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Summer 2022



The Academy Newsletter

A Message from the President

I hope everyone is off on a big COVID free vacation this Summer! Thanks to everyone for working so hard on the Austin, TX meeting last February! It was a big success, and we couldn't have done it without everyone. Whether it was participating on a committee or participation from one of our manufacturers or somewhere in between, it takes a perfusion village. For those of you that are Fellows and want to participate in some fashion please get in touch with me justin.resley@gmail.com or send an email to Office@theaacp.com Remember Fellows need to participate!

I am excited about Savannah, GA next February. I'm originally from El Paso, TX so having the meeting in my home state last year was fantastic and next year it will be in the state where I live....Georgia! Savannah is a fantastic foody town and recent improvements on River Street where there is a new JW Marriott with outdoor bars and restaurants only have added to the fun.

Just a few weeks ago I had the honor of giving the James P. Dearing memorial lecture to the graduating class at MUSC. It was a moving experience seeing all those new perfusionists about to take the next step into their new perfusion careers. It seems like yesterday I was starting my first day at INOVA Fairfax and then the next 31 years flew by!

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James Dearing's talent and hard work helped to create our professional perfusion identity. At the time Jim entered perfusion there were few academic credentials available and he himself didn't even have an undergraduate degree! He had the vision to create a degree of circulation technology. He was creating something that he himself couldn't even be a part of or obtain, which in my opinion was a selfless act. I implored the new graduates at MUSC to be inquisitive, ask questions, research something, be prepared, talk to others, network with your colleagues, write a protocol, publish a paper, mentor someone, let someone mentor you, and above all be active in your profession.

See you in Savannah!

Sincerely,

Justin Resley
President, American Academy of Cardiovascular Perfusion



Important Academy Dates

The ACADEMY ANNUAL MEETING DEADLINES

ABSTRACT DEADLINE **October 15, 2022**

MEMBERSHIP DEADLINE **December 1, 2022**

PRE-REGISTRATION **January 6, 2023**

HOTEL REGISTRATION **January 6, 2023**

2023 ANNUAL MEETING **February 1-4, 2023**

Taknesha Hawthorne

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Born and raised in Oklahoma City, Taknesha Hawthorne received her Bachelor of Science at the University of Oklahoma College of Nursing. She worked as a critical care cardiac nurse for eight years before being accepted as a perfusion student at Thomas Jefferson University.

The Effects of Corticosteroid Administration on the Cardiopulmonary Bypass Induced Systemic Inflammatory Response

Abstract

Cardiopulmonary bypass (CPB) is an essential component of most cardiac surgeries. Unfortunately, CPB is not without risks; it is associated with significant adverse effects that can result in multi-organ damage and even death. Cardiac surgery with the use of CPB provokes an intense response of the immune system which can lead to a systemic inflammatory response. Corticosteroids can prevent the migration of inflammatory immune cells into the circulation and enhance the release of anti-inflammatory cytokines in response to pro-inflammatory cells that are released. Due to the complexities of multiple pathways involved in the inflammatory response, it is unlikely that a single medication will be completely effective. There is limited evidence supporting the efficacy of standard corticosteroid administration in decreasing morbidity. However, there are certain procedures where corticosteroids are found to be beneficial.

Introduction

Cardiopulmonary bypass has become a fundamental part of modern cardiac surgery. CPB allows the surgical team to operate on the heart in a bloodless, motionless field while oxygenating and circulating the patient's blood. CPB is fundamental for many cardiac operations. It provides gas exchange, temperature modulation, systemic circulation, and diversion of blood from the heart in order to provide a bloodless surgical field. Unfortunately, CPB is not benign, it is associated with significant physiological disturbances that can result in end organ damage and death. Since the 1950s, there have been drastic improvements in the surgical procedures involving CPB; however, the risk of adverse effects persists. "Cardiopulmonary bypass and injury related to ischemia and reperfusion in cardiac surgery can induce a severe systemic inflammatory response" (Donneyong et al., 2018). While systemic activation can be potentially beneficial, triggering the immune system to promote healing and prevent infection, can also prove detrimental. Studies have shown that activation of the inflammatory response causes organ dysfunction and injury, adversely affecting the postoperative course. "For these reasons, numerous CPB has often been associated with the pathophysiologic changes that occur during sepsis known as the systemic inflammatory response (SIRS). Contact activation between blood and the artificial surfaces of the extracorporeal circuit is a main trigger of SIRS. The systemic inflammatory response is multi-factorial involving exposure of circulating blood to artificial surfaces of the extracorporeal circuit, shearing effects of roller pumps, hypothermia, and the non-physiological blood flow (Naase et al., 2020). The contact of blood

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with the foreign surfaces disrupts the delicate homeostatic balance that is maintained by the vascular endothelial system. These various triggers can complicate the perioperative and postoperative periods by causing the release of cytokines, leukocyte activation, and the release of many inflammatory mediators.

Several improvements have been made such as the use of centrifugal pumps, surface coated circuits, leukocyte-depleting filters, and hemofiltration. “Complications secondary to tissue damage and inflammatory response still remain and can have a profound impact on post-operative outcomes” (Naase et al., 2020). Therefore, a therapeutic strategy directed at attenuating the inflammatory effects is administration of intraoperative corticosteroids. Corticosteroids are particularly attractive because they are inexpensive, readily available, and highly effective at suppressing inflammation (Broniki et al., 2020). Corticosteroids have potent anti-inflammatory effects and have been shown to inhibit macrophage production, reduce the release of pro-inflammatory cytokines, and have favorable effects on C-reactive proteins (Donneyong et al., 2018).

Inflammatory Response

Despite many adjustments, CPB has been shown to induce cellular and immune response including release of cytokines, complement activation, activation of the proinflammatory cascade, activation of the coagulation-fibrinolytic system, and activation of the endothelium (Aljure & Fabbro, 2019). CPB induces the release of pro-inflammatory mediators such as tumor necrosis factor (TNF) and interleukin 6 and 8 (IL-6 and IL 8) (Perchermeier, 2021). The systemic inflammatory response is related to platelet, monocyte, neutrophil, macrophage activation, and cascade activation (coagulation, fibrinolytic, stimulating peptide enzyme); leading to increased endothelial permeability and blood vessel and organ parenchyma cell injury. Activation of the SIRS can also lead to respiratory failure, kidney dysfunction, liver dysfunction, nervous system dysfunction, myocardium injury and infarction, multiple organ dysfunction, and death. Activation of the complement system is achieved through the alternative pathway and the kallikrein-kinin system is also activated (He et al., 2020). Following the activation of the alternative pathway, several peptides are generated to increase the number of circulating leukocytes which promotes leukocyte adhesion to vascular endothelium and phagocyte attraction to sites of inflammation. Complement activation can cause physiological alterations that can complicate the perioperative period thus causing hemodynamic instability.

Therapeutic Strategies to Attenuate the Inflammatory Response

Attempts to inhibit the inflammatory response include avoiding CPB altogether, if possible, (off pump surgeries), modifying circuits to become bio-compatible, removing neutrophils with leukodepletion filters and the use of pharmacological treatments such as corticosteroids. However, prophylactic administration of corticosteroids has been debated and studied for more than 3 decades as a way to attenuate the systemic inflammatory response in cardiac surgery. (Donneyong et al., 2018). “Corticosteroids prevent migration of inflammatory immune cells into the circulation, reduce the release of intracellular cytokines, and decrease vascular permeability” (Perchermeier, 2021). In the context of cardiac surgery, corticosteroids are shown to attenuate complement activation, decrease the release of TNF and IL-6 and IL-8 also known as pro-inflammatory cytokines and enhance the release of IL-10, an anti-inflammatory cytokine. Therefore, corticosteroids are highly effective at suppressing virtually every aspect of the inflammatory cascade and have been shown to significantly ameliorate the inflammatory response to CPB. “What is much less clear is the impact of corticosteroids on the postoperative course and overall outcome” (Bronicki et al., 2020).

Several studies have demonstrated that the administration of corticosteroids attenuates the CPB-induced SIRS and improves the outcome of the patient. Existing evidence suggests that corticosteroids administration during cardiac surgery significantly reduces the risk of arrhythmias and shortens the length of hospital stay, without increasing the risk of infection or other complications (Donneyong et al., 2018). Corticosteroids also significantly reduced the incidence of pulmonary adverse outcomes

and the incidence of atrial fibrillation. (Ng et al., 2020).

Historical overview of corticosteroid administration during CPB

By the 1960s and 70s, the CPB induced systemic inflammatory response syndrome following cardiac surgeries was becoming well known. Methylprednisolone was the drug of choice due to its anti-inflammatory effects and minimal tendency to induce water and sodium retention. At the time the optimal dosage was 30 mg/kg due to its benefits in clinical shock studies; there were no studies showing the detrimental systemic effects yet. Towards the end of the 1970s, patients being treated with methylprednisolone were found to have longer necessity for post-operative respiratory support. However, another study showed that patients receiving methylprednisolone exhibited less vasoconstriction and significantly improved perfusion flows. Clinically the patients were also mentally alert earlier and left the ICU earlier. In 1978, methylprednisolone was revealed in a study to have cardioprotective properties. Perioperative myocardial biopsies revealed that methylprednisolone helped preserve cardiac cellular integrity by less mitochondrial damage, improved bypass graft flow rates (56% higher), improved postoperative urine output (67% higher), and fewer postoperative chest x-ray abnormalities (Chaney, 2002).

During the 1980s, the importance of the administration of a 1gram dose of methylprednisolone with the initiation of CPB to compensate for hemodilution was discovered. The 1980s also brought about the discovery that CPB was associated with the complement activation; leading to the majority of the subsequent investigations involving steroid administration to be focused on complement activation. Many studies during this time suggested that despite the inability of methylprednisolone to completely inhibit complement activation, it may be able to attenuate the complement mediated neutrophil activation that is associated with CPB (Chaney, 2002).

In 2018, a systematic review and meta-analysis of 56 randomized controlled trials that were published between 1977 and 2015, including both the Dexamethasone for Cardiac Surgery (DECS) and Steroids in Cardiac Surgery (SIRS) trials. The results determined that mortality did not significantly vary between the control groups and patients receiving perioperative corticosteroids. While the use of corticosteroids does exhibit increased cardiac index and significantly decreased SVR. Rates of postoperative infections were significantly lower in the steroid groups and there was also a statistically significant reduction both mean intensive care unit stay and hospital length of stay. "However, study authors questioned the clinical relevance of these differences because they were only 43 minutes and 9 hours, respectively" (Crawford & Townsley, 2019). The meta-analysis also found no significant effect of corticosteroids on neurologic outcomes or renal failure. The analysis also suggested that outcomes may potentially be age dependent. Patients younger than sixty-five appeared to have a lower risk of mortality when receiving corticosteroids, whereas patients older than eighty demonstrated an increased mortality risk with steroid administration (Crawford & Townsley, 2019). In contrast, a study by Hao and colleagues showed that the prophylactic administration of methylprednisolone during CPB did not decrease the number of inflammatory monocytes or T cells. (Hao et al., 2019)

The role of steroids in heart transplantation

Every year, there are about four thousand heart transplantations performed worldwide. The median survival rate is steadily improving; however, the long-term outcome is still far from ideal. The release of pro-inflammatory cytokines is even greater in patients undergoing heart transplants than coronary artery bypass surgery, due to the duration of CPB and ischemia time being much longer. Immunosuppressive therapy is essential to preserve graft function and is a standard component of induction, maintenance, and anti-rejection therapy in heart transplant recipients. High dose steroids are generally administered intraoperatively as well as postoperatively. Optimal immunosuppressive therapy will include a combination of different drugs in order to enhance the immunosuppressive effects as well as decrease their toxic effects with the lowering of the dosage of each. The main corticoster-

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oids that are used to treat allograft rejection are prednisone and prednisolone. According to Sandha et al., (2018), the addition of corticosteroids to the perfusion solution can minimize the development of myocardial edema and the generation of proinflammatory cytokines during normothermic heart transplantation.

The role of steroids in deep hypothermic circulatory arrest

Currently, there are no drugs that are specifically indicated for neuroprotection during open-heart surgery. “Cardiac surgery with use of deep hypothermic circulatory arrest (DHCA) is known to be associated with impaired cerebral oxygen metabolism and cerebral edema” (Fudulu et al., 2018). If the neuroinflammatory response associated with CPB is triggered by systemic inflammation, high-dose corticosteroids could potentially attenuate this neuroinflammatory response. Corticosteroids are used to treat cerebral edema; therefore, this is justification for their presumed neuroprotective effect during DHCA. According to Fudulu et al, while steroid administration had no effect in normothermic cells, in the deep hypothermia-treated cells methylprednisolone increased cell survival but decreased protective interleukins. However, there is no clear evidence that corticosteroid administration translated to better clinical outcomes.

Corticosteroids are associated with a significant improvement in cerebral oxygen metabolism and recovery of cerebral blood flow after DHCA. Although some studies have reported a neuroprotective effect, others have demonstrated no clinical advantage. Therefore, there is still inconclusive evidence of the neuroprotective effects of corticosteroids; however, some studies indicate that the administration of corticosteroids after termination of DHCA may have a beneficial effect on cerebral metabolism, reduce capillary permeability which prevents tissue edema, and enhances brain tissue perfusion (Gocoł et al., 2020). Further studies are necessary due to the discrepancy in variable treatment algorithms before widespread application is implemented.

The role of steroids in pediatric surgery

In pediatric surgery, there is believed to be a greater importance in modulating the inflammatory response due to the surface of the extracorporeal circuit relative to the reduced circulating blood volume, leading to more pronounced hemodilution, and the more frequent use of DHCA when compared to procedures in adults. “There are three main indications for corticosteroid use in pediatric heart surgery with the use of cardiopulmonary bypass (CPB): (1) to blunt the systemic inflammatory response (SIRS) induced by the extracorporeal circuit; (2) to provide perioperative supplementation for presumed relative adrenal insufficiency; (3) for the presumed neuroprotective effect during deep hypothermic circulatory arrest operations” (Fudulu et al., 2018). In its biochemical aspects, perioperative steroid administration can significantly attenuate the CPB-induced systemic inflammatory response. However, steroid administration doesn't have significant effects on mortality, although there is a slight trend of reduced mortality in steroid-treated patients. Bronicki et al., (2021) found through a meta-analysis of pediatric cardiac surgeries, corticosteroids have a favorable impact on postoperative fluid balance as well as being associated with shortening the duration of mechanical ventilation. Corticosteroids may be beneficial particularly for pediatric patients undergoing highly complex congenital surgeries and DHCA. “Cerebral protection during deep hypothermic circulatory arrest (DHCA) is the least studied indication for the application of steroid therapy in neonates undergoing cardiac surgery” (Crawford & Townsley, 2019). Therefore, more research is needed in order to study the effects of DHCA in pediatric patients.

Adverse effects of steroids

“The impact of corticosteroids on perioperative mortality is unclear and confirmation regarding the safety of their perioperative use in cardiac surgery is lacking” (Donneyong et al., 2018). Corticosteroid adverse effects appear to be related to dosage and duration; adverse effects are more common at higher dosages and with chronic use. The most common adverse effects of corticosteroids include immunosuppression, osteoporosis, hyperglycemia, adrenal suppression, myopathy, psychiatric

disturbances, hypertension, and dermatologic adverse effects (Yasir et al., 2021). In addition, corticosteroids have been associated with poor wound healing and increased risk of gastrointestinal bleeding (Ng et al., 2020). Corticosteroids also alter fluid and electrolyte balance and suppress the immune system (Donneyong et al., 2018). However, the addition of GI prophylaxis and a glucose control protocol may nullify some of the potential adverse effects of corticosteroids. There may also be a higher incidence of myocardial adverse effects related to patients receiving corticosteroids during surgery. However, these results need to be interpreted with caution due to the majority of cases of myocardial complications came from only the SIRS trial where a myocardial injury was defined as a rise in CK-MB and/or presence of new Q waves postoperatively (Ng et al., 2020). Older age, comorbidities such as diabetes mellitus, concurrent use of other immunosuppressive agents, and poor nutritional status can all influence the occurrence and magnitude of adverse effects (Yasir et al., 2021).

Discussion

Through a review of several meta-analyses, there was no significant effect on mortality regarding the administration of perioperative corticosteroids. However, it is not excluded that there is a possibility that there may be beneficial effects of corticosteroids. Although there are some results that conclude that the administration of corticosteroids can reduce infection, there is no conclusive evidence that they have a true impact on postoperative infections (Perchermeier, 2021). “The use of corticosteroids in patients undergoing cardiac surgery with cardiopulmonary bypass has not been shown to improve mortality rates beyond standard care” (Perchermeier, 2021). Therefore, the use of prophylactic corticosteroids is no longer routine in adult cardiac surgeries (Fudulu et al., 2018). The strength of corticosteroid anti-inflammatory effects and clinical side effects are related to dosage. There may be an appropriate dosage range that can effectively inhibit systemic inflammation and trigger protective function of corticosteroids without side effects. Corticosteroids may protect rather than destroy cardiomyocytes (He et al., 2020). In the pediatric population, there is evidence suggesting the administration of corticosteroids is beneficial. Of note, many of the older studies involving corticosteroids and CPB utilized bubble oxygenators which undoubtedly possess greater capability of inducing the SIRS response. The current standard of practice is to utilize membrane oxygenators. Further study of cardiopulmonary surgeries using membrane oxygenators, centrifugal pumps, surface modified circuits, and leukocyte depleting filters with the administration of a standardized dosing of corticosteroids in patients of all ages is necessary to determine the benefits and risks.

Conclusion

The use of cardiopulmonary bypass during open-heart surgery provokes an acute inflammatory response which is often unpredictable and carries a significant risk of mortality and morbidity due to the activation of blood and the synthetic perfusion circuits. The pros and cons of corticosteroid prophylaxis in patients undergoing open-heart surgery have been the subject of debate for many years. While corticosteroids can blunt inflammation, it does not necessarily translate into improved clinical outcomes. Complications of steroids are often dose and duration dependent; therefore, the administration of low dose steroids may attenuate the traditional adverse effects. Due to the intricacies and diversity of the multiple pathways that are involved in the inflammatory response, it is unlikely that a single drug will ever be completely effective. Patients undergoing CPB are so vulnerable to post-operative infection due to the inflammatory response, a thorough understanding and finite control of therapeutic interventions is necessary to optimize patient recovery.

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Intraoperative Goal Directed Perfusion Association with Postoperative Renal and Cerebral Malfunction

Introduction

When discussing cardiac surgery, it is essential to understand the potential complications that may occur intraoperatively and postoperatively based upon surgical events, patient hemodynamic monitoring, and perioperative risk factors. Cardiopulmonary Bypass (CPB) is a critical component of cardiac surgery but is not without its complications. CPB practices are operated in a way that attempts to protect the patient, provide a bloodless surgical field, and minimize systemic tissue damage all at once. However, current perfusion practices can lead to multiple potential sources of organ damage simply due to the nature of CPB. In large, the conduct of perfusion amounts to alterations in native organ perfusion, especially when analyzing the transition from pulsatile flow to laminar flow. In organs such as the kidneys and the brain, this changes the overall amount of blood flow being distributed to these areas. In turn the level of oxygen delivery to sustain adequate tissue perfusion to meet tissue metabolic demands is affected. Each of the physiological factors that perfusion practice controls intraoperatively, can correlate to patient postoperative outcomes and complications—most commonly acute kidney injury (AKI) and cerebral injury. Most previous research has assessed the effects of mean arterial pressure (MAP) and pulse pressure with the incidence and risk of the two postoperative outcomes (9, 20). However, recent studies have looked closer at the effect of oxygen delivery (DO_2) on postoperative kidney and cerebral function, as the value is directly influenced by blood flow on CPB—one of the main factors perfusionists control during the conduct of CPB. The events that influence DO_2 intraoperatively to the cerebral and renal systems are multifactorial and have been noted to lead to and increased incidence and risk of postoperative AKI as well as cerebral injury.

Oxygen Delivery (DO_2)

Oxygen delivery (DO_2) is the volume of oxygen delivered to the tissues throughout the body within in one minute. It is determined by the arterial blood flow (Cardiac output) and the arterial oxygen content (14). To have a full understanding of the physiological mechanism of oxygen delivery, it is imperative to discuss the relationship between DO_2 , arterial oxygen content (CaO_2), venous oxygen consumption (VO_2), and oxygen extraction rate (O_2ER). CaO_2 is the amount that hemoglobin is saturated by oxygen at a given moment and has a direct relationship with DO_2 —a rise in content will promote a rise in DO_2 (6, 16). VO_2 is represented as the amount of oxygen taken up and utilized by the body OR the amount of oxygen consumed by perfused tissues during one minute (6, 16). O_2ER is the ratio between VO_2 and DO_2 and thus, is the amount of oxygen extracted from the blood under the influence of consumption and delivery (6, 16). In a normal metabolic state, VO_2 is independent of DO_2 , and the body remains in aerobic metabolism (6, 16). When oxygen delivery matches the tissue oxygen demand, adequate tissue perfusion occurs. Normal DO_2 ranges from 900-1000ml O_2 /min and normal VO_2 ranges from 100-270ml O_2 /min equating to a normal O_2ER of ~20-30% (6, 16). Since DO_2 is dependent upon cardiac output, as well as arterial blood oxygen content, any change in these factors will influence oxygen delivery. Decreased cardiac output or flow will yield de-

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Sydney is a rising second year, graduate student at Thomas Jefferson University's MS in Cardiovascular Perfusion program—Class of 2023. By being a student member of both AmSECT and the American Academy of Cardiovascular Perfusion she has been able to become further involved in the patient safety and scientific advancement for perfusion practice. Her undergraduate education was completed with a BA in Health Science from Gettysburg College in December of 2020. In the interim, Sydney worked as a student research assistant II at Children's Hospital of Philadelphia under PI Dr. Todd Kilbaugh. Here she pursued her interest in Cardiovascular perfusion through the involvement in translational research projects pertaining to Cardiopulmonary Bypass and ECMO. She is currently placed at Virtua-Our Lady of Lourdes Hospital in Camden, NJ for a clinical rotation and will be moving on to Cooper University Hospital in Camden, NJ for the summer. She will finish second year at the Children's Hospital of Philadelphia for the fall and Thomas Jefferson University Hospital in Philadelphia, PA for the spring. Born and raised in Woolwich Township, NJ, she attended Kingsway Regional High School—Class of 2017—but has grown to appreciate all of the opportunities the city of Philadelphia has to offer while attending Jefferson.

creased oxygen delivery, and decreased oxygen content or hemoglobin will yield decreased oxygen delivery. Demand/ delivery mismatch will then occur (6, 16). As such, when a decrease in hemoglobin concentration, oxygen saturation, or blood flow occurs, organ O_2ER begins to increase to meet metabolic demands from VO_2 (6, 16). If the factors contributing to delivery are not corrected and maximum O_2ER is reached, a critical DO_2 level is met that stimulates abnormal cellular anaerobic metabolism—decreasing organ oxygen consumption, tissue ischemia, and increasing lactate levels inducing metabolic lactic acidosis (11). In this state VO_2 becomes dependent upon DO_2 . However, if DO_2 falls and metabolic demand decreases as a response to temperature changes or decreased tissue activity levels (as under anesthesia or the influence of paralytics), then this homeostatic response should not occur (6, 16).

Oxygen Delivery (DO_2) and Cardiopulmonary Bypass

One of the more recent developments in perfusion practice is the work towards implementation of Goal-directed perfusion for cardiopulmonary bypass. To ensure adequate flow on CPB, BSA and cardiac index are used to tailor each flow range to each specific patient (15). The established equation for the calculation of DO_2 is as follows: $DO_2 = Q_{blood} \times 10 \times CaO_2$ (15). The modified DO_{2i} equation to account for BSA is as follows: $DO_{2i} = DO_2 / BSA$ (15). Research shows that the known critical value for DO_{2i} is 280ml/min/m² to maintain adequate tissue oxygen delivery (16). With this information, an equation was derived to yield a “safe” CPB flow value to maintain DO_2 above the established critical DO_{2i} : $Q_{blood} = 280 \times BSA / [(Hgb \times 1.34) + 0.62] \times 10$ (15). This allows perfusionists to generate a minimum flow value prior to CPB conduction that will maintain adequate tissue oxygen delivery to meet metabolic demand, while only needing to take into consideration the patient's BSA and Hgb (15).

An imbalance between oxygen delivery and oxygen consumption (VO_2) leads to overall acute circulatory failure following cardiac surgery (1). The purpose of CPB is to provide a constant source of oxygen to tissues in place of the heart and lungs. Therefore, the control of DO_2 and the demand/ metabolism balance falls under the role of perfusion to prevent tissue hypoxia and organ dysfunction (1). Since flow, otherwise known as cardiac output, is used to determine native DO_2 , it is only fitting that the same principle be applied when determining adequate oxygen delivery on cardiopulmonary bypass. This is known as indexed oxygen delivery (DO_{2i}) and is determined by dividing calculated DO_2 by the patient BSA. The idea behind goal directed perfusion is to standardize the values for adequate oxygen delivery while introducing a level of specificity for each patient. During CPB, DO_{2i} is dependent upon hemoglobin concentration, oxygen saturation, pump flow, and the partial pressure of oxygen (14). However, the value is calculated differently depending upon the heart and lung machine model with subsequent flow probes and technology (2). All equipment uses a

modified version of the established Ranucci equation: $DO_2 = \text{pump flow} (\text{Hb} \times 1.36 \times \text{Hb saturation} + 0.003 \times \text{arterial oxygen tension})$ (2). However, LivaNova, Mirandola, and Italy use the CONNECT software which calculates DO_{2i} via: $DO_2 = \text{flow} (\text{Hct}/2.94 \times 1.36 \times \text{SaO}_2 + \text{PaO}_2 \times 0.003)10$ (2). Spectrum Medical, Gloucester, and England use the M4 software which calculates DO_{2i} via: $ecDO_2 = 10Q_{\text{blood}} \times \text{Hb} \times 1.34 (\text{SaO}_2/100)$ (2). Depending upon the HLM model as well as the software used, DO_{2i} varies per hospital equipment (2). It was also shown in recent studies that varying circuit types will influence the DO_2 value as well (2). This includes roller pumps vs centrifugal, open vs closed shunts, tubing type, and oxygenator type with a port for exhaust gas—release CO_2 (2).

Acute Kidney Injury and Cardiopulmonary Bypass

Following cardiac surgery with use of cardiopulmonary bypass, development of acute kidney injury occurs in 20-40% of patients less than 48 hours postoperatively from a rapid deterioration in renal function (14). Stage I expression of this deterioration presents as a reduced glomerular filtration rate (GFR) with urine output under 0.5cc/kg/hr and a rise in serum creatinine (SCr) levels greater than 150% over a baseline of 0.3mg/dl (4, 17). The manifestation of AKI is an impairment of renal function, persistent renal vasoconstriction, exaggerated response to exogenous vasoconstriction, and death of vascular endothelial and tubular epithelial cells due to ischemic necrosis (17, 19). There are three different scoring references with three different grades to diagnose the severity of AKI, however they all use serum creatinine and GFR as references and markers of injury (19). Each scoring reference is used to diagnose the severity of prerenal, intrinsic renal, and post renal presentation of the injury. The two most relevant common presentations of kidney injury for cardiac patients undergoing cardiopulmonary bypass are prerenal and intrinsic renal. Prerenal causes of AKI include any sudden and severe reduction in blood pressure or interruption of blood flow to the kidneys from severe injury or illness—blood loss, dehydration, heart failure, sepsis, and vascular occlusion (17). Intrinsic renal causes of AKI include any direct injury to the kidneys via inflammation, drugs, toxins, infection, or reduced blood supply (17). BUN/creatinine ratios differentiate between the two types, however CPB during cardiac surgery can lead to both postoperatively. Prerenal presents as a BUN/creatinine ratio greater than 20 whereas intrinsic renal presents as 10-20 (17).

Renal blood flow amounts to ~20% of overall cardiac output, so any adjustment to this factor will influence blood flow to the kidneys (3, 4). Normally, the renal medulla is naturally, chronically low in oxygen tension (pO₂) making its oxygen reserve limited (16). Normal renal oxygen delivery equates to 80ml/minute/100g tissue with oxygen consumption less than 10% of the total body usage—supply exceeds the demand (4). With the natural low tissue oxygen reserve, it is imperative that oxygen supply to the renal tissues remains significantly higher than the consumption (4, 16). The medullary region of the kidney—low oxygen reserve—maintains a lower volume of blood flow compared to the cortex but makes up the highest amount oxygen extraction from the oxygen delivered (4, 16). This is due to its high oxygen requirement for tubular reabsorption functionality (4). Therefore, any perioperative or intraoperative condition that led to oxygen/supply demand imbalances could easily induce periods of ischemia to the tissue if not monitored or controlled properly (4, 9, 11, 16).

Lannemyr et. al. conducted a study showing a decrease in renal DO_2 during CPB of ~20% as a result of renal vascular vasoconstriction and hemodilution leading to renal oxygen supply-demand mismatch. More specific conditions could also include low cardiac output/flow on CPB, hypotension, and loss of pulsatile flow as reviewed by Vives et.al. However, their study also found with the presence of sustained DO_{2i} during CPB, hemodilution still resulted in impaired renal oxygen supply-demand mismatch expressed by increased renal O₂ER. Even though overall DO_{2i} remained stable, renal DO_2 decreased resulting in reduced arterial O₂ content due to hemodilution at a constant renal VO_2 . On CPB, the kidneys may suffer from an imbalance between the amount of oxygen that is available and the renal metabolic demand. This is largely due to the decreased

hemoglobin concentrations that may ensue preoperatively as well as hemodilution intraoperatively which decreases oxygen carrying capacity to supply the renal tissue with oxygen (11). Based on the factors that influence DO_2 , increasing CPB flow should remediate the issue if not sustained for extensive periods of time as shown by a study conducted by Oshita et al. In this study they analyzed the largest area under the curve (AUC) that represented the time and depth DO_{2i} fell below the critical threshold to its return to above as an indicator for the risk of postoperative AKI. The critical DO_{2i} referenced here was $<262-272\text{ml}/\text{min}/\text{m}^2$ under mild hypothermia, and surgical procedures were non-specific. The largest AUC below the $DO_{2i\text{crit}}$ was referenced as an independent risk factor for postoperative AKI. However, the cumulative time and depth on CPB that DO_{2i} fell below the critical value and returned above was not identified as such. Therefore, it is the longest and deepest fall below that critical value that may indicate an increased risk for postoperative AKI, rather than the cumulative AUC throughout the conduct of CPB.

Cardiopulmonary bypass specifically alters regional blood flow to and through the kidneys as well as renal vasomotor tone. Both lead to a reduction in renal parenchymal pO_2 which decreases renal perfusion pressure, and overall increases the risk of ischemia-reperfusion injury (19). In a study conducted by Lui et. al., it was discussed that any decrease in the amount of oxygen supplying the renal tissues increases the risk of tissue ischemia in the area, which proves that a highlighting risk factor for AKI is decreased oxygen delivery (11). By using a critical DO_{2i} threshold of $<272\text{ml}/\text{min}/\text{m}^2$, they showed that they lowest DO_{2i} value during CPB was the best predictor of peak postoperative sCr levels and thus risk for AKI. Either way, the percentage of occurrence as well as the risk of postoperative AKI increases with prolonged CPB duration, severe hemodilution, and low oxygen delivery (11).

Cerebral Injury and Cardiopulmonary Bypass

Any cardiac surgery is particularly tricky when it comes to discussing cerebral safety especially. There are many sources of cerebral injury that can occur—ischemic/ micro embolic stroke and postoperative delirium (POD) or postoperative cognitive disorder (POCD) to name a few (18, 20). POD and POCD are common complications after cardiac surgery involving CPB and are defined as a functional impairment of essential nervous system activities (12). They occur in 30-80% of patients during the first postoperative week (8). POD arises within 1-3 days postoperatively (12) whereas POCD appears within one week (12) and can last up to several months in 50% of patients (8, 10). Neuropsychological tests are commonly used to assess and diagnose cognitive function, but the timing, specificity, and sensitivity of the tests influence the final diagnosis (7). All forms of cerebral injury present with a similar etiology, but the extent as to what postoperative symptoms present as depends upon the severity and location of the ischemic lesion (7). Diagnostic techniques for detecting potential cerebral injury, aside from a physical neuropsychological test, include MRIs to detect the presence of ischemic lesions as well as glucose monitoring (7). Hyperglycemia in general—not including diabetic patients—is a source of several mechanisms contributing to cerebral injury via cellular acidosis, oxidative stress, increased blood brain barrier permeability, and cerebral edema (7). Elevated serum glucose is common when conducting bypass due to a stress induced response to CPB itself (7). Therefore, perioperative, and postoperative glucose control and monitoring to keep levels between 80-110mg/dl are used to predict the severity of potential cerebral damage (7).

As CPB is conducted, determinants of cerebral blood flow and metabolism correlate with non-CPB cerebral conditions, however the two factors—Cerebral blood flow (CBF) and Cerebral metabolic rate ($CMRO_2$)—can still be highly affected by CPB conduction (4). Cerebral perfusion makes up about 15% of total cardiac output and adequate flow to maintain tissue perfusion is $\sim 10\text{cc}/\text{kg}/\text{min}$ (3, 4). The main determinates of adequate CPB perfusion are mean arterial blood pressure (MAP), hematocrit, cerebral metabolism, and $PaCO_2$ for autoregulation (4). When considering all of these factors together, each can be adjusted while on CPB. When approaching a critical MAP of 55mmhg on bypass, CBF as well as cerebral oxygen delivery, significantly declines with any amount of hemodilution—increase in hemodilution, and thus decrease in hematocrit, increases cerebral blood flow even

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with a change in MAP (4). At ~60mmhg cerebral autoregulation of flow and blood pressure over 15 minutes is disrupted (10). Cerebral autoregulation ensures a CBF of about 50ml per 100g of brain tissue per minute with a perfusion pressure ranging from 60-100mmhg (18) Therefore, cerebral metabolism becomes compromised as there is a lack of oxygen delivery to meet cerebral metabolic demand. In a study conducted by Wiberg et.al., an average MAP between 40-50mmhg and 70-80mmhg yielded no difference in the risk of postoperative ischemic injury indicating that CDO₂ is more likely to be “the driver.” At normal conditions, non-CPB, cerebral oxygen delivery (CDO₂) far exceeds the cerebral metabolic rate (CMRO₂) (5). Normal cerebral oxygen consumption is referenced as ~3.5ml/100g brain tissue/min which an average basal metabolic rate of 49mlO₂/min⁻¹ (3). When CDO₂ becomes significantly reduced—as with reduced hematocrit, MAP, and pump flow—adequate CMRO₂ is sustained via an increase in the oxygen extraction (5). Garrison et. al. defines DO₂crit as the boundary of shock delineating the region of physiological response between regional or global aerobic and anaerobic metabolism. Once the critical CDO₂ value is met, oxygen extraction hits maximum and cerebral tissue ischemia occurs (5). Contrary to renal DO₂ supply, increasing flow on CPB or CBF in general has little to no effect on increasing CDO₂ when necessary (5). As hemodilution decreases hematocrit, a critical hematocrit can be reached where the CBF response can no longer compensate for the severe reduction in arterial blood oxygen content with the use of oxygen extraction (5). Therefore, to subsequently ensure adequate CDO₂, hematocrit must be increased either with hemoconcentration or the addition of pRBCs (5). Otherwise, ischemic conditions will occur without the ability to increase oxygen delivery to meet demand.

Discussion

In a study conducted by Leenders et. al., significantly lower DO_{2i} was associated with patients who suffered postoperative delirium using a critical value higher than what was associated with AKI-<310ml/min/m² at normothermic conditions. This analysis furthers the idea of the difficulty to maintain a specific DO₂ value for goal directed perfusion. In a multitude of studies, DO₂ was noted to be easily influenced by factors that perfusionists can control while conducting CPB. However, the varying DO₂ requirements per tissue increases the difficulty to mitigate potential postoperative complications such as AKI and cerebral injury intraoperatively. This is without including the results from those patients that preoperatively present with renal insufficiency and cerebral impairment due to underlying pathophysiological conditions typically associated with cardiac injury. Needless to say, the topic of DO₂ and goal directed perfusion association with postoperative complications is an area that needs to be explored in greater detail as technology continues to change regarding perfusion practices.

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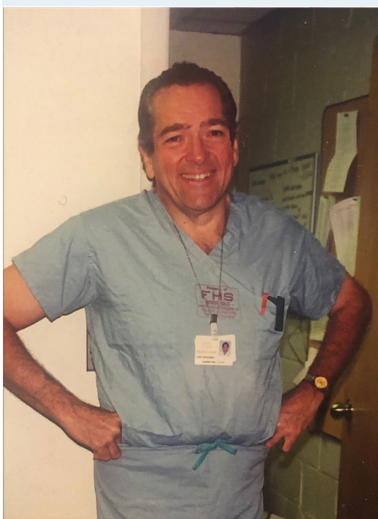
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