

Despite the HBF increase, HMI02, hemispheric carbon dioxide production, and hemispheric respiratory quotient decreased significantly immediately after the infusion of 10% glycerol (table 2); however the decrease was no longer significant 50 min later. Hemispheric glucose consumption was unaltered in the total group, but in the diabetic patients studied there was a stronger tendency to increase in hemispheric glucose consumption in keeping with previous reports. Systemic blood levels of pyruvate and lactate increased significantly after administration of glycerol but cerebral hemispheric production of pyruvate and lactate was not significantly altered.

After glycerol infusion, systemic levels of blood glycerol, as measured in the carotid artery, became markedly elevated (table 4). No significant cerebral AV difference for glycerol was detected before or after glycerol infusion (table 4, fig. 1), yet CSF glycerol levels became markedly increased (table 5). Systemic blood triglycerides increased after glycerol infusion at which time a large positive cerebral AV difference for triglycerides, not seen in the steady state, was recorded (table 4, fig. 1), together with an increase in CSF levels of triglycerides (table 5). Four patients had

| Table 2 |

Effect of Intracereous Infusion of 10% Glycerol on Hemispheric Blood Flow and Metabolism

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Steady state</th>
<th>After infusion completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBF (ml/100 g brain/min)</td>
<td>57</td>
<td>30.1 ± 4.0</td>
</tr>
<tr>
<td>HMI02 (ml/100 g brain/min)</td>
<td>56</td>
<td>2.16 ± 0.39</td>
</tr>
<tr>
<td>HMC02 (ml/100 g brain/min)</td>
<td>56</td>
<td>2.05 ± 0.53</td>
</tr>
<tr>
<td>HMI0Gl (mg/100 g brain/min)</td>
<td>37</td>
<td>2.97 ± 1.10</td>
</tr>
<tr>
<td>HG02 (mg/dl)</td>
<td>36</td>
<td>1.36 ± 0.52</td>
</tr>
<tr>
<td>HRQ</td>
<td>55</td>
<td>0.96 ± 0.20</td>
</tr>
</tbody>
</table>

* = Significant compared with steady-state values (<0.05).
Abbreviations: HBF = hemispheric blood flow; HMI02 = hemispheric oxygen consumption; HMC02 = hemispheric carbon dioxide production; HMI0Gl = hemispheric glucose consumption; HG02 = glucose to oxygen ratio; HRQ = hemispheric respiratory quotient.
received oral glycerol one to two weeks prior to the study which accounts for the relatively high mean values of both CSF glycerol and triglycerides recorded in the steady state (table 5).

Total FFA were elevated in systemic blood prior to glycerol but were significantly decreased after infusion. Individual analysis of components in seven patients indicated changes in palmitic and linoleic acid fractions (table 6). Cerebral AV differences for total FFA became positive after infusion suggesting brain uptake (fig. 1).

Systemic blood P1 levels were reduced after the intravenous infusion of glycerol (table 7) while total phosphate and phospholipid phosphorus levels did not change.

Cerebral AV differences for P1 were measured both by separate and continuous sampling. Continuous measurement of cerebral AV differences for P1 was carried out in a total of 23 cases also subdivided into acute and subacute, ischemic and hemorrhagic groups for analysis. In the total group studied, steady-state P1 concentrations in cerebral venous blood were significantly higher than those in arterial blood, which confirmed the movement of P1 into cerebral venous blood from ischemic brain seen on interval sampling measurements. During and up to 60 min after intravenous administration of glycerol, the negative AV difference for P1 was reduced as shown in table 7 and in the acute group in figure 2. Reduction of the P1 release into cerebral venous blood by glycerol was ap-

Table 3

Effect of Intravenous Infusion of 10% Glycerol on rCBF, rCBV, Blood Flow and Blood Volume in Gray and White Matter in Nonischemic, Ischemic, and Hyperemic Areas in 23 Patients with Recent Cerebral Infarction

<table>
<thead>
<tr>
<th></th>
<th>Steady state</th>
<th>After infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NI I H</td>
<td>NI I H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rCBF&lt;sub&gt;10&lt;/sub&gt;</td>
<td>29.3 ± 6.2</td>
<td>22.1 ± 6.1</td>
</tr>
<tr>
<td></td>
<td>35.7 ± 6.2</td>
<td>33.2 ± 8.0*</td>
</tr>
<tr>
<td></td>
<td>30.5 ± 6.0*</td>
<td>33.8 ± 7.7*</td>
</tr>
<tr>
<td>rCBV&lt;sub&gt;14&lt;/sub&gt;</td>
<td>4.62 ± 0.64</td>
<td>3.33 ± 0.92</td>
</tr>
<tr>
<td></td>
<td>5.32 ± 0.86</td>
<td>5.75 ± 1.39*</td>
</tr>
<tr>
<td></td>
<td>5.39 ± 1.19*</td>
<td>5.21 ± 1.25*</td>
</tr>
<tr>
<td>Fg</td>
<td>52.6 ± 7.9</td>
<td>33.8 ± 8.3</td>
</tr>
<tr>
<td></td>
<td>90.6 ± 20.3</td>
<td>68.9 ± 16.4*</td>
</tr>
<tr>
<td></td>
<td>65.8 ± 16.3*</td>
<td>75.8 ± 16.1*</td>
</tr>
<tr>
<td>Vg</td>
<td>8.29 ± 0.82</td>
<td>5.09 ± 1.25</td>
</tr>
<tr>
<td></td>
<td>13.50 ± 2.81</td>
<td>11.93 ± 2.85*</td>
</tr>
<tr>
<td></td>
<td>11.63 ± 2.96*</td>
<td>11.68 ± 2.61*</td>
</tr>
<tr>
<td>Fw</td>
<td>18.3 ± 4.0</td>
<td>9.9 ± 3.5</td>
</tr>
<tr>
<td></td>
<td>23.7 ± 5.9</td>
<td>20.1 ± 5.2*</td>
</tr>
<tr>
<td></td>
<td>17.4 ± 5.1*</td>
<td>19.3 ± 6.4*</td>
</tr>
<tr>
<td>Vw</td>
<td>2.57 ± 0.48</td>
<td>1.50 ± 0.52</td>
</tr>
<tr>
<td></td>
<td>3.53 ± 0.81</td>
<td>3.48 ± 0.90*</td>
</tr>
<tr>
<td></td>
<td>3.07 ± 0.92*</td>
<td>2.97 ± 0.98*</td>
</tr>
</tbody>
</table>

Values = mean ± standard deviation (ml/100 g brain/min).
* = Statistically significant compared with steady-state values.

Abbreviations: rCBF = regional cerebral blood flow; rCBV = regional cerebral blood volume; Fg = blood flow in gray matter; Vg = volume blood flow in gray matter; Fw = blood flow in white matter; Vw = volume blood flow in white matter; NI = nonischemic area; I = ischemic area; H = hyperemic area.

Table 4

Effects of Glycerol on Arterial and Cerebral Venous Concentrations of Triglycerides, Glycerol, Glucose, Lactate, and Pyruvate

<table>
<thead>
<tr>
<th></th>
<th>No. patients</th>
<th>Steady state</th>
<th>After infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A CV AV</td>
<td>A CV AV</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>37</td>
<td>124.8 ± 31.7 115.6 ± 31.5*</td>
<td>9.2 ± 3.4</td>
</tr>
<tr>
<td>Lactate (mg/dl)</td>
<td>14</td>
<td>6.93 ± 3.08  8.59 ± 3.16*</td>
<td>-1.66 ± 0.95</td>
</tr>
<tr>
<td>Pyruvate (mg/dl)</td>
<td>22</td>
<td>0.433 ± 0.200 0.517 ± 0.184*</td>
<td>-0.085 ± 0.061</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>13</td>
<td>76.0 ± 35.4 73.4 ± 50.2</td>
<td>2.6 ± 18.8</td>
</tr>
<tr>
<td>Glycerol (mg/dl)</td>
<td>10</td>
<td>3.13 ± 2.48  2.74 ± 2.31</td>
<td>0.39 ± 0.77</td>
</tr>
</tbody>
</table>

* = Statistically significant difference compared with arterial value.
† = Statistically significant difference compared with steady-state values.
‡ = Statistically significant difference with value before glycerol infusion.
§ = Statistically significant difference from zero.

Abbreviations: Values = mean ± sd; A = arterial concentrations; CV = cerebral venous concentrations; AV = arteriovenous difference.
EFFECTS OF GLYCEROL INFUSION DURING SHOCK

Table 5

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Steady state</th>
<th>After infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>9</td>
<td>14 ± 13</td>
</tr>
<tr>
<td>Glycerol (mg/dl)</td>
<td>11</td>
<td>0.31 ± 0.42</td>
</tr>
<tr>
<td>Inorganic phosphate (mg/dl)</td>
<td>15</td>
<td>1.40 ± 0.17</td>
</tr>
</tbody>
</table>

Values = mean ± sd.
* = Statistically significant difference compared with steady-state values.

Cerebral AV differences for total phosphate or phospholipid phosphorus showed neither release nor uptake across the blood brain barrier in the steady state or after glycerol so that the P1 release from infarcted brain observed in the steady state must be balanced by movement of organic phosphate compounds into brain.

Discussion

Steady-State Observations

Values for HBF measured by the hydrogen bolus technique and mean hemispheric regional cerebral blood flow (rCBF) values measured by clearance of 133Xe were found to be closely correlated. Due to some unavoidable extracranial contamination, steady-state values for mean hemispheric rCBF obtained by external counting from the head after carotid injection of 133Xe were slightly lower than those for HBF calculated by hydrogen clearance measured in blood from the transverse sinus within which virtually no blood of extracerebral origin is present.

HBF, HMIO2, and hemispheric carbon dioxide production of the infarcted cerebral hemisphere showed abnormally low values compared to those normally quoted. This finding was in keeping with many earlier studies of stroke patients performed in this laboratory. Blood flow and metabolism

Table 6

| FFA Fractions in Arterial and Cerebral Venous Blood in Seven Patients |
|-----------------|-----------------|-----------------|-----------------|
|                 | Steady state    | CV              | After infusion  |
|                 | A               | CV              | A               | CV              |
| Total FFA (mMol/l) | 0.65 ± 0.13    | 0.65 ± 0.14    | 0.52 ± 0.14*    | 0.51 ± 0.16*    |
| Palmitic acid (16:0) | 0.19 ± 0.06    | 0.19 ± 0.07    | 0.16 ± 0.06*    | 0.15 ± 0.06*    |
| Palmitoleic acid (16:1) | 0.03 ± 0.00    | 0.03 ± 0.01    | 0.02 ± 0.00     | 0.02 ± 0.01     |
| Stearic acid (18:0) | 0.06 ± 0.01    | 0.06 ± 0.01    | 0.06 ± 0.01     | 0.06 ± 0.02     |
| Oleic acid (18:0) | 0.29 ± 0.07    | 0.28 ± 0.07    | 0.23 ± 0.08*    | 0.22 ± 0.09*    |
| Linoleic acid (18:2) | 0.08 ± 0.01    | 0.08 ± 0.02    | 0.06 ± 0.01     | 0.06 ± 0.01     |

* = Statistically significant difference compared with steady-state value.

Abbreviations: A = arterial concentrations; CV = cerebral venous concentrations.
have previously been demonstrated to be similarly depressed, although to a lesser degree, in the cerebral hemisphere contralateral to the side of infarction, a phenomenon known as diaschisis. Such a finding militates against the use of the nonischemic hemisphere for normal control observations with which to compare changes in blood flow and metabolism of the infarcted hemisphere. Thus, normal values for healthy populations established by separate studies are customarily used for comparative purposes. Despite the obvious value of comparative observations on the effect of glycerol on blood flow and metabolism of both the nonischemic and ischemic hemispheres, it was considered that further procedures required for bilateral hemispheric blood flow measurement to study the duration and complexity of the present design might prove hazardous to the patient. Significance of change from steady-state values was therefore used in assessing the effects of glycerol on blood flow and metabolism in the infarcted hemisphere alone.

Cerebral Hemodynamic Effects of Glycerol

Increased HBF, mean hemispheric rCBF and rCBV in patients after infusion of 10% glycerol may be attributed to its well known hyperosmolar effect in decreasing intracranial pressure and cerebral edema. Increased rCBF and rCBV in foci of ischemia involving both gray and white matter can best be explained on the basis of decrease in regional brain tissue edema. As compression of the microcirculation is relieved effective redistribution of blood flow to previously ischemic areas occurs. After glycerol infusion, areas of hyperemia correspondingly became fewer as areas of ischemia were decreased. Nonischemic brain areas showed only mild increases in blood flow and blood volume after glycerol, probably secondary to over-all decrease in intracranial pressure. By the same mechanism, rCBF might reasonably be expected to increase to the same order in the nonischemic hemisphere.

The apparent disparity and greater increase in blood flow to the infarcted hemisphere after glycerol,

---

**Table 7**

*Effect of Glycerol Infusion on Continuous Recordings of Inorganic Phosphate Concentrations*

<table>
<thead>
<tr>
<th></th>
<th>Data sample</th>
<th>Steady state</th>
<th>During glycerol</th>
<th>After glycerol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>100 ml</td>
<td>500 ml</td>
</tr>
<tr>
<td>Total series</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial</td>
<td>Mean</td>
<td>1.88</td>
<td>1.79*</td>
<td>1.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±0.36</td>
<td>±0.37</td>
<td>±0.46</td>
</tr>
<tr>
<td>Arteriovenous</td>
<td>Mean</td>
<td>-0.07†</td>
<td>-0.05</td>
<td>-0.03‡</td>
</tr>
<tr>
<td>difference</td>
<td></td>
<td>±0.10</td>
<td>±0.12</td>
<td>±0.13</td>
</tr>
<tr>
<td>Acute infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous</td>
<td>Mean</td>
<td>-0.07†</td>
<td>0.03‡</td>
<td>-0.01†</td>
</tr>
<tr>
<td>difference</td>
<td></td>
<td>±0.10</td>
<td>±0.11</td>
<td>±0.13</td>
</tr>
<tr>
<td>Subacute infarction</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>N = 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous</td>
<td>Mean</td>
<td>-0.10†</td>
<td>-0.16‡</td>
<td>-0.10</td>
</tr>
<tr>
<td>difference</td>
<td></td>
<td>±0.13</td>
<td>±0.12</td>
<td>±0.12</td>
</tr>
<tr>
<td>Ischemic infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous</td>
<td>Mean</td>
<td>-0.07†</td>
<td>-0.05</td>
<td>-0.03‡</td>
</tr>
<tr>
<td>difference</td>
<td></td>
<td>±0.10</td>
<td>±0.13</td>
<td>±0.14</td>
</tr>
<tr>
<td>Hemorrhagic infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous</td>
<td>Mean</td>
<td>-0.07†</td>
<td>-0.06</td>
<td>-0.01</td>
</tr>
<tr>
<td>difference</td>
<td></td>
<td>±0.11</td>
<td>±0.12</td>
<td>±0.12</td>
</tr>
</tbody>
</table>

* = P < 0.05 significant changes of concentrations of P1 from steady-state value.
† = P < 0.05 significant difference from zero.
‡ = P < 0.05 significant changes of (AV) difference of concentrations of P1 from steady-state value.
EFFECTS OF GLYCEROL INFUSION DURING SHOCK

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Figure 2

Effects of intravenous infusion of 10% glycerol on continuous records of inorganic phosphate (Pi) in arterial and cerebral venous blood. This shows mean levels obtained by continuous measurement of inorganic phosphate (Pi) levels in arterial (○) and cerebral venous (△) whole blood before, during, and after intravenous infusion of 10% glycerol. Note the early fall in arterial Pi levels during infusion and the abolition of the initial negative AV difference for Pi toward the end of infusion. * = P < 0.05 significant changes of Pi of arterial and cerebral venous blood compared to steady-state values; N = number of measurements. Solid bar and broken bar represent so of arterial and cerebral venous blood, respectively.

detected by the isotope technique (mean hemispheric rCBF) compared to the hydrogen bolus method (HBF), is due in part to the different number of cases studied in the two groups but also may be attributed to the relatively larger increases of flow in ischemic areas that can be detected by rCBF measurements since mean hemispheric rCBF is a calculated value for the total regions. Furthermore, although HBF increases are small, redistribution with reperfusion of ischemic areas is highly effective. Increased blood flow and blood volume in ischemic regions also coincided with focal EEG improvement.

Systemic Metabolic Effects of Glycerol

After intravenous infusion of glycerol, systemic blood levels of glucose, lactate, pyruvate, and triglycerides increased while levels of FFA and Pi decreased. Total phosphate was unchanged. Concentrations of glycerol attained in the systemic circulation were also maintained.

Glycerol is an important endogenous precursor of glucose in the body where it is normally released from adipose tissue as a result of lipolysis. Gluconeogenesis in the liver with formation of the intermediate compound glycerol phosphate is the most likely ex-planation for increase in blood glucose and decreased blood Pi after infusion.27 The effect of glycerol on systemic blood glucose levels must be borne in mind when treating patients with diabetes mellitus and stroke.

Significant elevation of systemic blood pyruvate and lactate in patients given glycerol may be accounted for in part by elevation of blood glucose, which in normal individuals results in increased pyruvate and lactate turnover in skeletal muscle.28 Part of the decrease in circulating phosphate pool could also be explained on this possible promotive effect on skeletal muscle metabolism.

Esterification of glycerol with FFA to form triglycerides occurring in liver is believed to be largely responsible for the systemic elevation of triglycerides and reduction of FFA seen in the present study. However, systemic FFA reduction may also be caused by increased insulin secretion that occurs secondary to increased systemic glucose levels.29 Whereas increased blood triglycerides might theoretically increase blood viscosity, thereby predisposing collateral flow to ischemic brain areas,26 such a factor appears to be of minimal importance in view of the overriding beneficial hemodynamic changes produced by relief of regional brain edema.

Cerebral Metabolic Effects of Glycerol

Results of the present series of cases confirmed earlier studies in smaller series that intravenous infusion of 10% glycerol given to patients with acute cerebral infarction produces significant increases of HBF associated with decrease in HMI02, hemispheric carbon dioxide production, and hemispheric respiratory quotient despite EEG and clinical improvement. Decreases in HMI02 and hemispheric carbon dioxide production after glycerol are small compared to the extent of reduction in steady-state values from those normally quoted.30 However, increase in these parameters, even though of low order, has previously been reported in spontaneous recovery from cerebral infarction after several weeks.31 Attempts to explain this apparently paradoxical situation are offered below. It should be pointed out that patients who exhibit complete recovery of neurological function from previously sustained ischemic deficit still show marked reduction of HMI02 and hemispheric carbon dioxide production when compared to normal populations.

Hemispheric glucose consumption was not altered after glycerol but glucose to oxygen ratio tended to increase. Unaltered hemispheric glucose consumption after glycerol, in the face of rise in arterial glucose levels, makes it unlikely that the beneficial cerebral metabolic effects of glycerol reflect merely a transition.
from a fasting to a fed state. Infusion of glucose alone to fasting stroke patients has previously been shown in this laboratory to promote increased cerebral glucose consumption.\textsuperscript{18} Lactate and pyruvate release from brain were not significantly altered, suggesting absence of shift to increased anaerobic metabolism.

Results of continuous recording of cerebral AV differences again showed release of $P_I$ into cerebral venous blood and CSF. Inorganic phosphate release into cerebral venous blood observed in previous studies\textsuperscript{5,8} was therefore confirmed, and cannot be accounted for by random fluctuations in steady-state $P_I$ levels since both continuous observations made in the steady state and during glycerol infusion, in addition to intermittent sampling, exclude this possibility. Since no significant cerebral AV difference for total phosphate was observed, it may be concluded that over-all cerebral phosphate balance is maintained by movement of inorganic phosphate compounds into the brain to replace the $P_I$ loss. No significant brain uptake of phospholipid phosphorus was observed in the steady state. It seems that other organic phosphate compounds, e.g., glycerol phosphate, must move into brain to maintain cerebral $P_I$ balance after infusion. Further study is required to establish these events and the exact nature of the biochemical exchange.

Explanation of the cause for measurable $P_I$ release from infarcted brain can only be speculative. Increased cerebral $P_I$ pool in the presence of a damaged blood brain barrier appears to be the best since it has been consistently shown in animals that cerebral ischemia and anoxia impair cerebral mitochondrial oxidative phosphorylation with resultant depletion of cellular adenosine triphosphate and phosphocreatine with an accumulation of adenosine diphosphate and $P_I$.$^{32,33}$ The presence of both blood brain barrier damage and ischemic increase in cerebral $P_I$ pool is further supported in our study by an apparently greater effect of glycerol in preventing cerebral $P_I$ release in the more acute ischemic cases. Furthermore, other studies have suggested that cerebral ischemia may result in too large an accumulation of $P_I$ to be solely accounted for by concomitant reduction in the high energy phosphate pool,$^{34,35}$ so it seems reasonable to postulate that an important source for increased $P_I$ pool in infarcted brain might be breakdown of other phosphate-containing compounds such as phospholipids.

Significant FFA release from infarcted brain was again observed and is interpreted as indicative of increased FFA accumulation in ischemic brain tissue, an event that has been described in previous studies.$^{35}$ Mechanisms that bring about tissue FFA accumulation cannot be identified in this study. One explanation might be the breakdown of membrane components such as phospholipids and triglycerides in ischemic brain areas. This hypothesis is indirectly supported not only by findings suggestive of increased cerebral $P_I$ pool previously commented on but also by the steady-state findings of increased CSF triglyceride levels in the absence of significant cerebral AV difference for triglycerides to suggest origin from cerebral blood.

Measurement of cerebral AV differences and CSF levels for parameters studied can, of course, provide only indirect evidence of pathways for glycerol metabolism in the human brain. Glycerol increases in CSF after infusion confirms its entry into central nervous system compartments. The fact that a statistically significant positive cerebral AV difference for glycerol was not measured by the sampling method suggests rapid equilibration of glycerol into and out of central nervous system compartments.

Cerebral metabolic effects of glycerol, if any, also cannot be explained by increased systemic glucose production since cerebral glucose consumption is unaltered. Although controversy exists on the issue of glycerol metabolism in brain tissue, several studies strongly suggest that glycerol can be metabolized by brain$^{36-38}$ although the question remains as to the exact pathway. Authorities appear agreed that lipogenesis may be one result of glycerol metabolism,$^{39}$ but its role in supporting energy metabolism is uncertain. Entry of glycerol into metabolic pathways depends on glycerol kinase, an enzyme that is present in only small amounts in brain tissue.$^{40,41}$ Nevertheless, tracer studies with $^{14}$C glycerol provide evidence that glycerol is oxidized in brain tissue,$^{40}$ as well as demonstrate $^{14}$C glycerol uptake into phospholipids and triglycerides, probably through the intermediate formation of phosphatidic acid.$^{36,39,40}$

We believe that the findings of the present study support the hypothesis that glycerol is directly metabolized in brain tissue of patients studied. Reversal of $P_I$ release from infarcted brain after glycerol (evidenced by reduction of the negative AV differences for $P_I$ and fall in CSF $P_I$ levels) is in keeping with the increased utilization of cerebral $P_I$ pool, possibly because of high energy phosphate formation and improved energy metabolism. Similar reversal of FFA release after glycerol could result from improved cerebral lipogenesis leading either to increased phospholipid formation or perhaps esterification of FFA with glycerol to form triglycerides. Increased phospholipid formation would also utilize free $P_I$ pool. Although triglyceride formation probably only occurs to a minimal extent in brain tissue, the finding of increased CSF triglycerides after glycerol suggests that such a metabolic pathway may indeed exist. This assumption is further supported by the fact that the
patients who had been given oral glycerol one or two weeks prior to the blood flow measurement showed higher steady-state CSF concentration of triglycerides despite CSF glycerol levels being less elevated. However, a positive cerebral AV difference for triglycerides after glycerol infusion also suggests that systemic blood triglycerides may pass into CSF across a damaged blood brain barrier. More detailed analysis and comparison of serum and CSF triglyceride fractions might establish the source of the elevation.

Is brain tissue metabolism of infused glycerol the explanation for the paradoxical decrease in HMIO2 and hemispheric carbon dioxide production despite improved EEG and neurological function in the patients studied? The possibility that reduction in HMIO2 was an artifact of reestablishment of perfusion through nonperfused areas of infarcted brain leading to reduced withdrawal of oxygen from tissue can be rejected by the findings of constant cerebral glucose consumption and improved EEG. By the same process, the Crabtree effect (whereby inhibition of endogenous cell respiration occurs as a result of increased exogenous glucose utilization)49 can also be rejected. Enhancement of anaerobic glucose metabolism by glycerol could further impair neuronal metabolism by the deleterious effect of increasing tissue lactic acidosis. However, no shift to anaerobic metabolism was evident in the present study as judged by no change in the pyruvate and lactate production by brain.

Decreased HMIO2 despite increased rCBF and improved EEG after glycerol seems to us best explained by improved coupling of oxidative phosphorylation to cell respiration, assuming that such a condition exists regionally in focal areas of infarcted brain. The fact that HMIO2 was reduced does not exclude the possibility of regional uncoupling of oxidative phosphorylation existing in ischemic brain areas. However, direct support for this concept could not be obtained due to the unavailability of methods for measurement of regional cerebral oxygen consumption in our hospital.

Decreased HMIO2 after glycerol also coincides with decreased release of FFA from infarcted brain. Cellular FFA accumulation has been shown to impair mitochondrial respiratory control by uncoupling oxidative phosphorylation.44-46 This event appears coincidental with brain tissue and mitochondrial swelling.45, 46 Further study is required to explore the effect of increased circulating FFA on ischemic brain metabolism in the light of elevated plasma FFA also measured in the present study. Esterification of FFA with glycerol, as suggested in earlier paragraphs, could remove any deleterious effect that cellular FFA accumulation might exert on mitochondrial function and perhaps result in improved oxidative phosphorylation with recovery of cellular respiratory control. This should in turn lead to improved energy metabolism (supported by Pi uptake from cerebral pool) and neuronal function, the latter being evident in the present study by improvement of EEG and clinical functioning.

In conclusion, results of this study suggest that after intravenous infusion of 10% glycerol in patients with recent cerebral infarction, glycerol rapidly enters the CSF and brain compartments to favorably influence the stroke process; first, redistribution of cerebral blood flow with reperfusion of ischemic brain areas brought about by reduction in focal cerebral edema, and second, direct metabolism of glycerol by brain, either as substrate for energy metabolism, or is involved in lipogenesis, or both. Involvement of glycerol in lipogenesis with esterification to accumulated FFA might lead to improved coupling of oxidative phosphorylation with cell respiration, a hypothesis that we feel best explains the findings supportive of improved neuronal function despite further decrease in cerebral oxygen consumption of ischemic brain.

Acknowledgments

Dr. Henry McIntosh, Chairman, Department of Internal Medicine, Baylor College of Medicine, made available the Cardiac Catheterization Laboratory; and Dr. James Cole and Dr. Henry Hanley placed the catheters under fluoroscopic control and examined the patients in consultation prior to the procedure.

Drs. K. Shimazu, Y. Fukuchi, T. Ohuchi, A. Koto, A. Sari; Miss Judy Bond, R.N., Mrs. Dorothy Morgenroth, R.N., Mrs. Eileen Houston, and Mr. Peter Miller all made technical contributions to this investigation.

Dr. Evan Horning, Institute for Lipid Research, Baylor College of Medicine, kindly performed analysis of the free fatty acid components.

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Circulatory and metabolic effects of glycerol infusion in patients with recent cerebral infarction.

J S Meyer, Y Itoh, S Okamoto, K M Welch, N T Mathew, E O Ott, S Sakaki, Y Miyakawa, E Chabi and A D Ericsson

Circulation. 1975;51:701-712
doi: 10.1161/01.CIR.51.4.701

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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