Effect of Intravenous Infusion of Glycerol on Hemispheric Blood Flow and Metabolism in Patients With Acute Cerebral Infarction

BY JOHN STIRLING MEYER, M.D., YASUO FUKUUCHI, M.D., KUNIO SHIMAZU, M.D., TADAO OHUCHI, M.D., AND ARTHUR DALE ERICSSON, M.D.

Abstract:
Effect of Intravenous Infusion of Glycerol on Hemispheric Blood Flow and Metabolism in Patients With Acute Cerebral Infarction

The effects of intravenous infusion of 10% glycerol on regional blood flow and metabolism in infarcted hemispheres was investigated in 17 patients during the acute stage of stroke. Hemispheric blood flow (HBF) increased and cerebral oxygen consumption (CMRO₂) and carbon dioxide production decreased. Glucose consumption remained constant and hemispheric respiratory quotient (HRQ) decreased. The electroencephalogram improved, and in the majority of patients neurological function also improved. Cerebrospinal fluid pressure (CSFP) did not change during infusion but decreased afterward, and no rebound occurred. Central venous pressure (CVP) and mean arterial blood pressure (MABP) increased both during and after infusion. Intracerebral venous pressure (ICVP) increased during infusion. Mechanisms which may increase HBF following infusion of 10% glycerol are discussed. Expansion of the perivascular space by removal of edema fluid within the glia seems to be a primary factor causing increased HBF. Possible explanations for the measured effects of 10% glycerol on cerebral metabolism and brain function were considered. Inhibition of uncoupling of oxidative phosphorylation (recoupling) appeared to be the most likely explanation for the improvement in brain function and metabolic changes induced with this hyperosmolar solution. The decrease in HRQ is best explained by oxidation of glycerol in the infarcted hemisphere. Intravenous infusion of glycerol appears to be a useful form of therapy in patients with acute cerebral infarction.

ADDITIONAL KEY WORDS
hyperosmolar agents cerebral edema
recoupling intracranial pressure

Reduction of regional cerebral blood flow (rCBF) with localized areas of ischemic hypoxia frequently results in cerebral edema and tissue necrosis. Such zones of swollen brain may compress surrounding areas of normal brain and result in progressive cerebral infarction, which has been termed a "vicious cycle." Our approach to the treatment of cerebral infarction is prevention of this vicious cycle by prompt reduction of cerebral edema before a severe irreversible neurological deficit results. We have found little information concerning the management of cerebral edema or beneficial results of therapy in patients with acute stroke despite the fact that cerebral edema is known to increase intracranial pressure and to significantly alter cerebral hemodynamics and metabolism. Cerebral edema is also a common cause of fatal outcome during the first week following cerebral infarction.
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Since Weed and McKibben demonstrated that hyperosmolar agents reduce intracranial pressure, they have been used mainly in the field of neurosurgery to reduce brain tissue volume in order to facilitate surgical procedures and to prevent brain compression and herniation. Goluboff et al., in patients with brain tumor, found that infusion of mannitol or urea significantly increased cerebral blood flow (CBF) and decreased CSFP. Little is known about the effect of hyperosmolar agents on cerebral circulation and metabolism in infarcted brain. A recent investigation carried out in our laboratory in patients with cerebral infarction showed that injection of mannitol increased hemispheric blood flow (HBF) but had no effect on the hemispheric oxygen and glucose metabolism. Another investigation carried out in this laboratory revealed that infusion of mannitol or glycerol increased the rCBF in edematous brain induced by extradural compression in baboons.

Glycerol is converted to glucose mainly by the liver and has an antiketogenic effect in diabetic patients. One investigator demonstrated that glycerol may act as a substrate for brain metabolism. Virno et al., in 1961, were the first to report that orally or intravenously administered glycerol is highly effective in reducing experimental cerebral edema in rabbits. Cantore et al. reported that glycerol administered orally to patients with space-occupying lesions was extremely effective in reducing cerebral edema and CSFP. They also attempted to infuse a 30% solution intravenously but were discouraged by frequent hemoglobinuria. Sloviter, however, reported that a considerable quantity of diluted glycerol (5%) dissolved in normal electrolyte solutions can be administered intravenously to man without noxious effects.

Intravenous administration of glycerol has been evaluated in our laboratory in both animal experiments and clinical trials. Reversible brain swelling or progressive cerebral edema was induced in baboons by occluding the carotid and vertebral arteries bilaterally for ten minutes, and intravenous infusion of glycerol was found to be effective in reducing intracranial pressure and increasing CBF in these animals. Intravenous injection of a 10% glycerol solution resulted in significant clinical improvement in stroke patients with increased intracranial pressure and cerebral edema.

In the present communication the effect of intravenous infusion of glycerol on rCBF and metabolism in patients with cerebral infarction will be discussed.

Method

This study was carried out in 17 patients in whom acute cerebral hemispheric infarction was confirmed by clinical, angiographical electroencephalographical, and brain scan examinations. Age, sex, and interval of time between the clinical ictus and the measurement of cerebral hemodynamics and metabolism are included in table 1. There were eight men and nine women ranging in age from 47 to 74 years with a mean age of 64. CBF studies were carried out within two weeks of the ischemic attack in all but three patients. The mean time interval was 13 days. Thirteen patients suffered from right hemispheric infarction and four from left hemispheric infarction. All patients were examined in consultation by a cardiologist prior to the study and were considered to be in satisfactory physical condition to undergo blood flow studies.

Premedication consisted of intramuscular injection of 50 mg meperidine hydrochloride (Demerol) and 1.0 mg atropine sulfate. Local anesthesia was induced at all puncture sites by infiltration with 1% procaine hydrochloride. A catheter was inserted under fluoroscopic control via the basilic veins into each cerebral transverse sinus. Another catheter was placed into the innominate vein for measuring central venous pressure (CVP). Catheters also were inserted into the femoral or brachial arteries to sample arterial blood and to record the arterial blood pressure. A lumbar puncture was performed and a catheter inserted into the subarachnoid space to monitor CSFP. Arterial blood pressure (MABP), intracerebral venous pressure (ICVP), CVP, and CSFP were monitored with Statham pressure transducers. A catheter was placed in the bladder in order to measure urinary volume.

Arterial and cerebral venous oxygen tension (P O2), carbon dioxide tension (P CO2), and pH were recorded by means of electrodes mounted in flow-through cuvettes, and oxygen saturation (SO2) was monitored with a reflection oximeter. An infrared absorption CO2 gas analyzer was used to measure arterial and cerebral venous CO2 content, and glucose was measured continuously with the Technicon AutoAnalyzer.

The glycerol solution was prepared by adding 50 gm of glycerol (Glycerin USP 99.5%) to 500 ml of normal saline and was sterilized in a high vacuum autoclave turned to the liquid cycle for

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<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Sex</th>
<th>Interval of time from onset</th>
<th>HBF During</th>
<th>After</th>
<th>HMI0$_2$ During</th>
<th>After</th>
<th>CSFP During</th>
<th>After</th>
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<tr>
<td>1</td>
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<td>F</td>
<td>6 days</td>
<td>R</td>
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<td>2</td>
<td>66</td>
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<td>7 days</td>
<td>R</td>
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<td>R</td>
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<td>34.3</td>
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<td>R</td>
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<td>8 days</td>
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<td>N.E.</td>
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<td>L</td>
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<td>R</td>
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<td>50</td>
<td>M</td>
<td>14 days</td>
<td>R</td>
<td>36.4</td>
<td>41.4</td>
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<td>N.E.</td>
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<td>15</td>
<td>73</td>
<td>F</td>
<td>18 days</td>
<td>L</td>
<td>34.2</td>
<td>37.3</td>
<td>N.E.</td>
<td>2.09</td>
<td>1.97</td>
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<td>66</td>
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<td>25 days</td>
<td>L</td>
<td>30.2</td>
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<td>34.7</td>
<td>1.78</td>
<td>1.64</td>
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<tr>
<td>17</td>
<td>65</td>
<td>F</td>
<td>6 weeks</td>
<td>R</td>
<td>38.9</td>
<td>41.1</td>
<td>40.9</td>
<td>2.23</td>
<td>2.18</td>
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</table>

HBF = hemispheric blood flow (ml/100 gm brain/min), HMI0$_2$ = hemispheric metabolic index for oxygen (ml/100 gm brain/min), CSFP = cerebrospinal fluid pressure (mm H$_2$O), Before = values before infusion, During = values during infusion, After = values after infusion, and N.E. = not examined.
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30 minutes at 250°F. The bottle was capped immediately on cooling. This glycerol solution was infused at the rate of 100 ml per 15 to 20 minutes. Most of the patients were given a total of 500 ml with a mean dosage of 490 ml (0.8 gm/kg of body weight).

A bolus of 7 to 10 ml of hydrogen-saturated saline was injected into the carotid artery on the infarcted side, and HBF was calculated from the clearance curves of hydrogen of the transverse sinus blood measured with a hydrogen electrode. Hemispheric metabolic index for oxygen (HMI₀₂), carbon dioxide (HMICO₂), glucose (HMIG₁), glucose:oxygen utilization ratio (HG:O), and hemispheric respiratory quotient (HRQ) were calculated from the difference in concentration between arterial and ipsilateral transverse sinus blood and the HBF.

HBF and metabolism measurements were made in the infarcted hemisphere before and during the infusion of 200 to 500 ml of glycerol. The measurements were repeated in eight patients 5 to 20 minutes after completion of the infusion. Differences between the values before and during infusion and before and after infusion were analyzed using the standard t-test. Any difference having a standard error of less than 5% (p < 0.05) was considered statistically significant.

Results

EFFECTS OF INFUSION OF 10% GLYCEROL SOLUTION ON HBF AND METABOLIC INDEXES

Changes in HBF and metabolic indexes (HMI) following infusion of the 10% glycerol solution are shown in table 2. Mean changes from the values before infusion (ΔHBF and ΔHMI) and during and after infusion are shown in figure 1, and individual HBF and HMIO₂ values are listed in table 1.

During infusion HBF increased in all but one patient, and the mean increase of 8% was significant. HMIO₂ decreased in 13 out of 15 patients and the mean decrease of 8% was significant. HMICO₂, HMIG₁, HRQ, and HG:O decreased slightly.

After the glycerol infusion was completed, the mean HBF remained higher than before the infusion but the difference was no longer significant. HMIO₂ also was lower than before the infusion but not significantly so. HMIG₁ and HRQ both decreased significantly. HMIG₁ and HG:O both increased but not significantly.

CHANGES OF CVP, ICVP, CSFP, AND MABP BY INFUSION OF GLYCEROL

Mean CVP, ICVP, CSFP, and MABP values before, during, and after infusion are shown in table 3, and mean changes from the values before, during, and after infusion (ΔCVP, ΔICVP, ΔCSFP, and ΔMABP) are illustrated in figure 2. Individual values for CSFP are listed in table 1.

The mean CVP and ICVP both increased significantly during infusion, and ICVP returned to the preinfusion level when the
Changes in HBF and metabolism in infarcted hemisphere during 10% glycerol infusion in patients with acute cerebral infarction

The effect of an intravenous infusion of 10% glycerol solution on HBF and metabolic indexes in patients with acute infarction of one cerebral hemisphere. The resulting changes (Δ) in the parameters measured are shown. HBF increased and HMIO₂ decreased during infusion, and HMICO₂ and HRQ decreased after the infusion. HMIO₂ = hemispheric oxygen consumption; HMICO₂ = hemispheric carbon dioxide production; HMIGI = hemispheric glucose consumption; HG:O = hemispheric glucose:oxygen utilization ratio; HRQ = hemispheric respiratory quotient.

TABLE 3
Comparison of 10% Glycerol Infusion on Intracerebral Venous, CSF, and Arterial Pressures in Patients With Acute Cerebral Infarction

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>Mean and S. D.</th>
<th>During</th>
<th>Mean and S. D.</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 15)</td>
<td>(N = 14)</td>
<td>(N = 17)</td>
<td>(N = 16)</td>
<td>(N = 15)</td>
</tr>
<tr>
<td>CVP (mm H₂O)</td>
<td>197 ± 56</td>
<td>101 ± 70*</td>
<td>34 ± 38</td>
<td>103 ± 43*</td>
<td></td>
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<tr>
<td>ICVP (mm H₂O)</td>
<td>107 ± 48</td>
<td>146 ± 69*</td>
<td>85 ± 28</td>
<td>121 ± 31*</td>
<td></td>
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<tr>
<td>CSFP (mm H₂O)</td>
<td>170 ± 52</td>
<td>172 ± 77</td>
<td>154 ± 23</td>
<td>114 ± 23*</td>
<td></td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>100 ± 13</td>
<td>112 ± 21*</td>
<td>96 ± 13</td>
<td>114 ± 23*</td>
<td></td>
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</tbody>
</table>

*Statistically significant difference compared with value before infusion.
N = number of measurements.
The effect of intravenous infusion of 10% glycerol on cerebral hemodynamics and hydrodynamics. The difference of pressures from the value before the infusion (A) is illustrated. Note that CSFP remained unchanged during the infusion but decreased after infusion. CVP = central venous pressure; ICVP = intracerebral venous pressure; CSFP = cerebrospinal fluid pressure; MABP = mean arterial blood pressure.

A typical recording of arterial and cerebral venous blood gases, pH, and pressures during the infusion of glycerol together with samples of electroencephalographical (EEG) tracings are illustrated in figure 4. CVP, ICVP, CSFP, and MABP increased rapidly after the infusion was started. Cerebral venous P0₂ and SO₂ began to increase after infusion of 100 ml of solution, but arterial P0₂ and SO₂ remained unchanged, indicating an increase in HBF and a decrease in HMO2. Cerebral venous P0₂ and SO₂ continued to increase until the infusion of 500 ml was completed. CVP, ICVP, and MABP remained increased for the entire period of infusion, but despite this CSFP began to decrease after 400 ml had been infused and dropped below the steady state level following infusion of 500 ml. Sample A of the EEG shows marked high-voltage slow waves in the infarcted hemisphere prior to glycerol infusion. EEG (sample B) activity began to improve after infusion of 200 ml, and the EEG (sample C) which was recorded 40 minutes after completion of infusion of 500 ml revealed disappearance of the slow wave focus in the infarcted hemisphere. Nine of the 17 patients were improved clinically at the end of the infusion; they were more alert and responsive and showed improvement in strength in the paralyzed limbs.

**Discussion**

In 1919, in an attempt to determine whether any increase in the amount of sodium chloride in the CSF could be measured following intravenous injection of hypertonic solutions of sodium chloride, Weed and McKibben² noted that within a short period after the injection CSF could no longer be obtained. As a result of this observation, they made continuous recordings of CSFP in cats following intravenous injection of hypertonic solutions, and demonstrated a transient increase in CSFP followed immediately by a marked decrease. Since then, numerous hyperosmolar solutions, particularly urea and mannitol, have been used clinically to reduce intracranial pressure and brain tissue volume.

Glycerol was first shown by Virino et al.¹⁸ to be highly effective in reversing experimental cerebral edema. In 1963, the same investigators administered glycerol orally and showed that it was an effective drug for the reduction of intraocular pressure.²⁴ These observations were confirmed by Casey and Trevor-Roper.²⁵ Cantore et al.,³⁰ in 1964, gave glycerol orally to 258 patients before, during, and after neurosurgical procedures and reported that it reduced intracranial hypertension promptly and effectively with no evidence of the rebound phenomenon and a striking lack of toxicity. They found intravenous infusion of a 30% glycerol solution to be more effective even in their most serious cases. Infusion of such highly concentrated solutions of glycerol, however, frequently produced hemolysis, and furthermore intravenous injection of such high concentrations has been reported to produce hemoglobinuria, hypotension, tremor, and convulsions.²⁶,²⁷ On the other hand, Sloviter¹⁷ suggested that a 5% solution of glycerol in normal saline administered intravenously is useful as a nutritional agent. He reported no cardiorespiratory or central nervous system disturbances or any significant hemolytic effects.

In the present investigation, 50 gm of glycerol dissolved in 500 ml of saline was
infused over an average interval of one and one-half hours while continuously monitoring the electrocardiogram, electroencephalogram, respiration, CVP, and arterial pressure. No complications were observed during and after the infusion. Slight hemolysis could be detected when the rate of infusion was accidentally increased, but if the solution was administered slowly at 45 drops per minute hemolysis did not occur.18

Shenkin et al.7 studied the effects of reduction of increased intracranial pressure on the cerebral circulation in patients with brain tumor. They used two methods to reduce intracranial pressure—intravenous injection of 150 ml of 50% glucose and drainage of the CSF from the ventricles. Injection of hypertonic glucose was reported to increase CBF, but acute reduction of intracranial pressure by ventricular drainage apparently did not change the CBF despite the fact that ventricular drainage caused a greater reduction in CSFP than injection of 50% glucose. These investigators suggested that the increase in CBF following hypertonic glucose injection may have been caused by lowering the blood viscosity rather than by reducing the intracranial pressure; however, the skull must have been opened to permit ventricular drainage, and this factor was not considered. An increase in CBF following intravenous infusions of mannitol or urea was reported by Goluboff et al.3 in patients with brain tumor, while Harper and Bell28 reported no significant change in blood flow in normal dogs after intravenous administration of urea in spite of marked decreases in brain volume.

| TABLE 4 |
| Effects of 10% Glycerol Infusion on Cerebral Venous and Arterial Gases, pH, and Glucose in Patients with Acute Cerebral Infarction |

<table>
<thead>
<tr>
<th></th>
<th>Mean and S. D. Before</th>
<th>Mean and S. D. During</th>
<th>Mean and S. D. After</th>
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<tr>
<td>CVPO2 (mm Hg)</td>
<td>31.6 ± 4.9 (N = 14)</td>
<td>33.9 ± 5.4*</td>
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<td>CVSO2 (%)</td>
<td>52.6 ± 7.3 (N = 15)</td>
<td>59.6 ± 8.4*</td>
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<td>CVPCO2 (mm Hg)</td>
<td>58.5 ± 8.7 (N = 13)</td>
<td>51.9 ± 6.4*</td>
<td>58.2 ± 7.7 (N = 6)</td>
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<td>CVPH</td>
<td>7.250 ± 0.037 (N = 15)</td>
<td>7.235 ± 0.037</td>
<td>7.246 ± 0.046 (N = 7)</td>
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<tr>
<td>CVO2 (vol %)</td>
<td>8.5 ± 2.0 (N = 15)</td>
<td>9.6 ± 2.1*</td>
<td>8.6 ± 2.7 (N = 7)</td>
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<tr>
<td>CVCO2 (vol %)</td>
<td>54.7 ± 3.4 (N = 15)</td>
<td>53.5 ± 3.1*</td>
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<td>CVGI (mg/dl)</td>
<td>125.9 ± 44.7 (N = 15)</td>
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<td>PaO2 (mm Hg)</td>
<td>72.9 ± 6.4 (N = 16)</td>
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<td>SaO2 (%)</td>
<td>94.3 ± 6.7 (N = 17)</td>
<td>95.9 ± 3.5</td>
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<td>PaCO2 (mm Hg)</td>
<td>44.9 ± 6.2 (N = 13)</td>
<td>43.5 ± 4.8</td>
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<td>AO2 (vol %)</td>
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<td>apH</td>
<td>7.315 ± 0.032 (N = 17)</td>
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<td>ACO2 (vol %)</td>
<td>48.9 ± 5.0 (N = 16)</td>
<td>48.3 ± 4.2</td>
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<tr>
<td>AGI (mg/dl)</td>
<td>131.9 ± 44.1 (N = 16)</td>
<td>146.8 ± 46.8*</td>
<td>126.0 ± 34.7 (N = 8)</td>
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*Statistically significant difference compared with value before infusion.
N = number of measurements.
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Spector studied the effects of intravenous injection of 30% urea in rats subjected to anoxic-ischemic encephalopathy, and concluded that the reduction in cerebral edema not only decreased the mortality rate but reduced the severity of hemiplegia in survivors. Sundt et al. occluded the middle cerebral artery in cats and found a significant reduction in the size of the infarcted area in animals treated with intravenous urea compared with untreated controls.

In another series of 13 patients with cerebral infarction studied in this laboratory, HBF increased significantly after intravenous injection of 100 ml of 25% mannitol solution. Prior to trials in our patients, the effect of intravenous infusion of glycerol was investigated in seven baboons with brain swelling induced by temporary occlusion of both carotid and both vertebral arteries. In these animals, the CBF began to increase before the intracranial pressure decreased. Similar findings were observed in the present series of patients with acute cerebral infarction. During infusion of glycerol, HBF increased significantly while CSFP remained unchanged (see figs. 1 and 2). This is clearly illustrated in figure 4, in which cerebral venous $P_{O_2}$ and $S_O_2$ are seen to begin to increase soon after the beginning of the infusion in spite of a slight increase in CSFP. The mechanism by which hyperosmolar solutions cause an increase in HBF in the infarcted hemisphere appears to be due to extraction of regional water accumulations in glial processes.
EFFECT OF 10% GLYCEROL (500ml LV)

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<td>R-CVSO2</td>
<td>42.7%</td>
<td>80%</td>
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<td>R-CVPCO2</td>
<td>357</td>
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<td>R-CVPH</td>
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<tr>
<td>PaO2</td>
<td>79 mmHg</td>
<td>61%</td>
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<td>SaO2</td>
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<tr>
<td>SpO2</td>
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</table>

**FIGURE 4**

Example of continuous recordings of arterial and cerebral venous gases, pH, CVP, ICVP, CSFP, and MABP with intermittent EEG recordings. Note the early increase in CVPO2 and CVSO2 followed by a sustained increase and delayed decrease in CSFP. Also note the improvement in the EEG during and after the infusion.

Glycerol, because of its special properties as a metabolic substrate, changed cerebral metabolism as well as CBF. Infusion of mannitol in patients with brain tumor has been reported to increase cerebral oxygen consumption (CMRO2) as well as CBF, but in patients with cerebral infarction mannitol increases blood flow without changing HMIO2. The results of the present study indicate that glycerol decreases CMRO2, CO2 production, and the RQ of the infarcted hemisphere in spite of an increase in HBF. This was associated with improvement in the neurological status and reversal of the EEG abnormality (see fig. 4). These observations are not compatible with an expected depletion of cerebral energy production which usually occurs when CMRO2 and CO2 production are reduced. Another possible explanation for this dissociation of CMRO2 and energy production may be that glycerol caused a reversal of uncoupled oxidative phosphorylation, a situation in which surrounding the vessel rather than a decrease of intracranial pressure throughout the brain, an effect which Luse and Harris demonstrated in an electron microscopy study. They observed that intravenous injection of hyperosmolar solutions produced shrinkage of swollen glial cytoplasm in the water-intoxicated brains of rabbits, while in untreated animals a massive increase in volume of the glial cytoplasm occurred.
CMRO₂ and CO₂ production is increased but energy production by the brain is reduced. Some evidence for uncoupling of oxidative phosphorylation in infarcted or edematous brain has been reported. Păulescu et al. demonstrated partial uncoupling in edematous brain tissue and suggested that postanoxic uncoupling of oxidative phosphorylation was the primary metabolic disturbance. Teraura et al. reported that CMRO₂ increased despite slowing of EEG activity when cerebral edema was induced by experimental cerebral infarction, and suggested that uncoupling of oxidative phosphorylation might be an important concomitant of progressive cerebral edema since uncoupling agents such as dinitrophenol injected into the carotid artery produced an identical metabolic change accompanied by slowing of the EEG and cerebral edema. It is difficult to prove uncoupling of oxidative phosphorylation in patients with cerebral infarction due to the lack of methods for measuring regional oxidation and energy production. Carter et al. used a new method for measuring regional CMRO₂ and reported that it did not decrease in proportion to the reduction of rCBF in abnormal brain tissue. The fact that mean hemispheric CMRO₂ was reduced in these patients does not exclude the possibility of regional areas of uncoupling in edematous areas. Indeed, this seems a likely possibility since the majority of patients had hemiplegia, and yet CMRO₂ was reduced by less than half the normal level in the patients in our study.

Sato et al. proposed that release of free fatty acids may be a causative factor in uncoupling of oxidative phosphorylation associated with cerebral edema. Such impairment of oxidative phosphorylation might be due to accumulation of free fatty acids in cells as a result of increased breakdown of lipids or decreased metabolism of free fatty acids or both. Measurements of cerebral arteriovenous differences for inorganic phosphate and glycerol in patients with acute hemispheric infarction have shown the concentration of both in cerebral venous blood to be significantly higher than that in arterial blood on the infarcted side and that this difference was reversed after infusion of glycerol. This indicates that infarcted brain releases free fatty acids and phosphate and that glycerol infusion increases phosphate and fatty acid uptake by infarcted brain. Such a view is supported by the work of Pritchard, who presented evidence of incorporation of glycerol as glycerophosphatides in brain slices. From these studies, the most likely explanation for the decrease in CMRO₂ and CMRCO₂ following intravenous infusion of glycerol is inhibition of uncoupling of oxidative phosphorylation or recoupling through reduction of edema and improved metabolism of free fatty acids.

Another explanation for improvement of brain function in spite of the reduced CMRO₂ may be that glycerol enhances the activity of anaerobic glycolytic pathways. The increase of arterial concentration of glucose by 20 mg/dl indicates active conversion of glycerol into glucose in the liver; but HMIGI, calculated from the arteriovenous difference, did not change. Glycerol, however, can be incorporated by the brain into the intermediate steps of carbohydrate metabolism and can produce energy by means of the anaerobic glycolytic pathways.

Another possible explanation is inhibition of endogenous respiration within the brain by utilization of exogenous carbohydrates which has been termed the “Crabtree effect” after the investigator who discovered this effect in tumor cells in 1929. He believed the operative factor was the presence of a high aerobic glycolysis which, although not specific for tumor tissue, provides a rich source of energy for uncontrollable proliferation of tumor cells. This phenomenon may possibly contribute to the findings in the present study, namely, a reduction of cerebral oxidative respiration following the infusion of glycerol with resulting high levels of arterial glucose. This should result in increased glucose consumption, however, and this was not found to occur. Furthermore, the Crabtree phenomenon does not occur in the brain of patients with infarction during glucose infusion and has not been shown to occur in brain slices; however, it does occur in immature retinal tissue.

We have measured in recent studies the arteriovenous (A-V) differences for inorganic phosphate and glycerol in patients with acute cerebral infarction in an effort to identify changes in phosphorylation within the brain. For phosphate the arterial concentrations were significantly lower than the venous concentrations (negative A-V difference). After glycerol
infusion, this negative difference was significantly narrowed. Glycerol after infusion was shown to enter the infarcted brain. In other words, inorganic phosphate was taken up with glycerol by the brain after infusion of glycerol. This decrease in the amount of inorganic phosphate released from the brain following treatment with glycerol suggests improved phosphorylation or reincorporation of phosphate into either ATP, glycerol phosphate, glucose phosphate or phosphatides. In interpreting the A-V difference for phosphate, the blood-brain barrier for phosphate must be taken into consideration. Phosphate does not move easily into normal brain tissue from the blood, but the barrier is destroyed by cerebral infarction in man.

Certain technical factors were considered which might be responsible for an artifactual rather than a true reduction in CMRO2 after glycerol administration. The first possibility considered was the re-establishment of perfusion through nonmetabolizing zones of infarction, e.g., shunting of blood through dead brain. If blood flow is re-established in such areas of no flow, cerebral venous oxygen values will increase since there is little or no oxygen withdrawal by the tissue. Another possibility is that HBF measurements are less sensitive than blood gas determinations. Neither of these factors would account for the clinical and EEG improvement or the constant glucose utilization. Furthermore, the method used for measuring HBF detects changes of 5%.

Considerable evidence has been found that under abnormal circumstances glycerol can be utilized by the brain as a substrate. Voegtlin et al., in 1925, administered glycerol through a stomach tube to insulin-intoxicated rats and prevented insulin hypoglycemia and death. Sloviter et al. injected a 10% glycerol solution into the internal carotid artery of hypoglycemic rabbits and noted rapid improvement of the ipsilateral EEG, indicating that glycerol was rapidly metabolized and provided a source of energy for the hypoglycemic brain.

In the present investigation, HRQ decreased significantly after the infusion of glycerol, and this can be best attributed to direct oxidation of the glycerol by the infarcted hemisphere before it could be converted into glucose by the liver. Another possible explanation for this decrease in HRQ might be the oxidation of hydrogen molecules liberated in the reaction whereby glycerol is metabolized by the brain to glucose, but conversion of glycerol into glucose or glycogen in brain tissue has not as yet been established.

When hyperosmolar agents are administered to patients with cerebral edema and increased intracranial pressure, danger of the rebound phenomenon must be considered. In the present series, CSFP was monitored for at least 60 minutes after completion of infusion. In some of these patients as well as in another clinical series of patients treated with daily infusion of 10% glycerol solution, the CSFP was measured for 24 hours and no rebound occurred; i.e., the pressure remained low and did not exceed the intracranial pressure prior to the administration of glycerol. Rebound is thought to occur when the concentration of infused substances in the brain tissue becomes higher than that in plasma. Waterhouse and Coxon estimated the concentration of glycerol in CSF, brain tissue, and muscle during sustained intravenous infusion and found that the concentration in the brain tissue and CSF remained lower than one-half the concentration in plasma for measurements up to nine hours after infusion. The concentration of glycerol in muscle, however, reached the same level as that in the plasma within three hours. These results indicate incomplete penetration of glycerol into brain. This barrier might be expected to be disturbed in infarcted brain; nevertheless, infarcted brain appears to oxidize glycerol as evidenced by the reduction of HRQ and this would prevent any accumulation of glycerol in brain tissue. Cantore et al. mentioned that repeated administration of glycerol is unassociated with rebound. Javid et al. also found no evidence of rebound 17 hours after intravenous injection of glycerol in dogs.

In conclusion, intravenous infusion of a 10% glycerol solution appears to be an effective means of treating patients with acute cerebral infarction. This hyperosmolar agent increases blood flow to the infarcted hemisphere, reduces cerebral edema, and improves cerebral metabolism, energy production, and function.

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JOHN STIRLING MEYER, YASUO FUKUUCHI, KUNIO SHIMAZU, TADAO OHUCHI and ARTHUR DALE ERICSSON

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