Cerebral Blood Flow and Metabolism in Man Following Cardiac Arrest

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Joe Lee, M.D., F.R.C.P.(C), and W. L. MacKeen, R.R.T.

SUMMARY We measured cerebral oxygen extraction, cerebral blood flow (CBF), and cerebral metabolic rate (CMRO₂) in comatose patients during the first 60 hours after resuscitation from cardiac arrest. Each patient was studied 2 or 3 times. CBF was determined by a modification of the Kety-Schmidt method using inhaled Xenon⁰¹³. Over the study period jugular venous oxygen tension and saturation rose, while the oxygen content difference between arterial and jugular venous blood fell, indicating a progressive increase in the ratio of CBF to metabolism. CBF and CMRO₂ measurements confirmed this. Between 2 and 6 hours after resuscitation both measurements were severely but proportionately depressed to less than 50% of normal. After 6 hours CBF was increased disproportionately to CMRO₂, so that a relative hyperemia developed and persisted for the duration of the study.

Although regional inhomogeneity of flow and regional ischemia cannot be ruled out, we have found no evidence for global cerebral ischemia between 2 and 60 hours post-resuscitation as an explanation for failure of recovery.

In man following cardiac arrest restoration of levels of global cerebral blood flow, which can be considered adequate relative to the depressed metabolic state of the tissue, is achieved within 2 hours of resuscitation.

ANIMAL STUDIES suggest that recovery of neuronal function after severe ischemic-anoxia may be impaired by either early or delayed failure of cerebral tissue perfusion.¹⁻³ Although the evidence that this occurs in man is lacking, there is speculation that recirculation to the brain may be impaired after total cerebral ischemia, contributing to failure of neuronal recovery. We have investigated this question by measuring cerebral oxygen extraction, cerebral blood flow (CBF), and cerebral and metabolic rate for oxygen (CMRO₂) in patients during the first 60 hours after resuscitation from cardiac arrest.

References

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Methods

Patients were selected for study after successful resuscitation from unexpected cardiac arrest. The average age was 69 years and the male preponderance was 3 to 1. We did not study patients who exhibited no evidence of recovery of brain function (as determined by isoelectric electroencephalogram and absent cranial nerve reflexes), or patients who rapidly recovered consciousness after resuscitation. All patients in this study within the first few hours after resuscitation recovered vegetative and brain stem function, such as spontaneous respiration, cranial nerve reflexes, and other aspects of vegetative behavior. Cortical function, however, remained depressed in all and no patient was awake at the time of study. After the first few hours no consistent pattern of further neurologic improvement was evident over the duration of the study. It was, therefore, a select group with an estimated poor prognosis, and, as expected, eventual outcome was poor with 80 percent mortality. Death resulted from cardiac complications, or the pulmonary complications associated with protracted unconsciousness in the aged. Four patients eventually recovered consciousness and were discharged from hospital.

Immediate treatment in the intensive care unit consisted of mechanical ventilation to maintain Pco 2 in the normal range and PO 2 above 70 torr. Arrhythmias, congestive heart failure and metabolic acidosis were treated and the continuously monitored arterial blood pressure was maintained within normal limits for the patient’s age.

As soon as cardiovascular stability was assured, an internal jugular venous catheter was inserted cephalad and checked radiographically to determine its position at the base of the skull. A Teflon catheter was also placed in a femoral artery.

Twenty-five patients fulfilling the above criteria were included in the study. Arterial and internal jugular venous blood were sampled anaerobically on 2 or 3 occasions for blood gas analyses. Studies were spaced so as to form groups corresponding to the time intervals 2–6 hours, 6–24 hours, and 24–60 hours after resuscitation. Cerebral oxygen extraction was estimated by measuring oxygen tension (PO 2) in duplicate in the 2 samples in a Corning 116 blood gas analyzer and calculating saturation (SO 2), oxygen content, and arterial-jugular venous oxygen content difference (C(a-jv)DO 2). The calculation of SO 2 from PO 2 is based upon the assumption of a normal oxyhemoglobin dissociation curve corrected for variation in Pco 2, pH, and patient temperature.

In each of 14 patients cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMRO 2) were also determined 2 or 3 times and similarly grouped. A modification of the Kety-Schmidt method was used to measure CBF. The patient was ventilated with oxygen from a modified closed circuit anesthesia machine with an 8 liter reservoir bag. Carbon dioxide was removed by a soda lime cannister and O 2 added to maintain constant volume in the circuit. Five mCi of Xenon was added to the reservoir and controlled ventilation was continued for 20–30 minutes to achieve tissue equilibrium. After switching to open circuit ventilation, 10 paired femoral arterial and internal jugular blood samples were drawn in plastic syringes at timed intervals over a 15 minute washout period. The sample syringes were immediately capped and Xenon activity was counted in an Ortec 300 gamma well counter. Arterial and jugular venous washout curves for Xenon were plotted and CBF calculated by the height over area method. CMRO 2 was then calculated as the product of CBF and (a-jv)O 2 content difference:

\[
\text{CMRO}_2 = \frac{\text{CBF}}{100} \times \text{C(a-jv)DO}_2
\]

Results

Data from 56 paired arterial and internal jugular venous blood samples from 25 patients are shown in Table 1 and figure 1. While there were no changes in arterial Pco 2, and arterial oxygen saturation was near 100% in all groups, jugular venous PO 2 and oxygen saturation rose so that the a-jv oxygen content difference fell progressively over the period of measurement. This is indicative of a progressive increase in the ratio of CBF to metabolism.

CBF and CMRO 2 data obtained from 30 studies in 14 patients are shown in Table 2 and figure 2. From 2 to 6 hours after cardiac resuscitation both CBF and CMRO 2 were severely and proportionately reduced to less than 50% of normal. In a few cases the a-jv oxygen content difference was widened and jugular venous PO 2 was lower than normal, but in the group as a whole there was no evidence of impairment of CBF relative to brain metabolism at this time, both being equally depressed. After 6 hours CBF was increased disproportionately to CMRO 2 so that a relative hyperemia developed and persisted for the duration of the study. CBF at 24–60 hours exceeded normal values while CMRO 2 was still reduced to about 70% of normal. Thus, the calculated ratio of CBF to CMRO 2 increased above normal, suggesting an uncoupling of the normal metabolic regulation of CBF with a relative hyperemia or “luxury perfusion.”

### Table 1 Serial Analysis of Arterial and Internal Jugular Venous Blood Gases after Resuscitation from Cardiac Arrest

<table>
<thead>
<tr>
<th></th>
<th>2-6 hr.</th>
<th>6-24 hr.</th>
<th>24-60 hr.</th>
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<tbody>
<tr>
<td>PaCO 2</td>
<td>35.5 ± 6.1</td>
<td>35.4 ± 5.7</td>
<td>33.9 ± 6.0</td>
</tr>
<tr>
<td>PjvO 2</td>
<td>35.8 ± 6.6</td>
<td>41.4 ± 8.1</td>
<td>46.2 ± 8.6</td>
</tr>
<tr>
<td>SjvO 2</td>
<td>97.9 ± 1.7</td>
<td>98.4 ± 1.3</td>
<td>98.2 ± 2.1</td>
</tr>
<tr>
<td>C(a-jv)DO 2</td>
<td>65.3 ± 8.2</td>
<td>75.0 ± 9.9</td>
<td>80.1 ± 8.4</td>
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Statistical analysis by analysis of variance for independent samples.
**TABLE 2**  Cerebral Blood Flow and Metabolism During the First 60 Hours after Resuscitation From Cardiac Arrest

<table>
<thead>
<tr>
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<th>2-6 hrs.</th>
<th>6-24 hrs.</th>
<th>24-60 hrs.</th>
<th>P</th>
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<tbody>
<tr>
<td>PaCO₂</td>
<td>38.6 ± 5.2</td>
<td>38.5 ± 5.2</td>
<td>38.1 ± 5.6</td>
<td>NS</td>
</tr>
<tr>
<td>CBF</td>
<td>22.9 ± 6.3</td>
<td>45.9 ± 19.1</td>
<td>68.8 ± 23.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CMRO₂</td>
<td>1.62 ± 0.43</td>
<td>1.96 ± 0.56</td>
<td>2.40 ± 0.50</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>CBF/CMRO₂</td>
<td>14.2 ± 1.9</td>
<td>25.5 ± 9.7</td>
<td>30.2 ± 11.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

± 8D ( ) SEM  Statistical analysis by analysis of variance for independent samples.

**Discussion**

The mechanisms of irreversible anoxic-ischemic neuronal damage are not yet resolved. Experimental studies in animals suggest that portions of the brain may remain ischemic after resuscitation from total circulatory arrest, or that delayed ischemia may develop during the following hours. This has led to the hypothesis that failure to recover cerebral
neuronal function after total circulatory arrest may be due, at least in part, to failure of restoration or preservation of brain tissue blood flow. Although the experimental observations have been well documented, the experimental models are somewhat artificial, not confirmed by all studies, and it is not yet clear whether these observations represent an experimental curiosity or a true clinical entity. The appropriate studies of cerebral blood flow and metabolism in man during the early hours following resuscitation from circulatory arrest have not been published.

Brodersen (1974) has measured CBF and metabolism in the period from 1 to 12 days in comatose patients after cardiac arrest. Though the majority displayed a relative hyperemia, CBF was variable and generally varied in parallel with the cerebral oxygen consumption. There were too few studies in the early hours to compare to our data.

Our studies show severe and proportional depression of both CBF and CMRO2 in the earliest time interval, 2 to 6 hours postarrest, suggesting that a metabolic regulation of CBF is preserved.

There was no evidence indicating pathologic impairment of CBF in this time period. Further evidence supporting the conclusion that CBF, though reduced, is sufficient for the metabolic restoration of energy metabolism in brain tissue comes from a previous study (Kalin, et al., 1975) showing that acid-base balance and electrolyte composition in cisternal CSF became normal within 2 hours of resuscitation.

From 6 to 60 hours CBF is dissociated from metabolic control, and a relative hyperemia or "luxury perfusion" is evident. There is, therefore, no support for a "delayed ischemia" hypothesis in these studies. We recognize, however, that the method measures global CBF and areas of inhomogenous flow or regional ischemia would be undetected by this method. As well, no inference can be made based on this study either about occurrence of brain edema in the post resuscitation period, or its effect on rCBF.

It is of some interest that not only did CBF increase 300% over the 60 hour period of measurement, indicative of a relative hyperemia, but metabolism as well tended to follow this pattern, increasing 50%. This may indicate a progressive recovery of anoxically injured tissue, or may indicate recruitment of previously ischemic and depressed regional tissue compartments. Although increasing CMRO2 should parallel a progressively improving neurologic status, this was not clearly evident from the small number of patients studied. Although all regained active vegetative and brain stem activity, cortical function was depressed in all, none being awake at the time of study.

If global impairment of cerebral reperfusion following resuscitation is a clinically important entity, it must be looked for within the first 2 hours. Clinical investigations in patients in this unstable period are very difficult and we probably must continue to rely on well controlled animal models. Studies to date suggest that experimental "no-reflow" is at least partially reversed by several interventions: injection of epinephrine, increase in systemic blood pressure, and hemo
dilution. There is also evidence that better neurologic recovery is observed in animal preparations when these measures, aimed at improving systemic and cerebral circulation, are used in the early resuscitation period. It is reasonable to conclude, based on animal studies, that restoration of cerebral circulation is primarily related to adequate early restoration of systemic circulation, particularly arterial blood pressure.

This study suggests that in man, following cardiac arrest, restoration of levels of global cerebral blood flow which can be considered adequate relative to the depressed metabolic state of the tissue is achieved within 2 hours of cardiac resuscitation. This does not exclude, of course, regional imbalance between flow and metabolism and, therefore, the possibility of ongoing regional ischemia has not been ruled out.

Acknowledgment

The financial support of the Medical Research Council of Canada and the Sellers Foundation of Manitoba is gratefully acknowledged.

References

Evidence that intracranial hemorrhage is a recognized complication of subacute bacterial endocarditis,4 information linking this complication to the use of anticoagulants, those who advise against their use claim an increased incidence of intracranial hemorrhage as a major complication of this therapy. While intracranial hemorrhage is a recognized complication of subacute bacterial endocarditis,6 information linking this complication to the use of anticoagulants is largely based on case reports of few patients.6,7

In order to study the effect of anticoagulants during septic cerebral embolization, we administered anticoagulants to dogs while embolization was carried out, using a technique originally developed by Molinari.8

Effects of Anticoagulants in an Animal Model of Septic Cerebral Embolization

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SUMMARY

The effect of anticoagulation on lesions caused by cerebral emboli of different types was studied in 57 dogs. The resultant arterial and parenchymal lesions were assessed by pathologic and angiographic studies. Embolization with emboli that caused little or no inflammatory response in the artery (12 dogs) was not associated with hemorrhagic infarcts or with subdural or subarachnoid hemorrhage; furthermore, treatment with anticoagulants (9 dogs) did not change the character of the lesions. Embolization with emboli that caused arteritis, that is, bacterial contamination or presence of lead chromate in the embolus (21 dogs), was associated with hemorrhagic infaracts, focal subarachnoid hemorrhage, and increased incidence of acute subdural hemorrhage. Treatment with anticoagulants (16 dogs) was associated with a further increase in the incidence of subdural hemorrhage.

USE OF ANTICOAGULANTS

In the presence of septic cerebral embolism is controversial. Various authors have considered bacterial endocarditis to be an absolute,1 relative,2 or no contraindication3 to the use of anticoagulants. Those who advise against their use claim an increased incidence of intracranial hemorrhage as a major complication of this therapy. While intracranial hemorrhage is a recognized complication of subacute bacterial endocarditis,4 information linking this complication to the use of anticoagulants is largely based on case reports of few patients.6,7

In order to study the effect of anticoagulants during septic cerebral embolization, we administered anticoagulants to dogs while embolization was carried out, using a technique originally developed by Molinari.8

Methods

In 57 adult mongrel dogs weighing 10.4 to 17 kg, emboli were introduced into the cervical internal carotid artery, where they lodged most often in the proximal portion of the middle cerebral artery. Details of the surgical technique and preparation of the emboli have been described.4

Silastic emboli were prepared from medical-grade silicone rubber molding compound (Silastic, Dow Corning) and were injected either sterile or contaminated with β-lactamase-positive Staphylococcus aureus (MIC for penicillin G > 1.0 μg/ml). Contaminated emboli contained transversely oriented canals. Microfil emboli were prepared from a commercially available silicone rubber compound containing chrome yellow pigment (Microfil MV-122, Canton Biomedical Products, Boulder, CO) which produced an inflammatory reaction microscopically identical to that caused by the contaminated Silastic emboli. Dogs were placed into 6 groups on the basis of the type of embolus injected and the treatment with anticoagulants: group 1 (12 dogs), sterile Silastic emboli, not anticoagulated; group 2 (10 dogs), contaminated Silastic emboli, not anticoagulated; group 3 (9 dogs), sterile Silastic emboli, anticoagulated; group 4 (8 dogs), contaminated Silastic emboli, anticoagulated; group 5 (11 dogs), Microfil emboli, not anticoagulated; and group 6 (8 dogs), Microfil emboli, anticoagulated.

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