Cerebral Blood Flow in Humans Following Resuscitation From Cardiac Arrest

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Cerebral blood flow was measured by xenon-133 washout in 13 patients 6-46 hours after being resuscitated from cardiac arrest. Patients regaining consciousness had relatively normal cerebral blood flow before regaining consciousness, but all patients who died without regaining consciousness had increased cerebral blood flow that appeared within 24 hours after resuscitation (except in one patient in whom the first measurement was delayed until 28 hours after resuscitation, by which time cerebral blood flow was increased). The cause of the delayed-onset increase in cerebral blood flow is not known, but the increase may have adverse effects on brain function and may indicate the onset of irreversible brain damage. (Stroke 1989;20:761-765)

Cardiopulmonary resuscitation has increased the number of patients surviving cardiac arrest,1,2 but neurologic damage may result from global anoxic ischemia.3-5 A critical 4-minute interval has been reported during which resuscitation must be initiated to prevent central nervous system (CNS) damage.6,7 Animal studies suggest that this interval may be considerably lengthened while still allowing normal neurologic recovery8-11 and that brain damage of delayed onset12-14 may result from changes occurring after resuscitation.15-17 Because abnormalities in cerebral blood flow (CBF) during the postarrest period may contribute to brain damage,11,18-26 we measured CBF in humans resuscitated from cardiac arrest.

Subjects and Methods

We studied 13 inpatients, none with known pre-existing neurologic disease, 26-82 (mean 67) years of age, who were resuscitated from cardiac arrest. All patients were comatose and respirator-dependent. This study was approved by the Georgetown University School of Medicine Human Research Committee. Each patient's nearest relative signed informed consent before the study began. Although we studied every patient as early as possible, no patient was studied <6 hours after resuscitation. Delays were caused by difficulties contacting relatives for consent and by allowing time for the patients' cardiovascular status to become sufficiently stable to permit study of CBF. We also measured CBF in 32 control volunteers, 29-75 (mean 64) years of age, without history of neurologic or cardiovascular disease.

CBF was measured by the xenon-133 inhalation method.27 Xenon-133, 8 mCi/study, was administered by a Xenamatic 4000 (Diversified Products, Houston, Texas). The subject rebreathed the xenon-133 for 75-90 seconds. CBF was calculated by using a compartmental method,27 in which values for only the fast-flow compartment (f1) were reported, and by using the initial slope index (ISI) method,28 which includes both fast- and slow-flow compartments. Xenon-133 washout from the brain was monitored for 17 minutes by six NaI detectors (Harshaw, Solon, Ohio), 25 mm in diameter and with 45-mm collimation, in a helmet. Detectors were placed over the frontal, parietal, and parieto-temporal regions bilaterally. A detector over the patient's endotracheal tube determined end-tidal radioactivity, which was used to calculate arterial xenon-133 concentration.27 Radioactivity was counted continuously for 300 msec by each detector and was stored in a computer (Tektronix Inc. 4052, Beaverton, Oregon) as a single raw data point. Raw data points were subjected to 7-point smoothing, and 10 raw data points summed as a single point on the final curves were used to calculate CBF. Start-fit for the calculation of f1 began when end-expiratory radioactivity was 20% of that at initiation of the washout phase (1.7-1.9 minutes).27 ISI was calculated from head washout curves from Minute 2.
TABLE 1. Comparison of MABP, Arterial pH, PaO\textsubscript{2}, PaCO\textsubscript{2}, and Body Temperature During Measurement of Cerebral Blood Flow in Patients Following Resuscitation From Cardiac Arrest

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MABP (mm Hg)</th>
<th>pH (mm Hg)</th>
<th>PaO\textsubscript{2} (mm Hg)</th>
<th>PaCO\textsubscript{2} (mm Hg)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7</td>
<td>82±9.2</td>
<td>7.45±0.036</td>
<td>88±11.3</td>
<td>31±5.7</td>
<td>37.4±0.34</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>73±11.2</td>
<td>7.42±0.051</td>
<td>92±9.2</td>
<td>28±3.8</td>
<td>37.1±0.52</td>
</tr>
</tbody>
</table>

MABP, mean arterial blood pressure; Group I, patients regaining consciousness; Group II, patients not regaining consciousness. Data are mean±SD.

to Minute 3.\textsuperscript{28} Data are expressed as milliliters blood flow per 100 grams brain per minute.

Studies of the patients were repeated at intervals of 2–16 hours in all but one patient who had a single CBF determination. Studies were terminated if the patient died, if the patient regained consciousness, or if the family withdrew permission for further study. Arterial pH, PaO\textsubscript{2}, PaCO\textsubscript{2}, and pH were measured immediately before and after each study. Blood pressure and cardiac rhythm were continuously monitored. Mean arterial blood pressure (MABP) was maintained with dopamine only when pressors were required. Four of the seven patients who regained consciousness were receiving 4–18 \mu g/kg dopamine, as were all six patients who did not regain consciousness (3–22 \mu g/kg dopamine).

Differences in maximum CBF between patients regaining consciousness and patients not regaining consciousness were analyzed using Student’s t test.

Results

Seven patients (Group I) regained consciousness within 36 hours; two had subsequent cardiac arrests and were not resuscitated, but the remaining five patients survived to hospital discharge. Six patients (Group II) never regained consciousness and remained in deep coma until death. Hospital records revealed no differences between groups in the duration of cardiac arrest, the duration of resuscitation, or the drugs used during resuscitation. There were no differences between groups in MABP, arterial pH, PaO\textsubscript{2}, PaCO\textsubscript{2}, or body temperature at the time of CBF measurement (Table 1).

Group II had increased whole-brain CBF compared with Group I (Figure 1). This increase in CBF was seen as early as 15 hours after resuscitation. In three Group II patients, a decline in CBF from previously elevated levels was associated with an isoelectric electroencephalogram. Three Group II patients had their initial CBF measurement delayed 18–28 hours after resuscitation due to unavailability of xenon-133 (in one patient) or a delay in obtaining consent (in two patients); no other variables precluded earlier study. In each of these three Group II patients, the initial CBF measurement was elevated compared with that in Group I. Figure 2 demonstrates the maximum mean whole-brain CBF in each patient and control. Maximum CBF in Group II was significantly greater than that in Group I (p<0.01) or in controls (p<0.01), with no signifi-
The decline in CBF during the PRP appears to be transient. The longer animals live past the first 1–2 hours of reperfusion, the less heterogeneous ischemia is seen. The delayed effects of transient global ischemia in animals include hyperemia. We observed heterogeneous cerebral hyperemia in humans not regaining consciousness after resuscitation from cardiac arrest (Group II). Although our data suggest that there is a delayed onset of hyperemia in patients not regaining consciousness, initial CBF determinations were delayed in three patients (18, 19, and 28 hours, respectively), by which time hyperemia had already appeared. In these three patients we cannot exclude the possibility that the hyperemia was of earlier onset than that observed in the three Group II patients in whom earlier CBF measurements were obtained. Hyperemia was not observed in any Group I patient. Since we did not obtain CBF studies within the first few hours after resuscitation, we cannot comment on the role of CBF abnormalities in the early PRP in determining whether patients will regain consciousness or will experience delayed-onset hyperemia. However, in a previous study of CBF in patients resuscitated from cardiac arrest, a transient period of reduced CBF (2–6 hours after resuscitation) preceded the appearance of hyperemia.

One must interpret CBF data in ischemic brain with caution. Xenon-133 washout measurements may fail to detect areas of no or low blood flow mixed with areas of high blood flow. Ischemic insult may also cause “rate slippage,” in which damaged areas of the fast-flow compartment may be inappropriately analyzed as part of the slow-flow compartment, making CBF appear increased when it is actually diminished. However, the ISI method should not be subject to errors in CBF measurement created by compartment shifts. CBF was increased by both the $f_i$ compartmental and ISI methods of measurement in our Group II patients, reducing the possibility that the observed hyperemia was an artifact. Increased whole-brain CBF has also been observed using the Kety method in patients resuscitated from cardiac arrest.

Since there were no significant differences in MABP, arterial pH, PaO$_2$, PaCO$_2$, or body temperature, differences in CBF between our two groups of patients cannot be accounted for by these variables. Delayed-onset CNS cell death may be heralded by the hyperemia observed in our Group II patients. In the study by Beckstead et al, CBF and the cerebral metabolic rate for oxygen (CMRO$_2$) were both below normal from 2 to 6 hours after resuscitation. From 6 to 60 hours after resuscitation, cerebral hyperemia (with CBF as high as 300% of normal) was seen, but CMRO$_2$ fell to 70% of normal by 60 hours, demonstrating an uncoupling of CBF and CMRO$_2$. No relation between CBF, CMRO$_2$, neu-

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**Figure 2.** Scatter plot of maximum whole-brain cerebral blood flow (CBF) in Group II (nonsurviving, •) and Group I (surviving, Δ) patients following resuscitation from cardiac arrest and in 32 controls (○). CBF calculated by (left) two-compartment method, in which only fast-flow compartment ($f_i$) is shown, and (right) by initial slope index (ISI) method, which includes both slow- and fast-flow compartments. Data are mean±SD.

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Discussion

Brain damage from cardiac arrest may occur during the anoxic ischemic period, the degree of damage being related to the duration of the insult. Important changes contributing to cell death may also occur following resuscitation. Abnormalities in CBF during the postreperfusion period (PRP) may contribute to brain damage. A brief increase in CBF following global ischemia, probably the result of lactic acidosis, may be followed by diminished CBF, which may be heterogeneous in distribution. Areas of hyperperfusion are found close to the areas of greatest histologic and metabolic abnormalities. Preservation of neuronal function during the PRP has been demonstrated in brain subjected to prolonged ischemia when severe hyperperfusion was prevented, suggesting that preservation of CBF during the early PRP may be necessary for improved neurologic outcome.

We have not observed decreased CBF in humans, possibly due to our failure to measure CBF <6 hours after resuscitation. It is also possible that the decline in CBF during the early PRP observed in animals may be the result of the 15–60-minute periods of global ischemia generally employed. Global ischemia was of shorter duration in our patients.

The decline in CBF during the PRP appears to be transient. The longer animals live past the first 1–2 hours of reperfusion, the less heterogeneous ischemia is seen. The delayed effects of transient global ischemia in animals include hyperemia. We observed heterogeneous cerebral hyperemia in humans not regaining consciousness after resuscitation from cardiac arrest (Group II). Although our data suggest that there is a delayed onset of hyperemia in patients not regaining consciousness, initial CBF determinations were delayed in three patients (18, 19, and 28 hours, respectively), by which time hyperemia had already appeared. In these three patients we cannot exclude the possibility that the hyperemia was of earlier onset than that observed in the three Group II patients in whom earlier CBF measurements were obtained. Hyperemia was not observed in any Group I patient. Since we did not obtain CBF studies within the first few hours after resuscitation, we cannot comment on the role of CBF abnormalities in the early PRP in determining whether patients will regain consciousness or will experience delayed-onset hyperemia. However, in a previous study of CBF in patients resuscitated from cardiac arrest, a transient period of reduced CBF (2–6 hours after resuscitation) preceded the appearance of hyperemia.

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rologic status, and survival was established; this failure was attributed largely to the few surviving patients in the study of Beckstead et al. It would have been desirable to have measured CMRO$_2$ in our patients. Early studies reported reduced whole-brain CMRO$_2$ in comatose patients resuscitated from cardiac arrest, and Lassen suggested that hyperemia implied a reduction in brain arterial-venous oxygen difference relative to CBF, citing a patient in coma following head trauma who had normal CBF but a reduction in arterial-venous oxygen difference. Studies of regional CBF and regional CMRO$_2$ have demonstrated an uncoupling of CBF and metabolism following acute ischemic injury, and thus one cannot determine the metabolic state of brain following acute ischemia based on measurements of CBF alone. Positron emission tomography has verified the uncoupling of CBF and CMRO$_2$, following acute focal ischemic insults producing relative hyperemia in areas of permanent damage. Although these results were obtained in studies of acute focal ischemia, they are most likely relevant to global ischemic insults as well. Although these studies demonstrate that the uncoupling of CBF and CMRO$_2$ is a better indicator of tissue viability than CBF alone, the precarious clinical state of our patients precluded any invasive measure (in this case jugular venous catheterization) not directly related to their therapeutic management.

A possible mechanism of delayed-onset hyperemia is acidosis. Ischemia produces lactic acidosis, and acidosis in the CNS extracellular space produces hyperemia. Adenosine, a potent vasodilator, also accumulates in the extracellular space after ischemia. Restoration of CBF leads to the return of a normal pH and phosphocreatine and adenosine 5'-triphosphate (ATP) levels within 1-4 hours. Thus, the early effects of ischemia on pH are unlikely to cause delayed-onset hyperemia, although these biochemical events are probably responsible for the transient hyperemia seen in animals in the early PRP. Delayed-onset cell death must be associated with metabolic failure. Energy failure in dying cells would be associated with falling ATP levels, increased extracellular adenosine concentration, and acidosis and thus would be conducive to delayed-onset hyperemia. Severe CNS acidosis has been observed in patients dying of cardiac arrest but not in those successfully resuscitated. We were unable to measure CNS extracellular pH in our patients because ethical constraints prevented cisternal puncture, and lumbar spinal CSF pH is not a reliable measure of brain extracellular pH.

It is not known if delayed-onset hyperemia contributes to brain damage or is only a predictor of poor outcome. Hyperemia following CNS ischemia is associated with increased blood-brain barrier permeability and may contribute to the development of cerebral edema or increased intracranial pressure.

Future studies should measure CBF early after resuscitation to determine if the low-flow state occurring in the early PRP in humans is associated with subsequent hyperemia and poor clinical outcome and if prevention of the early low-flow state will alter neurologic outcome or delayed-onset CBF abnormalities. Whether the onset of CNS hyperemia is a harbinger of CNS cell death or its result, therapeutic strategies for protecting the brain probably must be initiated before its onset.

References

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