Emergency Cardiopulmonary Bypass: A Promising Rescue Strategy for Refractory Cardiac Arrest

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Emergency cardiopulmonary bypass (ECPB) has been investigated experimentally and clinically as an advanced resuscitation method that may rescue patients with refractory cardiac arrest or cardiogenic shock unresponsive to traditional medical interventions. By diverting blood flow from the patient to an extracorporeal heart and lung system capable of providing full cardiac output, ECPB can provide blood flow and gas exchange to the patient when there is not the capability of the patient’s heart or lungs to sustain these functions intrinsically. This method extends the time window for successful interventions to correct the underlying pathophysiology leading to arrest or shock.

Background of Cardiac Arrest and Post Cardiac Arrest Syndrome

There is no universal reporting system for cardiopulmonary arrests in the United States. However, it has been estimated that approximately 350,000 arrests occur each year, with 50% happening out-of-hospital and the other half to patients in a hospital setting.\textsuperscript{1} Less than 40% of these patients have return of spontaneous circulation (ROSC), and mortality for those with ROSC exceeds 60%.\textsuperscript{2} The 2010 American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR)
emphasize high-quality CPR including early defibrillation, chest compressions at the correct rate and depth, and appropriately sequenced advanced airway management, intravenous (IV) access, and drug administration to maximize the percentage of arrest patients achieving sustained ROSC.

Patients with ROSC after cardiac arrest fall on a continuum of neurologic injury sustained during the arrest ranging from those who are awake, alert, and neurologically intact to those who are comatose, unresponsive, and potentially neurologically devastated. Patients who manifest organ dysfunction after cardiac arrest have post-cardiac arrest syndrome (PCAS) and need targeted therapy to optimize outcomes. These therapies center around therapeutic hypothermia (TH), which has been demonstrated to improve survival and neurologic outcomes in PCAS patients.

The Three-Phase Model of Cardiac Arrest

One of the main factors that dictates the severity of the PCAS is the length of time from collapse to ROSC. In 2002, Weisfeldt and Becker proposed a three-phase time-sensitive model of cardiac arrests caused by shockable rhythms, suggesting that patients pass through sequential periods of arrest where different interventions should take priority. The first phase is the electrical phase, lasting approximately 4 minutes, during which defibrillation takes precedence. Approximately 5 minutes after the start of arrest the patient enters the circulatory phase, in which high-quality chest compressions take precedence over defibrillation. The notion of restoring some perfusion first followed by defibrillation is an attempt to restore some myocardial oxygen delivery, adenosine triphosphate (ATP), and action potentials so that electrical defibrillation attempts can be more successful. After the circulatory phase comes the metabolic phase wherein chest compression and defibrillation alone simply will not save the vast majority of patients. The endogenous injury from ischemia and no or low flow during the arrest accrues to a degree that it comes to dominate intraarrest physiology. At this point it is much more difficult to achieve ROSC, and most patients are pronounced dead. Survival and neurologic function decrease with increasing length of CPR and decreasing quality of advanced cardiac life support (ACLS) techniques. ROSC is difficult to achieve with increased length of resuscitation because a vicious cycle ensues: low cardiac output → further ischemia → refractory ventricular fibrillation (VF) or recurrent arrest → worsened metabolic phase.

Role of Emergency Cardiopulmonary Bypass

ECPB seems to have the best potential for patients in the lethal metabolic phase of cardiac arrest during which chest compressions and defibrillation fail the vast majority of the time. ECPB seems to be effective in three broad categories of clinical arrest: (1) patients for whom cardiac arrest would not be expected to be reversed by traditional ACLS, such as profound hypothermia or overwhelming drug intoxication; (2) patients with cardiac arrest refractory to standard ACLS, such as those in the metabolic phase or who have failed to respond to ACLS; or (3) for salvage of patients who achieve ROSC but show signs of postarrest deterioration such as profound cardiogenic shock or, less commonly, refractory hypoxemia from postarrest pulmonary injury. The fundamental principles behind ECPB are to provide exogenous full-body circulation and gas exchange to patients who can no longer adequately perform these functions endogenously. This method allows an extended window of investigation and intervention to determine the cause of the arrest and take the necessary steps to restore adequate endogenous organ function.
DEFINITION OF TERMS/CONCEPTS/TYPES OF EXTRACORPOREAL CIRCULATION

A number of different options for extracorporeal circulation exist including extracorporeal membrane oxygenation (ECMO), ECPB, continuous venovenous hemofiltration (CVVH), hemodialysis, and plasmapheresis. These modalities vary depending on their primary function: circulation, gas exchange, or filtration of electrolytes and other metabolically active substances. For this review the authors focus almost exclusively on ECPB, which can provide adequate circulation and gas exchange to replace native heart and lung function.

Percutaneous Cardiopulmonary Support Systems

Percutaneous cardiopulmonary support (PCPS) is a general term for portable battery-powered heart-lung machines, which can provide extracorporeal circulation in a number of venues for a variety of reasons.

Emergency cardiopulmonary bypass

ECPB uses a venous cannula to aspirate blood, usually via a femoral site, from the venous circulation to a centrifugal or, less commonly, a roller pump acting as an extracorporeal heart and to a membrane oxygenator, acting as an extracorporeal lung, before returning the blood to the body through an arterial cannula to be distributed throughout the body.

Extracorporeal membrane oxygenation

ECMO is a method of providing artificial cardiac or pulmonary support or both and is frequently used as a rescue strategy in the pediatric population. Like ECPB, it is initiated by placement of percutaneous cannulae, often via the femoral vasculature. ECMO has two main types: VA, or venoarterial, and VV, or venovenous. Whereas VA-ECMO provides both cardiac and pulmonary support, VV-ECMO provides only pulmonary support and is primarily used for treatment of patients with severe lung injury such as acute respiratory distress syndrome.

Continuous venovenous hemofiltration

CVVH is a technique of removing blood from a patient’s venous circulation, using a pump to pass the blood over a convection filter utilizing a pressure gradient, and removing specific solutes from the blood before returning the filtered blood to the patient’s venous circulation. It has been used in cardiac arrest patients to remove endotoxin and other inflammatory mediators from the PCAS patient’s blood. However, CVVH cannot be used to provide cardiac or pulmonary support.

Hemodialysis

Hemodialysis provides similar clinical interventions as CVVH but uses dialysate to produce diffusion of solutes across a semipermeable membrane. Like CVVH, hemodialysis is typically used to remove creatinine and urea along with other waste products of metabolism from the blood of patients with either acute or chronic renal failure. It provides no cardiac or pulmonary support and cannot be used as a primary therapy for treatment of refractory cardiac arrest. However, hemodialysis can be used as an adjunct therapy in patients postarrest.

Plasmapheresis

Plasmapheresis is typically performed by removing blood via a venous cannula, centrifuging the blood to separate the plasma from the cells in the blood, and then removing antibodies and other disease-causing proteins before returning the filtered
plasma to the patient. Many autoimmune disorders including Guillain-Barré syndrome, thrombotic thrombocytopenic purpura, and myasthenia gravis are treated by plasmapheresis. However, plasmapheresis is not typically used to treat cardiac arrest patients.

**Therapeutic hypothermia**

TH is the only therapy that has been systematically demonstrated to improve outcomes in comatose survivors of cardiac arrest and has become the standard of care in the treatment of neurologically injured PCAS patients. A number of different approaches to the induction of TH are available including induction with IV-chilled saline infusion, surface cooling with ice bags, rapid immersion systems, surface-cooling wraps, IV cooling catheters, and maintenance of TH with surface or IV devices. Importantly, TH can be induced and maintained using ECPB, ECMO, or CVVH circuits, and these have been used to deliver TH to postarrest patients. If ECPB is used as a rescue strategy for refractory arrest patients, most centers now advocate using ECPB together with TH.

**Ischemia/reperfusion and reperfusion injury**

During ischemia there is no blood flow or oxygen delivered to the tissues. CPR attempts to convert this no-flow state into a low-flow state until native circulation is restored. Whereas ROSC is the immediate goal of resuscitation, there is much evidence that some of the tissue injury observed is due to factors within the reperfusion phase. In other words, although the ischemia causes injury, the injury may be reversible depending on the conditions of reperfusion.

**BRIEF HISTORY OF EMERGENCY CARDIOPULMONARY BYPASS**

ECPB grew out of the initial use of cardiopulmonary bypass for surgical repair of cardiac defects. After conceptual and developmental advances in the early part of the 20th century, the first clinical applications of extracorporeal circulation were undertaken in the 1950s. As early as 1937, Gibbon proposed the idea of using cardiopulmonary bypass (CPB) to treat massive pulmonary embolism. The first known CPB-assisted operation was performed by Dr Clarence Dennis at the University of Wisconsin in 1951. Refinements in pump function leading to less blood damage and improvements in membrane function producing better gas exchange have allowed CPB to be used on a daily basis at hundreds of institutions around the world.

**Brief Introduction to Reperfusion Injury**

Understanding of reperfusion injury after ischemia continues to grow but remains incomplete. A fundamental question involved in ischemia and reperfusion is, “When does cell death occur?” Is cell death irreversible after a period of ischemia, or at the time of onset of reperfusion (ROSC) are cells still salvageable and cell death occurs during reperfusion? Events of prolonged ischemia set the biochemical stage for reperfusion injury: low ATP levels, elevated reactive oxygen/nitrogen species, reduced electron transport cytochromes, and intracellular calcium (Ca^{2+}) overload. Into this dangerously primed biochemical medium current reperfusion practice introduces sudden reoxygenation, creating a burst of new reactive oxygen species, lipid oxidation, mitochondrial Ca^{2+} overload, mitochondrial permeability transition, and the systemic amplification of destructive biochemical cascades. Metabolic strategies to attenuate reperfusion injury could in theory prevent some of these destructive cascades while allowing restoration of blood flow and promoting long-term neurologically intact survival. Groundwork for this concept comes from the laboratories of
Buckberg and colleagues. They proposed controlled reperfusion using a high osmolarity, low Ca\(^{2+}\) cocktail of antioxidants, which includes neuroprotective agents and leukocyte filtration to prevent reperfusion injury in a number of animal models and diverse types of ischemic injuries. This concept of reperfusion injury is vital to understanding the use of ECPB, because ECPB has the potential to control the conditions of reperfusion and reduce reperfusion injury. Thus, ECPB plus a strategy to control reperfusion injury is of growing scientific interest.

RATIONALE FOR ECPB IN CPR

The rationale for studying ECPB in CPR settings includes the following:

- A growing literature to support its effectiveness.
- In expert hands, can be rapidly initiated to maintain circulation.
- Bridge until effective native cardiac output is restored.

Emergency Department Patients May Be Ideal ECPB Candidates

In some cases, emergency department (ED) patients are perfect candidates for the novel ECPB resuscitation strategy: They are typically healthy at the time of their arrest and actively engaged in life, the cause of arrest is more likely to be cardiac, the initial rhythm is more often a shockable rhythm than in patients who arrest in a hospital setting, many out-of-hospital cardiac arrests receive bystander CPR, and automated external defibrillators are often used, providing early defibrillation. All of these actions increase the likelihood of the patient having ROSC and being a candidate for postarrest care; similarly, these actions prolong the period of arrest prior to irreversible neurologic injury and can allow patients still in arrest to be salvageable by alternative resuscitation strategies on ED arrival. However, a significant percentage of these patients do not achieve ROSC by conventional means and are, in the overwhelming majority of cases, pronounced dead at the location of the arrest or in the ED. In one sense these patients are “too healthy to die,” and alternative resuscitation strategies are desperately required.

Therapeutic Hypothermia with ECPB

Another attractive aspect of ECPB as a rescue strategy for patients with refractory cardiac arrest is that ECPB is an efficient and rapid means of delivering TH. Blood removed from a patient’s venous system can be rapidly cooled to a chosen temperature prior to reintroduction into the arterial side of the patient’s circulation. Using this approach, a patient can be cooled from the presenting temperature (often ~ 36°C) to the target temperature for therapeutic cooling (most commonly 33°C) over 20 to 30 minutes.

EXPERIMENTAL EVIDENCE SUPPORTING IMPLEMENTATION OF EMERGENCY CARDIOPULMONARY BYPASS

Animal models in species such as rats, dogs, and swine have been fundamental to the development of CPB and ECMO. In contrast to a vast literature on CPB, only a small number of studies have been published on the use of extracorporeal circulation technology as a resuscitative measure after cardiac arrest.

ECPB as an Alternative Method to Improve Survival from Prolonged Cardiac Arrest

More than two decades ago the Pittsburgh group led by Safar conducted a series of dog studies to systematically address two important questions: (a) Would ECPB
resuscitation be better than traditional advanced life support (ALS)? and (b) What is the longest duration of arrest that could be survived? Reich and colleagues examined the cardiac resuscitatability with ECPB in dogs after escalating durations of untreated VF. After 15 and 20 minutes of no-flow cardiac arrest, all dogs were successfully defibrillated, weaned off normothermic ECPB within 4 hours, and maintained stable spontaneous circulation to the end of the study. After 30 minutes from arrest all animals achieved ROSC, but only 5 of 10 dogs could be weaned off ECPB, and 100% deteriorated hemodynamically prior to the end of the study period. After 15 minutes from cardiac arrest all animals achieved normal neurologic function after 4 days, whereas this was not the case for any animals after longer arrest durations. In addition, the investigators demonstrated that basic life support (BLS; chest compressions) could markedly prolong the window of opportunity for successful ECPB. In these experiments, 2 minutes of untreated VF was followed by 30 minutes of BLS before ECPB was instituted. All animals achieved ROSC, and 70% survived neurologically intact to 72 hours. When ECPB was replaced with ALS, only 20% of the animals survived neurologically intact to 72 hours, thus demonstrating superiority of ECPB over standard ALS, perhaps due to better coronary perfusion pressure.

The Pittsburgh group also conducted a series of fundamental experiments directly comparing conventional CPR and ECPB after various lengths of untreated (no-flow) VF, the results of which were summarized concisely by Safar and colleagues in 1990 and are briefly outlined here. These studies collectively suggest ECPB to be superior to ALS. For example, after 20 minutes of no-flow VF, ALS restored stable ROSC in 7 of 9 dogs, whereas ECPB did so in 13 of 13 animals and produced a more favorable hemodynamic profile.

In a study to better simulate the out-of-hospital cardiac arrest (OHCA) scenario, 4 minutes of no-flow VF was followed by 30 minutes of BLS, and after these 34 minutes of cardiac arrest either ALS or ECPB was instituted. All animals in the ECPB group achieved ROSC versus 5 of 10 animals in the CPR-ALS group. In addition 70% of ECPB-resuscitated animals achieved intact neurologic function after 4 days, indicating that good neurologic outcome can be achieved with ECPB support after more than 30 minutes of high-quality CPR-BLS.

Refinement of ECPB

Physical optimization

ECPB-based strategies allow control of both physical and pharmacologic conditions under which reperfusion takes place. For example, TH improves survival when used with ECPB. Ao and colleagues compared the impact of hypothermic (33°C) versus normothermic (37°C) ECPB of 24 hours duration followed by 72 hours of intensive care on cardiovascular and neurologic recovery after 15 minutes of untreated VF. There was a pronounced treatment benefit of TH with regard to survival (6 of 7 vs normothermia, 0 of 8), neurologic function, hippocampal CA1 neuron degeneration, and myocardial infarction area. In a second study, the same investigators demonstrated that very rapid cooling (1.6 ± 0.8 minutes) compared with slow cooling (49.5 ± 12.1 minutes) to target temperature of 33°C may not have an impact on survival but improved functional and histologic neurologic outcome. The Pittsburgh group systematically evaluated the value of ECPB and hypothermia for resuscitation from prolonged cardiac arrest; ECPB was found to allow for rapid cooling to 33°C within 30 seconds of reperfusion and was associated with improved neurologic outcomes compared with normothermic reperfusion.

The authors found in their own rat ECPB model (Fig. 1) that bypass-administered cooling affords significant neurologic and survival benefit after asphyxial cardiac
arrest when compared with a normothermic strategy. In this study, Sprague-Dawley rats were resuscitated with ECPB after 8 minutes of normothermic cardiac arrest. With the initiation of bypass, animals were either cooled to 30°C or 34°C, or they were maintained at 37°C. Survival after ECPB resuscitation in different groups demonstrated the dramatic impact of hypothermia on 72-hour survival, with no animals surviving after normothermic ECPB, and 8 of 10 and 6 of 10 animals survived when treated with moderate and mild hypothermia, respectively (Fig. 2). However, it seems that cooling can be even more protective when it is initiated during the intraarrest period prior to reperfusion. Such intraarrest hypothermia preceding initiation of ECPB was studied by Nozari and colleagues, who compared early versus delayed cooling in a canine OHCA model. Rapid cooling to 34°C was either initiated very early prior to ROSC or was delayed by 10 minutes. Delaying cooling by only 10 minutes reduced survival from 78% to 13%. Moreover, the majority of the survivors (5 of 7) in the early cooling group had good neurologic outcomes at 72 hours. These earlier findings were corroborated by subsequent studies in the same laboratory that demonstrated the remarkable neuroprotective effects of early intraarrest (prereperfusion) cooling by aortic flush followed by ECPB resuscitation in a canine hemorrhagic arrest model. Further work on the protective effect of intraarrest cooling demonstrated that rapid induction of profound hypothermia (10°C tympanic temperature) after exsanguination cardiac arrest and subsequent resuscitation with ECPB

Fig. 1. The experimental setup of a simplified rodent ECPB model. The right atrium is cannulated with a 14-G cannula via the external jugular vein for venous outflow, whereas the arterial return occurs via the right femoral artery. A miniaturized membrane oxygenator is used for blood oxygenation and carbon dioxide removal. Total circuit volume is 30 mL. The letters indicate the location of monitoring components: (A) central venous oxygen saturation, (B) circuit pressure sensor, (C) oxygen partial pressure sensor, (D) circuit temperature, (E) rectal temperature, (F) esophageal temperature, (G) central venous pressure, (H) arterial blood pressure, (I) electrocardiography, (J) capnography.
allowed no-flow times with intact neurologic survival of up to 120 minutes in dogs. This principle of prolonged cold preserved no-flow cardiac arrest with delayed controlled ECPB resuscitation, known as suspended animation or emergency preservation and resuscitation, illustrates the powerful protective resuscitative potential of TH combined with ECPB. In addition to hypothermia, other physical modifications of ECPB-based reperfusion were shown to exert benefit. Hypertensive hemodilution achieved by administration of norepinephrine and dextran to a mean arterial pressure (MAP) greater than 140 mm Hg and a hematocrit of 20% and paired with ECPB was shown to prevent the occurrence of postarrest cerebral hypoperfusion and may improve neurologic function.

Neuroprotection during experimental CPB has also been reported in pulsatile bypass studies when compared with nonpulsatile bypass, with an improvement in cerebral blood flow, better autoregulation, and reduced markers for cerebral hypoxia. Moreover, Anstadt and colleagues tested the influence of pulsatile versus nonpulsatile ECPB on neurologic outcome measures in a dog model of prolonged (12.5 minutes) VF arrest and reported that nonpulsatile flow produced more severe hippocampal CA1 neuron dropout, more frequent ischemic changes in the caudate nucleus and cerebral cortex, and a trend toward more severe neurologic functional deficit 7 days after resuscitation. Although promising, clearly more study is required on the use of pulsatile-flow versus continuous-flow ECPB.

**Pharmacologic optimization**

ECPB also provides an opportunity to exert considerable control over chemical or pharmacologic constituents of the reperfusate with the target of mitigating ischemia and reperfusion injury. Several experimental studies demonstrate the ability of some drugs to improve outcome even when these drugs are given with the reperfusion after ischemia (ie, thereby preventing reperfusion injury). However, there is conflicting literature in this important area. For example, in early reperfusion the sodium...
hydrogen exchange antiporter opens after ischemia and leads to sodium influx and contributes to intracellular Ca\(^{2+}\) overload. There are studies that show both the effectiveness and noneffectiveness of sodium hydrogen exchange inhibitors with initiation of ECPB for resuscitation from prolonged cardiac arrest nonresponsive to ACLS.\(^{37}\) Similarly, the effect of an N-methyl-d-aspartate antagonist was examined in a canine cardiac arrest and ECPB model in order to minimize excitotoxicity associated with cerebral ischemia and reperfusion, but no protective effect was evident.\(^{22}\) These studies suggest that these agents when used alone in reperfusion have limited effectiveness against the cumulative injury.

Whereas most single agents fail to protect when used during reperfusion after ischemia, there is more enthusiasm for the use of combination therapy with multiple compounds added to the bypass circuit prime to improve outcome. The scientific rationale for these cocktail components is that because multiple destructive pathways are active during reperfusion, multiple agents are required to correct the complex intertwined injury cascades that unfold during and after ischemia and reperfusion. Therefore, such treatments lead to an overall enhanced additive or synergistic benefit effect compared with what would be achievable with single-agent therapy alone. Combinations of agents in the literature include the use of Ca\(^{2+}\) chelators or Ca\(^{2+}\) channel blockers added to the bypass prime to counteract intracellular Ca\(^{2+}\) overload during reperfusion.\(^{38}\) Magnesium sulfate was examined as an additional method to antagonize the intracellular effects of Ca\(^{2+}\) as well as for its neuroprotective potential after ischemia and reperfusion.\(^{38,39}\) The nonbicarbonate buffer tromethamine (THAM) was added in a dose that limits acidemia during reperfusion yet does not lead to normalization of the pH, because both severe acidosis and overzealous buffer administration were implicated in increased neuronal and myocardial injury after ischemia and reperfusion.\(^{38,40–42}\) Hetastarch or dextran was added empirically to the CPB prime in many experimental ECPB studies to limit a reduction in colloid osmotic pressure and to combat interstitial edema formation.\(^{13}\) Reperfusion from global ischemia after cardiac arrest as well as the use of ECPB itself leads to endothelial activation and vascular leakage.\(^{43}\) Mannitol to reduce intracellular edema in addition to its postulated radical scavenging effects was also a frequent component of controlled reperfusion cocktails.\(^{38}\) Complement and leukocyte activation and systemic inflammation are relevant pathophysiologic mechanisms after resuscitation from cardiac arrest but do also occur with CPB and cardiac surgery.\(^{44–46}\) Thus, filter-leukodepletion to remove the vast majority of leukocytes from whole blood containing prime and integration of leukodepletion filters into the ECPB circuit have been included in protective reperfusion strategies.\(^{47–49}\) In large animal models, post-cardiac arrest reperfusion combined with leukocyte depletion led to reduction of oxidative injury and complement C5b-9 (membrane attack complex) and was shown to improve functional myocardial and neurologic recovery.\(^{47–49}\) Finally, packed red blood cells have been used in the bypass prime to increase oxygen transport capacity of the reperfusate.\(^{37}\)

An example of the effectiveness of this cocktail approach can be seen in a piglet model of deep (19°C) prolonged (90 minutes) hypothermic cardiac arrest. Allen and colleagues\(^{47,48}\) compared a controlled, combinatorial global reperfusion and rewarming strategy (normoxia, citrate, magnesium sulfate, pH-stat, mannitol, leukodepletion blood prime, Na\(^{+}/\text{H}^{+}\) exchange inhibitor) with what was considered usual clinical practice (unmodified blood prime, 100% oxygen, alpha-stat). The animals receiving the cocktail had lower release of conjugated dienes (lipid peroxidation), endothelin-1 (vascular injury), and creatinine kinase (cellular injury) and better neurologic deficit scores. Trummer and colleagues\(^{38}\) described the use of a controlled reperfusion
strategy in a swine model of prolonged sudden cardiac arrest. In this study the bypass prime (cocktail) included lidocaine, citrate, magnesium sulfate, mannitol, and pH-stat. Next to the bypass prime, the study controlled physical aspects of reperfusion, which included initial low-flow and low blood pressure (30–40 mm Hg) reperfusion followed by full-flow CPB, fast induction of moderate hypothermia (30°C), and pH-stat to increase cerebral blood flow. Also, leukodepletion filters were included into the arterial bypass line. Conditions were controlled for 60 minutes. All animals (7 of 7) were successfully resuscitated with the cocktail versus zero animals getting standard CPR and ACLS. In addition, good neurologic functional recovery was observed in 6 of 7 animals.

There are many unknowns in the optimal reperfusion conditions following prolonged ischemia, including the proper level of reoxygenation to target after resuscitation. Proper oxygen level during reperfusion and avoidance of hyperoxia has been associated with reduced postresuscitation oxidative injury in experimental and clinical studies. It is possible that avoidance of early hyperoxic reperfusion during ECPB may improve myocardial and neurologic function. Yoshitake and colleagues demonstrated that in a canine model of prolonged VF (15 minutes), hypoxemic ECPB worsens outcome despite maintained blood flow. However, experimental studies are awaited to define a target partial pressure of oxygen in arterial blood (PaO₂) level during ECPB that is both safe and effective. Execution of such studies may be hampered by the lack of correlation between arterial and tissue normoxia or hyperoxia after ischemia and reperfusion injury and by technological limitations in determining actual levels of tissue oxygenation. The ideal oxygenation level following ischemia remains unknown.

**Limitation of Animal Models**

As much as cardiac arrest and ECPB studies are designed to mimic reality, subjects are anesthetized healthy adolescent and single-gender animals. This homogeneity leads to problems with the external validity and generalizability of the models, because attributes of the OHCA human population include older age, 1:2 female-to-male ratio, numerous comorbidities (eg, coronary artery disease, hypertension, diabetes mellitus), and highly variable cardiac arrest to CPR (no-flow) and CPR to ROSC (low-flow) intervals. Inhalant anesthetics that are a frequent part of experimental animal studies but are rarely part of human periarrest management are capable of inducing marked dose-dependent preconditioning and can lead to protection even hours after discontinuation of anesthesia when the vast majority of the anesthetic is washed out.

In ECPB models, prearrest heparinization is universally used to prevent clot formation in catheters placed during instrumentation of the animals, whereas this is rarely the case in humans. Findings in a canine ECPB model suggested that not only the presence or absence of heparin pretreatment but also the heparin dose may impact the resuscitation success. In that study, animals pretreated with 700 U/kg unfractionated heparin had better short-term hemodynamic outcome and survival rate (6 of 6 vs 2 of 6) compared with those animals treated with 200 U/kg. Moreover, the small size of some animals such as rats may be a benefit in many aspects, such as considerable cost savings and ease of handling compared with swine or dog models, but postresuscitation care is limited and dissimilar to contemporary medical critical care. This difference may limit the survivability of more severe injuries because of factors that would not necessarily be outcome-limiting in humans.
INITIAL CLINICAL TRIALS

ECPB is a new concept, with the bulk of human literature reported only during the last 12 years. There are some earlier studies investigating ECPB that are available only in Japanese-language literature. Preliminary English-language studies on treating a heterogeneous patient populations including cardiac arrest, refractory shock, and complicated myocardial infarction began to appear as early as 1976; however, the majority of reports on the human use of ECPB begin in 1999.60–62 The first major English-language publication of an investigation of ECPB as an alternate resuscitation strategy for patients in refractory cardiac arrest was published in Chest in 1999.63 In this pilot study, 10 VF patients between the ages of 14 and 65 were treated with ECPB. Inclusion criteria were patients with witnessed cardiac arrest (OHCA or in ED) of less than 30 minutes duration unresponsive to ACLS who had been intubated, defibrillated up to three times, and received at least one dose of epinephrine (1 mg) but remained in VF. CPB was initiated by an on-call ED research team consisting of emergency physicians with laboratory experience in deployment of CPB by a femoral-femoral route who were assisted by certified perfusion technologists. They used a Bard PCPS device. A 77-cm, 20 French venous catheter was placed with its tip in the right atrium and a 36-cm, 20 French arterial catheter was placed with its tip in the iliac artery. Blood was removed from the venous system and passed through a pump, membrane oxygenator, and heat exchanger before returning to the patient via the arterial cannula.

For the 10 cases described in this study, the mean time to pump was 32.0 ± 13.6 minutes, and the mean time on ECPB was 229 ± 111 minutes. All of the patients (10 of 10) had ROSC, 70% were weaned from CPB, and 60% survived discharge from ED to intensive care unit (ICU) admission. The mean cardiac output prior to weaning from ECPB was 4.09 ± 1.03 L/min. However, none (0 of 10) regained an acceptable level of neurologic function and none (0 of 10) survived to hospital discharge. The average time from ED arrival to death was 48 hours.

The investigators concluded, “The results of this study support the idea that CPB alone is not enough to ensure neurologically intact survival after resuscitation from prolonged cardiac arrest unresponsive to ACLS.” In addition, they noted the need for more systematic treatment of PCAS: “With increased awareness of the post-resuscitation disease and therapy aimed at alleviating ischemia reperfusion injury, more success with CPB as a resuscitative tool may be expected.”

The same year, Younger and colleagues64 published the results of their case series of refractory arrest patients treated with ECPB, which they termed extracorporeal cardiopulmonary resuscitation (ECPR). ECPR was attempted in 25 patients of whom 21 were successfully supported with CPB. Patients included in the study were either in cardiac arrest or immediately postarrest with poor systemic perfusion. Only 5 of the 25 patients (20%) included in the analysis sustained a cardiac arrest either in the prehospital or ED setting. Extracorporeal circulation was established by placing a drainage cannula in a central vein, most commonly the femoral, and the infusion cannula in a central artery, most commonly the femoral. After extracorporeal circulation was initiated, patients were treated with an aggressive hemodynamic optimization strategy, transfusing packed red blood cells to maintain a hematocrit of 40%, maximizing ECPR flow (~ 5 L/min) to minimize native cardiac work, and infusing sodium bicarbonate to maintain a minimum arterial pH of 7.30. In addition, lung rest was instituted using pressure control ventilation at a rate of 6 breaths per minute, and initial postarrest volume overload was treated with IV furosemide to maintain a urine output of at least 100 mL/hour. Survivors were on ECPR support for a shorter time.
than nonsurvivors (44 ± 21 hours vs 87 ± 96 hours; *P* = .21). Seven of the 9 patients who achieved ROSC survived to hospital discharge. All but one (an end-stage cardiomyopathy patient who received heart transplantation) had an arrest of pulmonary cause. Two other patients were transitioned to a left ventricular assist device and were awaiting transplant at the time of publication. Overall survival was 36%, with the majority neurologically intact.

In 2000, Nagao and colleagues from Tokyo published results of a prospective investigation of an alternative CPR strategy, which they dubbed *cardiopulmonary cerebral resuscitation*, combining ECPB with coronary reperfusion strategies and TH. Of the 50 patients treated, 36 were placed on ECPB. Inclusion criteria were age 18 to 74, OHCA with presumed cardiac cause, initial rhythm of VF, and coma on ED arrival. If ROSC could not be achieved shortly after ED arrival, placement of percutaneous ECPB cannulae and an intra-aortic balloon pump was attempted. After successful cannulation, cardiac catheterization was performed. Of the 36 patients placed on ECPB, 4 (11%) never achieved ROSC, and 23 (64%) never achieved adequate blood pressure to maintain native hemodynamics. The remaining 9 (25%) received extended postarrest care, including TH to 34°C for at least 48 hours. Overall survival in the cohort of 50 patients was 30% (15 of 50) with good neurologic outcomes in 24% (12 of 50); for patients treated with TH, survival was 65% (15 of 23), and good neurologic outcomes were achieved in 52% (12 of 23). Unfortunately, survival results for the patients placed on ECPB were not reported separately, and these data cannot be interpreted regarding the efficacy of this alternative resuscitation strategy.

In 2006, Athanasuleas and colleagues, a group of cardiothoracic surgeons, published a 9-year 34-patient convenience sample of cardiac arrest patients treated with an aggressive resuscitation strategy attempting to direct the scope of resuscitation to the heart and brain. This strategy was accomplished by applying three key interventions: (1) monitored CPR and blood pressure treatment to maintain a peak systolic blood pressure of at least 60 mmHg during resuscitation, (2) rapid transition to CPB, and (3) controlled coronary revascularization using amino acid-enhanced warm blood cardioplegia. The majority of these patients (20 of 36; 56%) arrested while having acute myocardial infarction: 3 of them arrested prior to arrival in the cardiac catheterization lab; the other 17 after undergoing percutaneous coronary interventions. The remaining 14 patients arrested in the context of cardiac surgery, most commonly in the ICU after coronary artery bypass graft (CABG) surgery. CPB was instituted in the operating room via a median sternotomy approach in the vast majority of patients (30 of 34; 88%). Warm blood cardioplegia reperfusate included potassium, THAM, dextrose, glutamate, and aspartate; was mixed in a blood-to-reperfusate ratio of 4:1; and was infused at 125 mL/min for 20 minutes. The length of cardiac arrest in this cohort of patients was prolonged, averaging 72 ± 43 minutes, and transfer to the operating room for CPB was delayed in some cases until invasive monitoring demonstrated adequate blood pressure to maintain cerebral perfusion. Regardless of whether CABG was performed, the aorta was cross-clamped during warm blood cardioplegia and the period of CPB was brief, being continued for 30 minutes after the aortic cross-clamp was discontinued. Survival in this select patient population was 74% (27 of 34), and all but 2 survivors were grossly neurologically intact. The investigators contrasted their impressive neurologically intact survival with the lack of survival seen in Martin and colleagues' case series as well as in another series of 29 patients with no survivors. The investigators suggest that ECPB must be part of an integrated strategy to preserve brain function before, during, and after correction of the pathologic condition precipitating the arrest.
The same year, Sung and colleagues from Seoul, South Korea, reported their experience with implementation of emergency PCPS in 22 patients with refractory cardiac arrest. Because of hospital limitations on PCPS expertise, the investigators chose a portable self-priming PCPS system (Capiox emergency bypass system; Terumo, Inc, Tokyo, Japan). Only one of the 22 patients was started on bypass in the ED; the rest had ECPB initiated in the ICU, catheterization lab, or operating room. The mean duration of PCPS was 52 ± 48 hours in the 13 patients (59%) who could be weaned from PCPS. Twelve patients had interventions to correct the cause of arrest including 4 percutaneous coronary interventions and 2 CABGs. Ten of these patients (83%) were able to be weaned from PCPS. Ten patients (44%) survived, all but one neurologically intact. The investigators argue that their success is directly related to the simplicity and rapid deployment of the PCPS combined with an aggressive search for reversible causes of arrest.

In 2008, Chen and colleagues from Taipei, Taiwan, published results of the use of ECPB for refractory in-hospital arrests. Inclusion criteria were 18 to 75 years old, cardiac cause of in-hospital arrest, and CPR duration less than 10 minutes. The extracorporeal CPB equipment had a heparin-coated circuit, centrifugal pump, and hollow-fiber oxygenator (Medtronic, Anaheim, CA, USA). Patients treated with ECPB were compared with patients during the same period who met inclusion criteria but were not treated with ECPB. The decision to initiate ECPB was made by the attending physician. A total of 113 conventional CPR and 59 ECPR patients were enrolled. A one-to-one matching was performed using propensity analysis to control for potential unbalanced covariates. These covariates included age, sex, initial arrest rhythm, time of day of arrest, and comorbidities. The ECPR group was more likely to have interventions directed at reversing the cause of arrest including percutaneous coronary interventions, CABG, and heart transplantation. One-year survival was higher in the ECPR than the conventional CPR group (18.8 vs 9.7%; \( P = .007 \)), and this survival was maintained in the propensity-matched comparison (19.6 vs 13.0%; \( P = .006 \)).

In 2010, Nagao and colleagues published the results of 10 more years of implementation of ECPB for refractory arrest. Between November 2000 and December 2007, 171 met inclusion criteria for this implementation study: witnessed, out-of-hospital cardiac arrest with less than 15 minutes from collapse to paramedic arrival; between 18 and 74 years old; presumed cardiac cause of arrest; defibrillation by either bystander use of an AED or by EMS; and persistent cardiac arrest on ED arrival. Conventional CPR was continued while the attending physician assessed whether the patient met the inclusion criteria for ECPB. Bypass was initiated by Seldinger technique, placing an outflow cannula in the femoral vein and a return cannula in the femoral artery. The CPB system included a centrifugal pump, a hollow-core oxygenator, and a heat exchanger. An intra-aortic balloon pump was also placed, and after pulsatile bypass was instituted, emergent coronary angiography was performed and culprit lesions treated with stent deployment. In addition, hemodynamics were optimized to a MAP of 90 to 120 mmHg and a pulmonary artery occlusion pressure of 15 to 20mmHg. Mild TH was instituted as soon as possible after the patient was on functional CPB with a target temperature of 34°C, which was maintained for 3 days after target temperature was reached (Fig. 3). Using this approach, 19.3% of the patients (44 of 171) survived to hospital discharge, and 12.3% (21 of 171) survived with favorable neurologic outcomes, defined as Glasgow-Pittsburgh Cerebral Performance score of 1 or 2.

A recent report from Japan is the first to attempt to compare the effectiveness of ECPB for refractory cardiac arrest versus standard ALS. The SAVE-J consortium
consisted of 46 participating EDs, with 26 using a protocolized ECPB strategy for refractory arrest and 20 departments using standard ALS care. All hospitals used standardized ALS for the initial 15 minutes of cardiac arrest treatment and included TH and hemodynamic optimization in their postarrest management protocol. At the ECPB hospitals, ECPB was performed on eligible patients who were observed at some point to have a rhythm of VF, were under 75 years old, required less than 45 minutes from collapse to the ED, and who remained pulseless after 15 minutes of full ED ALS efforts. With standard ACLS and protocolized postarrest care centered on TH, there were 2 survivors (1.6%) with good neurologic function at 30 days out of 134 patients treated, whereas with ECPB there were 22 survivors out of 183 patients treated (12%). This study is ongoing, but the large difference in survival is the first attempt to directly compare ECPB versus standard ALS care.

**SUMMARY**

ECPB is a relatively new, advanced resuscitation method that is growing in technical sophistication, shows promising experimental data, and is expanding in clinical practice. Experimental data and clinical studies suggest its ability to be highly effective at producing ROSC for refractory cardiac arrest. Currently, however, the majority of patients who achieve ROSC with ECPB do not survive long-term with good neurologic function. Despite this limitation, survival rates may be far better than standard ALS care.

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**Fig. 3.** Protocol of ECPR for induction of hypothermia with percutaneous coronary intervention (PCI). After arrival at the emergency room, ECPR using emergency cardiopulmonary bypass plus intra-aortic balloon pumping was immediately performed. Subsequently, emergency coronary angiography with PCI was performed in cases of suspected acute coronary syndrome. The goal was to reach a target temperature of 34°C within 6 hours in the post-ROSC cooling group (upper dotted part and dotted line), and within 30 minutes in the intraarrest cooling group (lower gray part and gray line). (From Nagao K, Kikushima K, Watanabe K, et al. Early induction of hypothermia during cardiac arrest improves neurologic outcomes in patients with out-of-hospital cardiac arrest who undergo emergency cardiopulmonary bypass and percutaneous coronary intervention. Circ J 2010;74:77–85; with permission.)
Nicol and colleagues performed a systematic review of PCPS for cardiac arrest and refractory shock and identified 85 studies with a total of 1494 treated with PCPS for refractory shock or cardiac arrest. Overall survival was 47.4%. When limited to PCPS used to treat cardiac arrest, the investigators found 54 studies with 674 patients, 44.9% of whom survived to discharge. In funnel plot analyses of survival versus sample size for cardiogenic shock and cardiac arrest patients, they found that the plots were skewed to the left—with higher survival in publications with fewer patients. This result suggests publication bias, as is typical of early technologies. The investigators concluded that their review demonstrated that PCPS is an efficacious intervention in cardiogenic shock and cardiac arrest. However, they acknowledged that “high-quality, adequately controlled trials are required to determine whether percutaneous bypass is effective.” In preparation for the 2010 AHA CPR guidelines, members of the International Liaison Committee on Resuscitation reviewed the data for efficacy of ECPB to treat refractory arrest. They recommended that a “further prospective control trial for out-of-hospital cardiac arrest with long-term follow-up is desired to clarify . . . [the] effectiveness of . . . extracorporeal cardiopulmonary support.”

THE FUTURE

The future of ECPB will depend on new data gathered in the next decade. There are significant opportunities and methodologies that may be further optimized to improve survival using ECPB. The collective data on ECPB suggest that it may be the best hope available for survival in patients with refractory cardiac arrest.

REFERENCES


