

The Adverse Effects of the Cardiopulmonary Bypass Machine

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Abstract

Throughout the United States, the use of the cardiopulmonary bypass (CPB) machine during cardiac surgery has become a widely employed practice. Although this machine has simplified cardiac surgery by allowing the heart to be stopped, the technology also causes adverse effects on a patient's body and cognitive functions. These include complications of the inflammatory system, heart, lungs, kidneys, and brain. Using the CPB can not only cause physical harm, but it can also lead to cognitive decline that can affect the patient's quality of life. Studying the CPB in terms of its adverse effects is imperative to making any effort to diminish the complications. Evidence-based research shows that methods utilizing equipment such as a membrane oxygenator, heparin-coated circuits, and ultrafiltration, as well as several medications may reduce the negative physical and neurocognitive outcomes.

The Adverse Effects of the Cardiopulmonary Bypass Machine

The human heart is a miraculous organ. It is continuously, involuntarily pumping blood so that every muscle, every artery, and every cell in one's body can get the oxygen it requires. However, sometimes this process does not work as it should and the body does not adequately receive the blood, and consequently the oxygen, it needs. This is oftentimes due to a blockage in one or more of the coronary arteries, the vessels carrying blood to the heart itself. If the heart is not getting enough blood, it is not getting enough oxygen. Therefore, the heart may infarct and portions of the heart may begin to die. When some of the cardiac tissue dies, the heart's pumping ability is decreased which further continues the cycle of inadequate blood supply. Scenarios such as this one need to be corrected immediately.

Blockages in the heart are often corrected with coronary artery bypass graft surgery while the heart is on the cardiopulmonary bypass (CPB) machine (Lewis, Heitkemper, Dirksen, O'Brien, & Bucher, 2007). While the use of this machine during the surgery has been beneficial in stopping the heart for surgery, it poses many physical, emotional, and cognitive risks that could possibly lead to a diminished quality of life and on the rare occasion, death. Each of these negative outcomes will be further discussed.

The Cardiopulmonary Bypass Machine and How it Works

The CPB is the machine that allows surgeons to operate on a nonmoving, bloodless heart. It allows the heart to be stopped so that it can be cut open and the blockage can be corrected. This machine is the main component in a type of circulation known as extracorporeal circulation, or circulation that takes place outside of the body. Blood normally enters the heart in the right atrium and travels just below that to the right

ventricle. From there the blood exits the heart into the lungs where carbon dioxide is taken out of the blood and replaced with oxygen. After traveling through the lungs, the blood is sent back into the heart in the left atrium, enters into the left ventricle, and from there is injected into the aorta where it travels to the rest of the body. The cardiopulmonary bypass does nearly the same incredible process, outside of the body, in a machine (Hessel & Edmunds, 2003).

Stilling the Heart

In order to use the CPB, the heart must be stopped. Cardiac surgery with CPB cannot occur if the heart is still beating. Cardioplegia is the act of stopping the heart so a surgeon can operate on it. This process is done by using a solution composed of eight to twenty mEq/L of potassium, magnesium, and other components (Hessel & Edmunds, 2003). This solution may be injected into the aortic root (portion of the body's main artery that is connected with the heart) that is proximal to the clamp. Using this method will allow the solution to enter only the heart and not travel systemically. When the solution is injected into the aortic root it is known as antegrade; inserting it into the coronary sinuses is called retrograde. This mixture will arrest the heart during diastole within 30 to 60 seconds and may be combined with either a crystalloid solution or blood (Hessel & Edmunds, 2003).

The Use of Hypothermia

There has been much research and debate on whether or not the patient should be placed in a hypothermic state during CPB. Whether warm or cold cardioplegia is used, research shows that using a potassium solution will decrease oxygen consumption of the heart by 90%, but using a hypothermic state will decrease the oxygen consumption even

further by an additional 5% to 20% (Flynn, Adams, & Alligood, 2003). The patient may be chilled to a temperature of 25°C-34°C for moderate hypothermia and even less for deep hypothermia. Chilling the body showed to reduce oxygen consumption in the heart to preserve the muscle, as well as protect neurological function. According to Nussmeier (2005), every 1°C that the temperature is lowered, cerebral metabolic rate is decreased by 7%. Decreasing the metabolic rate lessens the brain's need for oxygen which helps to preserve its function. One particular study found that patients who underwent hypothermia to 34°C as opposed to 37°C had a significantly reduced decline in attention and dexterity by 55.6% and 41.3% (Nathan, Wells, Munson, & Wozny, 2001). Although many benefits to hypothermic cardioplegia have been found, warm cardioplegia has shown to be advantageous as well (Flynn et al., 2003).

How the CPB Works

After the heart is stopped, cannulas can either be placed in the superior and inferior vena cava or a single cannula can be placed in the right atrium (Hessel & Edmunds, 2003). Placing the cannulas in these locations collects the blood before it enters into the heart. From there, the blood travels into the venous reservoir. The reservoir is a great holding place for up to one to three liters of blood. It also helps to trap any venous bubbles and is the site for adding any medications or extra blood if necessary. After the reservoir, the blood enters into the membrane oxygenator. This is the vital section of the CPB that acts as the lungs of the machine. The membrane oxygenator consists of an extremely thin microporous membrane made of either polypropylene or silicone rubber. This membrane separates the gases from the blood. Although carbon dioxide is diffusible in plasma, oxygen is not and the blood must be spread very thin so

the oxygen may diffuse into the blood. Membrane oxygenators add up to 470 mL of oxygen and extract 350 mL of carbon dioxide from the blood every minute (Hessel & Edmunds, 2003).

A heat exchanger is also used in conjunction with the oxygenator. This device is typically placed just before the oxygenator because it helps to prevent bubbles from forming in the blood. The heat exchanger may be used to either warm or cool the blood based on the institution's policies, but generally the blood is cooled to minimize oxygen consumption. Monitoring the temperature of the blood during the operation as well as observing the speed and temperature of rewarming afterward is important. Rewarming too quickly or to too great a temperature may cause significant problems. It is also necessary that the cardioplegia system has its own separate heat exchanger (Hessel & Edmunds, 2003).

During the surgery and through the use of the CPB, many microemboli are produced. These are tiny clots formed either by gases or blood particles. Emboli have been found to be the cause of many difficulties following surgery. Because the brain receives 14% of cardiac output, it is especially vulnerable to receiving one or more of the microemboli which oftentimes lead to stroke (Hessel & Edmunds, 2003). Therefore, the CPB must reduce the number of microemboli to decrease the chance of plugging a vessel throughout the body. Prevention of microemboli is accomplished through the use of a membrane oxygenator, the prevention of air entering the circuit, and the use of a microfilter. Whether the microfilter is a depth filter or a screen filter, it will effectively trap microemboli and prevent them from reentering the blood stream (Hessel & Edmunds, 2003).

Once the blood is oxygenated and filtered, it enters the body, again bypassing the heart completely. A cannula into the ascending aorta is usually the entrance point of choice, but the femoral or iliac arteries are options as well. The surgeon may choose to use the femoral or iliac arteries if plaque lines the aortic wall. Atherosclerosis in the aorta is dangerous, because if pieces of the plaque become dislodged, these pieces may travel to the brain and cause a stroke (Hessel & Edmunds, 2003).

Negative Effects of the Cardiopulmonary Bypass

Physical Adverse Effects

Systemic inflammatory response. When the blood travels through the CPB, it is traveling through something much different than its usual familiar environment. Instead of traveling through the vessels that it was designed to go through, the blood is now flowing through polyvinyl chloride tubing (Hessel & Edmunds, 2003). Although the tubing is compatible with blood, blood was obviously not made to travel through the tubing. Because the blood is being introduced to this foreign material, it is only natural that the body tries to protect itself. Therefore, the systemic inflammatory response syndrome (SIRS) often occurs after CPB as the body's reaction to the new substance. It is characterized by the body producing at least two of the following characteristics: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or $\text{PaCO}_2 < 32$ mmHg, or leukocytes $>12,000$ (Laffey, Boylan, & Cheng, 2002).

Several factors may account for SIRS in many patients. One of them is the fact that the blood comes in contact with the foreign substances of the tubing and the machine itself. The second is known as an ischemia-reperfusion injury. Once the aorta is clamped

off, organs such as the brain, heart, lungs, and kidneys may not receive adequate oxygenation and may therefore experience some ischemia. But once these are reperfused when the clamp comes off, studies show that components of the inflammatory response are released, contributing to SIRS. Another factor that may indirectly lead to SIRS is the release of endotoxins from the abdominal organs after they incur injury. This injury occurs because the splanchnic vessels (vessels supplying the abdominal viscera) are generally hypoperfused during and after use of CPB (Laffey et al., 2002). Once this damage occurs, the endotoxins are released and are thought to be a cause of inflammatory response activation (Cremer et al., 1996; Laffey et al., 2002). Other factors not specifically noted with CPB that activate the response include surgical trauma, blood loss, and hypothermia, all of which also occur during cardiac surgery, leading to greater inflammation (Laffey et al., 2002).

Once the inflammatory response is activated, the body releases many different components. Complement is one of these inflammatory components that consists of several different elements. Two of these, C5a and C3a, show to be significantly elevated after CPB during a study of the inflammatory process after on-pump cardiac surgery (use of CPB) and off-pump (use of beating heart) (Ascione et al., 2000). Cytokines, such as tumor necrosis factor (TNF) and several of the interleukins (IL), are also a major component of the inflammatory response that may be increased (Laffey et al., 2002). When studying the effects of on-pump surgery, it was found that IL-8 increased and remained elevated after surgery (Ascione et al., 2000). IL-6 levels were also elevated after CPB and again at 3 hours past surgery (Cremer et al., 1996). Other elevated inflammatory components due to CPB include monocytes, neutrophil and leukocyte

elastase, and white blood cell counts (Ascione et al., 2000; Cremer et al., 1996; Edmunds, 1998; Laffey et al., 2002). The coagulation-fibrinolytic cascades are also two very important responses to inflammation. Certain plasma factors activate during CPB to form thrombin which in turn forms an insoluble fibrin clot. This process is pivotal to the understanding of how CPB can affect the body. Once the endothelium of a vessel is damaged by inflammation, its surface becomes more susceptible to platelet and clot adhesion. This has been linked to the progression of atherosclerosis and other cardiovascular complications (Laffey et al., 2002).

Approximately 20% of *low-risk* patients develop complications following CPB (Laffey et al., 2002). Not only does SIRS damage the blood vessels throughout the body, it affects the rest of the body as well. Systemic inflammatory response syndrome is a generalized inflammatory process that contributes to multi-organ failure (Laffey et al., 2002). When inflammatory mediators are elevated, impairment of organ function also occurs. A study concludes that inflammation causes the rise in transaminases, urea, creatinine, and amylase, which each indicate failure of certain body organs following surgery (Cremer et al., 1996).

Cardiovascular effects. Although the purpose of using the cardiopulmonary bypass is ultimately to correct heart problems, using this machine often leads to other adverse cardiovascular effects. These effects may be due to the inflammatory response causing aggravation to the heart, or just due to the fact that the heart is being operated on, manipulated, often frozen, and changed. One common problem after CPB is that the heart develops an arrhythmia which is any abnormal heart rhythm or speed. The most common arrhythmia following CPB is atrial fibrillation (AF), which occurs in up to 40-50% of

patients (Auer et al., 2005; Gunaydin et al., 2007). Atrial fibrillation is defined as “rapid randomized contractions of the atrial myocardium, causing a totally irregular rapid atrial rate” (Fibrillation, 2003, p. 672).

This arrhythmia that commonly happens within four days of surgery may cause hypotension, tachycardia, heart failure, stroke, and other potentially fatal events (Auer et al., 2005; Gunaydin et al., 2007). It is not known exactly what causes AF post-CPB, but it is probably due to a multitude of factors. One study found that inflammation from SIRS plays a direct role in causing atrial fibrillation. Two groups undergoing CPB were studied. When the first group underwent cardiac surgery, their cardiopulmonary bypass machine was supplied with leukofiltration and the surface of the inside of the machine and tubing was modified with a Polymethoxyethylacrylate coating. These are two methods thought to reduce the inflammatory response. The second group did not have either of these methods, and the CPB was left as it normally is. After surgery, results showed that in the first group with the leukofiltration and coating, the inflammatory mediators, such as IL-2, C3a, and white blood cells, were significantly lower. Only 10% of the first group developed atrial fibrillation whereas 35% of the group with no modification developed this arrhythmia. This study shows that inflammation plays a significant role in the development of cardiac issues after surgery (Gunaydin et al., 2007).

While the inflammatory process may play an important role in causing AF, other factors may relate to its development. Increased age may be a primary factor. Sixty-nine was the median age for those that developed AF, while 64 was the median age for those that did not (Auer et al., 2005). This same study found that the type of cardiac surgery may be a risk factor. As opposed to a coronary artery bypass graft surgery, the research

from this study showed that surgery for valvular heart disease led to a greater number of patients with postoperative AF. This may occur because valvular heart surgery often requires manipulation of the nerve fibers that cause heart conduction. Any damage to the conduction system may increase the likelihood for AF (Auer et al., 2005). Creswell et al (2005) researched many studies to find the risk factors for AF. Patients that were placed in a mild hypothermic state (34°C) during surgery had fewer incidences of postoperative AF than those in moderate hypothermia (28°C). Other factors found in this review that are associated with less AF incidences are the use of posterior pericardiotomy and the use of heparin-coated circuits (Creswell, Alexander, Ferguson, Lisbon, & Fleisher, 2005).

The heart may be damaged in other ways besides developing an arrhythmia. Using CPB was found to release a greater amount of troponin T within the first 72 hours postoperative compared with patients who had beating heart surgery (Khan et al., 2004). Troponin T is a cardiac specific protein that is released after myocardial injury. Therefore, since the level was elevated even higher after CPB, it shows a greater amount of injury to the heart muscle. Another study found that there was moderate biventricular dysfunction in nearly every patient immediately after bypass. Based on the patient's preoperative ejection fraction and degree of cardiac dyssynergy (muscular incoordination), some patients were able to recover from the biventricular dysfunction while others were not (Mangano, 1985).

Pulmonary dysfunction. Another important finding after CPB is that the lungs are also oftentimes negatively affected. Up to 20% of patients after cardiac surgery with CPB need to be ventilated for more than 48 hours because of the pulmonary dysfunction (Shlensak & Beyersdorf, 2005). Studies have shown that this pulmonary dysfunction is

caused by a variety of factors such as inflammation and ischemia (Ng, Wan, Yim, & Arift, 2002; Rajmakers et al., 1993; Shlensak & Beyersdorf, 2005).

The inflammation caused by CPB as discussed earlier plays a role in pulmonary dysfunction. This often leads to pulmonary edema and excessive pulmonary secretions (Shlensak & Beyersdorf, 2005). One study examined a lung biopsy post-surgery and found that the pneumocytes and endothelial cells of the lungs were swollen and necrotic. This damage was due to alveolar edema caused by the leakage of neutrophils and erythrocytes caused by inflammation. The edema, coupled with the facilitation of inflammatory cells and the buildup of alveolar protein, causes decreased lung compliance. This reduced compliance is evidenced by an increase in lung permeability, an increase in pulmonary vascular resistance, and changes in lung surfactant (Ng, Wan, Yim, & Arift, 2002). One study researched the increase in lung permeability caused by CPB using the ^{67}Ga -transferrin pulmonary leak index. This study showed that CPB causes a pulmonary vascular leak that was identified using ^{67}Ga kinetics. The researchers concluded that this leakage may be leading to pulmonary injury as well as the increased permeability (Rajmakers et al., 1993).

This inflammatory process may also rarely cause acute respiratory distress syndrome (ARDS). In a study of 3,278 patients undergoing CPB, 13 of them developed ARDS that resulted from the toll the inflammation took on the lungs. Although this is only 0.4% of the total population, two of those patients died. ARDS is often associated with a high mortality rate. In this study it was 15%, but other studies show the mortality rate of ARDS after CPB to be between 30-70% (Milot et al, 2001).

Ischemia of the lungs can also be a factor leading to pulmonary dysfunction. During CPB, the pulmonary artery through which deoxygenated blood enters the lungs is oftentimes clamped. This leaves only the bronchial arteries to supply blood to the lungs. Studies show that circulation of the bronchial artery (main vessel supplying oxygenated blood to the lungs) is greatly reduced during CPB, and this may be causing ischemia of the lungs (Shlensak & Beyersdorf, 2005).

In a separate study, two groups of piglets on CPB were examined. The first group was on CPB for 90 minutes and the pulmonary artery was clamped. The second group was also on CPB for the same amount of time; however the pulmonary artery was not clamped. In the end, both groups showed lung injury. This injury was determined by the increase in pulmonary vascular resistance, increased alveolar-arterial oxygen gradients, and decreased pulmonary compliance. Although both groups on CPB demonstrated pulmonary dysfunction, the first group whose pulmonary artery was clamped showed significantly greater damage. This study suggests that partial CPB in which the pulmonary artery is not clamped may be a better choice to decrease pulmonary injury (Chai et al., 1999).

One study discovered that CPB alone may not be the cause of the lung injury. It may be the result of several factors. These may include general anesthesia, sternotomy, violation of the pleura, administration of heparin-protamine, hypothermia, and others (Ng, Wan, Yim, & Arift, 2002). In one study, atelectasis, as opposed to vascular lung injury, is the main cause of pulmonary dysfunction (Groeneveld, Jansen, & Verheij, 2007). The authors concluded that the atelectasis was not caused by CPB. The amount of pulmonary injury caused by CPB has yet to be determined and is still currently being

researched. No conclusive evidence has been found (Groeneveld, Jansen, & Verheij, 2007).

Renal complications. The kidneys are very susceptible to injury after cardiac surgery with CPB. Up to 30% of these patients using CPB develop acute renal failure (ARF) and approximately 1% then requires dialysis (Rosner & Okusa, 2006). This kidney injury may then further lead to higher mortality, longer stays in the intensive care unit, and a greater risk for infectious complications. The type of cardiac surgery may play an integral role in the development of ARF. Combined coronary artery bypass grafting/valvular surgery poses the greatest risk for developing ARF (4.6% of patients), while typical coronary bypass grafting has the lowest incidence (2.5%; Rosner & Okusa, 2006).

Although the main focus of most studies is how the CPB affects renal function, Rosner and Okusa stated that most patients who are about to undergo cardiac surgery have already sustained minor or major renal insults (Rosner & Okusa, 2006). If the patient has had a myocardial infarction, then his left ventricular function was probably reduced which in turn minimizes cardiac output and reduces renal perfusion. This and other causes of renal injury preoperatively may add to the adverse effects of the CPB.

Glomerular filtration rate (GFR) is the most important determinant of renal function (Sear, 2005). The GFR is oftentimes measured by creatinine clearance. Any reduction in GFR below the normal limit illustrates that the kidneys are not functioning properly to filter urine. In a study comparing on-pump versus off-pump, the on-pump group showed a significant decrease in GFR as demonstrated by a decrease in creatinine clearance (Ascione, Lloyd, Underwood, Gomes, & Angelini, 1999). An increase in the

albumin-to-creatinine ratio and an increase in N-acetyl glucosaminidase activity in the on-pump groups showed renal dysfunction as well. Each of these renal tests shows that CPB can be harmful to kidney function. In a separate study comparing on and off-pump cardiac surgery, patients undergoing on-pump surgery had more severe cases of acute kidney injury (Massoudy et al., 2008). In this particular study, acute kidney injury was defined by having an increase in serum creatinine $\geq 50\%$ or $\geq 0.3\text{mg/dl}$ within 48 hours. Although the off-pump group did show signs of kidney injury, these patients developed it less often and had milder cases. The on-pump group also needed more renal replacement therapy (Massoudy et al., 2008).

Many suggestions have been made as to why the kidneys in particular are injured during CPB. As with most organs, the inflammatory response plays a role. The study comparing on and off-pump patients found the level of C-reactive protein and IL-6 (2 inflammatory markers) to be increased in the on-pump group. This was the group that also had more severe and frequent kidney complications postoperatively. This increase in the inflammatory response may be one of the reasons for the injury (Massoudy et al., 2008). CPB also stimulates several complements, other cytokines, and oxygen free radicals. These inflammatory mediators lead to leukocyte extravasation and edema, causing kidney injury (Rosner & Okusa, 2006).

The kidneys receive 20% of cardiac output and are incredibly sensitive to hypoperfusion (Sear, 2005). Therefore, when the kidneys are not receiving adequate perfusion, cellular injury takes place. These hemodynamic effects play a large part in the occurrence of injury (Rosner & Okusa, 2006). Ascione et al. (1999) identified this injury with hypoperfusion as well as loss of pulsatile perfusion. Other factors associated with

causing renal injury may be emboli that enter renal circulation as well as the effects of different vasoactive and nephrotoxic medications (Rosner & Okusa, 2006). A study found that preoperative mild dysfunction plays a major role in postoperative complications. In this study the following complications were common: increased mortality, renal replacement therapy, new onset of atrial fibrillation, and a longer stay in the intensive care. Since the kidneys play a large part in ridding the body of waste, any injury or failure of these organs will have detrimental effects if not taken care of immediately (Ramakrishna et al., 2008).

Adverse cerebral effects. Although adverse outcomes affecting all bodily organs can be very serious, those affecting the brain can be most damaging. Damage to the brain is most commonly caused by cerebral emboli (Patel et al., 2002). These may consist of atherosclerotic plaque, air, fat, and platelet aggregates (Roach et al., 1996). Other causes of brain injury may be hemodynamic fluctuations, cerebral hyperthermia after CPB is discontinued, and inflammation. Hypoperfusion with the ischemia/reperfusion cycle to the brain may also be another cause of damage (Hogue, Palin, & Arrowsmith, 2006). Although membrane oxygenators and arterial line filters help reduce these possible causes of injury, neurological adverse effects still occur because of CPB (Carrascal et al., 1999; Hessel & Edmunds, 2003).

Whichever the cause, there are several commonly noted cerebral outcomes. One certain study characterized the types of injuries into four different categories: persistent neurological focal deficits, stupor or coma, temporary neurological focal deficits, and seizures (Carrascal et al., 1999). Results from this study showed that 3% (76 patients) developed some type of complication. Of this 3%, 13 patients developed persistent

neurological focal deficits, 18 had a stupor or coma following CPB, 18 had temporary focal deficits, and 27 had a seizure. Twenty-nine percent of these patients died following surgery. In a separate study, adverse cerebral outcomes took place in 6.1% of the patients. They fell into one of the following categories: focal injury, stupor or coma, deterioration in intellectual function, memory deficit, or seizure (Roach et al., 1996).

When comparing off-pump and on-pump cardiac surgery, there was a 65-fold increase in cerebral microemboli produced during on-pump surgery (Bowels et al, 2001). Although there was not a significant number of deaths or strokes in this study, this massive increase in microemboli helps to show that CPB can very easily present fatal problems. In a similar study comparing off-pump and on-pump surgery, 1.6% of on-pump patients developed a focal neurologic deficit (Patel et al., 2002). These deficits may have been aphasia, loss of vision, homonymous hemianopia, hemiparesis, or comatose state. Compared with the on-pump, off-pump with aortic manipulation had only 0.4% of patients develop one of these deficits while off-pump without aortic manipulation had 0.5% develop one (Patel et al., 2002).

Although these are not high percentages, each of these studies demonstrates that use of CPB leads to an increase in neurological injury. These injuries may not lead to death, but they can be debilitating and life-changing. There are several identified risk factors: advanced age, prior stroke, systolic hypertension, diabetes, female gender, and atherosclerosis of the ascending aorta (Hogue et al., 2006).

Cognitive Adverse Effects

One subject that has varying results is that of adverse cognitive function after CPB use. One definition of cognitive decline is a 20% decrease in baseline performance

in at least 20% of the main variables such as motor skills, verbal memory capacity, and attention (Van Dijk et al., 2002). Cognitive decline can occur in up to three quarters of patients after cardiac surgery and continue for six months in a third of these patients (Newman et al., 2001a). The causes of this decline are similar to those that cause adverse cerebral effects such as a microembolism, inflammation, and hypoperfusion (Newman et al., 2001a).

In a study of 261 patients who underwent cardiac surgery, 53% of those had cognitive decline at discharge, 36% at six weeks, 24% at six months, and 42% at five years (Newman et al., 2001b). Cognitive decline in this study was defined as a drop of at least one SD in the scores on tests of any one of four domains. A drop of one SD is equal to a decline in cognitive function of about 20%. The domains studied are verbal memory and language comprehension, abstraction and visuospatial orientation, attention, processing speed, concentration, and visual memory. From this same study, the author took a different approach and also studied how neurocognitive function affected the patients' quality of life five years after surgery (Newman et al., 2001a). The researchers found that cognitive function postoperatively was directly correlated with long-term quality of life. When the cognitive function immediately after surgery was reduced, the patients generally had lower overall health and were working less productively. Through these results, this author believes that this decline in cognitive function may have negative financial and social implications (Newman et al., 2001a).

The P300 auditory-evoked potentials test measured brain function in a separate study (Kilo et al., 2001). This study reflects information processing, alertness, and memory updating. When this test was used on patients who used CPB, the P300 was

significantly impaired at seven days after surgery. However, this test showed the results to be almost normalized at four months. Although this particular test found that cognitive function may improve around four months, Newman et al. believes that patients who have cognitive decline immediately after surgery are at increased risk for long-term decline (Newman et al., 2001b).

The problem is that CPB alone may not be the cause for cognitive decline. In a study comparing on-pump with off-pump patients, the results for cognitive decline did not vary significantly (Van Dijk et al., 2002). At three months postoperatively, cognitive decline occurred in 21% of off-pump patients while it occurred in 29% of on-pump. This study shows that CPB did have slightly more patients develop cognitive dysfunction, but it also occurred in off-pump patients. These findings may demonstrate that CPB might not be the main cause. It could be a contributor, but other factors may play a role. Whether CPB is the major causative factor or not, this study shows that surgery in general may cause adverse cognitive effects. These adverse effects cause a diminished quality of life years later, including a reduction in rehabilitation abilities, work performance, and financial obligations (Van Dijk et al., 2002).

Reducing the Risks of Cardiopulmonary Bypass

The very first successful cardiac surgery using the cardiopulmonary bypass was in May of 1953 by its inventor Dr. John H. Gibbon. Although the machine helped to save lives, many patients died because of emboli; and many others who survived showed neurocognitive dysfunction after surgery. Components of the CPB such as the bubble oxygenator proved to be the cause of many of the complications such as emboli (Edmunds, 2003).

Since that first successful use of the heart-lung machine, there have been many advances in CPB. Each new change or addition to the machine has been in attempt to reduce the risks that are described above and to ultimately save lives. Because the patient's blood is introduced into an entirely new environment, no matter how close the machine is to the human's natural setting, there will always be some type of physiological reaction. "But in reality 50 years after the first successful use of the heart-lung machine and the extension of millions of lives, blood and the heart-lung machine remain incompatible" (Edmunds, 2003, p. 2223). Ways to increase compatibility and reduce these risks such as inflammation, microemboli, and heart and lung complications will be discussed here.

Membrane Oxygenators

Throughout the years, the CPB machine has made several changes in order to have better outcomes and save more lives without adverse effects. One such change is the use of a membrane oxygenator instead of a bubble oxygenator. As stated earlier, bubble oxygenators were once used to oxygenate the blood and collect carbon dioxide to be carried out of the body. However, bubble oxygenators may be allowing more microemboli to escape into the body and possibly the brain (Edmunds, 2003).

Although both the membrane and bubble oxygenators perform the same job, they do it through different means. The membrane oxygenator is either made of a microporous membrane or sheaves of hollow fibers that spreads blood out so that carbon dioxide and oxygen can be diffused. A bubble oxygenator differs in that carbon dioxide and oxygen are diffused around actual small bubbles. Although the bubbles produced increase the surface area for gas exchange, membrane oxygenators have been proven to produce less

microemboli, are less reactive to blood elements, and allow for better control of blood gases (Hessel & Edmunds, 2003).

One study in 1987 compared the microemboli produced when using the two types of oxygenators. The ten patients that used membrane oxygenators as well as an arterial line filter had zero microemboli. This varies greatly with those that used bubble oxygenators. Each of these 17 patients had between 4 and 39 microemboli detected by a Doppler ultrasound (Padayachee et al., 1987).

Heparin-Coated Circuits

Another method that is often used to reduce risks of CPB is the use of heparin-bonded circuits. Heparin is an anticoagulant drug that blocks the conversion of prothrombin to thrombin to prevent new clot formation (Hodgson & Kizior, 2009). While reducing clot formation was the original use for heparin-coated circuits, other positive benefits have been identified. Although difficult to prove clinically, heparin has some anti-inflammatory benefits; and studies show that the drug helps other portions of the body such as the lungs and heart and can reduce hospital stay (de Vroege, Huybregts, van Oeveren, van Klarenbosch, Linley, et al., 2005; Jessen, 2006; Mangoush et al., 2007).

Since the systemic inflammatory response can be so damaging to the body after CPB, understanding why it occurs and how it can be reduced is vital. Once blood comes in contact with the CPB machine, the body generally begins to defend itself with the use of defense mechanisms such as complements, interleukins, and cytokines. If these proinflammatory mediators cannot be controlled by antiinflammatory mediators, systemic inflammation will occur. These mediators lead to widespread vasodilation and increased vascular permeability, allowing fluid to seep into the body's tissues.

Endothelial damage also occurs, as well as increased heart rate and fever. The production of the cytokine tumor necrosis factor also produces thrombin which assists in the body's coagulation. This factor coupled with endothelial damage caused by proinflammatory mediators increases the body's risk of developing thrombi throughout the vascular system (Laffey et al., 2002).

Although it is not entirely known how they work, heparin-coated circuits are of some benefit in reducing this inflammatory response. In one study, 51 patients undergoing a coronary artery bypass graft were separated into those who would get a heparin-coated circuit and those whose circuit would be uncoated. After two hours in the intensive care after surgery, those patients with heparin-bonded circuits had significantly lower leukocyte counts. They also had lower concentrations of the complement C3b/c in their blood, indicating that their inflammatory response did not activate as many complements because of the heparin (de Vroege et al., 2005). One analysis of other studies found that heparin-coating inhibits contact activation and reduces complement activation (Mangoush et al., 2007). Another found that using heparin decreased complement activation, suppressed leukocyte activation, and decreased release of cytokines (Jessen, 2006).

Mainly due to the decrease in inflammation, heparin-coated circuits help to improve lung function following surgery. Inflammation causes an increase in capillary permeability and thus fluid buildup. When this inflammation occurs in the lungs, as it will with SIRS, pulmonary edema and decreased function often occurs. During the same study, de Vroege researched pulmonary function in heparin and non-heparin coated circuits. The non-heparin coated circuits demonstrated increased pulmonary shunt

fraction, decreased Pao₂/FiO₂ ratio, and increased pulmonary vascular resistance index. Each of these pulmonary indices indicates a decrease in pulmonary function (de Vroege et al., 2004).

Heparin-coated circuits reduce the need for blood transfusions and the occurrence of re-sternotomy after surgery. The drug also decreases the duration of ventilation and the patient's length of stay in the hospital (Mangoush et al., 2007). Another study comparing heparin-coated and non heparin-coated circuits showed that non heparin-coated circuits had an increased level of bradykinin (causes vasodilation and therefore decreased blood pressure) and an increase in creatine kinase. An increased level in this indicates an injury to either the heart, brain, or skeletal muscle (de Vroege et al., 2005).

Ultrafiltration

Ultrafiltration is a widely used process in pediatric cardiac surgery but has not yet been generally accepted for adult surgery. Research has shown that this procedure may be beneficial in adults as well as children. Ultrafiltration is a practice whereby the patient's blood is passed through a filter with tiny pores. Pressure throughout the filter pushes excess solutes and fluid out and then the blood is returned to the body. Two main types of ultrafiltration exist: conventional and modified. Conventional ultrafiltration is completed during CPB only, and not after it is discontinued. The blood is taken from the venous reservoir and replaced into the oxygenator. Modified ultrafiltration, on the other hand, is run after CPB is completed. Blood during this type is taken from a sideport in the aortic cannula into a hemofilter and returned to the right atrium. These processes cause a decrease in plasma volume, leading to an increase in concentration of red blood cells. This increased concentration requires that the blood be returned with crystalloid solutions

to prevent hypovolemia. Hopefully, through this process, not only are excess solutes and volume removed, but inflammatory mediators as well, thereby decreasing the inflammatory response (Boodhwani et al., 2006).

A study, although on pediatric patients, found that ultrafiltration does in fact reduce the inflammatory response as well as help pulmonary function (Huang et al., 2003). This study used a combination of modified ultrafiltration and balanced ultrafiltration, calling it continuous ultrafiltration. The article indicated that balanced ultrafiltration is similar to conventional in that it runs throughout the course of CPB and removes harmful solutes. Using this type of ultrafiltration, the tested group had much lower levels of the inflammatory mediator IL-6. This group also had lower levels of thromboxane b₂, a metabolite of thromboxane A₂ that deals with platelet aggregation. A higher serum hematocrit and albumin level was also noted in the ultrafiltration group. The authors attributed the increased serum concentration and decrease in inflammatory mediators to be the cause of the pulmonary preservation. The treated group had increased pulmonary compliance and decreased airway resistance and improved gas exchange as evidenced by decreased alveolar-arterial oxygen difference. The authors concluded that using ultrafiltration is a very beneficial choice during CPB (Huang et al., 2003).

Another study of ultrafiltration on adults showed extremely positive outcomes for the patients as well. Using combined conventional and modified ultrafiltration, patients showed higher hemoglobin, hematocrit, and platelet levels. Hemodynamically, patients treated with ultrafiltration also had increased mean arterial pressure and cardiac index. The alveolar-arterial PO₂ gradient was also decreased in this study, showing pulmonary improvement (Kiziltepe et al., 2001). A meta-analysis looking at the effects of

ultrafiltration showed a decrease in postoperative bleeding by 70ml/patient and a decrease in the need for blood products by 0.7units/patient. Modified ultrafiltration showed the greatest benefit in this analysis (Boodhwani et al., 2006).

Corticosteroids

Corticosteroids are drugs with the primary purposes of preventing and suppressing immune responses and decreasing the inflammatory response (Hodgson & Kizior, 2009). Their use with cardiopulmonary bypass has been controversial. On one hand, they have the potential to reduce inflammation, but steroids also have the potential to reduce the patient's immune system so much that they become even more susceptible to infection and wounds. Although debate exists on the use of these drugs during CPB, several studies have shown benefits to using them (Halonen et al, 2007; Whitlock et al., 2006).

Knowing that using steroids in excess may cause more adverse effects, one study researched using low doses of these throughout the procedure. Pulsing low-dose methylprednisolone, a type of adrenal corticosteroid, during CPB proved to be beneficial compared with a group that received a placebo (Whitlock et al., 2006). Those that received steroids had lower levels of IL-6, less blood loss, higher mean arterial pressure (MAP), less incidence of onset of atrial fibrillation, and shorter length of intubation when compared with the placebo group (Whitlock et al., 2006). Another study concluded that corticosteroids were successful in decreasing the incidence of postoperative atrial fibrillation, the most commonly developed cardiac dysrhythmia following surgery. Using hydrocortisone, the incidence of atrial fibrillation was 30% as opposed to 48% in the placebo group (Halonen et al, 2007). These studies indicate that corticosteroid therapy

during cardiac surgery and CPB can prevent issues such as atrial fibrillation, but may also improve other adverse effects such as inflammation and blood loss (Halonen et al, 2007; Whitlock et al., 2006).

Conclusion

Cardiac surgery has certainly advanced over the years, particularly with the development of the cardiopulmonary bypass machine. Being able to operate on a completely motionless heart is an incredible progression that may help save many lives. The CPB machine itself has come a long way in development since the first surgery and will continue to develop to enhance every patient's quality of life.

Although the CPB is an amazing machine, many adverse effects can occur. A systemic inflammatory response is the most common due to the blood being introduced to an entirely new environment. This inflammatory response can lead to many other problems throughout the body and ultimately organ failure may occur. Other adverse effects are atrial fibrillation, pulmonary damage including edema and ischemia, renal failure, and neurocognitive deficits. While some of these are not common effects, research has shown that they certainly are possible and harmful.

The goal of any surgery, in particular cardiac surgery, is to fix the previous problem and prevent adverse effects. Preventing these adverse effects is an ongoing process and will continue to be so. Using membrane oxygenators and adding filters throughout the machine have been useful in preventing microemboli from travelling throughout the body. Research has shown that coating the circuit with heparin may reduce inflammation, bleeding, the need for blood transfusions, and pulmonary injury. Ultrafiltration is being studied and found to reduce inflammation and pulmonary harm as

well. Medications such as corticosteroids are also identified to be beneficial in reducing cardiac complications and reducing the inflammatory response. It is the hope of all healthcare professionals that the incidence of harmful consequences of cardiopulmonary bypass will continue to decline and someday the risks associated will be close to zero. Until that day, research will continue and new methods will be tested to improve this already incredible machine.

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