CARDIOPULMONARY ARREST remains a frequent critical care emergency. The ultimate prognosis for any patient following resuscitation from cardiac arrest is often difficult to assess immediately following resuscitation, as restoration of normal function can be seen despite initially severe neurologic deficits. The critical vulnerability of the central nervous system to hypoxic/ischemic injury has been a cornerstone of classic medical doctrine for centuries. In classical doctrine, the normothermic brain can tolerate only 4-8 minutes of total cerebral ischemia (TCI) without suffering permanent damage.1,2 However, there has been a growing number of reports3-7 which have demonstrated recovery of neurologic function in animals following prolonged cerebral ischemia. Primary neuronal ischemic damage, damage to the vascular supportive cells and glia, and alteration in microcirculatory control of cerebral blood flow have all been implicated as limiting factors in the tolerance of the nervous system to global ischemia. Although treatments designed to ameliorate brain damage following global ischemia remain controversial,8,9 there is suggestive evidence in both focal and global ischemia that some of the neurologic damage seen in these ischemic states is not directly related to primary neuronal damage which has fully developed by the time of restoration of adequate perfusion pressure.

Post-ischemic hyperperfusion ("no-reflow"), initially proposed by Ames and his colleagues,10 has been shown to occur in a number of model systems with methods for measuring cerebral blood flow ranging from carbon black perfusion to xenon clearance techniques.11,12 These studies have shown approximately a 50% reduction in cerebral blood flow between one and two hours post-resuscitation after approximately 15 minutes of TCI. In many of these studies, extensive intrathoracic surgery and/or the use of vasoactive drugs may have altered CBF independently of any post-ischemic changes in vascular resistance. Additionally, the applicability of the xenon clearance technique for measuring cerebral blood flow during low flow states has recently been questioned.13

Consequently, we utilized a new double balloon aortic arch/inferior vena cava occlusion technique for the induction of total cerebral ischemia.14 Regional cerebral blood flow in dogs was sequentially measured using radiolabelled microspheres following 12 minutes TCI. The patterns of change in regional cerebral blood flow were determined at up to 5 different times for grey and white matter flows both were reduced (60 ± 3%, 41 ± 5% respectively). Similar differences in brain stem and cerebellar flow were also observed. The majority (71-86%) of the reduction in total CBF seen at one hour post-TCI is due to increased cerebrovascular resistance, with 14-29% of the decrease related to arteriovenous shunting.
were given to maintain light surgical anesthesia (no response to pain, cough reflex still present) until the induction of TCI. No additional anesthesia was required after the induction of cerebral ischemia. Dogs were intubated and respiration controlled on a volume respirator (Harvard apparatus Model 607). PCO₂ was maintained at 32 ± 1 mm Hg. Electrocardiogram, one-channel transparietal electroencephalogram, pulmonary artery capillary wedge pressure, central venous pressure, and left and right axillary artery blood pressures were recorded on a six-channel recorder (Brush Model 2600). All pressures were measured using standard pressure transducers (Statham Model P23D). Cardiac output was determined in duplicate by the thermodilution technique (Instrumentation Laboratory Model 601). Arterial PCO₂, PO₂, and pH were measured on a blood gas analyzer (Instrumentation Laboratories, Inc. Model 301). In 4 animals early in the series, a 19 gauge plastic catheter was inserted percutaneously in the cisterna magna for cerebrospinal fluid pressure monitoring. This was discontinued since pressures were normal over the 6 hours of hemodynamic monitoring and blood flow measurements, and it was desirable to avoid any potential CSF leak around the catheter.

Total cerebral ischemia was produced by the occlusion of the aortic arch just proximal to the brachiocephalic artery by a Fogarty 43 mm occlusion balloon (Edward’s Laboratories) introduced through the femoral artery. The balloon is positioned by observing the effects of balloon inflation on the simultaneous recording of left and right axillary pressure. The second occlusion balloon was placed in the proximal portion of the inferior vena cava to the femoral vein and inflated just prior to final aortic arch occlusion. Preload reduction was carried out until mean arterial pressure fell to ≤ 60 mm Hg, followed by inflation of the aortic arch balloon. This was necessary to prevent the development of pulmonary edema from acute left ventricular pressure overload when the aorta was suddenly internally occluded. Maintenance of coronary perfusion during balloon inflation permitted the rapid return of cardiopulmonary function to pre-ischemic status shortly following deflation of the occlusion balloon. The details and validation of this technique for producing total cerebral ischemia have been previously reported. After 12 minutes of aortic arch occlusion, the aortic and inferior vena cava balloons were deflated and withdrawn through the femoral artery and vein respectively. Intravenous bicarbonate (0.1 mEq/kg/min of ischemia) was administered. Each dog was hyperventilated for approximately 5 min to correct the hypercarbia which developed during the occlusion. PO₂ was maintained at ≥ 80 mm Hg (≥ 90% saturation) with supplemental oxygen during the occlusion and in the immediate post-resuscitation period. PCO₂ was returned to pre-ischemic level of 32 ± 1 mm Hg within 10–15 minutes following resuscitation by sequentially adjusting the mechanical ventilator. Body temperature was monitored using a pulmonary artery thermodilimeter and maintained within the range of 38.0 ± 1.0°C by heating lamps. Total and regional cerebral blood flows were measured before induction of cerebral ischemia and at 0.5, 1, 3, and 6 hours after restoration of cerebral perfusion following 12 minutes of TCI by the left ventricular injection of 15μ polyethylene microspheres labelled with 14Ce, 113Sn, 85Sr, 90Nb, and 48Sc (Minnesota Mining and Manufacturing Company).

Sham-operated dogs (n = 3) were maintained on thiopental anesthesia over a 6-hour period. Cardiac output decreased 8–15% over this period, and mean arterial blood pressure was maintained within 10% of initial control value. Regional and total cerebral blood flow was measured 4 times over the 6 hours. The variability of the sequential flow measurements over time was only 5% greater than the variability measured when the 4 microspheres were injected simultaneously. Microspheres were suspended in the 6% hydroxyethyl starch and 0.9% saline solution. Aggregation was minimized by adding 0.05% final concentration of 2-14. Before initial use, the stock suspension of microspheres was sonicated for 10 minutes and vortexed for 5 minutes before each use. Two to three *10⁶ spheres were withdrawn into 5 cc plastic syringe with continual agitation maintained by flushing the sphere suspension back and forth between 2 syringes on a 3-way stopcock until injection. The spheres were injected over 60 seconds through a multi-holed left ventricular catheter inserted through the femoral artery. Its position was verified before and after injection by pressure tracing. An arterial reference sample was withdrawn through the left axillary artery using a Harvard pump and calibrated glass syringe at a withdrawal rate of 2.45 ± 0.01 cc/min. Withdrawal was begun 5 seconds before injection and continued for 90 seconds after completion of injection. The approach to microsphere use developed in this laboratory has been reported previously.

After the completion of each experiment, the animal was sacrificed by the intravenous injection of a saturated solution of KCl. The brain was rapidly removed and wet weight determined. The brain was fixed in buffered 10% sodium formaldehyde for 48+ hours. After fixation, the brain was divided into frontal, occipital, parietal, and anterior and posterior temporal lobes. Grey and white matter samples were separated from thin sections of each lobe. Left and right halves of the brain stem were separated into the diencephalon/basal ganglion, midbrain, pons, medulla, and cerebellum. The fixed tissue samples were minced and placed in preweighed counting vials and tissue sample weight determined. Calculation of blood flows based on wet tissue sample weight, fixed tissue sample weight, and dessicated dry weight all showed the same pattern of flow changes. "Wet sample" weights

\[
\text{fixed sample weight} \times \left( \frac{\text{brain wet weight}}{\text{brain fixed weight}} \right)
\]

were used in calculating the flow data presented below. Arterial reference blood samples, pure isotope samples for fractional distribution of isotope activity,
and tissue samples were counted in a 3 channel gamma spectrometer (Beckman Model 300). Isotope separation and blood flow calculations were performed using a matrix algebra approach to the solution of simultaneous equations. Statistical analysis of grouped data was performed using analysis of variance on a statistical program utilizing a PDP 11-45 computer (Digital Equipment Company).

Results

Following aortic occlusion, the EEG became isoelectric within 20 to 30 seconds. Pupils were fixed and dilated and all reflexes abolished within one minute. After 12 minutes of circulatory arrest, administration of bicarbonate and hyperventilation restored mean arterial pressure to pre-ischemic level within 2 minutes. Occasional moderate (33%-50%) increases in mean arterial pressure were observed briefly following resuscitation, but returned to normal within 5 minutes. Intracranial pressure (ICP) was reduced during the ischemic period. There was an increase in ICP between 5 and 15 minutes following balloon release, but this returned to normal within 15-30 minutes and remained normal for the 6 hours following resuscitation. Arterial blood gases had returned to pre-ischemic values within 10-15 minutes after balloon release. Serial hematocrits, serum electrolytes, and osmolality were unchanged from pre-ischemic levels at each time for post-resuscitation flow determination (30-360 minutes post-TCI). Mean arterial blood pressure fell from a control mean of 135 to a mean of 120 over the 6 hour period, but the difference was not statistically significant. Cardiac output was reduced 40% at 1-3 hours post-"resuscitation" (p < 0.05). The ECG revealed sinus tachycardia without evidence of acute myocardial injury. Table 1 summarizes the hemodynamic/physiologic variables observed in the control period and over the 6 hours following 12 minutes of TCI. Thus, in this model system the major determinants of cerebral blood flow are at our near pre-ischemic levels during the measurement of post-ischemic cerebral blood flow. During microsphere injection and distribution, there were no significant changes in blood pressure, heart rate, ECG, or cardiac output. Control values for the pre-ischemic period for total and regional cerebral blood flow for the 15 experimental animals are shown in table 2. Total cerebral blood flow during the control period was 0.46 ml/gm/min. Grey matter flow was 0.55 ml/gm/min while white matter flow was 0.34 ml/gm/min. This was remarkably constant in all lobes of the cerebral cortex for both grey and white matter.

Serial changes in total cerebral blood flow following balloon release after 12 minutes of circulatory arrest are shown in figure 1. Total cerebral blood flow was slightly decreased ½ hour after balloon release (0.28 ml/gm/min) though not statistically significantly different from control values. However, 1 hour following balloon release, total cerebral flow has decreased to 0.22 ml/gm/min (53 ± 4%) mean % original value ± SE). This was significantly lower than control flow (p < 0.005). This was observed despite maintenance of cerebral perfusion pressure and control pre-ischemic blood gases values. Cerebral blood

<table>
<thead>
<tr>
<th>Table 1. Hemodynamic and Physiologic Parameters After Resuscitation From 12 Minutes &quot;Circulatory Arrest&quot;</th>
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</thead>
<tbody>
<tr>
<td><strong>No of Dogs</strong></td>
</tr>
<tr>
<td>(15)</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
</tr>
<tr>
<td>(beats/min)</td>
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<tr>
<td><strong>Mean Arterial</strong></td>
</tr>
<tr>
<td>(mm Hg)</td>
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<tr>
<td><strong>Pulmonary Capillary</strong></td>
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<tr>
<td>Wedge Pressure (mm Hg)</td>
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<tr>
<td><strong>Cardiac Output</strong></td>
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<tr>
<td>(L/min)</td>
</tr>
<tr>
<td><strong>pH</strong></td>
</tr>
<tr>
<td><strong>PO&lt;sub&gt;2&lt;/sub&gt;</strong></td>
</tr>
<tr>
<td>(mm Hg)</td>
</tr>
<tr>
<td><strong>PO&lt;sub&gt;2&lt;/sub&gt;</strong></td>
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</tbody>
</table>

*Room Air
**4 L Supplemental Oxygen Flow

Table 2. Pre-Ischemic Total and Regional Cerebral Blood Flow

<table>
<thead>
<tr>
<th>Blood Flow cc/min/gm</th>
<th>Mean ± SEM</th>
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<tbody>
<tr>
<td>Total Brain</td>
<td>0.46 ± .04</td>
</tr>
<tr>
<td>Cerebrum Grey Matter</td>
<td>0.55 ± .03</td>
</tr>
<tr>
<td>White Matter</td>
<td>0.34 ± .03</td>
</tr>
<tr>
<td>Brain Stem Medulla</td>
<td>0.35 ± .02</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.45 ± .04</td>
</tr>
<tr>
<td>Pons</td>
<td>0.36 ± .03</td>
</tr>
<tr>
<td>Diencephalon</td>
<td>0.48 ± .03</td>
</tr>
<tr>
<td>Midbrain</td>
<td>0.47 ± .02</td>
</tr>
</tbody>
</table>

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Changes in total cerebral blood flow following 12 minutes total cerebral ischemia (TCI).

Changes in regional grey matter flow following 12 minutes TCI.

Changes in regional white matter flow following 12 minutes TCI.

Changes in cerebellar/diencephalon blood flow following 12 minutes TCI.

Changes in total cerebral blood flow following 12 minutes TCI.

Changes in regional brain blood flow following 12 minutes TCI.

Changes in regional grey matter flow following 12 minutes TCI.

Changes in regional white matter flow following 12 minutes TCI.
were simultaneously injected in 6 dogs. These 2 injections were made in 2 control, non-ischemic animals, in 2 animals ½ hour following TCI, and in 2 animals 1 hour following TCI. Total cerebral blood flow was then calculated for each animal independently for each sphere size. A ratio of the flow rate calculated from the 15μ microsphere data to the flow calculated from 50μ microsphere data was then calculated. In the control animals, the ratio of 15μ/50μ flow was 0.95 and 0.96. At ½ hour following global ischemia, the ratio was 0.79 and 0.92. One hour following global ischemia, the 15/50 ratio was 0.71 and 0.86. Thus, at the point of maximally decreased blood flow calculated by 15μ microspheres (1 hour post-ischemia), approximately 14 to 29% of the decrease in the blood flow calculated from 15μ microspheres can be attributed to the shunting of the 15μ microspheres through newly opened “arteriovenous thoroughfares” between 15 and 50μ in diameter. In the dog, “pure” cerebral venous blood cannot be obtained without intracranial surgery (see Discussion). However, no 50μ spheres were detected in samples of jugular venous blood withdrawn during and for 3 minutes after the simultaneous microsphere injections.

Discussion

Despite considerable effort, the basic mechanism underlying progressive central nervous system damage following resuscitation from total circulatory arrest remains unclear. Ames and his co-workers suggested a pathologic basis for the “no-reflow” or impaired reperfusion phenomenon based on endothelial blebs and edema of the glial foot processes causing intrinsic compression of the capillaries within the central nervous system. Snyder and his colleagues subjected anesthetized dogs following thoracotomy to 15 minutes of global ischemia induced by aortic cross-clamping and demonstrated a 50% reduction in cortical blood flow 40–120 minutes after resuscitation using xenon clearance techniques. Some of these dogs required vasopressor (norepinephrine) infusion to maintain arterial pressure at pre-ischemic levels. In this study, post-ischemic hypoperfusion, which developed by 30–60 minutes after TCI, was not associated with any increase in intracranial pressure. Hossmann and his colleagues reported a 50 to 75% reduction in post-ischemic cerebral blood flow, again utilizing xenon clearance techniques, in anesthetized rats subjected to 30–60 minutes of circulatory arrest produced by clamping of the aortic arch combined with trimethaphan-induced hypotension. Vasoactive drugs were required to maintain post-ischemic perfusion pressure. The extensive intrathoracic surgery in both these studies and the use of vasoactive agents complicate the interpretation of the post-ischemic blood flow data. Lin and his colleagues reported decreased cerebral blood flow using radiolabelled microspheres technique in a model combining open thoracotomy, ventricular fibrillation, aortic cross-clamping, and open chest cardiac massage during the period of cross-clamping. The effect of light barbiturate anesthesia in many studies, including our own, is an important factor to consider in assessment of cerebral blood flow data. However, since cerebral blood flow is diminished by barbiturate anesthesia in non-ischemic animals, use of thiopental anesthesia prior to the induction of global ischemia would decrease control flows, particularly in the grey matter. This would act to decrease any difference noted between control values and post-ischemic values. In our model, no anesthesia is administered after the induction of cerebral ischemia.

The use of xenon (133Xe) and other gas clearance methodologies for the measurement of cerebral blood flow has been challenged for low flow states. Diffusion bypass of 133Xe between arteries and veins has been demonstrated in anesthetized dogs. This could contribute to a small underestimation of cerebral blood flow, particularly in low flow states. Waltz has shown that the washout curves in many experimental animal species can not always be readily resolved into a bimodal pattern, with a fast component representing grey matter flow rates and a slow component representing white matter flow rates. “Total” cerebral blood flow can be calculated using a non-compartmental approach. It is, however, unclear what, if any, relationship these flow data bear to grey or white matter regional CBF.

In our present studies, 15μ microspheres radio-labelled with 5 different isotopes were used to measure regional cerebral blood flow during control periods and after 12 minutes of total cerebral ischemia in lightly thiopental anesthetized dogs. Major determinants of cerebral blood flow (cerebral perfusion pressure Po2, pH, PO2) were not significantly different in the post-ischemic period from the pre-ischemic control values. The validity of 15μ microspheres as a technique to measure cerebral regional blood flow has been previously established. The 53% reduction in total cerebral blood flow 1 hour following 12 minutes of total cerebral ischemia in this study is similar to the 50% decrease seen post-ischemia in cortical blood flow in the dog reported by Snyder. This reduction in cerebral blood flow...
without any significant change in perfusion pressure usually indicates increased cerebrovascular resistance. However, post-ischemic flows measured with 15µm microspheres may be underestimated if that size sphere passes through low resistance vascular channels ("arteriovenous thoroughfare") instead of being trapped at the capillary and small arterial level, as in the pre-ischemic state. 27 The cerebral circulation in the dog does have arteriovenous anastomotic channels, more numerous, but appearing similar on anatomic studies to arteriovenous connections seen in primates. 28 The standard methodology for measuring arteriovenous shunting with microspheres requires a sample of pure venous effluent from the organ under study. Since numerous vascular communications between extracranial and intracranial circulation occur in the dog, obtaining a pure sample of cerebral venous blood is technically difficult without invasive neurosurgical intervention. 24 In this study, the effect of sphere loss through the opening of dilated vascular channels or true arteriovenous anastomosis (> 15µm but < 50µm) was studied non-invasively by comparing blood flow calculated from both 15µm microspheres and 50µm microspheres injected simultaneously. In the control state, the blood flow calculated from the 50µm sphere data is 4 to 5.5% higher than the value from the 15µm sphere data. This is likely accounted for by rheologic differences between the 50 and 15µm spheres, as well as the possibility of some low level of shunting during the control period. No spheres were detected in the jugular venous blood samples obtained during the control injections. Also, no 50µm spheres were detected in jugular venous blood in the post-ischemic period, although jugular venous blood in the dog is a mixture of (predominantly) extracranial and intracranial venous blood. The absence of any 50µm spheres is at least suggestive that any arteriovenous shunts that were present were in either extra- or intracranial circulation were not larger than 50µm in diameter. From the data on simultaneous injection of 15 and 50µm microspheres, it appears that approximately 15 to 30% of the reduction of cerebral blood flow measured by 15µm microspheres at 1 hour after TCI can be accounted for by the opening of "arteriovenous thoroughfares" or arteriovenous anastomosis in the 15–50µm diameter size range. However, the major factor (70–85%) in the reduction in cerebral blood flow measured post-ischemia with 15µm microspheres cannot be accounted for by shunting using this technique. This demonstration of the major role played by increased cerebral vascular resistance in the delayed (30–60 min post-TCI) development of the post-ischemic impaired reperfusion supports the use of microsphere CBF data in this study. We believe that this portion of the post-ischemic reduction in flow measured with 15µm microspheres represents an increase in cerebrovascular resistance at the resistance vessel level.

The data on regional CBF and A-V shunting following global cerebral ischemia strongly suggest that the alterations in cerebral blood flow are primarily mediated by heterogeneous changes in small vessel cerebrovascular resistance. The mechanism of such resistance changes remains unsettled. A number of mechanisms have been proposed, including glial edema and capillary endothelial "blebs", 26 disseminated intravascular coagulation, 29 and localized vasodilatation secondary to extracellular fluid hyperkalemia (Wade et al., 1975). The increase in blood flow in the white matter and cerebellum ½ hour post-ischemia while brain stem structures and gray matter flows are reduced suggests a difference in the time course in these tissues for resolution of the initial post-resuscitation hyperemia noted in a number of cerebral ischemia model systems. 19, 31 This may be related to structural differences between gray and white matter, including the cellular and capillary density. It is clear from more recent work in Ames lab that extrinsic compression of the capillaries by either endothelial blebs or glial foot process swelling does not occur in a time course or to an extent consistent with the regional cerebral blood flow changes seen in this study. Direct visualization of pial arterioles in the post-ischemic period has shown early vasodilatation followed by vasoconstriction. 27

The occurrence of impaired cerebral perfusion following restoration of perfusion pressure after total cerebral ischemia has led to the suggestion that there is a potentially reversible component to the central nervous system damage seen following cardiac arrest. If the final neurologic outcome is not based totally on the immediate neuronal ischemic damage occurring during the period of circulatory arrest, the continuing ischemia related to the observed increase in cerebrovascular resistance may be amenable to therapeutic intervention. There are experimental data in animal models that post-ischemic reduction in cerebral blood flow is associated with poor neurologic outcome. 38 Therapy designed to improve cerebral microcirculation has been reported to ameliorate neurologic damage following 12 minutes of ventricular defibrillation in dogs. 7 The data presented in this study suggest that therapy designed to reduce cerebrovascular resistance in the small arterial resistance vessels might increase nutritive cerebral blood flow in the post-ischemic period. Whether increased cerebral blood flow during the impaired reperfusion period will improve neurologic outcome or be associated with an exacerbation of the cerebral edema which develops later in the national history of severe global cerebral ischemia remains to be examined.

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D L Jackson, W P Dole, J McGloin and J I Rosenblatt

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