The Heart Surgery Forum #2009-1049
12 (3), 2009 [Epub June 2009]
doi: 10.1532/HSF98.20091049

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Patient-Centered Cardiopulmonary Bypass Concepts

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ABSTRACT

This review outlines and discusses the newest technologies used for cardiopulmonary bypass (CPB) including changes in pump technology, oxygenators, filters, and priming. In addition, evidence-based and experience-based procedures are presented in line with the recommendations given on what CPB-related practices are safe and effective.

INTRODUCTION

The introduction of the heart–lung machine into clinical surgery for heart disease by John Heysham Gibbon (1903-1973) and colleagues in 1953 was a milestone in the development of cardiac surgical procedures. By 1961, the use of cardiopulmonary bypass (CPB) together with mild hypothermia was considered safe for coronary artery bypass grafting (CABG). Since then, hundreds of thousands of operations have been performed; in fact, CABG surgery with the use of the heart–lung machine today is the second most frequently performed operation worldwide. Some of the technical principles of the setup are still the same as in the 1950s; however, the extensive subsequent research in all aspects of CPB has led to improvements in many aspects of extracorporeal circulation. Since the mid-1990s, a number of structured reviews have aimed to provide evidence that CPB practice is in fact safe and effective. It turns out that aside from the existence of the large number of publications, only a few controlled randomized trials have produced evidence-based guidelines for performing safe, patient-centered, and effective CPB practice [Shann 2006; DioDato 2008].

The present review outlines and discusses the newest technologies used for CPB, including changes in pump technology, oxygenators, filters, and priming. In addition, evidence-based and experience-based procedures are discussed in line with the recommendations given on what CPB-related practices are safe and effective. The review focuses on evidence-based techniques for reducing the organ injury and inflammation that are associated with CPB by (1) maintaining pH and euglycemia, (2) reducing hemodilution by minimizing circuits and priming, (3) processing of pericardial and mediastinal shed blood, and (4) managing the ascending and arch aorta (Table 1).

Presented at the 4th Integrated Coronary Revascularization (ICR) Workshop for Interventional Cardiologists and Cardiac Surgeons, Innsbruck, Austria, December 4-6, 2008.

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INFLAMMATION AND ORGAN INJURY ARE PATHOPHYSIOLOGIC CONSEQUENCES OF CPB

Even though extracorporeal circulation and hypothermic cardioplegic arrest enable the surgeon to perform cardiac surgery under safe conditions, optimization of organ protection remains a major concern in clinical cardiac surgery. In particular, ischemia and reperfusion, hypothermia and rewarming, hemodilution, changes in tissue pH and blood glucose levels lead to activation of the systemic inflammatory response, as well as considerable cellular and organ damage that is associated with substantial postoperative morbidity [Seghaye 1996]. In this regard, several attempts have been made to improve organ protection by providing extracorporeal circuits and oxygenators with precoated surfaces for enhanced protection of circulating blood cells, by modifying cardioplegic solutions, by minimizing the circuits, or by pharmacologically modifying the reperfusate [Jensen 2001; Menasché 2001; Shimpo 2001; Wildhirt 2001].

Ischemia and reperfusion-induced injury are mediated by various mechanisms, including increased adhesion of leukocytes to the endothelium contributing to "no reflow," generation of oxygen-derived free radicals with subsequent peroxidation of cellular structures, and excessive increases in intracellular Ca^{2+} levels, which lead to reversible and/or irreversible malfunction of the contractile apparatus.

One key element in the cascade of ischemia and reperfusion-induced injury is the activation of the vascular endothelium as the primary target for circulating blood cells and cytokines. Activation of endothelial cells leads to altered production of vasoactive mediators, including nitric oxide, endothelin, and cytokines that subsequently causes endothelial dysfunction. Impaired endothelial function leads to a prothrombotic state of the vasculature due to increased adhesion of activated platelets and neutrophils. In addition, the impaired availability of endothelium-derived nitric oxide and the activation of the endothelin system produce an enhanced vasoconstrictor tone and impaired regulation of organ blood flow. These pathophysiologic sequelae affect essentially every organ system and increase morbidity and mortality [Jensen 2001; Levy 2003]. To date, many attempts have been made to avoid the organ damage caused by CPB, but they have largely failed.

ATTEMPTS TO REDUCE MORBIDITY AND MORTALITY

Changes in Pump Technology

Two types of blood pumps are commonly used in extracorporeal circulation. The roller pump, originally patented in 1855, is a positive-displacement pump that physically pushes the fluid through the system. The roller pump is safe, cost-effective, and used best in high pressure/resistance–low volume situations, such as in CPB or dialysis settings. The speed of a roller pump is proportional to the flow, but the mechanical trauma to the circulating cells is significant.

Another common type of pump is the rotary pump. In a centrifugal pump, the rotary motion of the pump is used to circulate the blood. Centrifugal pumps act as "afterload sensitive" pumps by nature of their design and respond to changes in pressure by decreasing the flow when the pressure increases or by increasing the flow when the pressure decreases, although the pump speed remains constant. The rotary-type pumps have been introduced into the medical field because of their reduced trauma to circulating blood cells, their small size, and their reduced priming needs. Full anticoagulation is still required. Centrifugal pumps have increasingly been used in cardiac-assist devices. Such systems will become more important in the near future as destination therapy evolves into a major therapeutic option for patients with end-stage heart failure when transplantation is not an option. In the setting of CPB, however, the roller pumps will remain the gold standard, because of both technical aspects and costs.

Miniaturized Circuits (Minimized Extracorporeal Circuits) and Priming

Reducing the exposure of circulating cells to foreign surfaces has been an active goal for many years. Four aspects are of importance: reducing the surfaces of foreign materials used (tubing, oxygenators), reducing the blood–air interface (open versus closed systems), reducing reexposure and shear forces (cardiotomy suction), and reducing hemodilution.

There is class I, level B evidence that direct reinfusion into the circuit of unprocessed blood exposed to pericardial and mediastinal blood should be avoided. On the other hand, processing of blood cells and secondary filtration can be considered to decrease the deleterious effects of reinfused shed blood (class IIb, level B evidence). Caguin and Carter demonstrated that neurologic dysfunction is increased in patients when cardiotomy-suction blood exposed to pericardial and mediastinal surfaces is reinfused into patients. This effect was attributed in part to the increased fat content and increased hemolysis of the scavenged blood [Caguin 1963]. In fact, Brooker and colleagues reported the association of lipid microemboli and cerebral emboli after CPB when cardiotomy-suction blood was reinfused in a canine model [Brooker 1998]. In addition, reinfusion of pericardial suction blood has been demonstrated to cause increased blood loss by exacerbating mediators of coagulation and fibrinolysis [De Haan 1995]. Another important issue is the increase in inflammatory mediators, such as endotoxins, as shown by Spanier et al [2000].

Table 1. Evidence Levels for Important Aspects of Modern Cardiopulmonary Bypass Concepts*

Level A	
pH management with alpha-stat for moderate hypothermia	Class I
Arterial line filters	Class I
Reduction of hemodilution	Class I
Level B	
Maintenance of euglycemia	Class I
Avoid unprocessed reinfusion of pericardial suction blood	Class I
Aortic assessment by TEE or EAS to detect nonpalpable plaque	Class I
Aortic assessment by TEE or EAS to reduce cerebral emboli	Class II
Reduction of circuit surface area to attenuate SIRS	Class IIa
Use biocompatible surface-modified circuits	Class IIa
Limit arterial line temperature to 37°C to avoid hyperthermia	Class IIa
Blood cell processing to reduce deleterious effects of shed blood	Class IIb

*TEE indicates transesophageal echocardiography; EAS, epiaortic scanning; SIRS, systemic inflammatory response syndrome.

Moreover, others have demonstrated thrombin activation during CPB with activation of the coagulation cascade, fibrinolysis, and systemic inflammation [Schönberger 1995; Neuhof 2001; Chung 2005].

Strategies for improving the techniques that reduce fat microemboli include avoiding retransfusion of suction blood or using a cell saver with or without secondary filtration before returning such blood to the patient [Borowiec 1997; Jewell 2003; Kaza 2003]. The introduction of minimized extracorporeal circuits (MECCs) into clinical practice some years ago promised to significantly improve outcomes in CABG patients. In fact, some groups reported reductions in inflammation and hospital stays for patients for whom a MECC system was used [Immer 2007; Kofidis 2009]. In this regard, Stalder et al [2007] showed reduced cardiac troponin levels and faster postoperative recoveries in a series of 1799 patients when the suction blood was processed prior to reinfusion. These findings are supported by results of a randomized trial of 400 patients in which the patients in the MECC group showed improvement in their biological profiles compared with the patients who underwent their operations with the conventional extracorporeal circulation system [Remadi 2006].

Despite changes in the blood–air interface, reductions in shear forces, and overall reductions in foreign surfaces exposed to blood, hemodilution is a tremendous factor contributing to adverse patient outcomes, neurologic injury in particular. Hemodilutional anemia during CPB can lead to inadequate oxygen delivery and, consequently, to ischemic organ injury [DeFoe 2001]. In a study of Jehovah's Witnesses, Vaislic and colleagues [2003] showed that reduction of demodulation led to higher hematocrits and higher hemoglobin levels, as well as less myocardial damage. Miura et al [2007] reported that extreme hemodilution of the hematocrit to less than 15%

was associated with a high incidence of neurologic injury. The authors concluded that further studies are required to determine the safety limits of the hematocrit during pediatric CPB.

The Neurologic Outcome Research Group of the Duke Heart Center reported that neurocognitive impairment was significantly more pronounced, particularly in older patients, when the patient experienced extreme hemodilution. In this prospective randomized study of hemodilution during cardiac surgery with CPB in adults, the authors reported early termination of the study because of an increase in adverse events [Mathew 2007]. Similarly, Fang et al [1997] found an increased risk of postoperative death for patients with hematocrits ≤14% in 2738 patients who underwent CABG. For high-risk patients, there was a significantly increased risk of mortality for patients with hematocrits ≤17%. Habib and colleagues [2003] retrospectively analyzed 5000 consecutive patients and found that increased hemodilution severity during CPB was associated with worse perioperative vital organ dysfunction/morbidity and with increased resource use, as well as with greater short- and intermediate-term mortality. They speculated that these results derived from inadequate oxygen delivery that caused ischemic and/or inflammatory injury to vital organs, as was recently demonstrated in cerebral tissues [Sungurtekin 1999]. The analysis of a large observational study offers evidence that links low on-pump hematocrit values to these adverse outcomes. Further prospective randomized trials are needed (1) to establish whether a causal effect of hemodilution on poor outcomes actually exists and (2) to test the potential efficacy of maintaining on-pump hematocrits >22% for improving the outcomes of CPB [Habib 2003]. The current literature indicates class I, level A evidence for reducing hemodilution, including reducing the priming volume [Shann 2006].

Temperature Management: Hypothermia and Rewarming

Hypothermia is a well-established tool for minimizing organ damage and increasing the time available for surgery during CPB. The kidneys and brain in particular are target organs for hypothermic protection [Grigore 2002]. Experimental studies have demonstrated significant protective effects of hypothermia in the setting of ischemic injury.

In the clinical setting, however, the protective effects of hypothermia are not as obvious. Swaminathan et al [2001] examined the effects of warm (35.5°C-36.5°C) versus cold (28°C-30°C) CPB management but found no difference between the patient groups with respect to renal outcome. Similarly, others reported comparable urinary protein measurements in a randomized trial with 3 different temperature-management protocols [Regragui 1995].

In contrast, hyperthermia has been associated with increased renal damage in a rodent model [Zager 1989; Delbridge 2007]. The effects of temperature on tissue metabolic rate and related effects on energy and nutrient demand, as well as the amount of oxidant-mediated tissue injury, may be responsible in part.

Recent data from randomized trials with more than 450 patients have demonstrated that postoperative renal dysfunction occurred frequently in 16% of low-risk CABG patients [Boodhwani 2009]. The authors showed that mild hypothermia did not improve renal outcome but, more importantly, that rewarming caused increased renal injury. In fact, the authors showed that rewarming to between 34°C and 37°C increased renal dysfunction and subsequently recommended avoiding active rewarming [Boodhwani 2009]. This observation may be important because acute postoperative renal failure is known to occur in 1% to 4% of patients, leading to a tremendous increase in mortality; however, the rarity of renal failure makes it a difficult outcome measure in clinical trials.

Hypothermia is widely used during CPB to protect vital organs such as the brain to reduce metabolism and oxygen demand; however, induction of hypothermia requires a rewarming phase to compensate for the adverse outcomes associated with hypothermia, ie, platelet dysfunction and impaired hemostasis [Insler 2000].

An ischemic neurologic event in the setting of CPB typically occurs during the early and late phase of CPB at times when patients are usually perfused at warmer temperatures. Sahu et al [2009] recently found that neurocognitive function in CABG patients was significantly influenced by 2 rewarming strategies. The authors stated that weaning from CPB at 33°C may be a simple and useful strategy for lowering the postoperative impairment of neurocognitive function and may be useful as a tool to decrease morbidity after coronary revascularization [Sahu 2009].

Therefore, aggressive temperature measurement during hypothermia and rewarming may be helpful for protecting target organs from injury. Bar-Yosef and colleagues studied the effect of limited rewarming and surface warming on cerebral hyperthermia and the risk of postoperative hypothermia. The authors found that limiting rewarming during CPB in combination with surface warming, can prevent cerebral hyperthermia while minimizing the risk of postoperative hypothermia [Bar-Yosef 2004].

Another important issue concerns the sites where temperature is measured. Stone et al [1995] reported that despite other temperature-measurement sites, management of nasopharyngeal temperature matches well to the brain temperature. In contrast, Cook et al [1996], Johnson et al [2002], and others have shown that nasopharyngeal temperature measurement underestimates the jugular vein temperature and therefore exposes the brain to unintended hyperthermia. Kaukuntla and colleagues reported that in the absence of monitoring systems and attentive management, the arterial inflow temperature of the CPB circuit will likely exceed body temperatures and expose the brain and other vital organs to unintended but avoidable hyperthermia [Kaukuntla 2004].

Shann et al [2006] summarized the results of 10 randomized controlled trials and 2 prospective cohort studies that evaluated neurologic outcomes associated with temperature measurement during CPB. Six of the studies reported no differences between normothermic and hypothermic CPB, 3 studies reported poorer outcomes with normothermic management, and 1 study reported poorer outcomes with

hypothermic CPB. In addition, 3 nonrandomized trials found conflicting results, with 1 trial favoring hypothermia and 2 studies showing no statistically significant difference between groups. The authors concluded from the available evidence that the arterial line temperature should be limited to 37°C, because it might be useful for avoiding cerebral and organ hyperthermia (class IIa, level B evidence) [Shann 2006].

Management of the Ascending and Arch Aorta and the Arterial Inflow

Neurologic dysfunction and stroke following cardiac surgical procedures are related to various factors, including patient characteristics (such as preexisting vascular pathology), procedural characteristics (such as manipulation of the great vessels and hemodynamic alterations), anesthesia, and CPB per se. Unlike other operative procedures, manipulation of the ascending aorta is routine in cardiac surgery and often inevitable. Dislodgement and embolization of atheromas from the ascending and aortic arch have clearly been associated with manipulations during cardiac surgery [Whitley 2008]. In the clinical setting, it is difficult to identify the initial event responsible for neurologic injury; however, the advanced age and increased comorbidities of the cardiac patient population require the establishment of standardized protocols on how to assess and handle the great vessels prior and during the surgical procedure.

In fact, in a recent autopsy study, Mazighi et al [2009] studied the prevalence of proximal extracranial atherosclerosis in patients who died from stroke and found that proximal extracranial atherosclerosis was frequent and significantly associated with brainstem infarcts. Their findings confirm the importance of a systematic (preoperative) workup, including evaluation of proximal extracranial atherosclerotic lesions.

As reported by Likosky et al [2003] among others, atheroemboli are the major cause of cerebral type I (stroke) outcomes after CABG surgery. In particular, noncalcified plaques, which are often not palpable by the surgeon, contribute to embolic stroke [Dávila-Román 1994, 1999]. The risk factors for noncalcified atheromatosis of the aorta are advanced age, diabetes mellitus, and peripheral vascular disease, all of which are well-known factors for atherosclerosis. In fact, Mizuno and colleagues reported that approximately 20% of patients who underwent CABG showed significant atherosclerosis of the aortic arch, defined as intimal thickening of greater than 5 mm [Mizuno 2000]. Such atherosclerosis is associated with an increased rate of stroke and, as suggested by Djaiani [2006a], is presumably caused by true embolic events.

The same group also showed that routine assessment of the ascending and arch aorta by epiaortic scanning (EAS) led to modifications in intraoperative surgical management in almost one third of the patients who underwent CABG surgery; however, the use of EAS did not reduce the number of transcranial Doppler–detected cerebral emboli before or during CPB [Djaiani 2008]. With regard to the mode to use to assess the aorta at risk, Dávila-Román et al [1999] showed that EAS is significantly more sensitive than transesophageal echocardiography (TEE) for the identification of atherosclerosis. Similarly, a metaanalysis by Van Zaane et al [2008] suggested that a negative result for aortic atherosclerosis by TEE requires additional testing by EAS because of the former's low sensitivity.

Once significant aortic atherosclerosis has been detected, strategies should be considered to avoid manipulation and dislodgement. Such strategies may include the use of off-pump techniques in CABG patients to avoid cannulation and side-clamping of the ascending aorta, alternative cannulation of the femoral or axillary vessels for retrograde CPB, or replacement of the ascending aorta under hypothermic circulatory arrest prior to the surgical procedure [Djaiani 2006b; Zingone 2007; Etz 2008]. The decision-making process remains challenging in individual cases but is mandatory to reduce neurologic events and mortality. For patients who are to undergo CPB and are at increased risk of adverse neurologic events, strong consideration should be given to intraoperative TEE or epiaortic ultrasonographic scanning of the aorta for 2 reasons: (1) to detect nonpalpable plaque (class I, level B) and (2) to reduce cerebral emboli (class IIa, level B) [Shann 2006].

pH Management

As a component of the strategies for organ protection in general and neurologic protection in particular, the management of pH in accordance with the acid–base status and CO_2 regulation is of fundamental importance. In this regard, Murkin and colleagues demonstrated more than 20 years ago that when a non–temperature-corrected $PaCO_2$ of approximately 40 mm Hg was maintained, cerebral blood flow (CBF) was lower, and analysis of the pooled data suggested that CBF regulation was better preserved. That is, CBF was independent of pressure changes and was dependent on cerebral oxygen consumption [Murkin 1995, 2000]. Various randomized clinical trials subsequently demonstrated that the initiation of alpha-stat management is associated with improved neurologic and neuropsychological outcomes in adult patients undergoing moderately hypothermic CPB. In fact, alpha-stat blood gas management preserves the coupling of CBF with metabolism such that hypothermia-induced decreases in metabolic rate are accompanied by proportional decreases in CBF [Murkin 1995]. In a review of the evidence, Shann et al [2006] concluded that the clinical team should manage adult patients undergoing moderate hypothermic CPB with alpha-stat pH management (class I, level A).

Maintenance of Blood Glucose Levels

There is both experimental and clinical evidence for maintaining blood glucose levels within an institution's reference intervals for all patients, including nondiabetic patients. In this regard, McAlister and colleagues showed that for each 1-mmol/L increase in blood glucose above 6.1 mmol/L (1 mmol = 18 mg/dL), the risk for each outcome parameter (stroke, myocardial infarction, septic complication, or death) increased by 17% [McAlister 2003]. In a prospective nonrandomized interventional study of nearly 5000 patients undergoing cardiac procedures, Furnary et al [2004] showed that perioperative hyperglycemia was directly associated with an

increased risk of death, deep sternal wound infection, length of stay, and hospital costs. This study and others suggest that a target glucose range of <150 mg/dL is favorable for maintaining euglycemia. Garber and colleagues summarized the evidence on inpatient diabetes and metabolic control. This systematic review was sponsored by the American College of Endocrinology, the American Association of Clinical Endocrinologists, and the co-sponsoring organizations (including the Society of Thoracic Surgeons). A consensus statement supported the need early detection and aggressive management of hyperglycemia to improve patient outcomes [Garber 2004]. This statement was recently revised and extended [Garber 2008]. In the setting of CPB, it remains difficult to treat hyperglycemia adequately, particularly in the presence of insulin resistance and intense gluconeogenesis, as identified by Groban et al [2002]. In this regard, Finney et al [2003] reported that measuring blood glucose levels rather than insulin levels in the setting of critically ill patients produces apparent benefits with respect to mortality.

With the goal of improving neurologic outcomes, Murkin suggested the following to be important for effectively limiting hyperglycemia: (1) avoiding or limiting glucose-containing intravenous, cardioplegic, and pump-priming solutions; (2) enhanced awareness and treatment of catecholamine-induced hyperglycemia; and (3) more aggressive insulin-dosing strategies [Murkin 2000]. According to Shann et al [2006], there is class I, level B evidence that the clinical team should maintain the perioperative blood glucose concentration within the institution's reference interval in all patients, including nondiabetic individuals.

Perfusion technology has developed tremendously in the past 2 decades. In particular, compression and miniaturization of the systems have improved patient care. In addition, passive modifications and coatings of surfaces, including heparin or phosphorylcholine, have been developed, predominately to reduce the inflammatory response associated with the use of CPB. Our group showed that a phospholipid coating significantly reduces systemic increases in proinflammatory and anti-inflammatory cytokines and P-selectin. Despite the comparable clinical outcomes in this study, the observed significant reductions in values for systemic inflammatory parameters suggest improved biocompatibility of extracorporeal circuit materials when they are coated with phospholipids [Schulz 2002]. In addition, others have shown a clear reduction in inflammation with coated extracorporeal circuits. Videm and colleagues demonstrated a reduction in complement activation with the use of heparin-coated systems [Videm 1999]. Others have reported improved platelet preservation with the use of CPB circuits coated with biocompatible surface additives. We have recently shown that adding nitric oxide directly into the oxygenator of the CPB circuit significantly improves platelet function and reduces platelet activation [Chung 2005]; however, there is class IIa, level B evidence in the available studies to indicate that reducing the surface area and using circuits with surfaces modified with biocompatible materials might be useful/effective for attenuating the systemic inflammatory response and improving outcomes [Shann 2006].

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