more normal flow. In contrast, the radionuclide static scan or computerized tomographic scan may be negative in the first days following ischemic infarction and may become abnormal at a later time. Patients with neoplasms, arteriovenous malformations, carotid-cavernous fistulas, and fistulas in the neck have been studied in our laboratory by multi-view radionuclide angiography. The pattern of arterial feeding vessels supplying the lesion and the venous drainage channels can be identified. In Patient No. 2, the location and the prominent ACA and MCA feeding vessels were demonstrated and were confirmed by cerebral angiography (fig. 2). In some patients with neoplasms and fistulas, intracerebral steal of blood may occur, i.e., the blood flow to normal regions of the brain may be diverted to feed the vascular lesion.

Radionuclide angiography is a quick, noninvasive diagnostic tool which provides different information from computerized axial tomography. These techniques can best be used in combination to arrive at a correct clinical diagnosis.

References

Cerebral Blood Flow and Metabolism in Man Following Cardiac Arrest

J. E. Beckstead, M.D., F.R.C.P.(C), W. A. Tweed, M.D., F.R.C.P.(C), 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 Xenon109. 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. 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 metabolic rate for oxygen (CMRO2) in patients during the first 60 hours after resuscitation from cardiac arrest.
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 Pco2 in the normal range and PO2 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 (PO2) in duplicate in the 2 samples in a Corning 116 blood gas analyzer and calculating saturation (SO2), oxygen content, and arterial-jugular venous oxygen content difference (C(a-jv)DO2). The calculation of SO2 from PO2 is based upon the assumption of a normal oxyhemoglobin dissociation curve corrected for variation in Pco2, pH, and patient temperature.

In each of 14 patients cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMRO2) were also determined 2 or 3 times and similarly grouped. A modification of the Kety-Schmidt method9 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 O2 added to maintain constant volume in the circuit. Five mCi of Xenon133 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.12 CMRO2 was then calculated as the product of CBF and (a-jv)O2 content difference:

$$CMRO_2 = \frac{CBF}{100} \times (a-jv)O_2$$

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 Pco2, and arterial oxygen saturation was near 100% in all groups, jugular venous PO2 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 CMRO2 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 CMRO2 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 PO2 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 CMRO2 so that a relative hyperemia developed and persisted for the duration of the study. CBF at 24-60 hours exceeded normal values while CMRO2 was still reduced to about 70% of normal. Thus, the calculated ratio of CBF to CMRO2 was 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>Time</th>
<th>PaCO2</th>
<th>PjvO2</th>
<th>SaO2</th>
<th>SjvO2</th>
<th>C(a-jv)DO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6 hr</td>
<td>35.5 ± 6.1</td>
<td>35.4 ± 5.7</td>
<td>97.9 ± 2.3</td>
<td>65.3 ± 8.2</td>
<td>6.3 ± 1.8</td>
</tr>
<tr>
<td>6-24 hr</td>
<td>35.4 ± 6.0</td>
<td>41.4 ± 5.1</td>
<td>98.2 ± 0.6</td>
<td>75.0 ± 9.0</td>
<td>4.6 ± 1.8</td>
</tr>
<tr>
<td>24-60 hr</td>
<td>33.9 ± 6.0</td>
<td>46.2 ± 5.6</td>
<td>98.2 ± 1.7</td>
<td>80.1 ± 8.4</td>
<td>3.5 ± 1.5</td>
</tr>
</tbody>
</table>

**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>
<th></th>
<th>2-6 hrs.</th>
<th>6-24 hrs.</th>
<th>24-60 hrs.</th>
<th>P</th>
</tr>
</thead>
<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>49.3 ± 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

Probability analysis by analysis of variance for independent samples.

Probable because of the small number of patients who recovered, no consistent relationship between CBF, CMRO₂ and neurologic status could be identified. In particular, no pattern of improving neurologic status paralleling increasing CMRO₂ was evident, nor were the 4 patients who survived clearly distinguishable on the basis of CBF or CMRO₂ from those who did not.

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 preser-
vation of brain tissue blood flow. Although the ex-
perimental 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)\textsuperscript{17} has measured CBF and
metabolism in the period from 1 to 12 days in coma-
tose 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 depres-
sion of both CBF and CMRO\textsubscript{2} in the earliest time in-
terval, 2 to 6 hours postarrest, suggesting that a
metabolic regulation of CBF is preserved.

There was no evidence indicating pathologic im-
pairment 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\textsuperscript{16}) 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 “lux-
ury perfusion” is evident. There is, therefore, no sup-
port 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, indi-
cative 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 CMRO\textsubscript{2} 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 follow-
ing resuscitation is a clinically important entity, it
must be looked for within the first 2 hours. Clinical in-
vestigations 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, in-
crease in systemic blood pressure, and hemo-
dilution.\textsuperscript{19-21} There is also evidence that better neuro-
logic recovery is observed in animal preparations
when these measures, aimed at improving systemic
and cerebral circulation, are used in the early resuscitation period.\textsuperscript{19, 20} 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
1. Ames A, Wright RL, Kowada MD et al: Cerebral ischemia II.
2. Fischer EG: Impaired perfusion following cerebrovascular
3. Ginsberg MD, Myers RE: The topography of impaired
microvascular perfusion in the primate brain following total cir-
4. Harrison MJG, Sedal L, Arnold J, Russel RWR: No reflow
phenomenon in the cerebral circulation of the gerbil. J Neurol
Neurosurg Psychiatry 38: 1190-1193, 1975
32: 457-461, 1975
6. Snyder JV, Nemoto EM, Carroll RG, Safar P: Global ischemia
in dogs. Intra cranial pressures, brain blood flow and metab-
7. Twed WA, Wade JG, Davison WJ: Mechanism of the “low-
flow” state during resuscitation of the totally ischemic brain.
8. Wade JG, Amstrup O, S rensen SC: No-flow state following
cerebral ischemia. Arch Neurol 32: 381-384, 1975
9. Kety SS, Schmidt CF: The determination of CBF in man by the
use of nitrous oxide in low concentration. Am J Physiol 143:
53-56, 1945
10. Lassen NA, Munck O: The cerebral blood flow in man deter-
mined by the use of radioactive krypton. Acta Physiol Scand
33: 30-49, 1955
11. Lassen NA, Feinberg I, Lane MH: Bilateral studies of cerebral
oxygen uptake in young and aged normal subjects and in
12. Kety SS, Schmidt CF: The nitrous oxide method for the quan-
titative determination of cerebral blood flow in man: theory,
13. Lin SR, Komano M: Cerebral circulation after cardiac arrest:
Microangiographic and protein tracer studies. Stroke 8:
182-188, 1977
14. Little JR, Kerr FWL, Sundt TM Jr: Microrcirculatory obstruc-
tion in focal cerebral ischemia: an electron microscopic in-
vestigation in monkeys. Stroke 7: 25-30, 1976
15. Lang R, Zimmer R, Oberndörfer G: Post ischemic O\textsubscript{2}
availability and O\textsubscript{2}-consumption of the isolated perfused brain
of the dog. Pflügers Arch 334: 103-113, 1972
Effects of Anticoagulants in an Animal Model of Septic Cerebral Embolization

ROBERT A. FOOTE, M.D., THOMAS J. REAGAN, M.D., AND BURTON A. SANDOK, M.D.

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, relative, or no contraindication 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, information linking this complication to the use of anticoagulants is largely based on case reports of few patients.

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.

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. 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.
Cerebral blood flow and metabolism in man following cardiac arrest.
J E Beckstead, W A Tweed, J Lee and W L MacKeen

Stroke. 1978;9:569-573
doi: 10.1161/01.STR.9.6.569

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/9/6/569