Total Cerebral Ischemia: A New Model System for the Study of Post-Cardiac Arrest Brain Damage

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SUMMARY The pathophysiology of post-cardiac arrest brain damage is not well understood. Many of the model systems presently used to study global ischemia have serious limitations. A new model system for total cerebral ischemia (TCI), using aortic and inferior vena caval occlusion balloons, is described. This model system produces verifiable TCI and avoids surgical invasion of the thorax or the use of vasoactive drugs. It does not impede cerebral venous return and protects the cardiopulmonary system from damage. This model system can be used to study the efficacy of various therapeutic interventions following a standardized CNS global ischemic insult.

CARDIAC ARREST is a frequent critical care emergency, which can arise from dysfunction of many different organ systems. Cessation of effective myocardial function is a "final common pathway" for many disparate processes. Attempts to resuscitate patients following cardiac arrest have been reported for centuries. In 1878 Boehm demonstrated that compression of the thorax in animals could cause circulation of blood. However, it has only been in the last 20 years that an effective clinical regime for cardiopulmonary resuscitation has been widely available. This required the introduction of external electrical defibrillation and a demonstration of the effectiveness of closed chest cardiac massage. More effective supportive therapy and sophisticated monitoring capabilities have also increased the possibility of survival of patients in such critical care situations.

Approximately 50% of patients experiencing cardiac arrest in a modern intensive care unit are initially successfully resuscitated. However, only a total of 20% of all patients experiencing cardiopulmonary arrest in this setting survive to discharge from the hospital. The ultimate prognosis for a patient following cardiac arrest is often difficult to assess in the immediate post-arrest period, as survival with full restoration of function may be seen despite early evidence of severe damage to the nervous system. However, many of the patients who die following initially successful resuscitation remain in deep coma with markedly abnormal neurological examinations and electroencephalograms.

The critical vulnerability of the central nervous system (CNS) to hypoxic/ischemic injury has been a cornerstone of classical medical doctrine. In the traditional view, the normothermic brain tolerates only 4-8 minutes of total cerebral ischemia before significant permanent damage is caused. Recently, however, Hossmann and colleagues have demonstrated recovery of significant neurologic function in animals following 30-60 minutes of "total cerebral ischemia." Cerebral microcirculatory changes may be a limiting factor in the tolerance of the CNS to ischemia. Ames and his colleagues first popularized the concept of the "no reflow phenomenon." They described a failure to reestablish flow when the perfusion pressure in the CNS was restored following circulatory arrest. This phenomenon is seen not only in the CNS, but also in the myocardium. The pathophysiologic and anatomical bases for these changes remain obscure. Safar and colleagues have reported recovery of significant neurologic function in dogs following 12 minutes of ventricular fibrillation if vigorous "anti-no-reflow" therapy is instituted.

Many experimental model systems have been employed to study total cerebral ischemia, including intrathoracic cross-clamping of the aorta, inflation of an external pneumatic cervical pressure cuff, inducing ventricular fibrillation, and clamping various arteries (carotid/vertebral) in the neck. Many of...
these techniques are fraught with technical difficulties and some may not induce "total" cerebral ischemia (see Discussion). The limitations of previously described model systems led to a search for a new model system. Optimal design characteristics for such a system included an ability to induce "total" cerebral ischemia in a completely reproducible and verifiable manner, avoidance of surgical invasion of the thorax, minimizing the use of vasoactive drugs, protection of cardiopulmonary function, and permitting unobstructed cerebral venous return. The following report details the development of such a model system and presents data to support attainment of these optimal design criteria.

Methods

Adult mongrel dogs 14–17 k were lightly anesthetized with thiopental (18–20 mg/kg induction dose) for the first hour of the experiment. Additional doses (1 mg/kg) were given to maintain light surgical anesthesia. No additional anesthesia was required after induction of cerebral ischemia. The dogs were intubated orotracheally, with respirations controlled on a volume respirator (Harvard Apparatus Model 607). Pco₂ was maintained at 32 ± 1 mm Hg. The ECG, one channel transparietal electroencephalogram, pulmonary artery/pulmonary capillary wedge pressure, and both left and right axillary arterial pressures were recorded on a 6-channel recorder (Bedil Model 2600). All pressures were recorded via pressure transducers (Statham Model P-23D). Cardiac output was determined by the thermodilution technique (Instrumentation Laboratories Model 601). Arterial Po₂, Pco₂ and pH were measured on a blood gas analyzer (Instrumentation Laboratories Inc.). Serial hematocrits and serum electrolytes were also determined. In some early animals a catheter was inserted percutaneously into the cisterna magna for monitoring cerebrospinal fluid (CSF) pressure either continuously or at time of sacrifice. The totality of ischemia was evaluated using carbonized radioactive labeled microspheres (15 micron: 3M Company). A description of the microsphere technique and the computer programs for calculation of tissue sphere content and blood flow developed in this laboratory have been reported previously.23 Neurological examinations before total cerebral ischemia (TCI) (both before and after thiopental anesthesia) were conducted and compared with serial neurologic examinations during the period of 12 minutes of total cerebral ischemia and over the 6 hours to 1 week of observation following TCI. Examination included evaluation of pupil size and reactivity, corneal and blink reflexes, motor tone, posturing, deep tendon reflexes, and response to noxious stimulus.

TCI was induced by the insertion of a 45 mm Fogarty arterial occlusion balloon (Edwards Labs), introduced via the femoral artery to the aortic arch. A second occlusion balloon catheter was placed in the proximal portion of the inferior vena cava via the femoral vein. Totality of the cerebral ischemia induced by inflation of the aortic balloon was quantitated in two dogs by the injection of 2 million 15μ ¹⁴Ce labeled microspheres into the left atrium during a control period, followed by a similar number of ⁸⁵Sr labeled microspheres injected during the balloon occlusion. In these control animals a limited thoracotomy was performed with insertion of a left atrial catheter. Calculation of the number of microspheres in each tissue sample was based on quantitation of radioactivity on a 3-channel gamma spectrometer (Beckman Model 300). In 3 other control animals, left anterior descending coronary artery blood flow was measured before and during aortic occlusion by an electric magnetic flow probe (Micron Instrument Co., RC-1000).

Results

Analysis of the anatomy of the aortic arch in the dogs revealed that appropriate placement of an arterial occlusion balloon in the arch could produce total cerebral ischemia (fig. 1). The induction of ischemia can be monitored by simultaneous measurement of left and right axillary blood pressures during occlusion balloon inflation. As the balloon catheter is sequentially advanced into the aortic arch from the femoral artery, inflation will cause the blood pressure to rise in both axillary arteries until the balloon reaches the left subclavian artery. When balloon inflation occludes the left subclavian artery, the left axillary blood pressure will fall, but right axillary blood pressure will increase. With either slightly more inflation or slight advancement of the balloon, the blood pressure will fall sequentially, first in the left and then the right axillary artery. If inflation is stopped at this point, the cerebral ischemia can be maintained for the period of observation.
EKG

L. Axillary Pressure

Pulmonary Artery Pressure

R. Carotid Flow

Figure 2. Pattern of right and left axillary blood pressures with inflation of correctly placed aortic occlusion balloon.

point (fig. 2), “total cerebral ischemia” can be induced.

Placement of the balloon by this technique will occlude all blood flow to the head and the rest of the body, while permitting continued perfusion of both coronary arteries. In early attempts with this model system, the sudden increase in left ventricular afterload caused by aortic balloon inflation resulted in acute pulmonary edema in many of the dogs. However, when one inflates an occlusion balloon in the inferior vena cava just below the diaphragm prior to aortic balloon inflation, the pulmonary circulation can be “unloaded” with a progressive decline in pulmonary artery pressure and mean arterial systemic pressure. If the mean arterial pressure is allowed to fall to 60 mm Hg before the aortic occlusion balloon is inflated, occlusion of aortic outflow can be accomplished minimizing the development of either myocardial infarction or pulmonary edema.

Eighty-four percent of dogs undergoing this dual intravascular balloon occlusion acutely survived 12 minutes of occlusion without significant change in post-occlusion ECGs. Early in the occlusion period most animals developed a supraventricular tachycardia. During the last half of the occlusion period, the ECG revealed sinus tachycardia. In 16% of the dogs, particularly in the early phases of model system development, acute ECG changes consistent with myocardial ischemia occurred during the occlusion. This was most often related to placement of the balloon in a more proximal location than optimal, leading to coronary ostia occlusion. In all of the animals who developed acute ST elevation and T wave inversion during the occlusion, blood pressure did not recover following release of the occlusion balloon and these animals were excluded from the study.

Verification of Totality of Cerebral Ischemia

In 2 animals, radioactively labeled microspheres were injected in the left atrium during both the control period and the occlusion period (see table 1). When one injects the same number of microspheres labeled with 2 different isotopes, 1 (148Ce) during a control period (“control spheres”) and 1 (85Sr) during the aortic occlusion (“occlusion spheres”), the number of spheres labeled with each isotope appearing in different tissue samples can be calculated. The animals...
were sacrificed with the occlusion balloon still inflated. Each cerebral hemisphere of these verification animals was cut into small pieces and approximately 1/3 of the hemisphere placed in preweighed counting vials for differential (2 channel) gamma spectrometry. The standard arterial reference sample technique for microsphere blood flow determination was used for the control injection, with control total cerebral blood flows of 0.35 and 0.38 ml/gm/min. Since there is no peripheral arterial flow during aortic balloon inflation, the total number of spheres in the brain was used to compare the flow during the control period with that during aortic occlusion. The sums of "control spheres" in the 6 hemisphere samples for these animals were 8,000 and 14,000, respectively. The number of "occlusion spheres" was reduced 99.99+% with less than 1 sphere in each hemisphere. This reflects essentially "total" cerebral ischemia during the occlusion. A similar reduction of 99.9% in renal blood flow was also documented. During occlusion, there is a 9 fold increase in the number of myocardial spheres. In 3 other control animals, coronary bloodflow measured by left anterior descending artery electromagnetic flow probe increased 2.5-4.5 fold from baseline during balloon occlusion. The remaining "occlusion spheres" could be accounted for in the lungs and in the blood pool in the heart and aortic root (4 "occlusion spheres"/gm of left atrial blood at the time of sacrifice).

Thus, this model system achieves "total" cerebral ischemia by a relatively non-invasive occlusion technique. The data also emphasize the relative protection of myocardial blood flow during this period. In all animals, (the 2 control animals and all experimental animals) totality of aortic occlusion was also assessed by monitoring right axillary artery blood flow from min 1 to min 12 of TCI. The average flow was less than 0.5 cc/min in all animals.

Return of Cardiovascular, Hemodynamic and Blood Gas Values following 12 Min of Total Cerebral Ischemia

At the end of 12 min of aortic occlusion, inferior vena cava and aortic balloons were deflated and in travenous bicarbonate (0.1 mg/kg/min of TCI) was administered. Each dog was also acutely hyper-ventilated for 5-10 min following release of the occlusion balloons to correct hypercarbia seen following occlusion release. With this technique, and without the administration of any vasoactive drug, the mean arterial blood pressure was restored to > 60 mm Hg within 1 min and was > 110 within 2-4 min following balloon release. The pH was > 7.30 within 10 min and the Po2 was maintained at > 80 mm Hg with supplemental oxygen during the occlusion and in the immediate post-occlusion period. The supplemental oxygen was tapered and discontinued by the end of a 6 hour observation period. PCO2 was initially elevated at the termination of the occlusion but returned to 32 ± 1 mm Hg within 10-15 min after balloon release. Cardiac output measured by thermodilution technique was at or above control values during the first 15-20 min following release, and remained at least at control values for the first half-hour. Cardiac output is generally reduced 20-60% at 1-3 hours following balloon release (table 2). Intracranial pressure is not elevated at 30 min to 3 hours following TCI (table 2). Thus, the major determinants of cerebral blood flow in the normal dog (i.e. mean arterial pressure, CSF pressure, PCO2, pH, Po2) all returned to baseline or were only slightly changed within 3-15 min following the period of TCI. During the 6 hours of monitoring following termination of TCI, all animals survived which initially had restoration of blood pressure without evidence of acute myocardial infarction. At the end of the 6 hour period

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<th>Table 1 Verification of Total Cerebral Ischemia 12 minutes TCI: Left Atrial Injection</th>
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<td>Sample</td>
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<tr>
<td>Left hemisphere</td>
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<td>Right hemisphere</td>
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<td>Heart (n = 2)</td>
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<th>Table 2 Pattern of Changes in Cardiac Output, Mean Arterial Pressure, and Intracranial Pressure Following 12 minutes TCI</th>
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<tr>
<td>Time</td>
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<tr>
<td>A) Cardiac output</td>
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<td>B) Mean arterial pressure</td>
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<tr>
<td>C) Intracranial pressure</td>
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<td>D) Mean cerebral perfusion pressure</td>
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mean arterial blood pressure was always greater than 110 mm Hg, the ECG pattern was sinus tachycardia, a low-normal pulmonary capillary wedge pressure was recorded and adequate oxygenation without respiratory support on room air was documented.

**Acute and Chronic Neurologic Outcome**

Following aortic occlusion, the EEG became isoelectric within 20–30 sec. All dogs had fixed and dilated pupils within 1 min and lost corneal blink and deep tendon reflexes in the same time period. There was thus clear physiologic and clinical evidence of a severe CNS insult that coincided with the quantitative validation of the totality of cerebral ischemia produced by this model system. Following 12 min of total cerebral ischemia, low voltage, slow EEG activity returned over the first 48 hours in 12/15 animals (80%). This activity returned between 90 minutes and 2 days following release of the balloon. In no animal did the post-TCI EEG return to normal. Pupils became constricted and minimally reactive within 5 to 15 min post-oclusion. Deep tendon reflexes and corneal reflexes generally returned within 15–60 min following release of the occlusion. In most cases, hyperreflexia developed within 1 to 2 hours. During the subsequent period of observation for each animal, 13/15 developed decerebrate rigidity with increased muscle tone. Forty percent (6/15) of the animals died within the first 24 hours. All of these animals had normal ECGs except for sinus tachycardia at the end of the 6 hour intensive observation period and had an adequate blood gas except for hypocarbia secondary to hyperventilation. In the animals which survived for 5–7 days no recovery of neurologic function was noted. All remained deeply comatose with only rudimentary posturing to deep pain stimulus. There was no recovery of “normal” EEG activity in serial daily observations. Two sham-operated dogs recovered normal neurological function over 24–36 hours.

**Discussion**

The study of cerebral ischemia has been pursued in many laboratories with the development of a wide variety of model systems. All model systems have their strengths and weaknesses. In attempting to define more precisely the pathophysiologic basis for the damage to the nervous system following cardiac arrest, a thorough review of all potential model systems was undertaken. The study of focal cerebral ischemia has been developed using many different model systems in various animal species. However, all models of focal ischemia are physiologically quite different from the total cerebral ischemia seen following a cardiac arrest. The most physiologic model system is true “cardiac arrest” with induced ventricular fibrillation. However, in such models, one must validate carefully that all effective cardiac action has ceased. The absence of cardiac output and, hence, of cerebral perfusion during the period of fibrillation should be documented. If one wishes to study extended periods of ventricular fibrillation without using cardiac massage and without using vasoactive drugs (e.g. epinephrine) post-resuscitation, many animals cannot be successfully resuscitated. Safar reported that only 1/3 of the dogs could be successfully resuscitated following 12 min of ventricular fibrillation. Not only are 2/3 of the dogs lost because of unsuccessful resuscitation, but also there is variable and difficult-to-quantitate damage to the cardiopulmonary system in different dogs during the 12 min of ventricular fibrillation. Thus, cardiopulmonary dysfunction may add to the ischemic neurologic damage seen in the surviving animals. Therapy designed to minimize CNS damage in this model system may have its primary effect on cardiopulmonary function rather than on reversing any specific pathogenetic mechanisms for post-ischemic CNS damage.

There are 2 major problems in interpreting those total cerebral ischemic experiments which utilize intrathoracic cross-clamping of the aorta. First, such models require an intrathoracic operative procedure. Secondly, the sudden imposition of a markedly increased left ventricular afterload upon sudden cross-clamping of the aorta often leads to acute pulmonary edema, which can result in cardiopulmonary damage. Use of a pneumatic cervical collar in conjunction with drug-induced systemic hypotension, as described by Safar et al., has 2 potentially confounding aspects. First, one would prefer to study both the natural history and the therapeutic response of the cerebral vasculature to such an ischemic/hypoxic insult in the absence of any even short acting exogenous vasoactive substances. Secondly, any system which progressively occludes the circulation to the head may transiently occlude cerebral venous return prior to total occlusion of arterial in-flow. This system, however, does protect cardiopulmonary function and minimizes surgical invasion.

There have also been attempts to achieve total cerebral ischemia by clamping or tying off various combinations of extrathoracic vessels in an attempt to achieve total cerebral ischemia. In many experimental animals, particularly the dog, the luxuriant collateral circulation in the head and neck region makes such techniques poor model systems for the study of total cerebral ischemia. Ligation of both carotid arteries and both vertebral arteries in the dog is associated with significant residual cerebral blood flow via the multiple collateral channels. The recent description by Hallenbeck and colleagues of the induction of total cerebral ischemia by increasing intracranial pressure appears to be an interesting and effective way to achieve cerebral ischemia. However, the alterations in total cerebral blood volume and the elicitation of cardiovascular and possibly cerebrovascular reflexes by the sudden imposition of marked intracranial hypertension is physiologically quite different from the conditions seen following cardiopulmonary arrest.

The data presented from this intravascular balloon...
occlusion model system for the study of total cerebral ischemia support the contention that this model system fulfills the optimal design characteristics noted above. Using radio-labeled 15μ microspheres, essentially "total" cerebral ischemia following proper placement and inflation of the occlusion balloon, was documented. Cardiopulmonary function was protected by combining decreased venous return to the heart by occlusion of the inferior vena cava, followed by intra-aortic balloon occlusion. Cardiopulmonary protection was evidenced by the rapid return to normal hemodynamic function after balloon release following 12 min of occlusion. This model system adopts a relatively non-invasive surgical technique, requiring only superficial axillary and femoral area cut downs and short-term low dose thiopental anesthesia. No anesthetics are administered after induction of total cerebral ischemia. The model system does not require the use of any vasoactive drug. Injection of radioactive-labeled microspheres, either through an indwelling left atrial catheter or, for acute studies, through a femoral artery/left ventricular catheter, can be a powerful tool in future regional microcirculatory studies on the natural history and therapy of total cerebral ischemia. Such future studies must also emphasize delineation of the underlying pathogenetic mechanism(s) for the CNS damage seen following TCI.

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