Cerebral Oxygen, Glucose, Lactate, and Pyruvate Metabolism in Stroke

Therapeutic Considerations


SUMMARY

Cerebral blood flow, oxygen, glucose, lactate, and pyruvate metabolism were measured in 13 subjects with completed stroke. Cerebral blood flow and oxygen consumption were reduced, glucose consumption and pyruvate production were normal, and lactate production was increased, suggesting a shift from aerobic to anaerobic cerebral glycolysis.

To test this hypothesis, cerebral blood flow and oxygen delivery were decreased by hyperventilation and increased by inhalation of 5% CO₂ in air. Hyperventilation decreased cerebral oxygen consumption (CMRO₂) and increased cerebral lactate production. Inhalation of 5% CO₂ in air increased cerebral blood flow and oxygen delivery and increased both glucose and oxygen consumption. Relationships between reduction in PaCO₂ and cerebral venous PO₂ and increased cerebral lactate production were found.

Increasing cerebral blood flow by 5% CO₂ inhalation improved circulation and oxygen delivery to ischemic cerebral areas and improved oxygen and glucose metabolism in the majority of cases since these procedures do not alter CMRO₂ in normal persons. Intravenous injection of glucose increased cerebral glucose uptake but insulin did not.

Additional Indexing Words:

Stroke treatment Cerebral metabolism
Cerebral ischemia Cerebral anaerobic glycolysis
Five per cent CO₂ plus air Cerebral oxygen consumption
Cerebral glucose consumption Cerebral lactate production

In a previous study, it was adduced from indirect evidence that, in occlusive cerebrovascular disease, cerebral anaerobic glycolysis was increased. In the present study, measurements of cerebral lactate and pyruvate production were added in a series of patients with cerebrovascular disease to ascertain directly whether or not cerebral anaerobic glycolysis is increased in such cases by ischemic hypoxia. The question was tested further by increasing and decreasing cerebral blood flow by the use of carbon dioxide inhalation and hyperventilation to note whether either procedure would improve or enhance cerebral anaerobic glycolysis if present. The question is a practical one since it is relevant as to whether or not agents which dilate cerebral vessels (such as the inhalation of mixtures of carbon dioxide in air or the oral or intravenous administration of papaverine) are rational forms of treatment in occlusive cerebrovascular disease.

Some have questioned whether carbon dioxide or other cerebral vasodilator agents may divert blood from ischemic areas by lowering the cerebral vascular resistance in surrounding areas of normal brain. Others hold the opposite point of view and consider...
that increasing cerebral blood flow may enhance the blood flow to ischemic areas in some cases.\textsuperscript{2, 5, 7}

Shalit and associates\textsuperscript{3} measured the intraluminal pressure of a ligated middle cerebral artery in the dog during inhalation of carbon dioxide and concluded that, since the pressure decreased, collateral flow to the ischemic lesion was reduced. However, the reduction in pressure noted may indicate increased regional flow due to lowering of regional vascular resistance. Hyperventilation has even been suggested as possible therapy in cases of stroke with reactive hyperemia, in order to reduce the so-called "luxury perfusion syndrome."\textsuperscript{4}

The opposite view considers the possibility that carbon dioxide (or other effective vasodilator agents), by increasing blood flow, might improve delivery of oxygen and removal of acid waste products in areas of poor cerebral perfusion having depressed metabolism with regional functional paralysis rather than necrosis.

Although it has been reported that inhalation of carbon dioxide or intravenous administration of papaverine significantly increased average cerebral venous oxygen tension in subjects with cerebral vascular disease,\textsuperscript{5, 6} it has been questioned whether such increases necessarily improved regional cerebral metabolism in ischemic areas.\textsuperscript{7}

It appears logical that, if an increased cerebral blood flow and cerebral venous oxygen tension were induced in human subjects with cerebral vascular disease by cerebrovasodilator drugs and this was shown also to be associated with a \textit{measurable increase in average cerebral oxygen consumption}, then it could reasonably be assumed that areas of cerebral ischemia had been metabolically improved since there is no evidence in this or other laboratories that increasing cerebral blood flow to normal brain (even by 70\%) increased cerebral oxygen consumption.\textsuperscript{8-10}

Inhalation of 5\% carbon dioxide \textit{plus} oxygen has been reported to increase significantly cerebral oxygen consumption in subjects with occlusive cerebrovascular disease within 10 minutes of its institution,\textsuperscript{9} but improved cerebral oxygen consumption has not been reported for inhalation of 5\% carbon dioxide in air. The beneficial effect of 5\% CO\textsubscript{2} plus oxygen on cerebral oxygen consumption may have been due to the administration of oxygen rather than the carbon dioxide. Some evidence has been reported by Geraud and associates\textsuperscript{11} that an increase in cerebral blood flow produced by the administration of papaverine in subjects with stroke was accompanied by an increase of cerebral oxygen consumption.

The question is of theoretical as well as practical importance for if increasing cerebral blood flow in subjects with ischemic cerebrovascular disease rapidly increases cerebral oxygen consumption, this should provide insight into metabolic factors responsible for the appearance of symptoms and recovery from stroke.

The present investigation was designed to measure cerebral blood flow and metabolism in a sample of subjects with cerebrovascular disease and to compare them with reported values in normal subjects. The sample consisted of a group of subjects who had recovered from ischemic cerebrovascular symptoms. The group had the measurements made before, during, and after inhalation of 5\% CO\textsubscript{2} and hyperventilation. Measurements of cerebral pyruvate and lactate metabolism were recorded during these procedures. Details of the methods used for lactate monitoring are published elsewhere\textsuperscript{10} but lactate measurements are reproducible within 0.1 mg/100 ml.

The experimental design included measurements of cerebral blood flow and metabolism before and after the administration of intravenous glucose or insulin because these procedures might improve any deficient cerebral glucose consumption. Gottstein and co-workers\textsuperscript{12} have reported that insulin injected simultaneously with glucose increased cerebral glucose uptake in subjects with cerebral arteriosclerosis. In all measurements in which therapeutic procedures were assayed, the patient acted as his own control, measurements being made before, during, and after the experimental procedure. Since there were no
significant alterations in the control values before and after the hyperventilation and 5% carbon dioxide inhalation, the original steady-state values were used for purposes of calculation.

Case Material

Measurements were made in 13 volunteer patients,* all of whom had experienced one or more episodes of neurologic deficit due to occlusive cerebrovascular disease. At the time of study, complete recovery had occurred in some cases, while others had some residual neurologic deficit which had remained static for at least 6 weeks (table 1). The present series of cases were, therefore, clinically different from a previously reported series of patients who had suffered from acute stroke with more severe neurologic deficit and whose mean age was older.1

The age, sex, and diagnosis of the present series are listed in table 1. The diagnosis was based on arteriographic as well as clinical evidence, since complete aortocranial arteriography was performed in every case. Ten subjects had hypertension but none had serious cardiac or pulmonary disorder at the time of the measurements. The group consisted of seven male and six female subjects, with a mean age of 50.1 years.

Measurements consisted of cerebral blood flow and cerebral oxygen, and glucose, lactate, and pyruvate metabolism. After obtaining values in the steady state, these measurements were repeated during or after one or more of the following therapeutic trials: active hyperventilation, inhalation of 5% CO2 mixture in air, intravenous injection of 12.5 g of glucose as 25 ml of 50% glucose and injection of 10 units of regular insulin after glucose. A time interval of 20 to 30 minutes was allowed to elapse between the measurements and the steady-state values were repeated to verify that they had not greatly altered before the next therapeutic trial. To simplify the tables, only the mean values are given.

Thirty minutes prior to measurement, each subject was given an intramuscular injection of 50 mg of meperidine hydrochloride (Demerol) and 0.4 mg of atropine sulfate. Local anesthesia was induced by infiltration of the puncture sites with procaine hydrochloride. At the time of the measurements, the subjects were heparinized by intravenous injection of 100 mg of sodium heparin through the catheter immediately after it was inserted into the lateral sinus above the jugular bulb via a needle using the Seldinger technique and a catheter guide. Details of the procedure have been described in a previous communication.1

Methods

Average cerebral blood flow was measured by the automatic nitrous oxide method using infrared gas analyzers and the Fick principle.1 Values for cerebral blood flow (CBF) in ml/100 g brain/min were calculated from continuous recordings of the arterial and cerebral venous nitrous oxide differences in the desaturation phase. With use of this modification of the nitrous oxide method, cerebral blood flow is reproducible upon repeated examinations in the same individual at time intervals comparable to those used in the present series, with an average error of 4.8%. The CBF values by our modification of the method were not significantly different from simultaneous determinations with the method reported by Scheinberg and Stead.13

Arterial and cerebral venous PO2, PCO2, and pH were monitored with special electrodes mounted in flow-through cuvettes. Oxygen saturation was monitored by reflection oximeters calibrated by the manometric method of Van Slyke and Neill. Arterial and cerebral venous oxygen contents were calculated from recorded oxygen saturation, capacity, and dissolved oxygen measure as the PO2.14 Cerebral oxygen consumption in ml/100 g brain/min was derived from the product of CBF and mean cerebral arteriovenous oxygen difference ([A-V]O2), which was determined from the mean of minute-to-minute values during measurement of CBF, that is, 10 minutes. The same procedure was applied to calculate mean values of all other metabolic variables during each CBF determination. Continuous records give greater accuracy than conventional sampling methods since all parameters were not necessarily constant throughout the determination of CBF, considerable respiratory fluctuations regularly occurring in arterial PO2, PCO2, pH, and oxygen saturation values, although glucose, lactate, and pyruvate values were more stable.

Arterial and cerebral venous glucose concentrations were measured continuously by two Technicon auto-analyzers and a colorimetric reduction method for glucose, with potassium ferricyanide as the indicator.1 Cerebral glucose: oxygen utilization ratio (G/O) was derived as the ratio

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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. A written form giving permission for the procedure was signed by the patient in the presence of a witness.
### Table 1

**Cerebral Blood Flow and Metabolism after Recovery from Symptoms of Stroke**

| No.* | Age | Sex | Clinico-arteriographic diagnosis | CBF | MABP | CVR | PaCO₂ | CVO₂ | (A-V)O₂ | CMRO₂ | (A-V)G1 | CMRG1 | G/O | (V-A) Lact | CMR Lact | (V-A) Pyruvate | CMR Pyruvate |
|------|-----|-----|---------------------------------|-----|------|-----|-------|------|---------|--------|--------|--------|------|-------|---------|-----------|---------------|---------------|
| 1    | 71  | M   | Bil-ICA and R-VA stenosis, parietal infarct, hypertension | 45.7 | 102  | 2.28 | 42.0  | 25.0 | 4.81   | 2.20   | 11.2   | 5.11   | 2.33 | 1.60 | 0.73     | —         | —              | —              |
| 2    | 57  | F   | Bil-VA stenosis brain-stem infarct, hypertension | 47.8 | 126  | 2.64 | 41.8  | 30.0 | 6.81   | 3.26   | 8.1    | 3.87   | 1.19 | 0.41 | 0.20     | —         | —              | —              |
| 3    | 52  | F   | L-MCA occlusion, L-ICA stenosis, R. hemiparesis, hypertension | 46.3 | 100  | 2.16 | 38.9  | 32.5 | 3.32   | 1.54   | 5.5    | 2.54   | 1.65 | 0.57 | 0.26     | —         | —              | —              |
| 4    | 55  | M   | Diffuse cerebral arteriosclerosis TIA, hypertension | 40.1 | 128  | 3.15 | 37.0  | 27.7 | 7.05   | 2.83   | 7.3    | 2.93   | 1.04 | 1.43 | 0.57     | —         | —              | —              |
| 5    | 48  | F   | Bil-VA stenosis, TIA, hypertension | 46.1 | 100  | 2.18 | 32.0  | 28.3 | 5.71   | 2.63   | 15.2   | 7.01   | 2.67 | 0.63 | 0.29     | —         | —              | —              |
| 6    | 56  | F   | L-MCA occlusion, R. hemiparesis, hypertension | 57.0 | 105  | 1.84 | 33.0  | 27.0 | 5.26   | 3.00   | 8.2    | 4.67   | 1.56 | 1.65 | 0.94     | —         | —              | —              |
| 7    | 49  | M   | V-B insufficiency, TIA, hypertension | 59.7 | 90   | 1.51 | —     | 30.5 | 5.44   | 3.25   | 16.8   | 10.03  | 3.09 | 2.03 | 1.21     | 0.135     | 0.081         | —              |
| 8    | 58  | M   | L-ICA and L-VA stenosis, L. cerebral infarct, hypertension | 29.3 | 141  | 4.81 | 35.2  | 29.9 | 0.67   | 2.83   | 13.2   | 3.67   | 1.37 | 1.70 | 0.50     | 0.015     | 0.004         | —              |
| 9    | 52  | F   | L-ICA, TIA, post L. carotid endarterectomy | 41.8 | 111  | 2.66 | 39.1  | 26.3 | 4.55   | 1.90   | 9.0    | 3.76   | 1.98 | 1.00 | 0.42     | 0.023     | 0.010         | —              |
| 10   | 40  | F   | L-MCA occlusion, hemiparesis, L-ICA stenosis | 28.8 | 107  | 3.72 | 28.3  | 24.4 | 7.06   | 2.03   | 11.8   | 3.40   | 1.67 | 1.48 | 0.43     | 0.155     | 0.045         | —              |
| 11   | 60  | M   | L-cerebral infarct, L-VA stenosis, hypertension | 55.0 | 123  | 2.25 | —     | 36.0 | 4.93   | 2.71   | 10.2   | 5.63   | 2.08 | 1.84 | 1.01     | 0.028     | 0.015         | —              |
| 12   | 16  | M   | L-MCA hemiparesis (dissecting aneurysm) | 54.4 | 77   | 1.42 | 36.7  | 35.5 | 4.36   | 2.37   | 12.2   | 6.60   | 1.84 | 4.79 | 2.61     | 0.122     | 0.066         | —              |
| 13   | 44  | M   | Bil-MCA occlusion, quadriparesis, hypertension | 33.0 | 126  | 3.82 | 36.3  | 35.0 | 6.31   | 2.08   | 9.8    | 3.24   | 1.56 | 0.78 | 0.26     | —         | —              | —              |
| 14   | 41  | M   | Bil-MCA occlusion, quadriparesis, hypertension | 41.5 | 117  | 2.82 | 36.3  | 27.2 | 6.82   | 2.83   | 15.5   | 6.45   | 2.28 | 0.57 | 0.11     | 0.343     | 0.142         | —              |
|      | 50.1|     | Mean ± SD | 45.8 | 111.3| 2.69 | 36.1  | 29.7 | 6.16   | 2.76   | 11.2   | 5.21   | 1.87 | 1.45 | 0.69     | 0.118     | 0.055         | —              |

*In cases 5, 7, 8, 11, 13 therapeutic trials were repeated at intervals of 1-2 weeks.

Abbreviations: Bil = bilateral; R = right; L = left; ICA = internal carotid artery; VA = vertebral artery; MCA = middle cerebral artery; TIA = transient ischemic attacks; SD = standard deviation; CBF = cerebral blood flow; MABP = mean arterial blood pressure; CVR = cerebrovascular resistance; PaCO₂ = arterial carbon dioxide tension; CVO₂ = cerebral venous oxygen tension; (A-V)O₂ = arteriovenous oxygen difference; CMRO₂ = cerebral oxygen consumption; (A-V)G1 = arteriovenous glucose difference; CMRG1 = cerebral glucose consumption; G/O = glucose: oxygen ratio; (V-A) Lact = venous-arterial lactate difference; CMR Lact = cerebral lactate production; (V-A) Pyruvate = venous-arterial pyruvate difference; CMR Pyruvate = cerebral pyruvate production.
of cerebral arteriovenous glucose difference to that of oxygen, that is, \((A-V)\, GI/(A-V)/O_2\).

Contents of arterial and cerebral venous lactate were measured by the enzymatic method of Hochella and Weinhouse\textsuperscript{15} with modifications for continuous recording.\textsuperscript{10} Cerebral lactate production (CMR Lact) in mg/100 g brain/min was calculated as the product of CBF and mean cerebral venoarterial lactate difference \([IV-A]_{\text{Lact}}\).

Arterial and cerebral venous pyruvate levels were measured continuously by a modification of the enzymatic method of Segal and associates.\textsuperscript{16} This modification for continuous blood analysis with the use of two Technicon autoanalyzers and fluorometers will now be described for the first time. The apparatus was similar to that used for lactic acid measurements\textsuperscript{10} except that oxidation of DPNH, which is proportional to pyruvic acid present in the blood, was measured with a fluorometer.\textsuperscript{*}

The sample line of one Technicon system was connected to the internal jugular catheter and the other to the arterial catheter. The blood was propelled through the sample lines by a peristaltic proportioning pump at 0.23 ml/min. The blood was proportioned automatically, each proportion separated by an air bubble and mixed with phosphate buffer (pH 7.40) added at 1.60 ml/min.

Pyruvic acid was dialyzed from the blood through a thin cellophane membrane into phosphate buffer (pH 7.40), pumped through a reaction line, and mixed with an enzyme solution containing DPNH, lactic dehydrogenase of rabbit muscle, and 10% Triton X-100 solution (the latter was added at the same flow rate of 0.10 ml/min). Triton X-100 is a colloidal solution which was added to make the mixture homogeneous and to prevent precipitation.

The mixture was propelled into the heating bath (37 C) and the pyruvic acid was reduced to lactic acid by the coupling of DPNH to DPN in the presence of lactic dehydrogenase. The flow rate in the reaction line was constant, so that each sample was incubated for 9 minutes and 40 seconds. Hence, the amount of DPNH oxidized and recorded by the fluorometer at a wave-length of 366 m\textmu was proportional to the levels of blood pyruvate.

The time delay from sampling to recording was 16.5 minutes, and the response time from the base line to the level of a known standard solution was 40 seconds. Blood pyruvate con-

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
& \textbf{CBF} & \textbf{MABP} \\
\hline
\textbf{CMR} & \textbf{CyR} & \textbf{CMR} & \textbf{CyR} & \textbf{CMR} & \textbf{CyR} & \textbf{CMR} & \textbf{CyR} & \textbf{CMR} & \textbf{CyR} \\
\hline
\textbf{Gibbs et al.\textsuperscript{14}} (N = 50) & \textbf{54} ± 12 & \textbf{86} ± 7 & \textbf{86} ± 7 & \textbf{86} ± 7 & \textbf{86} ± 7 & \textbf{86} ± 7 & \textbf{86} ± 7 & \textbf{86} ± 7 & \textbf{86} ± 7 \\
\textbf{Kety et al.\textsuperscript{13} (N = 14) } & \textbf{64.7} ± 6.1 & \textbf{55} ± 6.1 & \textbf{64.7} ± 6.1 & \textbf{55} ± 6.1 & \textbf{64.7} ± 6.1 & \textbf{55} ± 6.1 & \textbf{64.7} ± 6.1 & \textbf{55} ± 6.1 & \textbf{64.7} ± 6.1 \\
\textbf{Scheinberg et al.\textsuperscript{13} (N = 29-32) } & \textbf{64.7} ± 6.1 & \textbf{55} ± 6.1 & \textbf{64.7} ± 6.1 & \textbf{55} ± 6.1 & \textbf{64.7} ± 6.1 & \textbf{55} ± 6.1 & \textbf{64.7} ± 6.1 & \textbf{55} ± 6.1 & \textbf{64.7} ± 6.1 \\
\textbf{Gaffney et al.\textsuperscript{13} (N = 32-59) } & \textbf{64.7} ± 6.1 & \textbf{55} ± 6.1 & \textbf{64.7} ± 6.1 & \textbf{55} ± 6.1 & \textbf{64.7} ± 6.1 & \textbf{55} ± 6.1 & \textbf{64.7} ± 6.1 & \textbf{55} ± 6.1 & \textbf{64.7} ± 6.1 \\
\hline
\end{tabular}
\caption{Reported Values for CBF and Metabolism in Normal Subjects}
\end{table}

centrations were reproducible within 0.015 mg/100 ml in the physiological range. Cerebral pyruvate production (CMR Pyr) in mg/100 g brain/min was calculated from the product of CBF and mean cerebral venoarterial pyruvate difference ([V-A]Pyr).

Blood pressure was recorded with a Statham pressure transducer. Mean arterial blood pressure (MABP) was calculated as diastolic pressure plus one-third pulse pressure. Cerebrovascular resistance (CVR) was derived in mm Hg/ml/100 g brain/min by dividing MABP by CBF. An eight-lead electroencephalogram (EEG) and end-tidal CO$_2$ tension ($P_e$CO$_2$) were also recorded. Comparison before and after each procedure was made by standard statistical tests (t-tests). Any difference having a risk of error of less than 5% ($P < 0.05$) was considered significant.

**Results**

**Values for Cerebral Blood Flow and Metabolism after Recovery from Stroke**

Values for cerebral blood flow and metabolism in the steady state are summarized in table 1. They were compared to normal values reported by several authors which are summarized in table 2, the values cited being limited to determinations by comparable methods. Eighteen measurements were made in the 13 subjects. It will be noted that cerebral blood flow and oxygen consumption were reduced but not so much as in a sample of the stroke population with more severe and acute neurologic deficit and of older age.$^1$

Mean arterial blood pressure was considerably higher in these patients than in normal subjects, and cerebral vascular resistance was increased. Cerebral glucose consumption and pyruvate production were within normal limits. Mean cerebral lactate production and the glucose:oxygen utilization ratio were higher than normal. Other values not tabulated in table 1 were as follows: Mean arterial pH (apH) and cerebral venous pH (CvPH) were 7.368 ± 0.048 and 7.347 ± 0.062, respectively. Mean arterial glucose (aGl) and cerebral venous glucose (CVGI) were 104.3 ± 13.2 and 93.1 ± 12.7 mg/100 ml, respectively. Mean arterial lactate (aLact) and pyruvate (aPyr) were 7.82 ± 2.03 and 0.475 ± 0.198 mg/100 ml, respectively, and those of cerebral venous blood were 8.66 ± 2.51 and 0.579 ± 0.239 mg/100 ml, respectively.

**Effect of Hyperventilation on Cerebral Anaerobic Glycolysis**

The effects of active hyperventilation for 10 minutes are summarized in table 3. Only statistically significant results will be mentioned here. Accompanying the well-known decrease in arterial carbon dioxide tension and increase in apH, there was an increase in cerebral vascular resistance, a decrease in CBF, and a decrease in cerebral venous oxygen tension (CVPO$_2$). Cerebral arteriovenous oxygen and glucose difference widened, and there was a small but significant reduction in cerebral oxygen consumption.

During hyperventilation, both arterial and cerebral venous lactate increased but cerebral venous lactate increased far more than arterial lactate. This change was due to both a decrease in CBF and an increase of cerebral lactate production.

Figure 1 is a graph plotting mean changes for CMR Lact against changes in CVPO$_2$. 

**MEAN VALUES FOR CMR-LACTATE PLOTTED AGAINST CVPO$_2$ IN CEREBRAL VASCULAR DISEASE**

![Figure 1](http://circ.ahajournals.org/)

In this graph, corresponding values for CMR Lactate were plotted against the values for CVPO$_2$ after placing them in groups below 20 mm Hg, between 20 and 25, between 25 and 30, between 30 and 35, and between 35 and 40 mm Hg. Note that as the CVPO$_2$ fell below 25 mm Hg during hyperventilation, CMR Lactate increased to a remarkable degree. The values were plotted from data obtained in the steady state, during hyperventilation, and during 5% CO$_2$ breathing.
during hyperventilation and 5% CO₂ breathing. Figure 2 is a graph showing changes in CMR Lact plotted against changes in PaCO₂ during hyperventilation and 5% CO₂ breathing. Cerebral lactate production increased in every case during hyperventilation; this correlated with decreases in PaCO₂, a mirror image increase of apH, and a decrease of CVPO₂. There was no correlation of CMR Lact with changes in cerebral venous pH. Cerebral pyruvate production showed no change during hyperventilation or 5% CO₂ inhalation. Increases of CMR Lact occurred when PaCO₂ and CVPO₂ decreased below 25 mm Hg.

**Effect of Inhalation of Five Per Cent Carbon Dioxide in Air on Cerebral Metabolism**

The effects of inhalation of a gas mixture containing 5% CO₂ in air are summarized in table 4. Cerebral vascular resistance decreased while CBF and CVPO₂ increased.

Cerebral oxygen consumption increased, but the increase in CMRO₂ was noted only in cases with a CBF of more than 40 ml/100 g
brain/min. In cases 8 and 13, both with a CBF lower than 40 ml/100 g brain/min and clinical signs of more advanced disease, CMRO\textsubscript{2} slightly decreased during CO\textsubscript{2} breathing. For the entire group, cerebral glucose consumption also increased significantly and was noted in every case except case 8, the patient with the lowest cerebral blood flow of the group.

**Effects of Intravenous Injection of Glucose or Insulin**

A bolus of 25 ml of 50% glucose (12.5 g) was injected intravenously over a 5-minute interval and 10 minutes prior to repetition of the measurements. The results are summarized in table 5. Since each measurement of CBF took 10 minutes, values for all metabolic parameters were calculated from the mean of minute-to-minute values obtained between the tenth and twentieth minutes after injection.

Both the arterial and cerebral venous glucose levels increased remarkably but the arterial levels were consistently larger than
glucose:oxygen utilization ratio. Arterial lactate and pyruvate levels increased.

Ten units of regular insulin were injected intravenously 20 minutes after the glucose injection, and measurements of cerebral blood flow and metabolism were repeated. Arterial glucose levels decreased, but arterial pyruvate and lactate levels increased; there was no change in cerebral lactate or pyruvate production.

In order to correlate levels of arterial glucose with cerebral glucose uptake, data before and after injection of glucose and insulin were divided into four groups according to the levels of arterial glucose (fig. 3). The cerebral glucose uptake significantly increased when the arterial glucose was raised to 150 mg/100 ml from levels of 100 mg/100 ml or below.

**Discussion**

**Correlation of Deficit of Cerebral Blood Flow and Metabolism with Clinical Status**

In the group of patients studied, the diagnosis of complete recovery or improved and stable neurological deficit resulting from cerebrovascular disease was based on detailed history, physical examination, and laboratory tests, including examination of the cerebrospinal fluid and complete aortocranial arteriography. Every patient but one appeared to have suffered from atherosclerotic occlusion, stenosis, or embolism of the cerebral vessels on the basis of this evaluation and follow-up examination in the clinic over the past 6 months. The single exception, case 12, suffered thrombosis of the left middle cerebral artery from a dissecting aneurysm of that vessel following head trauma.

Mean CBF and oxygen consumption for the 13 subjects were below normal but not so much as in similar measurements reported in 22 older subjects with more advanced disease as judged by arteriography and neurological evaluation. The mean value for cerebral glucose consumption (CMRGl) in the present study was found to be within the normal range, while in the previously reported group mentioned above, the cerebral glucose consumption was also reduced. The cerebral glucose uptake increased without any change in CMRO2 but with an increase of the cerebral venous levels. Cerebral glucose uptake increased with the steady state and pyruvate levels increased.
blood flow and metabolic disturbance appear, therefore, to correlate with the severity of the stroke as judged by the criteria named.

**Evidence for Cerebral Anaerobic Glycolysis**

The mean value for cerebral glucose:oxygen utilization ratio (G/O) in the present group was 1.87 ± 0.65, which is higher than reported normal values and higher than reported in two previous series of cases with advanced arteriosclerotic cerebrovascular disease.1,18

The mean values for cerebral veno-arterial lactate differences in the present series with occlusive cerebral vascular disease was 1.45 ± 0.92 mg/100 ml, and the mean value for CMR Lact was 0.69 ± 0.55 mg/100 g brain/min. Reported values for normal cerebral (V-A) Lact levels have varied according to the method used for their measurement. Gibbs and associates17 reported a mean value of 1.6 mg/100 ml in 50 normal young subjects by the method of Edwards. Scheinberg and co-workers21 found it to be 0.009 mM/liter, or about 0.008 mg/100 ml, in 25 normal subjects by a paper chromatographic method, but since this difference was not significant, they concluded that lactate was not added to the cerebral venous blood.

Using recently developed enzymatic methods similar to those used in the present study, Gottstein and associates22 gave 0.8 mg/100 ml as the mean value for (V-A) Lact and 0.42 mg/100 g brain/min as the mean value for cerebral lactate production in 45 normal subjects. It is not surprising that the normal brain should produce lactate since values reported for the cerebral glucose:oxygen utilization ratio in normal subjects exceed the theoretically calculated value of 1.34. This suggests that even in normal subjects some cerebral anaerobic metabolism occurs.1,12

Gurdjian and associates20 suggested 20 years ago that ionized lactate may pass slowly through the blood-brain barrier, since their experimental measurements indicated that cerebral venous lactate was not exactly proportional to concentrations measured in the brain. In the present study cerebral venous lactate increased during hyperventilation, indicating that in these subjects at least lactate passed the blood-brain barrier. Alexander and associates23 reported a similar rapid release of lactate in the cerebral venous blood as the PaCO2 was reduced by passive hyperventilation during anesthesia in subjects without cerebrovascular disease and have reviewed the evidence for and against the passage of lactate and pyruvate across the blood-brain barrier.

It appears that in man lactate does pass the blood-brain barrier since many laboratories have found cerebral venous lactate to be higher than arterial, as was found in the present series of subjects. In the present group of subjects with completed stroke, cerebral venous lactate was considerably higher than that of arterial blood, the (V-A) Lact difference being larger than that reported by Gottstein and associates22 for normal subjects. This suggests that in cerebrovascular disease, cerebral lactate production is increased because of increased cerebral anaerobic glycolysis, with a greater release of lactate into cerebral venous blood.

Increased cerebral lactate production, together with decreased CMRO2, normal CMR glucose, and increased cerebral glucose:oxygen utilization ratio, presents a metabolic pattern considered typical of increased anaerobic glycolysis. If this pattern were due to increased anaerobic glycolysis, cerebral pyruvate production should be unchanged,23 which it was. The question could be raised whether differences in the blood-brain barrier for the passage of lactate versus pyruvate might account for this. Since lactate and pyruvate molecules are similar, it would seem highly unlikely that lactate would pass the blood-brain barrier while pyruvate would not; furthermore, cerebral venous pyruvate levels in the steady state are higher than arterial values, indicating some passage of pyruvate across the blood-brain barrier.

The mean values for cerebral veno-arterial pyruvate difference and cerebral pyruvate production in seven subjects in the present series of cases were within normal limits according to the values reported by Gottstein and co-workers22 using the same enzymatic method.
The fact that cerebral lactate production was increased further by hyperventilation in the present series without any change in cerebral pyruvate production tends to confirm the view that anaerobic glycolysis was increased and the increase of lactate production was not due to a total increase in cerebral glycolysis.23-25

Numerous authors have reported that the decrease in CBF caused by hyperventilation did not measurably reduce CMRO2 of normal brain,8, 9, 10, 26 nor, in cases having more advanced cerebral vascular disease, more severe neurologic deficit,1 more present consumption remains under the critical level of 1046 mm Hg, the reduction of cerebral blood flow plus oxygen consumption, and in this type cerebral glucose consumption is reduced also.1 In the second type, it seems likely that irreversible cerebral infarction has occurred. In the first type, cerebral ischemia results in anaerobic glycolysis, which may remain reversible.

The present study was concerned primarily with cases of the first type which were selected because of good restoration of collateral circulation as demonstrated arteriographically. Apparently such restoration of circulation to ischemic areas tenuously maintains oxygen demand of the brain tissue but further reduction of cerebral blood flow by hyperventilation depresses CMRO2 further. On the other hand, increasing the CBF by inhalation of 5% CO2 temporarily increases CMRO2. In cases of the second type the brain appears to be irreversibly infarcted and is unable to respond metabolically to either increases or decreases of the cerebral circulation.1, 27

Inhalation of 5% CO2 in air in the present group of patients demonstrated that the metabolic defect in cerebral metabolism was rapidly reversible, although such metabolic improvement promptly regressed as soon as 5% CO2 inhalation was discontinued. In the present study, no attempt to correlate such metabolic improvement with clinical changes was made.

**Considerations of Special Effects of 5% CO2 Inhalation on Cerebral Metabolism**

It will be noted from tables 3 and 4 that occlusive cerebrovascular disease reduced both the capacity for vasodilatation during inhalation of CO2 and vasoconstriction during hyperventilation. During inhalation of 5% CO2 in air, cerebral oxygen metabolism was increased in eight measurements with six subjects, but decreased in two cases. Despite these two exceptional cases, the increase for the group was statistically significant. The two cases in which CMRO2 was decreased had markedly reduced CBF (both below 40 ml/100 g brain/min) and had the most advanced disease as judged by arteriographic and clinical evaluation. The increase in CBF during inhalation of CO2 in these cases was
minimal. It is admitted that the decrease in CMRO₂ in these two cases might be due to stealing blood away from the ischemic area or due to induction of acidosis within the ischemic regions. From a therapeutic view, if inhalation of 5% CO₂ were limited to 15 minutes of every hour, any danger from such minimal depression of CMRO₂ would seem to be negligible. During inhalation of the 5% CO₂ mixture, CMRGl was also significantly increased in every case except one.

Effects of Glucose and Insulin on Ischemic Cerebral Metabolism

Glucose is well known to be the most important substrate utilized by the brain for its energy metabolism³⁰ and appears to pass more rapidly through the brain-blood barrier than other substances such as fructose and glycerol whose molecular weight is similar to glucose.³²⁻³⁵ Some have claimed that insulin facilitates the cerebral uptake of glucose.¹²

In the present study, measurements of cerebral blood flow and metabolism were made in five cases with occlusive cerebrovascular disease before and after intravenous injection of 12.5 g of glucose. The only significant changes were an increase in cerebral glucose uptake after glucose injection with an increase in the ratio of glucose to oxygen utilization (table 5). Both arterial lactate and pyruvate increased ($P < 0.05$), but there was no change in CMR Lact and CMR Pyr.

The amount of glucose taken up by the brain appeared to increase as arterial glucose levels rose. It was not thought that the amount of glucose consumed by the brain was increased since CMRO₂ and CMR Lact did not increase following the injection of glucose. It seems likely that glucose was taken up by the brain in the form of storage, as has been previously considered, from indirect measurements during hypoglycemic coma in man.³⁶ Another possibility is that the glucose entered the cerebrospinal fluid as well as the brain.

References


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Therapeutic Considerations

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