The Effect of Extracorporeal Life Support on the Brain: Cardiopulmonary Bypass

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This article reviews the mechanisms of brain injury associated with cardiopulmonary bypass. These include embolic injury of both a gaseous and particulate nature as well as global hypoxic ischemic injury. Ischemic injury can result from problems associated with venous drainage or with arterial inflow including a steal secondary to systemic to pulmonary collateral vessels. Modifications in the technique of cardiopulmonary bypass have reduced the risk of global hypoxic/ischemic injury. Laboratory and clinical studies have demonstrated that perfusion hematocrit should be maintained above 25% and preferably above 30%. Perfusion pH is also critically important, particularly when hypothermia is employed. An alkaline pH can limit cerebral oxygen delivery by inducing cerebral vasoconstriction as well as shifting oxyhemoglobin dissociation leftwards. If deep hypothermia is employed, it is critically important to add carbon dioxide using the so-called “pH stat” strategy. Oxygen management during cardiopulmonary bypass is also important. Although there is currently enthusiasm for using air rather than pure oxygen, ie, adding nitrogen, this does introduce a greater risk of gaseous nitrogen emboli since nitrogen is much less soluble than oxygen. The use of pure oxygen in conjunction with CO₂ to apply the pH stat strategy is recommended. Many of the lessons learned from studies focusing on brain protection during cardiopulmonary bypass can be applied to the patient being supported with extracorporeal membrane oxygenation.

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rain injury is the most important complication associated with the use of cardiopulmonary bypass (CPB). It can take the form of a massive global insult which leaves the child neurologically devastated; it may result in a focal injury such as hemiplegia; and it may be subtle, resulting in a slight loss of motor or cognitive skills. The most difficult problem in analyzing brain injury associated with the use of both CPB and extracorporeal membrane oxygenation (ECMO) is that children who are supported with these systems are at risk of brain injury from multiple other sources in addition to the extracorporeal life support (ECLS) itself.1 The child with a congenital heart anomaly may have been chronically cyanosed, may have a genetic anomaly associated with developmental delay such as microdeletion of chromosome 22, or may have had a cardiac arrest requiring extended resuscitation before successful emergency institution of ECMO. The child with a diaphragmatic hernia may have been profoundly acidic and hypoxic before the institution of ECMO. However, it is important to bear in mind that the excellent cerebral perfusion that is possible with ECMO that is performed correctly also has the potential to reverse the brain injury that might otherwise result after respiratory or cardiac causes of hypoxia and/or ischemia. In fact, there is reasonable evidence that the traditional concept of brain injury becoming irreversible after a defined period such as 4 minutes of complete ischemia is wrong and that, in fact, the conditions of reperfusion strongly influence the maximal duration of ischemia that can be tolerated.2 If the circulation is well maintained after the ischemic insult rather than the usual marginal cardiac output after a cardiac arrest, then the brain can tolerate a considerably longer period of ischemia, perhaps up to 20 minutes. Thus, ECLS should be thought of as a method of reversing or reducing brain injury as well as a potential cause of injury.
Mechanisms and Strategies to Reduce Brain Injury Associated with ECLS

Embolic Injury

Gaseous Emboli
Cardiac surgeons frequently have the opportunity to witness the macroscopic effects of air emboli. Despite careful attention to removal of air from the cardiac chambers at the conclusion of the cross-clamp period, it is not unusual to see occasional small bubbles enter the right coronary artery system. For several minutes, the distribution area of the vessel involved will appear poorly perfused and will contract weakly. However, with appropriate support from the pump and the passage of time, the affected area appears to recover completely. Higher perfusion pressure and pulsatile flow accelerate recovery.

It is difficult to know what inferences to draw from the response of the heart to air emboli with respect to brain injury. Various studies have documented that endothelial injury results from the passage of even a single air bubble through a microvessel. Massive air embolus can result in seizures, coma, and brain death. But accurate quantitation of injury from small amounts of air introduced by ECLS has not been performed.

Minimizing Air Emboli During ECLS
Modern circuits should be equipped with a safety cut-off relay which will respond to detection of a large amount of air in the arterial line. The technician conducting ECLS should be sure that safety systems such as the pump cut-off relay which responds to inadequate venous return (usually a collapsible bladder system) are in good working order. There should be an arterial filter from which any trapped air can be bled out. Although a centrifugal pump head supposedly adds an extra level of safety, it is important to understand that when air is introduced in sufficient quantities it will be pumped even by a centrifugal pump head.

Debubbling of the circuit tubing and components is an important part of reducing exposure of the patient to gaseous microemboli. The oxygenator is a source of trapped bubbles, particularly if it is a silicone membrane type rather than hollow fiber. The centrifugal pump head also requires careful attention. Filling the circuit with low pressure carbon dioxide is a helpful technique for expediting the deairing process.

Entrainment of air through the venous cannula can be an ongoing source of air in the circuit. Usually this can be remedied by placement of an additional pursestring and tourniquet, but occasionally further measures are required. Air entrainment will not occur if right atrial pressure is sufficiently positive, so addition of volume to the circuit may be helpful. Other techniques are essentially the reverse of those that are usually applied to increase venous drainage, such as lowering the patient height relative to the bladder or reducing the rpm of the centrifugal pump. However, these latter measures are likely to reduce flow and may not be acceptable.

Particulate Emboli
Modern ECLS circuits are usually equipped with 40-μm arterial filters that will remove particles larger than 40 μm in diameter. This might include plastic particles from the circuit or oxygenator. However, the most important particles are fibrin and platelet aggregations which can form downstream from the filter often at points of turbulence such as cannula connectors or Y connectors. Constant vigilance to detect early clot formation is a critically important part of the conduct of ECLS.

Minimizing Particulate Emboli During ECLS
The most important technique for reducing particulate emboli during ECLS is to maintain adequate anticoagulation with heparin. Generally this requires an ACT level of 200 seconds or above. However, this may be problematic in the patient who has recently had cardiac surgery in whom even this low level of anticoagulation may result in excessive bleeding. Antifibrinolytic agents such as Amicar (epsilon amino caproic acid) or aprotinin add an additional level of risk of fibrin emboli. A low flow rate, eg, less than an index of 1.8l/min/m², also places a patient at higher risk of clot formation in the circuit. Patients should not be maintained at extremely low flow rates, eg, less than 0.5l/min/m², for more than short periods of time such as 30 minutes or so when a decision is being made regarding weaning from ECLS. Finally, if clots are detected in the circuit, either the patient should be weaned off if this is an option or the circuit should be changed out.

Global Ischemia

The Basic Problem: Lack of Monitoring
The brain is at constant risk of inadequate perfusion during ECLS because of the fundamental limitation that cerebral oxygen delivery is not monitored. Traditional monitoring methods such as mixed venous oxygen saturation (eg, >70%), perfusion pressure, or even base deficit and lactate levels are insensitive and do not distinguish inadequate whole body perfusion from inadequate cerebral perfusion. Occlusion of a venous cannula draining the brain is likely to result in an increase in mixed venous oxygen saturation (because most of the flow is now directed only to the lower half of the body) and an increase in perfusion pressure which will falsely reassure those depending on these monitoring modalities. Newer methods of cerebral monitoring such as near infra-red spectroscopy must be introduced and refined if the problem of brain injury during ECLS resulting from cerebral ischemia is to be reduced.

An equally important monitoring problem in addition to cerebral oxygen delivery is a common misunderstanding of central venous pressure (CVP) monitoring during ECLS. Veno-arterial ECMO, for example, is a pump system that runs in parallel with the body’s pump, ie, the heart. There is a common but incorrect belief that the CVP should be manipulated simply by changing the pump flow rate, ie, if the CVP is rising pump flow is increased and if falling it is decreased. However, the correct way to conceptualize the situation is that there are two pumps, one being the ECMO pump.
and one the patient’s right heart, and these compete to empty the right atrium. Adding volume to either the patient or the pump circuit will increase CVP. If the right heart is still working on the ascending limb of the Starling curve, this will result in an increase in right heart output to the left heart which will also increase its output if it too is functioning on the ascending limb of its Starling curve. A further complicating factor is the location of the tip of the CVP catheter. If this is upstream to the venous cannula, eg, a jugular venous cannula, it may be providing very misleading information regarding the preload of the right heart.

**Causes of Brain Ischemia**

**Venous Drainage**

**Cannula Obstruction.** Inadequate venous drainage is an extremely important risk during ECLS. The use of neck cannulation using a relatively large cannula in the superior vena cava (SVC) can cause almost complete occlusion of venous drainage. Once again it is essential to understand that cerebral blood flow may be zero and yet perfusion flow rate, right atrial pressure (if this is the location of the tip of the CVP monitoring catheter), and mixed venous saturation will all appear normal or better than normal. Great care must be taken if neck cannulation is selected to avoid an oversized cannula that will wedge in the SVC with occlusion of side holes. Ideally, cannulation should be directly in the right atrium, eg, via a median sternotomy in the early postoperative cardiac patient; in the patient over approximately 10 to 15 kg, femoral venous cannulation should be used for at least some if not all the venous drainage. Even in small children less than 10 kg it may be possible to achieve better flows at lower cerebral venous pressure if a double venous cannulation system is used by connecting a smaller jugular venous cannula with a Y to a thin-walled femoral venous cannula rather than attempting to use one large jugular cannula.

In the early years of ECMO, intracranial hemorrhage was an extremely common complication that frequently resulted in devastating neurological injury. Although part of the solution to this problem was to add antifibrinolytics such as amicar, another often overlooked part of the solution was to reduce the size of venous cannulas placed in the SVC and to add multiple side holes to thin-walled cannulas.

**Circuit Design.** Not all venous drainage problems are a result of mechanical problems with the venous cannula. The design of the circuit will influence venous drainage to an important degree. Simple decisions such as the height of the bed and patient relative to the lowest point in the circuit if gravity drainage is used (as is the case with a collapsible bladder with roller pump in which blood drains through a siphon effect), the diameter of the venous tubing and connectors, and the characteristics of the bladder inflow all affect drainage. A centrifugal pump head adds negative venous pressure (essentially vacuum-assisted drainage) which may allow greater perfusion flow for the same venous cannula and circuit but introduces additional expense and problems.

**Arterial Inflow**

**Inadequate Perfusion Flow Rate.** A normal cardiac index is 3.5 to 4.0 l/min/m². Nevertheless, the traditional maximal flow used for ECLS whether in the form of ECMO or regular cardiopulmonary bypass is 2.4l/min/m². Thus, even “full flow perfusion” already represents a significant flow reduction relative to a normal cardiac output. The situation is further complicated by the changing ratio of surface area of the child relative to weight. The very small premature child has a much greater surface area relative to weight so that a flow rate of 2.4l/min/m² corresponds to approximately 150 to 200 mL/min/Kg in the preemie, while in the older infant who may be 10 kg or so, the flow index of 2.4l/min/m² corresponds to a flow rate of approximately 100 mL/Kg/min. Thus, there is a risk particularly in the smaller child that if flow is being calculated relative to weight an inadequate flow index will be employed.

There is little evidence that the deleterious effects of ECLS are significantly magnified by higher flow rates. Therefore, if venous drainage will support a higher flow rate, there is no reason to avoid a flow index of 3 to 4 l/min/m². On the other hand, the additional perfusion being added to the pump flow rate by the true cardiac output should be estimated and factored in by observing the area under the curve of the arterial pulse when there is cardiac ejection. This should be taken into account in choosing a perfusion flow rate. There are additional factors that should be considered:

**Arterial Steal:**

**Bronchial Collaterals, Left Heart Return**

In the absence of congenital heart disease approximately 3% of the cardiac output (or pump flow during total cardiopulmonary bypass) returns to the left atrium without perfusing the systemic vascular bed. In patients with congenital heart problems, particularly those with cyanotic anomalies, this “left heart return” can be greater than 3%, sometimes massively so. It is possible for more than 30% to 40% of the pump flow to pass directly back to the left heart. Often these collateral vessels are diffuse, though they can be large discrete vessels. In the latter situation, it is often possible to eliminate such vessels by coil embolization in the catheterization laboratory. Not only do collaterals steal from the systemic bed, but the large amount of return can result in distention of the left atrium, left ventricle, and the pulmonary bed when left heart function is inadequate to handle the left heart return. Although placement of a left atrial vent, eg, a trans PFO cannula, will reduce the risk of pulmonary edema and myocardial injury from distention, it does not reduce the problem of global underperfusion secondary to the steal.

**Perfusion Hematocrit**

Hemodilution during cardiopulmonary bypass was introduced in 1960 as a means for reducing exposure to homologous bank blood. Because early circuits had massive priming volumes, cardiopulmonary bypass required exposure of patients to many donors. As circuit volumes have decreased in the last decade in particular, the rationale for hemodilution has evolved to become a perceived enhancement of microcirculation secondary to the reduced viscosity of dilute blood.
We undertook laboratory studies using immature piglets in which we compared the structural and functional neurological outcome using three different hemodilution protocols. In the initial studies, animals were cooled to deep hypothermia and underwent circulatory arrest. Histological outcome was significantly worse with a hematocrit of 10% relative to 20% and 30%. Behavior was significantly improved with a higher hematocrit. Direct observation of the cerebral microcirculation using intravital microscopy failed to demonstrate any decrease in functional capillary density with a higher hematocrit. In fact, both structural and functional outcomes were improved with the use of a higher hematocrit.

We subsequently undertook a prospective randomized clinical trial in which infants less than 9 months of age undergoing cardiopulmonary bypass and correction of congenital heart anomalies were randomized to a perfusion hematocrit of 20% versus 30%. Although the actual hematocrit difference that was achieved was only 6.3% (21.5 + 2.9 versus 27.8 + 3.2), a highly significant difference in developmental outcome at 1 year of age was observed. In fact, the study was terminated by the NIH Data and Safety Monitoring Board because the Psychomotor Development Index of the Bayley Scale was 8 points higher in patients with the higher hematocrit (P = 0.008) (Fig. 1). Other interesting findings of the study were that myocardial protection was improved with a higher perfusion hematocrit. Cardiac index was significantly higher in the first 24 hours with higher perfusion hematocrit. There was less whole body edema and lower lactate one after bypass. The use of blood products was almost identical for the two groups.

In response to the clinical trial, we changed our strategy for regular cardiopulmonary bypass so that we now aim for a hematocrit of at least 30 throughout the procedure. Conventional ultrafiltration is used during the warming phase of the operation to bring the hematocrit up to 35% to 40%. Although no data are available regarding optimal hematocrit in the setting of ECMO or other forms of ECLS, it would seem prudent to aim for a perfusion hematocrit of at least 30. If emergency institution of ECMO is required with a nonblood prime, ultrafiltration should be performed together with addition of blood products as soon as they are available to raise the hematocrit as rapidly as possible to the minimum of 30%. During the period when the hematocrit is lower than 30%, the perfusion flow rate should be increased in an attempt to compensate for the low hematocrit, thereby increasing oxygen delivery.

**Perfusion pH**

Another factor that should influence choice of perfusion flow rate is the perfusate pH. Cerebral perfusion is particularly sensitive to changes in pH. An alkaline pH reduces cerebral blood flow and shifts oxyhemoglobin dissociation leftward, thereby reducing oxygen availability. A more alkaline pH also increases cerebral metabolic rate and therefore oxygen demand. Both laboratory studies and a randomized clinical trial have demonstrated that use of an alkaline pH during hypothermic bypass can result in a suboptimal developmental outcome.

**Background.** When blood is cooled, the pH of neutrality shifts in an alkaline direction. Two strategies have been used during regular cardiopulmonary bypass to manage pH: the “pH stat” strategy involves addition of carbon dioxide to compensate for the alkaline shift with a respiratory acidosis. The alternative “alpha stat” strategy involves no compensation and is therefore a much more alkaline strategy. Cerebral blood flow during bypass is significantly lower with the alpha stat strategy. This may be helpful for the adult with atherosclerosis who is at risk of particulate microembolization dur-
ing bypass and who is supported with full flow bypass. However, for the child with congenital heart disease who may have marginal cerebral blood flow, use of a very alkaline pH may critically reduce cerebral blood flow. For example, when the alpha stat strategy was introduced into clinical practice at Children’s Hospital Boston in 1985, we experienced an epidemic of choreoathetosis, particularly in patients with multiple aortopulmonary collaterals undergoing deep hypothermic circulatory arrest. In retrospect, we believe that the alkaline strategy resulted in a steal of blood from the systemic to the pulmonary circulation in view of the opposite effects of pH on the pulmonary and systemic circulations. Several laboratory studies confirmed that cerebral perfusion was reduced with the alpha stat strategy and that cerebral oxygenation determined by Near Infra-red spectroscopy was also reduced. Studies with magnetic resonance spectroscopy also documented reduced levels of high energy phosphates during the critical cooling phase of bypass when the brain is still warm and the blood is cold and alkaline.

Between 1992 and 1996, we randomized 182 infants to either the alpha stat or pH stat strategy during repair of congenital heart anomalies. All perioperative complications occurred more frequently in the alpha stat group, even death (4 in the alpha stat group, 0 in the pH stat group achieved a P value of 0.058). Time in the ICU and time in hospital were significantly shorter in the homogeneous group of patients with transposition. Developmental studies showed a consistent trend to an improved outcome in patients with transposition and tetralogy, though in the small subgroup with VSD, patients with pH stat had a higher score.

**Inferences for pH Management During ECMO.** As is the case for hematocrit, it is difficult to know how to translate the experience with pH manipulation during regular cardiopulmonary bypass including the use of deep hypothermia to the situation of patients undergoing support with ECMO. It is important to remember that a mild degree of hypothermia should often be employed during ECMO so that a pCO₂ of 40 to 50 mm Hg often will be appropriate. An alkaline pH should definitely be avoided for all the reasons discussed above. If the pH is alkaline, consideration should be given to compensating for the consequent reduced oxygen availability for the brain by increasing perfusion flow rate until the pH can be pushed in an acidic direction by raising pCO₂.

**Perfusate Temperature**

Another very important factor to consider when selecting perfusion flow rate is the patient’s temperature. One of the great advantages of ECMO is that incorporation of a heat exchanger in the circuit allows the patient’s temperature to be under the direct control of the ICU team. A mild degree of hypothermia is often advisable for several reasons. By lowering the patient’s metabolic rate and therefore oxygen demands, it is possible to build in a greater safety margin between oxygen supply and demand for a given flow rate. A mild degree of hypothermia is also likely to reduce neuronal injury that may be in process consequent to the circumstances at the time of the institution of ECMO. Post insult hyperthermia has been demonstrated to be particularly hazardous in exacerbating ischemic neuronal injury (Fig. 3).

There is considerable evidence in the neuroscience literature that neuronal cell death does not always occur immediately after ischemia/reperfusion and may be delayed for hours to days. This process, termed delayed neuronal death, provides an opportunity for cell loss to be either reduced or exacerbated by various interventions. Postischemia brain temperature has been shown to be critically important in influencing delayed neuronal death. Busto and coworkers and Chopp and coworkers have demonstrated that a very mild degree of postischemic hypothermia (2-4°C) when initiated within 30 minutes of reperfusion is beneficial. In a laboratory study at Boston Children’s Hospital, three groups of young piglets were subjected to 100 minutes of deep hypothermia.
pothermic circulatory arrest. Control animals (group II) had their brain temperature maintained at 37°C for 24 hours postoperatively. One group of animals had their brain temperature maintained at 33 to 34°C for 24 hours (group I), while the third group had their brain temperature maintained at 39°C (group III). There was significantly worse neurological recovery during the next 4 days of observation, and histological outcome was also worse in the hyperthermic group.

**Perfusate Oxygen Management**

In the early years of regular cardiopulmonary bypass, pure oxygen was used as a safety measure to ensure sufficient blood oxygenation. However, hyperoxygenation is now achieved with modern oxygenators if 100% oxygen is used. Concern has been expressed that this might aggravate ischemia–reperfusion injury through generation of oxygen free radicals, particularly in the heart. Normoxia has therefore been advocated both for regular cardiopulmonary bypass as well as for ECMO and is now part of clinical practice in many centers. In normoxic CPB and ECMO, oxygen is replaced by nitrogen. Because nitrogen is less soluble than oxygen, we speculated that normoxic CPB might increase gaseous microemboli as well as placing the brain at greater risk of reduced oxygen supply, with the potential to overwhelm any beneficial effects against reoxygenation injury. Therefore, we designed a study to investigate the effects of normoxic and of hyperoxic CPB on neurologic outcome in a piglet model of prolonged deep hypothermic circulatory arrest.

**Laboratory Studies of Perfusate Oxygen Strategy.** In the first phase of the study, the influence of normoxia on the number of gaseous emboli passing to the brain was investigated. We studied 10 young piglets and found that gaseous emboli count was greater with lower rectal temperature (P < 0.001), use of a bubble oxygenator relative to a membrane oxygenator (P < 0.001), and lower oxygen concentration (P = 0.021), but in contrast to traditional dogma was not affected by the temperature gradient between blood and body during cooling or rewarming. In phase 2 of this study, we studied the hypothesis that normoxic perfusion increases the risk of hypoxic brain injury after deep hypothermia with circulatory arrest. Once again we studied 10 young piglets, 5 of which were exposed to normoxic bypass and 5 to hyperoxic bypass including hypothermic circulatory arrest. While there was evidence of increased oxygen free radicals with the hyperoxic strategy, nevertheless normoxic cardiopulmonary bypass significantly increased histologically graded brain damage compared with hyperoxic cardiopulmonary bypass. Near-infrared spectroscopy suggested that the mechanism was hypoxic injury, which presumably overwhelmed any injury caused by increased oxygen free radicals.

**Inferences for Oxygen Strategy for ECMO.** The patient receiving ECLS, particularly ECMO, is at risk of inadequate cerebral oxygen delivery for all the reasons noted above. Although the setting is often one of ischemia/reperfusion, nevertheless our recommendation is to focus more on maximal oxygen delivery and avoidance of nitrogen microemboli rather than on the injury that might result from free radical generation. Thus, there should be no concern about using high FiO2 levels and pO2 levels of several hundred.

**Conclusions**

There have been many improvements in both the hardware and conduct of cardiopulmonary bypass over the last decade that have improved the outcome for neonates and infants in particular who undergo cardiopulmonary bypass. Probably the most important change has been to reduce the level of hemodilution used so that today a hematocrit of 30% is considered satisfactory and a hematocrit of less than approximately 25% is inadequate. The danger of a very alkaline pH in reducing cerebral blood flow and cerebral oxygen delivery particularly in the setting of hypothermia has been learned. Relatively high oxygen levels appear to be acceptable and do not result in an important risk of dangerous free radical formation. A mild degree of hypothermia can be extremely helpful in minimizing brain injury.

Many of the lessons learned from cardiopulmonary bypass can be applied to the child who is placed on ECMO. Continuing improvements can be anticipated both for ECMO systems and cardiopulmonary bypass hardware and techniques as a result of ongoing laboratory and clinical research studies.

**References**


