Monitoring Cerebral Blood Flow, Oxygen, and Glucose Metabolism

Analysis of Cerebral Metabolic Disorder in Stroke and Some Therapeutic Trials in Human Volunteers

By John S. Meyer, M.D., F. Gotoh, M.D., M. Akiyama, M.D., and S. Yoshitake, M.D.

SUMMARY

More accurate methods for monitoring cerebral blood flow, oxygen, and glucose metabolism with results of their application in human volunteers are described.

Subjects with various types of cerebral vascular disease showed decreased cerebral blood flow and oxygen and glucose metabolism but anaerobic glycolysis appeared to be increased. Inhalation of 100% oxygen decreased anaerobic glycolysis, and mixtures of oxygen, 5% CO₂ plus oxygen, 5% CO₂ plus air, and hyperventilation all showed that cerebral vascular reactivity is reduced in cerebrovascular disease. Nevertheless, inhalation of 5% mixtures of CO₂ in air or oxygen significantly increased cerebral blood flow. Inhalation of 5% CO₂ plus oxygen significantly increased cerebral oxygen consumption in cerebrovascular disease within 10 minutes of its institution. The depression of cerebral glucose metabolism and oxygen consumption appears to be amenable to rapid improvement in some subjects with stroke. Intravenous administration of nylidrin hydrochloride decreased cerebral vascular resistance but did not increase cerebral blood flow or metabolism, presumably by autoregulation. Intravenous injection of 100 ml of low molecular-weight dextran increased cerebral blood flow and oxygen consumption but not to the level of statistical significance. A case of brain-stem ischemia showed a large increase of cerebral blood flow, oxygen metabolism, and glucose consumption after surgical reconstruction of the left vertebral artery accompanied by clinical recovery.

Additional Indexing Words:

Cerebral oxygen consumption Cerebral glucose consumption Stroke therapy

Hypertension Carbon dioxide inhalation Nylidrin

QUANTITATIVE MEASUREMENT of cerebral blood flow and metabolism was made possible by the nitrous oxide method introduced by Kety and Schmidt in 1945. Although this method has proved to be extremely reliable, it has some limitations. Frequent sampling of arterial and venous blood is required, and Van Slyke analysis of so many samples is subject to human error.

This laboratory has directed efforts toward recording cerebral blood flow and metabolism automatically with minimal loss of blood. The nitrous oxide content of the blood was graphed without loss of blood after diffusing the gas through a silastic membrane. Quantitative measurement of the gas was recorded either colorimetrically with the Technicon

From the Department of Neurology, Wayne State University, Detroit General Hospital and the Wayne Center for Cerebrovascular Disease, Harper Hospital, Detroit, Michigan.

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Circulation, Volume XXXVI, August 1967 197
autoanalyzer* or with two Beckman infra-red nitrous oxide gas analyzers.\(^2\) Hydrogen has also been used as the inert gas indicator, and arterial and venous curves were monitored by means of hydrogen electrodes.\(^3\) The application of methods using polarography, oximetry, and membrane-covered electrodes made possible simultaneous monitoring of oxygen tension, oxygen saturation, carbon dioxide tension, and pH of the cerebral arterial and venous blood or brain surface.\(^5\)–\(^9\)

Methods for continuous monitoring of cerebral arteriovenous differences for glucose were achieved by modifying the Technicon apparatus. Preliminary trials showing the validity of this method in monkeys will be reported elsewhere.\(^10\) Continuous monitoring of cerebral arterial and venous glucose content provides more accurate measurements of small (within 1 mg per 100 ml) and rapid changes in the cerebral metabolic rate for glucose than is possible on use of multiple sampling techniques.

The present study was designed to monitor cerebral blood flow, oxygen consumption, and glucose metabolism by the use of these techniques in subjects with proven cerebrovascular disease (stroke) before and after trials of several types of therapy.

**Methods**

**Monitoring Cerebral Blood Flow**

Cerebral blood flow was measured by the automatic nitrous oxide method.\(^2\) This method is a modification of the classical nitrous oxide method of Kety and Schmidt.\(^1\)\(^,\)\(^11\) Two methods have been devised to record automatically the nitrous oxide content of blood. The possible application of a colorimetric nitrous oxide method was first suggested by Spencer and associates,\(^12\) but considerable technical improvements were made in this laboratory before it was successfully applied to animals and man. Furthermore, the blood was returned to the subject by means of an extracorporeal circulation so that there was no loss of blood.

Blood from the internal jugular vein and an artery was propelled by a Technicon proportioning pump at 2.9 ml per minute through a diffusion coil which is 3 feet in length. The coil was fabricated with an inner silastic tube (I.D., 0.020 inch; O.D., 0.037 inch) and an outer Kel-F tube. Nitrous oxide diffused rapidly from the blood into a stream of dried air in the outer diffusion coil, while the blood in the inner silastic tube was returned to the subject via the brachial veins. The diffused nitrous oxide was carried by the stream of air into a microcombustion tube* heated to 1,000°C which converted nitrous oxide to nitrite. After mixing with a reagent consisting of sulfanilic acid and 1-naphthylamine, by the use of a Technicon proportioning pump, a purplish color resulted which was proportional to the nitrous oxide content of the blood. The colorimeter graphed the nitrous oxide content of the arterial and cerebral venous blood on the chart of a Technicon recorder or Grass polygraph\(^†\) during inhalation of a gas mixture containing 15% nitrous oxide, 21% oxygen, and 64% nitrogen. Thus, for each inhalation of gas, values of cerebral blood flow were obtained in both saturation and desaturation.

Later, a simpler and more satisfactory method for continuous recording of the nitrous oxide content of the blood was devised by the use of two Beckman infra-red nitrous oxide gas analyzers. The nitrous oxide was diffused from the blood as before and carried by the stream of air directly through the pick-up cells of the gas analyzers. Values for cerebral blood flow were calculated in the usual way from the difference in the area between the curves of the arterial and cerebral venous blood during saturation and desaturation phases and expressed in ml/100 g brain/min.

**Monitoring Cerebral Oxygen Consumption**

Cerebral arteriovenous oxygen differences were calculated from oxygen capacity measured by manometric methods, from oxygen saturation, and from continuous measurements of pH and oxygen pressure (\(P_{O_2}\)) in the arterial and cerebral venous blood.\(^18\) Cerebral oxygen consumption in ml/100 g brain/min was derived from the product of cerebral blood flow and the cerebral arteriovenous oxygen difference.

**Monitoring Cerebral Glucose Consumption**

The glucose contents of arterial and internal jugular blood were monitored by means of two Technicon autoanalyzers with a standard colorimetric method for glucose determination. One of the two sample lines was connected to the

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*Technicon Co., Chauncey, New York.

†Grass Instrument Co., Quincy, Massachusetts.

Circulation, Volume XXXVI, August 1967
MONITORING CEREBRAL BLOOD FLOW

arterial catheter and the other to the venous catheter (instead of the sampler as originally intended for the Technicon apparatus). By this means continuous records of the glucose contents of cerebral arterial and venous blood were obtained. The principle of the method requires that the glucose be dialyzed from the blood with potassium ferricyanide reagent, then heated in a heating bath to 95°C. The yellow color of the potassium ferricyanide is reduced to colorless potassium ferrocyanide in proportion to the glucose present in the blood. The color changes are graphed by two colorimeters using 420 filters. The quantity of blood required for monitoring cerebral arteriovenous glucose difference is 0.32 ml/min. The method has proven far more reliable than conventional sampling methods; there is reproducibility of ±1% transmission (1 mg per 100 ml in the physiological range) with a time delay of 5 minutes. Cerebral glucose consumption was calculated in mg/100 g brain/min from the cerebral blood flow and cerebral arteriovenous glucose differences. The enzymatic glucose method provided by Technicon was also used but proved to be less stable.

Clinical Investigation

Cerebral blood flow, oxygen utilization, and glucose consumption were repeatedly measured in 22 patients* between the ages of 40 and 78 years, all of whom suffered from various types of cerebral vascular disease. At the time of study complete recovery had occurred in some, while others had a permanent neurological deficit. All had a history of neurological deficit, and many had suffered from numerous attacks with recovery (transient ischemic attacks). Table 1 gives the age, sex, and diagnosis based on complete clinical and arteriographic investigation. The anatomic diagnosis of arterial stenosis and occlusion was confirmed by arteriographic as well as clinical evidence since aortocerebral arteriography was performed in every case. Eight patients had hypertension, but none had serious cardiac or pulmonary disorder at the time of the measurements.

The following therapeutic trials were made so that any effect on cerebral blood flow and metabolism could be estimated: inhalation of 5% carbon dioxide in air for 10 minutes, inhalation of 5% carbon dioxide in oxygen for 10 minutes, inhalation of 100% oxygen for 10 minutes, hyperperventilation for 10 minutes, intravenous injection of 0.3 to 0.5 mg of nyldrin hydrochloride, intravenous injection of 100 ml of low molecular-weight dextran, and the effect of endarterectomy for removal of severe stenosis of the vertebral artery in a single subject suffering from bilateral vertebral artery stenosis with brain stem ischemia and hypoventilation syndrome.

Thirty minutes prior to measurement the subjects were premedicated with intramuscular injection of 50 mg of meperidene hydrochloride (Demerol) and 0.4 mg of atropine sulfate. Procaine hydrochloride (2%) was infiltrated at the injection sites for local anesthesia, and one jugular vein was catheterized along with the median cubital veins and the brachial or femoral artery. Sodium heparin (100 mg) was injected through the jugular venous catheter. A schematic diagram of the apparatus for monitoring the cerebral blood flow and the cerebral metabolic rates for oxygen and glucose is shown in figure 1.

The arterial and jugular venous blood were propelled by peristaltic pumps and divided into three channels. Blood for monitoring cerebral metabolic changes was propelled through two cuvettes each containing the electrode sensors. In the cuvettes the blood was analyzed continuously by electronic methods² and returned to the median cubital veins. The electronic sensors monitored oxygen tension (P_o₂), oxygen saturation (S_o₂), carbon dioxide tension (P_co₂), and pH of the arterial and internal jugular blood. Oxygen tension electrodes, reflection oximeters, carbon dioxide electrodes, and small pH electrodes were used. In some cases, hydrogen electrodes were mounted in the cuvettes to determine cerebral blood flow using hydrogen gas as the indicator.

The second channels of blood were propelled through silastic diffusion coils and the nitrous oxide content was analyzed. In cases 1 to 13, the blood nitrous oxide content was automatically analyzed by the colorimetric nitrous oxide method, and in cases 14 to 22, infra-red gas analyzers were used. The third channels of blood were propelled through the systems for monitoring blood glucose.

The arterial catheter had an attachment for recording blood pressure and the end-tidal carbon dioxide tensions of the expired air (P_co₂) were monitored with a Beckman infra-red gas analyzer. Respiration was recorded by changes

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*Each subject volunteered for these metabolic studies after the procedures, including the nature of jugular venous puncture, were explained to them or their legally responsible guardians. A written form giving permission for the procedure was then signed by the individual or the guardian in the presence of a witness.

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*Kipp and Sons, Delft, Holland.
†Beckman Instruments, Inc., Fullerton, California.
### Table 1

**Cerebral Blood Flow and Mean Cerebral Metabolic Rates for Oxygen and Glucose in Human Subjects with Cerebrovascular Disease**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr), sex</th>
<th>Diagnosis</th>
<th>CBF</th>
<th>MABP</th>
<th>CVR</th>
<th>AO2</th>
<th>JO2</th>
<th>A-VO2</th>
<th>CMRO2</th>
<th>A-Gl</th>
<th>J-Gl</th>
<th>A-VGl</th>
<th>CMRGl</th>
<th>A-VGl</th>
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<tbody>
<tr>
<td>1</td>
<td>63 M</td>
<td>R. intracerebral hemorrhage</td>
<td>38.5</td>
<td>80</td>
<td>2.08</td>
<td>12.61</td>
<td>5.07</td>
<td>7.54</td>
<td>2.90</td>
<td>84.3</td>
<td>70.6</td>
<td>13.7</td>
<td>5.27</td>
<td>1.82</td>
</tr>
<tr>
<td>2</td>
<td>59 F</td>
<td>Diffuse cerebral arteriosclerosis</td>
<td>38.3</td>
<td>93</td>
<td>2.43</td>
<td>15.21</td>
<td>8.83</td>
<td>6.38</td>
<td>2.44</td>
<td>103.0</td>
<td>95.5</td>
<td>7.5</td>
<td>2.87</td>
<td>1.18</td>
</tr>
<tr>
<td>3</td>
<td>54 F</td>
<td>L. internal carotid occlusion; diabetes mellitus</td>
<td>31.7</td>
<td>76</td>
<td>2.40</td>
<td>13.56</td>
<td>6.31</td>
<td>7.25</td>
<td>2.30</td>
<td>149.4</td>
<td>138.2</td>
<td>11.2</td>
<td>3.55</td>
<td>1.54</td>
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<td>4</td>
<td>77 M</td>
<td>R. internal carotid stenosis; bilateral vertebral stenosis</td>
<td>33.7</td>
<td>88</td>
<td>2.61</td>
<td>16.91</td>
<td>10.90</td>
<td>6.01</td>
<td>2.03</td>
<td>138.4</td>
<td>126.2</td>
<td>12.2</td>
<td>4.11</td>
<td>2.03</td>
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<td>L. internal carotid occlusion</td>
<td>35.4</td>
<td>97</td>
<td>2.74</td>
<td>17.48</td>
<td>9.37</td>
<td>8.11</td>
<td>2.87</td>
<td>87.5</td>
<td>77.0</td>
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<td>3.72</td>
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<td>6</td>
<td>60 F</td>
<td>Alcoholic neuropathy; alcoholic pseudotabes; diffuse cerebral arteriosclerosis</td>
<td>45.7</td>
<td>82</td>
<td>1.79</td>
<td>14.18</td>
<td>7.75</td>
<td>6.43</td>
<td>2.94</td>
<td>61.0</td>
<td>53.5</td>
<td>7.5</td>
<td>3.43</td>
<td>1.17</td>
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<td>7</td>
<td>60 M</td>
<td>Bilateral internal carotid stenosis; R. subclavian occlusion</td>
<td>36.7</td>
<td>87</td>
<td>2.37</td>
<td>13.40</td>
<td>7.37</td>
<td>6.03</td>
<td>2.21</td>
<td>79.8</td>
<td>61.3</td>
<td>18.5</td>
<td>6.79</td>
<td>3.07</td>
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<tr>
<td>8</td>
<td>70 M</td>
<td>Bilateral internal carotid occlusion; bilateral vertebral stenosis; hypertension; polycythemia</td>
<td>29.5</td>
<td>140</td>
<td>4.75</td>
<td>19.14</td>
<td>9.86</td>
<td>9.28</td>
<td>2.74</td>
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<td>9</td>
<td>71 M</td>
<td>R. internal carotid stenosis</td>
<td>37.8</td>
<td>85</td>
<td>2.25</td>
<td>15.50</td>
<td>7.79</td>
<td>7.71</td>
<td>2.91</td>
<td>127.2</td>
<td>112.9</td>
<td>14.3</td>
<td>5.41</td>
<td>1.85</td>
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<td>10</td>
<td>52 M</td>
<td>R. middle cerebral artery occlusion</td>
<td>50.8</td>
<td>104</td>
<td>2.05</td>
<td>16.34</td>
<td>10.89</td>
<td>5.45</td>
<td>2.77</td>
<td>83.8</td>
<td>78.2</td>
<td>5.6</td>
<td>2.84</td>
<td>1.03</td>
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<tr>
<td>11</td>
<td>40 F</td>
<td>L. internal carotid occlusion</td>
<td>44.3</td>
<td>103</td>
<td>2.33</td>
<td>11.65</td>
<td>5.98</td>
<td>5.67</td>
<td>2.51</td>
<td>123.9</td>
<td>112.1</td>
<td>11.8</td>
<td>5.23</td>
<td>2.08</td>
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<tr>
<td>12</td>
<td>49 M</td>
<td>Bilateral vertebral stenosis; hypertension; hyperventilation syndrome</td>
<td>23.5</td>
<td>127</td>
<td>5.40</td>
<td>15.73</td>
<td>10.05</td>
<td>5.68</td>
<td>1.33</td>
<td>80.3</td>
<td>77.2</td>
<td>3.1</td>
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<td>0.55</td>
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<tr>
<td>13</td>
<td>63 M</td>
<td>Bilateral internal carotid occlusion; L. vertebral stenosis; hypertension</td>
<td>34.7</td>
<td>115</td>
<td>3.31</td>
<td>14.14</td>
<td>8.89</td>
<td>5.25</td>
<td>1.82</td>
<td>106.3</td>
<td>96.0</td>
<td>10.3</td>
<td>3.57</td>
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<td>14</td>
<td>49 M</td>
<td>R. internal carotid occlusion; L. internal carotid stenosis; diabetes mellitus</td>
<td>49.7</td>
<td>75</td>
<td>1.51</td>
<td>17.28</td>
<td>10.85</td>
<td>6.43</td>
<td>3.20</td>
<td>120.7</td>
<td>113.6</td>
<td>7.1</td>
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<td>30.2</td>
<td>92</td>
<td>3.05</td>
<td>13.69</td>
<td>7.25</td>
<td>6.44</td>
<td>1.94</td>
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<td>10.1</td>
<td>3.05</td>
<td>1.57</td>
</tr>
<tr>
<td>16</td>
<td>62 F</td>
<td>Bilateral carotid stenosis; bilateral vertebral stenosis; hypertension</td>
<td>25.7</td>
<td>120</td>
<td>4.67</td>
<td>16.66</td>
<td>7.69</td>
<td>8.97</td>
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<td>74 F</td>
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<td>29.8</td>
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<td>68 F</td>
<td>R. carotid occlusion; L. vertebral stenosis</td>
<td>28.2</td>
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<td>2.91</td>
<td>16.37</td>
<td>10.33</td>
<td>6.04</td>
<td>1.70</td>
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<td>1.32</td>
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<tr>
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<td>62 M</td>
<td>Diffuse cerebral arteriosclerosis; hypertension</td>
<td>27.5</td>
<td>155</td>
<td>5.64</td>
<td>16.34</td>
<td>8.26</td>
<td>8.08</td>
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<td>92.6</td>
<td>71.4</td>
<td>21.2</td>
<td>5.83</td>
<td>2.62</td>
</tr>
</tbody>
</table>
in transthoracic impedance. Electroencephalograms and electrocardiograms were recorded throughout.

The extracorporeal circulating system was sterilized by exposure to ethylene oxide (Ben Venue sterilizer) and circulating benzalkonium (Zephran).

Immediately before the recording of cerebral blood flow and metabolism, samples of arterial and jugular blood were obtained and analyzed for oxygen content, oxygen capacity, and carbon dioxide content using the standard method of Van Slyke and Neill.

After a satisfactory recording of cerebral metabolism was obtained in the steady state, the subject inhaled a gas mixture containing 15% nitrous oxide and 21% oxygen until equilibrium of nitrous oxide was achieved in arterial and internal jugular blood. The mask was then removed so that for each inhalation in the steady state two values of cerebral blood flow were obtained, one during saturation and the other during desaturation. Desaturation values were slightly higher than those made in saturation, but the difference was not statistically different.7-9

In some cases a mixture of 2.5% hydrogen, 21% oxygen, and 15% nitrous oxide was inhaled by the subject so that measurements of cerebral blood flow (CBF) by the two methods could be compared.7-9

For evaluation of the therapeutic trials three CBF values were obtained in the steady state using nitrous oxide values, and the last steady state value was made during the saturation phase. The effect of the therapeutic trial was evaluated thereafter, during the desaturation phase. The subjects were cooperative and tolerated the procedure without ill effects.

Results

Steady State Values

Cerebral blood flow and metabolism were measured in the steady state in 22 patients who suffered from various types of cerebrovascular disease (table 1). Mean cerebral blood flow (CBF) was 35.5 ± 7.5 ml/100 g brain/min and mean arterial blood pressure (MABP) was 103 mm Hg with a mean cerebral vascular resistance (CVR) of 3.11 units. Mean arterial and cerebral venous oxygen contents (A\(\text{O}_2\), J\(\text{O}_2\)) were 15.58 ml% and 8.74 ml%, respectively; mean cerebral arteriovenous oxygen difference (A-VO\(\text{O}_2\)) was 6.84 ml%; and mean cerebral metabolic rate for oxygen (CMRO\(\text{O}_2\)) was 2.37 ± 0.46 ml/100 g
Figure 1

Schematic diagram of the apparatus used for automatically recording the cerebral blood flow and metabolism of the human volunteers. $H_2$ = hydrogen electrode; $PCO_2$ = partial pressure of blood carbon dioxide electrodes; $P_ECO_2$ = partial pressure of carbon dioxide in expired air; $PO_2$ = partial pressure of blood oxygen electrodes; $pH$ = pH electrode; $T$ = temperature monitor (thermistor) for monitoring cuvette at 37°C; ref. = reference electrode; and oximeter = Kipp reflection oximeter for oxygen saturation of blood.

Relationship of Arterial Glucose to Cerebral A-V Glucose Difference and Cerebral Metabolic Rate for Glucose

In general, if the arterial glucose content was high, the cerebral arteriovenous glucose difference was wider than if the arterial glucose content was low, but there were some exceptions in which the arterial glucose content was low and the arteriovenous glucose difference was wide. There was no consistent correlation between arterial glucose content and cerebral metabolic rate for glucose.

Relationship of CBF to Cerebral A-V Glucose Difference, Cerebral Metabolic Rate for Glucose and A-V Glucose: A-V Oxygen Ratio

Little correlation was found to exist between CBF and cerebral A-V glucose dif-
CEREBRAL BLOOD MONITORING

The graph correlates cerebral arteriovenous glucose difference (A-J • Gl) in mg/100 ml plotted on vertical axis with cerebral blood flow (CBF) in ml/100 g brain/min plotted on horizontal axis. In general, the higher the CBF the lower the cerebral A-V glucose differences, but this did not reach the level of significant correlation (r = -0.18, 0.2 < P).

Figure 2

Graph correlating values of cerebral glucose consumption (CMR • Gl) in mg/100 g brain/min (vertical axis) plotted against cerebral blood flow (CBF) in ml/100 g brain/min in the group of subjects with different types of cerebral vascular disease. Some correlation exists but does not reach the level of statistical significance.

Figure 3

In general, the higher the CBF values the lower the cerebral A-V glucose differences and vice versa, but this correlation did not reach the level of statistical significance. Similarly, little correlation was found between CMR glucose and CBF as shown in figure 3. No correlation was found to exist for the total group between CBF and ratio cerebral A-V glucose to cerebral A-V oxygen.

Relationship Between Cerebral Metabolic Rate of Oxygen and Cerebral Metabolic Rate for Glucose

No correlation existed for the group as a whole between CMRO2 and CMRG1. In general, the majority of cases showed reduction of both but the possible significance of exceptions where CMRO2 was reduced while CMRG1 was normal or nearly normal will be considered in the discussion.

Relationship of Mean Arterial Blood Pressure on Cerebral Metabolic Rate for Glucose

In general, the higher the mean arterial blood pressure the lower the cerebral metabolic rate for glucose while the patients with normal levels for MABP tended to show higher values for cerebral consumption of glucose. This correlation did not reach the level of statistical significance (r = -0.19, 0.2 < P) as shown in figure 4. When the hypertensive group was separated on the basis of a mean arterial blood pressure in excess of 110 mm Hg from the normotensive group, the cerebral metabolic rate for glucose in the 14 normotensive subjects was 4.08 ± 1.96, while in the hypertensive group it was 2.87 ± 1.41, but this difference did not reach the level of statistical significance (0.2 < P).

Effect of Inhalation of 100% Oxygen

The effect, if any, of inhalation of 100% oxygen on CBF and on the cerebral metabolic rates for O2 and glucose was examined in 12 subjects with cerebral vascular disease during desaturation phase following inert gas inhalation. The results are summarized in table 2. Cerebral blood flow decreased from mean values of 38.7 to 34.2 ml/100 g
Cerebral Blood Flow and Mean Cerebral Metabolic Rates for Oxygen and Glucose before and after Therapeutic Trials in Cerebrovascular Disease

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Cases</th>
<th>CBF C</th>
<th>E</th>
<th>A\textsubscript{O2} C</th>
<th>E</th>
<th>JO\textsubscript{2} C</th>
<th>E</th>
<th>A-VO\textsubscript{2} C</th>
<th>E</th>
<th>CMRO\textsubscript{2} C</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% O\textsubscript{2} inhalation</td>
<td>Mean 12</td>
<td>38.7</td>
<td>34.2</td>
<td>14.72</td>
<td>17.15</td>
<td>8.76</td>
<td>9.98</td>
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Abbreviations: C = control; E = evaluation of therapeutic trials. For other abbreviations and units of measurement see table 1 and text.

The graph correlates mean arterial blood pressure (MABP) plotted on the horizontal axis and cerebral metabolic rate for glucose (CMR \cdot Gl) plotted on the vertical axis in the group of subjects with different types of cerebral vascular disease. Some correlation exists in that the hypertensive group showed lower CMR \cdot Gl than the normotensive group but the relationship is not statistically significant ($r = -0.19$, $0.2 < P$).

Effect of Inhalation of 5% Carbon Dioxide in Air

As shown in table 2, inhalation of a gas mixture containing 5% carbon dioxide in air by nine subjects with cerebrovascular disease increased mean cerebral blood flow from 35.3 to 45.3 ml/100 g brain/min which was statistically significant $(0.001 < P < 0.01)$. Arterial oxygen content slightly increased, and jugular oxygen content consistently increased $(P < 0.001)$. The cerebral arteriovenous oxygen difference decreased 17% $(0.001 < P < 0.001)$.
MONITORING CEREBRAL BLOOD FLOW

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<th>AGI C</th>
<th>JGI C</th>
<th>A-VG1 C</th>
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0.01), but cerebral metabolic rate for oxygen was not significantly altered. Arterial glucose content slightly increased and jugular glucose content significantly increased (0.01 < P < 0.02). Cerebral arteriovenous glucose difference decreased by 11% which did not reach the level of statistical significance (0.05 < P < 0.1). The cerebral metabolic rate for glucose and the ratio of cerebral arteriovenous differences of glucose to oxygen were not significantly altered.

**Effect of Inhalation of 5% Carbon Dioxide and Oxygen**

The effects of inhalation of 5% CO₂ in oxygen on five patients suffering from cerebrovascular disease is shown in table 2. Cerebral blood flow increased significantly by 31% (0.02 < P < 0.05), and arterial and jugular oxygen content both increased. The cerebral arteriovenous oxygen difference slightly decreased, and the cerebral metabolic rate for oxygen increased by 17% which was statistically significant (0.001 < P < 0.01). There were no consistent changes in cerebral metabolic rate for glucose.

**Effect of Hyperventilation**

As shown in table 2, the effect of active hyperventilation for 10 minutes on cerebral blood flow and metabolism was evaluated in eight subjects with cerebrovascular disease. Cerebral blood flow decreased 25% which was statistically significant (0.001 < P < 0.01). Arterial oxygen content increased (0.001 < P < 0.01), and jugular oxygen content decreased (0.001 < P < 0.01), hence the cerebral arteriovenous oxygen difference was widened (P < 0.001). Cerebral metabolic rate for oxygen, however, did not significantly change. Cerebral venous glucose values significantly decreased (0.001 < P < 0.01), but arterial glucose values did not change, hence cerebral arteriovenous glucose difference increased significantly from 8.3 to 12.0 mg/100 ml (0.001 < P < 0.01). Cerebral metabolic rate for glucose increased, but this did not reach the level of statistical significance, and the ratio of cerebral arteriovenous differences for glucose to oxygen was not changed.

Of the eight patients tested, five had electroencephalographic (EEG) slowing and the three showed no EEG change. Despite this there was no significant difference between the group with EEG slowing compared to the group without EEG change for cerebral blood flow, cerebral oxygen and glucose consumption, and the ratio of cerebral arteriovenous differences for glucose to oxygen. The mean
jugular oxygen content for the group with
EEG slowing was lower (7.78 vol %) than for
the group without it (8.33 vol %), but this
difference did not reach the level of statisti-
cal significance.

Effect of Intravenous Injection of Nylidrin
Hydrochloride (Arlidin*)

Nylidrin hydrochloride (Arlidin) was in-
vestigated as a possible cerebral vasodilator
drug. The drug was administered by intra-
venous injection immediately before desatur-
ation (CBF measurement) in doses of 0.3 to
0.5 mg dissolved in 20 ml of physiological
saline. There was no change in cerebral blood
or cerebral metabolic rate for oxygen. Mean
arterial blood pressure was decreased from
102 to 91 mm Hg (0.001 < P < 0.01), and
cerebral vascular resistance decreased by
13%, but this did not reach the level of statis-
tical significance. Both arterial and jugular
glucose values were significantly increased
(0.001 < P < 0.01), but cerebral glucose con-
sumption was not altered.

Intravenous Injection of Low Molecular-Weight
Dextran (Rheomacrodex†)

In eight cases of occlusive cerebrovascular
disease, cerebral blood flow and metabolism
were measured before and after intravenous
injection of 100 ml of low molecular-weight
dextran (Rheomacrodex). Cerebral blood
flow and cerebral metabolic rate for oxygen
and for glucose all increased but not to the
level of statistical significance (0.2 < P < 0.3,
0.05 < P < 0.1, and 0.2 < P < 0.3, respec-
tively). Cerebral metabolic rate for oxygen was
increased.

Discussion

Continuous recordings of cerebral blood
flow, cerebral oxygen consumption, and cere-
brovascular disease, which was confirmed in
cases by the history, general medical and
neurological examinations, examination of the
cerebrospinal fluid, evaluation for metabolic
disorders, and complete aortocranial arteri-
ography. The group included one patient with
cerebral hemorrhage and all the rest suffered
from atherosclerotic occlusion or stenosis of
major cerebral vessels associated with signs
and symptoms of completed stroke, progressive
stroke, and transient ischemic attacks. In
all cases cerebral blood flow and oxygen
consumption were decreased from normal val-
es*11, 14 determined by the nitrous oxide tech-
nique. Mean cerebral blood flow for the en-
tire group was 35.5 ml/100 g brain/min and
cerebral metabolic rate for oxygen was 2.37
ml/100 g brain/min. This confirms previous
reports of similar measurements in subjects
with cerebrovascular disease using the con-
ventional nitrous oxide method,15 modifica-
tions of it, and other methods for measuring
cerebral blood flow and metabolism includ-
ing the hydrogen method.2-4

The mean value for cerebral metabolic rate
for glucose was also found to be reduced to
3.64 ml/100 g brain/min which is considerably
lower than widely accepted normal val-
es.*14, 16, 17 Some patients showed normal or
nearly normal values for cerebral metabolic
rate for glucose despite reduced cerebral oxy-
gen consumption. This tended to occur in
subjects showing transient attacks with good
recovery, the absence of severe hypertension,
and good collateral circulation by cerebral
arteriography. This metabolic pattern pre-
sumably indicates some cerebral anaerobic
glycolysis in areas of poor perfusion with func-
tional impairment which theoretically might be
improved by therapeutically induced or sponta-
naneous restoration of blood flow. Anaerobic
glycolysis utilizes considerably more glucose
and, of course, less oxygen to produce the
same unit of energy compared to aerobic
cerebral metabolism. In such cases with com-
pleted stroke, the ratio for the cerebral arterio-
venous differences for glucose: oxygen tended
to be higher than in the other cases.

*Arlidin was kindly supplied free of charge by the
U. S. Vitamin & Pharmaceutical Corporation, Arling-
ton-Funk Laboratories, Division, New York.
†Rheomacrodex was provided free of charge by
Pharmacia Laboratories, Inc., Piscataway, New Mar-
et, New Jersey.
MONITORING CEREBRAL BLOOD FLOW

Gibbs and associates\textsuperscript{18} in 30 healthy young men reported arterial glucose values of 92 mg/100 ml and jugular glucose values of 82 mg/100 ml with an average cerebral arteriovenous difference of 9.8 mg/100 ml. The mean arteriovenous differences in the present series of cases of stroke were comparable, but the cerebral blood flow values were consistently below normal, hence it may be inferred that cerebral glucose utilization was reduced in our subjects. Scheinberg and Stead\textsuperscript{14} reported that in 29 normal subjects the cerebral arteriovenous glucose difference was 9.94 mg/100 ml and cerebral glucose consumption was 6.20 mg/100 g brain/min. Gottstein and co-workers\textsuperscript{18} reported that in 27 subjects with normal cerebral blood flow and metabolism the cerebral arteriovenous glucose difference was 9.9 mg/100 ml and the cerebral metabolic rate for glucose was 5.30 mg/100 g brain/min. They\textsuperscript{17} also reported a decrease of cerebral glucose utilization in 17 patients with cerebral arteriosclerosis. In this second group the cerebral metabolic rate for glucose was 3.27 mg/100 g brain/min with a ratio of cerebral arteriovenous differences for glucose to oxygen of 1.23. They concluded that in cerebral arteriosclerosis the brain takes up more oxygen than would theoretically be required for glucose oxidation, which they interpreted to mean that in cerebral arteriosclerosis cerebral oxidative metabolism was supported by substances other than glucose. Theoretically, 6 vol of oxygen are required to oxidize 1 vol of glucose, or in other words, 1 vol % of oxygen is required to oxidize 1.34 mg of glucose.\textsuperscript{19} Unfortunately, this ratio varies in the reports of different authors. Gibbs and associates\textsuperscript{20} reported the value as 1.49 in healthy subjects. Scheinberg and Stead\textsuperscript{14} gave the ratio as 1.67 in 20 normal subjects, and Gottstein and associates\textsuperscript{18} found it to be 1.43 in 32 subjects with normal cerebral blood flow and metabolism. The fact that all values are higher than the predicted value of 1.34 has been attributed to some degree of anaerobic glycolysis normally present in the brain since lactate and pyruvate are added to cerebral blood by the brain in human subjects.\textsuperscript{18}

Recently, Reinmuth and co-workers\textsuperscript{19} measured total cerebral blood flow and metabolism using the radioactive iodo antipyrine \textsuperscript{131}I Fick method in 22 patients with cerebrovascular disease and in cerebral arteriosclerosis with hypertension. They reported a mean cerebral arteriovenous glucose difference of 8 mg/100 ml in cerebrovascular disease and a mean total cerebral glucose consumption of 38 mg/min, which was 64% lower than normal values. In cerebral arteriosclerosis with hypertension, the cerebral arteriovenous glucose difference was 10 mg/100 ml and cerebral glucose consumption was 52.3 mg/min; both were 45% lower than their normal values. They observed that the difference of cerebral glucose consumption between nonhypertensive and hypertensive subjects was close to the level of statistical significance, although the reason for this difference was not clear.

In the present study of subjects with cerebral vascular disease, cerebral glucose consumption was lower in the hypertensive than in the normotensive group. We conclude that in subjects with focal cerebral ischemia or infarction plus long-standing hypertension there is generalized plus localized vascular disease with more severe depression of glucose metabolism. Steady state value for cerebral metabolic rate for glucose in the present group of subjects with cerebrovascular disease was 3.64 mg/100 g brain/min which is lower than the normal reported values, and the cerebral arteriovenous ratio for glucose-oxygen was 1.55, which is higher than most reported values for normal. It is, therefore, concluded that in cerebrovascular disease of all types there is probably an increase of anaerobic glycolysis due to cerebral ischemic anoxia. Later in the discussion further evidence to support this conclusion will be based on experimental observations during therapeutic trials designed to clarify this important question.

Additional evidence from the relevant literature supports the view that in cerebral vas-
cular disease, anaerobic glycolysis is increased. Gottstein and associates \(^{21}\) reported improved cerebral glucose consumption in such cases when glucose and insulin were infused intravenously, although cerebral glucose consumption was not increased by infusion of glucose alone. However, this increase of glucose consumption provoked by insulin was not accompanied by an increase of oxygen utilization but by increased lactate and pyruvate release from the brain into the jugular blood, indicating an increase of anaerobic glycolysis by the brain.

The effects on cerebral blood flow of inhalation of mixtures of 100% oxygen, 5% carbon dioxide in air, 5% carbon dioxide in oxygen, and hyperventilation in this group of subjects with cerebrovascular disease is remarkably similar to effects reported in normal subjects. \(^{22}\) With the exception of inhalation of carbon dioxide gas mixtures, when both arterial and cerebral venous CO\(_2\) partial pressure (P\(_{\text{CO}_2}\)) increased, any changes noted in CBF or cerebral metabolism by the therapeutic trials did not appear to be brought about by changes in blood pressure or P\(_{\text{CO}_2}\) of the blood. Inhalation of 100% oxygen in subjects with stroke decreased cerebral blood flow by 12% and minimally increased cerebral oxygen consumption. The statistically significant decrease of the cerebral metabolic rate for glucose by 21% during oxygen inhalation is of particular interest. This tends to confirm the state of cerebral anaerobic glycolysis in cerebrovascular disease which is reversed by inhalation of 100% oxygen, by the Pasteur effect, since more oxygen is made available to ischemic brain.\(^5\)\(^-\)\(^9\)

Inhalation of 5% carbon dioxide in air in subjects with cerebrovascular disease caused a significant increase of cerebral blood flow by 29%. This was not as great as the CBF increase of 75% noted during inhalation of 5% CO\(_2\) plus air in healthy subjects by Kety and Schmidt. \(^{22}\) This is to be expected because of the reduced cerebrovasodilator capacity in subjects with cerebrovascular disease. \(^{23}\) Cerebral oxygen and glucose metabolism increased, but this did not reach the level of statistical significance.

Inhalation of a mixture of 5% carbon dioxide plus 95% oxygen produced remarkable results since cerebral blood flow and oxygen consumption both showed a statistically significant increase. Furthermore, cerebral glucose consumption increased by 15%, although this did not reach the level of statistical significance. These data are believed to show rapid reversibility of the depression of cerebral oxygen metabolism in some forms of cerebral ischemia by therapy. Inhalation of 5% CO\(_2\) plus oxygen therefore appears to be a valuable form of therapy in cerebral vascular disease, and the improved cerebral oxygen consumption is believed to mean that increased cerebral blood flow and oxygen are effectively delivered to the ischemic tissue, since tissue with normal flow presumably has a normal metabolism which will not be increased by increasing flow, as shown by Kety and Schmidt. \(^{22}\) This question of whether cerebral vasodilators improve regional blood flow in the ischemic area has been hotly debated in the past. \(^{24}\) For example, it has been shown previously that cerebral blood flow and oxygen delivery were increased by large doses of papaverine over a 10-day period in subjects with occlusive cerebrovascular disease and that this was accompanied by clinical improvement. \(^{25}\) The fact that the increase in CBF was effective in regional areas of ischemia is believed to be established by the fact that the increase in cerebral blood flow produced by papaverine was accompanied by an increase of cerebral metabolic rate for oxygen. \(^{26}\)

Active hyperventilation in this group of subjects with cerebrovascular disease resulted in a reduction of cerebral blood flow by 25% which is not as great as the 38% reported in normal, healthy subjects by Kety and Schmidt \(^{27}\) and the 29% reported by McHenry and associates. \(^{28}\) Thus, in cerebrovascular disease, the capacity for vasoconstriction during hyperventilation is reduced as well as the capacity for vasodilation during inhalation of 5% CO\(_2\). Arterial oxygen content rose significantly while jugular oxygen content fell.
Cerebral metabolic rate for oxygen did not change. Arterial glucose values remained constant, but jugular glucose content fell rapidly and significantly during hyperventilation, hence cerebral arteriovenous difference for glucose also widened rapidly and significantly. This was due, in part, to the reduction of cerebral blood flow and possibly in part to increased anaerobic glycolysis. Cerebral metabolic rate for glucose increased by 14%, but this did not reach the statistically significant level. There was no correlation between EEG change and cerebral oxygen or glucose metabolism. These findings were in keeping with previous reports that EEG slowing during hyperventilation is due to a fall in tissue oxygen tension resulting from a combination of cerebral vasoconstrictive anoxia and the Bohr effect, whereby cerebral capillary pH becomes sufficiently alkaline to interfere with the oxyhemoglobin dissociation curve.29 Nevertheless, the rapid decreases shown in the continuous records of internal jugular glucose levels were remarkable and account for the predisposition to EEG slowing during hyperventilation in subjects with hypoglycemia, since hyperventilation in such cases would render the blood perfusing the brain more hypoglycemic as well as hypoxic, a situation that would tend to provoke EEG slowing more easily than when hypoxia occurs without hypoglycemia.

Nylidrin hydrochloride (Arlidin) is widely used as a peripheral vasodilator drug. It was evaluated as a possible cerebral vasodilator in subjects with cerebrovascular disease. Intravenous injection of 0.3 to 0.5 mg caused an acute decrease of mean arterial blood pressure in all cases. Cerebrovascular resistance decreased, but cerebral blood flow remained constant. This appears to confirm that autoregulation occurs in man and is still preserved as a phenomenon measureable by determinations of average blood flow despite the presence of regional cerebral vascular disease. Eisenberg10 reported a 43% increase of cerebral blood flow in subjects with cerebrovascular disease after oral administration of the drug for more than 2 weeks. In the present study, the drug was administered intravenously and resulted in a fall of blood pressure and no change in cerebral blood flow or cerebral oxygen and glucose consumption. Arterial and cerebral venous glucose content both increased, possibly due to the similarity of the chemical structure of this drug to epinephrine which might account for the apparent release of glucose from glycogen stores into the systemic circulation.

Some experimental evidence suggests that low molecular-weight dextran may improve cerebral blood flow in cerebral ischemia.31 Low molecular-weight dextran increased cerebral blood flow but not to the level of statistical significance; cerebral oxygen and glucose metabolism were also increased but not significantly. Possibly, if a larger volume had been infused over a longer interval of time, the changes might have reached the level of significance.

Cerebral blood flow and metabolism were measured before and after vertebral endarterectomy in a single patient with severe stenosis of the origins of both vertebral arteries, who had suffered three attacks of brain-stem ischemia with hemiparesis, ataxia, drowsiness, and depression of the respiratory center resulting in a central type of hyperventilation syndrome. The patient, a 49-year-old Negro male, had long-standing hypertension. Reconstruction of the left vertebral artery was proven to be successful by postoperative arteriography, and the patient made a complete neurological recovery with loss of the hemiparesis, ataxia, and drowsiness and return of normal pulmonary function. Cerebral blood flow and metabolism were measured immediately before, and 3 weeks after, surgery. Cerebral blood flow and oxygen consumption increased by more than 50% but were still below normal, and cerebral metabolic rate for glucose increased by more than 35% to normal values. The cerebral arteriovenous difference ratio for glucose-oxygen increased from 0.55 to 1.81. This pattern of metabolic change presumably indicates an increase of cerebral oxidative metabolism to higher levels but not to normal levels by amelioration of cerebral ischemia. Presumably, some ischemic hypoxia was also
substituted for anoxia since anaerobic glycolysis was also increased as evidenced by the disproportionately large increase in cerebral glucose consumption and in the ratio of cerebral arteriovenous glucose to oxygen.

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References


MONITORING CEREBRAL BLOOD FLOW

211


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JOHN S. MEYER, F. GOTOH, M. AKIYAMA and S. YOSHITAKE

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