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Complications in Cardiac Surgery

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COMPLICATIONS IN CARDIAC SURGERY

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Nursing at the University of Kentucky

By
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ABSTRACT OF DISSERTATION

COMPLICATIONS IN CARDIAC SURGERY

Quality of care and outcomes from cardiac surgery have always been of primary importance to providers and the entire health care team when caring for cardiac surgical patients. Providers in cardiac surgery have had a long history of tracking procedural morbidity and mortality rates in programs nationally and internationally. Morbidity and mortality rates vary widely among hospitals. In most studies in which procedural outcomes from cardiac surgery are evaluated, the focus has been on operative morbidity and mortality and the probability of death after a cardiac surgical procedure. Less attention has been paid to predictors of perioperative complications, and sample sizes have been relatively small in the studies done. The focus of this dissertation was identification of perioperative predictors of perioperative complications associated with cardiac surgery to identify patients who could be at risk for morbidity or mortality related to the cardiac surgical procedure. We used a large hospital registry and had large sample sizes for our studies. By identifying those patients at risk for perioperative complications, modifiable risk factors can be addressed in order to prevent untoward outcomes.

The purpose of this dissertation was to identify demographic, clinical and surgical predictors of selected common perioperative complications that can lead to morbidity and mortality in the cardiac surgical patient and the contribution of these complications to length of stay in the Intensive Care Unit (ICU) and overall length of stay in the hospital after an open chest cardiac surgical procedure with cardiopulmonary bypass. By identifying predictors of perioperative complications, we can identify patients preoperatively who may be at higher risk and intervene before a complication occurs. There are three manuscripts included in this dissertation.

The aim of the first study (N = 2399) reported in manuscript one was to determine demographic, clinical and surgical predictors of perioperative packed red blood cell transfusion in coronary artery bypass graft surgery patients undergoing cardiopulmonary bypass, and to test gender-specific models. The following predictors of transfusion were included: 1) age; 2) gender; 3) previous coronary artery bypass graft surgery; 4) body surface area; 5) number of grafts; 6) hematocrit prior to surgery; 7) hypertension; 8) diabetes mellitus; 9) history of heart failure; 10) dyslipidemia; 11) cardiopulmonary bypass time; and 12) elective versus emergent surgery. In the overall sample the
following predictors were identified: 1) age; 2) body surface area; 3) cardiopulmonary bypass time; 4) prior coronary artery bypass graft surgery; 5) preoperative hematocrit; and 6) elective versus emergent surgery. Older age, lower body surface area, longer cardiopulmonary bypass time, history of prior coronary artery bypass graft surgery, lower preoperative hematocrit and emergent surgery were independently predictive of transfusion. In the male only model (n = 1721) the following were predictors of transfusion: 1) preoperative hematocrit; 2) body surface area; 3) cardiopulmonary bypass time; and 4) elective versus emergent surgery. In the female only model (n = 678) the following were predictors of transfusion: 1) preoperative hematocrit; 2) cardiopulmonary bypass time; and 3) body surface area.

The aim of the second study was to determine the association of number of major perioperative complications of open-chest cardiac surgery and cardiopulmonary bypass (N = 2350) with ICU and hospital length of stay. The number of complications was predictive of a prolonged length of ICU stay and overall hospital length of stay. Major complications were considered to be neurological complications, specifically stroke, renal insufficiency and failure, respiratory failure, myocardial infarction, heart failure and bleeding which led to reoperation. We showed that one complication did increase the length of stay in the ICU but when there were two or more complications the length of stay increased significantly, revealing that it is imperative to optimize the patient as much as possible before surgery to avoid potential complications.

The purpose of the third study was to (1) determine predictors (i.e. gender, age, surgical procedure, body mass index, last creatinine level, chronic lung disease, diabetes control, history of stroke in the past, history of myocardial infarction, class of heart failure, hypertension, cerebrovascular disease prior to surgery, previous cardiac procedure, post-surgical complications, re-operative bleeding, and number of major complications) of ischemic and hemorrhagic stroke in patients who had undergone cardiothoracic surgery and (2) determine if neurological complications prolonged patient length of stay. We found three significant predictors of post-surgery stroke: body mass index (Wald(1) = 6.21, p = 0.01), having chronic lung disease (Wald(1) = 5.37, p = 0.02), and having diabetes control at the time of surgery (Wald(1) = 4.82, p = 0.03). More specifically, the results indicated that (1) having a higher body mass index decreased the odds of patients experiencing post-surgery stroke with a one unit increase in body mass index decreasing the odds of experiencing post-surgery stroke by 91%, (2) having chronic lung disease increased the odds of patients experiencing post-surgery stroke by 196%, and (3) diabetes control at the time of surgery decreased the odds of patients experiencing post-surgery stroke by 31%.

This dissertation has filled an important gap in the evidence base for complications related to cardiac surgery in patients by identifying complications that could lead to a prolonged length of stay as well as predictors of stroke and the use of blood transfusion. The results of these studies can lead to the prevention of these complications and therefore the reduction in perioperative morbidity and mortality. The findings from this dissertation provide further evidence of the value of identifying patients at higher risk of complication undergoing cardiac surgery.
KEYWORDS: cardiac surgery, stroke, cardiopulmonary bypass, blood transfusion, complications

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COMPLICATIONS IN CARDIAC SURGERY

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Chapter One

Introduction

Coronary artery bypass grafting (CABG) and valvular open-heart surgeries have become commonplace with the advent of cardiopulmonary bypass (CPB). Although CPB is lifesaving and has vastly increased the effectiveness and reach of cardiac surgery, its use is associated with serious complications. Developed in the early 1950s, CPB allows a surgeon to repair life-threatening problems of the heart by stopping the heart and emptying it of blood while maintaining body functions. Cardiac surgery with CPB is a process whereby a heart-lung machine temporarily takes over the function of the heart and lungs during surgery. Unfortunately, while on CPB the heart-lung machine damages blood cells, thus leading to many adverse reactions within the body (Cohn, 2012; J.K. Kirklin et. al., 1983).

Cardiopulmonary bypass surgical teams have a long history of tracking procedural morbidity and mortality rates. For example, in the Society of Thoracic Surgery national database, most evaluations of outcomes in cardiac surgery with CPB focus on perioperative morbidity and mortality (Ahmed, Butler, & Novick, 2014). The current perioperative mortality rates for CABG and valvular open-heart procedures are 3.4%, with 15% of these deaths occurring within the first 24 hours following surgery. Cardiac complications account for approximately 62.1% of these deaths within the first 24 hours. Respiratory failures account for 11.8%, infections 7.7%, and neurological injury, 6.0% of the perioperative mortality (Mazzeffi et al. 2019).

The purpose of this dissertation was to (1) identify the most common major complications associated with cardiac surgery with CPB, and (2) identify modifiable risk
factors or predictors for these complications. There were no studies done with large
groups of patients undergoing open chest cardiac surgery in a single institution that
identified possible predictors that could lead to complication perioperatively. A single
institution that collects meticulous prospective databases on all of their patients can
provide pilot data for future multi-center studies. To fill this gap in the literature, I used a
large comprehensive database with well-validated measures. The goal was to provide
data that can lead to practice changes to improve perioperative outcomes. The knowledge
gained through this dissertation could be used in order to prepare a patient by optimizing
their health preoperatively for the surgical procedure more efficiently to improve the
postoperative outcomes. Each chapter of the dissertation illustrates some common
complications associated with cardiac surgery and addresses some possible interventions
to alter negative outcomes. The specific aims of this dissertation were to:
Specific Aim 1: determine predictors of need for packed red blood cell (PRBC)
transfusion during or after CABG surgery with CPB.
Specific Aim 2: determine gender differences in predictors of need for packed red blood
cell (PRBC) transfusion during or after CABG surgery with CPB.
Specific Aim 3: determine the relationship between occurrence of one or more major
cardiac surgery complications (i.e., pulmonary, neurological renal and cardiac
complications) and length of stay in the ICU as well as overall hospital length of stay in a
large sample of 2350 patients undergoing cardiothoracic surgery with CPB.
Specific Aim 4: To define predictors (i.e. gender, type of surgical procedure, mortality,
last creatinine level, diabetes control, hypertension going into surgery, cerebrovascular
disease prior to surgery, previous cardiac procedure, post-surgery complication, and
reoperation because of bleeding) of stroke in patients who have undergone cardiothoracic surgery with CPB.

Morbidity and mortality after cardiac surgery with CPB are driven by the use of CPB. Although CPB is lifesaving and has vastly increased the effectiveness and reach of cardiac surgery, its use is associated with a number of serious complications. Cardiopulmonary bypass was developed in the early 1950s in order to repair life threatening problems of the heart by stopping the heart and emptying it of blood. It is a simple concept based upon the fact that the heart is really two blood pumps, the right and the left heart, working continuously to supply oxygenated blood to the body. The lungs provide a surface through which oxygen and carbon dioxide can be exchanged where the primary function of the heart is to deliver this oxygenated and decarboxylated blood to all other organs in the body (Cohn, 2012).

The conceptual framework used in this dissertation (Figure 1) was based on the physiological description of CPB and the changes that the body undergoes while on CPB. Complications may arise after a patient is on CPB for open chest cardiac surgery and is described in the model (Figure 1).

Cardiopulmonary bypass totally replaces the function of the heart and lungs during cardiac surgery (Figure 1). In order to maintain organ function and viability during cardiac surgery, the pump must sufficiently oxygenate and circulate blood to all vital organs to prevent ischemia and reperfusion injury, minimizing cell swelling and edema, and prevent intracellular acidosis. Minimizing time on CPB is important because the ability to perform these functions is not as good as that of a normal heart and there are
The term failure to rescue (FTR) has been used to quantify the risk of morbidity and mortality in the past after a cardiac surgical procedure. It is an indicator of hospital quality. Hospitals used the quantification of morbidity and mortality to determine how well their patients did postoperatively in the past rather than looking at the complications themselves (Edwards et al., 2016). A larger hospital may report lower morbidity and mortality than smaller hospitals but have higher complication rates and this is why the complication rate needs to also be reported (Ahmed et al., 2014; Edwards et al., 2016).

The analysis of FTR rates for patients with CPB yields information about the performance of specific institutions and their surgical complication rate which institutions can use to modify protocols for their specific patients (Ghaferi et. al., 2011). However, lower mortality rates do not directly correlate with fewer complications; it is crucial to identify and track perioperative complications in addition to mortality rates because complications prolong length of stay as well as can predict further complication during the perioperative period (Reddy et al., 2013).

In a study by Ghaferi et al. (2011), the analysis of FTR rates and complication rates in the context of a hospital's available resources prevent mortality through successful management of perioperative complications, resulting in patient outcome improvement. Ghaferi et al. posit that the successful management of complications and the positive behaviors and attitudes of those providing care, improve patient outcomes (Ghaferi, Birkmeyer, & Dimick, 2011). Poor performing hospitals with low successful FTR rates have the opportunity to improve their patient outcomes through better
teamwork and patient care and management of complications (Gonzalez, Dimick, Birkmeyer, & Ghaferi, 2014).

**Cardiopulmonary Bypass**

Once the patient’s blood begins to interact with the surface of the bypass machine there is risk for organ and tissue damage as well as platelet activation and red blood cell damage (J. Larmann & G. Theilmeier, 2004). What sets blood apart from other body fluids and liquid is that it begins to clot shortly after it is exposed to any surface other than vascular endothelium (Cohn, 2012; Kortekaas et al., 2012; Yuh, 2014). Clots will destroy the function of the vascular system whether they are macro- or microscopic (Yuh, 2014). In addition to activation of the clotting cascade, cellular and chemical components of blood are very fragile and prone to injury because they are hitting the surface of the CPB, with both insidious and subtle consequences as well as more catastrophic consequences (Cohn, 2012; Karkouti, Beattie, et al., 2005; Yuh, 2014).

Other problems, in addition to the fragility of the blood components when the blood is exposed to non-physiological surfaces like the cardiopulmonary bypass circuit, include the maintenance of adequate perfusion pressure, the use of non-pulsatile flow, and maintenance of blood homeostasis (Cohn, 2012; Yuh, 2014).

**Pulsatile Flow**

During CPB, the systemic vascular resistance of the patient changes, causing increased venous tone and decreased oxygen consumption suddenly once the cardiopulmonary bypass circuit switches to laminar flow, or non-pulsatile flow (J. Larmann & G. Theilmeier, 2004). There is also a depression of the cell-mediated immune
response, metabolic acidosis, and catecholamine release once the blood becomes in direct contact with the surface of the circuit (Raja & Dreyfus, 2005).

**Damage to Blood Components**

The blood is exposed to not only the abnormal environment of the synthetic nonendothelial cell surfaces but also abnormal blood flow with turbulence in the CPB circuit (Yuh, 2014). This exposure can potentially result in hemolysis and/or clotting resulting in micro- and macro-emboli and anemia, increasing the risk of death through hemodynamic instability and low cardiac output organ damage (DeFoe et al., 2001). Defoe et. al. (2001) found that a low hematocrit makes coming off bypass at the end of the operation difficult as well as necessitating intraortic balloon pump support for hemodynamic stability (DeFoe et al., 2001). Williams et. al. (2013) found preoperative hematocrit to be a strong independent predictor of perioperative mortality as well as renal failure and deep sternal wound infections (Williams, He, Rankin, Slaughter, & Gammie, 2013b). Lower hematocrits increases the likelihood of perioperative allogenic blood transfusion which has been shown to increase the morbidity and mortality of cardiac surgical patients in itself (Kumar, 2009). CPB requires anticoagulation because the surface of the circuit itself is procoagulant and will overwhelm the natural coagulants to produce thrombin (Cohn, 2012), initiating the clotting cascade and increasing the risk of not only extensive clotting but also, once the clotting factors have been depleted, increased risk of hemorrhage (Yuh, 2014).

**Fluid Status Fluctuation**

There are several factors affecting fluid balance during CPB: 1) body temperature; 2) plasma colloidal pressure; 3) interstitial pressure; 4) capillary
permeability; and 5) urinary output (Yuh, 2014). Fluid balance will also be affected by the presence or absence of heart failure in the patient preoperatively (Sirvinskas et al., 2008). In the oxygenator of the CPB machine there will be a denaturation of protein and destabilization of soluble fat both affecting the colloidal property of the blood (Raja & Dreyfus, 2005). This loss of protein function increases plasma viscosity and decreases the solubility of plasma, producing macromolecules that aggregate, causing emboli (Yuh, 2014). Denatured proteins are removed from the plasma by the reticuloendothelial system because the damage to the protein is irreversible, and therefore the specific function as well as the polarity of the protein is damaged. Platelets and white blood cells are also damaged in the oxygenator as well, causing release of vasoactive substances and micro-emboli, contributing to edema (Yuh, 2014). Hematocrits will increase because plasma volume shifts to the interstitial space if it is not excreted into the urine. It can take up to five days to regain normal total body water content after cardiopulmonary bypass (Sirvinskas et al., 2008).

Potential Cellular Damage Leading to Inflammation

Initially, on CPB, there is a drastic drop in systemic vascular resistance once the circuit changes to laminar flow, and there is a release of histamine (J. Larmann & G. Theilmeier, 2004). Along with this histamine release there is activation of endothelial cells because of the mechanical stress of the cells hitting the surface of the CPB circuit (Jan Larmann & Gregor Theilmeier, 2004). Damage to these cells causes a release of nitrous oxide synthase, which will result in inflammation (J. Larmann & G. Theilmeier, 2004). When bypass begins, the aorta is cross clamped causing a burst of transient ischemia. This ischemia/reperfusion can cause reversible as well as irreversible cellular
injury (Yuh, 2014). This transient ischemia is termed oxidative stress (J. Larmann & G. Theilmeier, 2004) and contributes to the endothelial damage as well as to cardiac tissue damage (J. Larmann & G. Theilmeier, 2004). Complement activation occurs because of surgical trauma-induced tissue thromboplastin release (Kortekaas et al., 2012; J. Larmann & G. Theilmeier, 2004). The purpose of the complement system is to reduce tissue damage by clearing pathogens from an organism, and consists of proteins and proteases that release cytokines (Janeway, 2005). Complement control proteins regulate the complement system, but when the CPB circuit changes the blood flow and the myocardium experiences the transient ischemia endotoxin, damage can begin the cascade (J. K. Kirklin et al., 1983). Damage to host tissue may occur because the membrane attack complex of the complement system causes cell lysis (Janeway, 2005). The components of the complement system, C3a and C5a, are also potent pro-inflammatory mediators known as anaphylatoxins and are produced once the complement system is activated (Hugli, 1986).

These mediators result in tissue changes, including vasoconstriction, increased vascular permeability, and induction of histamine release and modulation of host immune responses (Raja & Dreyfus, 2005). The overall levels of C3a are directly dependent on the duration of cardiopulmonary bypass, however Kortekass et. al. (2011) found that there may already be circulating complement in patients who have heart failure (Kortekaas et al., 2012). Neutrophils damaged by the CPB circuit will also stimulate the complement system, releasing further enzymes and proteases and leading to further tissue damage (J. Larmann & G. Theilmeier, 2004).
**Renal Failure**

Many patients experience the complication of renal failure related to CPB. Reduction in glomerular filtration rate or increased tubular reabsorption during cardiopulmonary bypass due to the non-pulsatile flow of the CPB circuit result in alterations in glucose transport (Yuh, 2014). End organ damage may occur due to embolization as well as homeostatic changes. Perioperative renal dysfunction is associated with an increased length of stay in the hospital and intensive care unit with a reported incidence of 5% to 30%. Of those, 1.5% of patients end up needing dialysis (Bahar et. al., 2005). Sirvinkas et. al (2008) found that renal insufficiency is associated with a more complex perioperative course and can increase the risk of mortality by up to 80% (Sirvinkas et. al., 2008). Bahar et. al. (2005) reported a mortality rate of 79% in a group of cardiac surgical patients with acute renal failure (ARF) as compared to 4.8% in the group who did not develop ARF (Behar et. al., 2005).

Because the kidneys, like the brain, are relatively sensitive to ischemia, acute postoperative renal dysfunction or failure goes hand in hand with ischemic brain injury. The renal failure itself also may contribute to postoperative encephalopathy, and these patients with acute renal failure likely represent an important high-risk subgroup worthy of careful neuropsychological assessment.

Ischemia is a major factor in renal dysfunction associated with CPB and is related to multiple factors, however one of the most significant factors is decreased renal perfusion during bypass time (Karkouti, Beattie, et. al., 2005). The glomerular filtration rate has been found to decrease as much as 30% during bypass (Bahar et. al., 2005). Karkouti et. al., 2005 found that there is a significant association between length of
bypass and its associated hemodilution and perioperative renal failure subsequently needing dialysis (Karkouti, Beattie, et. al., 2005). Other risk factors for postoperative renal injury include age over 70, diabetes mellitus, and a history of previous cardiac surgery (Yuh, 2014).

Vascular effects of CPB also can potentially damage the kidney as circulating catecholamine is decreased due to hemodilution and hypotension with resulting decreased renal perfusion (Yuh, 2014). This hypotension and non-pulsatile flow of the blood during CPB also causes an endocrine response as when the left atrial pressure is low, antidiuretic hormone (ADH) is released. The hormone ADH is also known as vasopressin and has major effects on the kidneys in preventing water loss and antidiuresis, or concentration of urine (Schrier, 2006). Activation of the renin angiotensin system through ADH release and a low renal perfusion pressure will further decrease renal blood flow (Yuh, 2014).

As with all organs, the micro-emboli and hemolysis of the red blood cells associated with CPB can damage the kidney and cause renal dysfunction from ensuing edema and then renal tubular necrosis (Bahar et. al., 2005). The destruction of the tubules can lead to infection with the potential for activation of the inflammatory and coagulation process already in place. This increases the risk of sepsis (Almassi, et. al., 1999).

**Blood Glucose Fluctuation**

Glucose may be obtained from exogenous sources through glycogenolysis or gluconeogenesis as there is also increased glycogenolysis secondary to epinephrine increase during CPB. The catecholamines epinephrine and norepinephrine are both increased with CPB, and after CPB begins blood glucose levels rise with a decrease in
insulin resulting in insulin resistance. There is also an abnormal pancreatic insulin response due to the hypothermia associated with CPB, and this, along with the binding of insulin to the artificial surface of the CPB, will result in a cascading effect of osmotic diuresis, dehydration, and increased cerebral edema. Maintenance of blood chemistry and pH, temperature, glucose management, adequate oxygen carrying capacity and adequate oncotic pressure are also important as is maintenance of normal hormonal function (Cohn, 2012; J. W. Kirklin & Kouchoukos, 2003; Yuh, 2014).

**Neurological Complications**

Another danger during CPB is the cross clamping of the aorta in order to maintain a bloodless field and to allow the CPB to be connected to the aorta. Injury may occur with the manipulation and clamping especially if it is calcified or friable (Yuh, 2014) (J. W. Kirklin & Kouchoukos, 2003). If the aorta is calcified, atheromatous debris could detach and travel to organs increasing the risk for perioperative stroke, aortic dissection, and postoperative renal dysfunction (Iijima et al., 2010; Yuh, 2014). There is also a risk for ventricular arrhythmia once the aorta is cross clamped due to electrical stimulation of the aorta. The risk of having a calcified aorta increases with age, especially after the age of 60 (Yuh, 2014).

Normally, cerebral blood flow is maintained at a constant rate irrespective of systemic blood pressure through autoregulation, a process whereby small cerebral resistance arterioles vasodilate or vasoconstrict as needed in response to a wide range of systemic blood pressures (Murkin, Farrar, Tweed, McKenzie, & Guiraudon, 1987). The brain in a resting state consumes 20% of cardiac output (Murkin et al., 1987). The reason constant cerebral perfusion is so important and highly conserved through autoregulation
is that the brain is very sensitive to ischemia (Ono et al., 2012). In circumstances of complete cardiac standstill such as in sudden cardiac arrest, permanent ischemic brain injury can occur in as little as two minutes (Yuh, 2014). Unfortunately, the systemic perfusion pressure generated by CPB in some patients may drop below the lower blood pressure limits of cerebral autoregulation, creating an opportunity for ischemic brain injury (Murkin et al., 1987; Ono et al., 2012). Cerebral neurons are also sensitive to low pH, or acidosis (Ono et al., 2012), and in fact one of the single most important factors linked to mortality rate status post cardiac arrest is post-arrest pH.

Anesthetic agents used during cardiac surgery can also alter cerebral blood flow, but they also reduce cerebral metabolic needs, potentially offering a protective as well as a hemodynamic effect (Sirvinskas et al., 2013). Cerebral infarction both due to a generalized or global compromise of cerebral perfusion called a watershed infarction, and/or emboli which are generated during CPB may occur (Karkouti, Djaiani, et al., 2005). Emboli occlude cerebral arteries and may damage specific anatomical regions of the brain, causing focal neurological deficits (Yuh, 2014). Therefore, given that there are several ways that the brain can be damaged during CPB, ranging from subtle to catastrophic, it is very important that neurological, especially neuropsychiatric, function be assessed both before and after surgery. It is necessary to document all types of injury which might impair one’s quality of life and functional capacity. In instances where a patient’s perioperative cardiac output is so poor that they are hypo-perfusing the brain, as well as other organs, that restoration of normal or less abnormal cardiac output after surgery may in some instances improve neurological (Yuh, 2014) and neuropsychiatric function.
Older age increases the risk of stroke, cognitive impairment or behavioral change especially after the age of 60 (Yuh, 2014). Identifying what specific demographics and physiological factors predispose individual patients to cerebral hypoperfusion injury during CPB could potentially greatly improve patient selection for CPB and/or better quantify the risks of CPB for individual patients so they can make as informed a decision as possible before proceeding with, or not proceeding with, cardiac surgery.

**Lung Injury**

Pulmonary impairment after cardiac surgery and CPB is multifactorial but can contribute to increased morbidity and prolonged extubation times (Raja, 2005). Because of excessive pulmonary capillary fluid filtration from capillary damage by complement release and activation of the coagulation cascade there can be increased pulmonary endothelial permeability, and changes in alveolar surfactant composition (Cohn, 2012; J. K. Kirklin et al., 1983; Raja, 2005; Yuh, 2014). During CPB, blood flow to the lungs is minimal or may be absent altogether which will increase the risk for ischemic changes and, because of the decrease in plasma oncotic pressure as well as hemodilution, there will be an increase in interstitial lung water (Cohn, 2012). These changes in lung tissue and function will compromise the function of the lungs and result in altered oxygenation as well as increase the risk of infection (Cohn, 2012).

**Emboli**

The CPB system produces a variety of gaseous and foreign emboli and can result in regional organ ischemia (Rozsa, Szabo, Gombi, Balazs, & Sztermen, 1989). Air embolism is considered to be the most dangerous type of embolism because nitrogen is poorly absorbed by the blood. Since carbon dioxide is easily absorbed in the blood it is
often used in the surgical procedure to displace the air that may have entered into the CPB circuit (Yuh, 2014). The CPB cannot prevent the generation of emboli but the membrane oxygenator of the circuit is designed to prevent or remove macroemboli through filtration. Massive air embolism, macrogasious emboli, nitrogen emboli, fat, and platelet aggregates usually are generated from the surgical field from the location of the cardiotomy, the incision made into the heart (Brooker et al., 1998). Blood aspirated from the surgical field at this point has the greatest risk of emboli (Brooker et al., 1998). Massive air embolism is a catastrophic event requiring the termination of CPB and removal of air in the circuit (Yuh, 2014).

**Infection**

To gain access to the heart and to place a patient on CPB, an incision must be made along the sternum and then the sternum divided. Because this is a large bone with very little blood flow to help with healing, there is a risk for infection and dehiscence. McDonald et al. (1990) found that independent risk factors for median sternotomy dehiscence were female sex, obesity, those with diabetes mellitus, and prolonged postoperative ventilation (McDonald, Brame, Sharp, & Eggerstedt, 1989). Even when CPB is necessary a smaller incision may be made to expose the heart. Advantages of a partial sternotomy are reduction in in surgical trauma and blood loss, and less risk to cardiac structures (Saleh, Alwair, & Chitwood, 2013). This smaller sternotomy has the advantage of fewer pulmonary complications as well because of earlier extubation time and less anesthesia and analgesia postoperatively (J. W. Kirklin & Kouchoukos, 2003).
Hypothermia

Cardiac surgery in adults is routinely performed with mild hypothermia of 29 to 32 degrees Celsius, and this allows for organ protection because of the decreased metabolic requirements. A lower temperature than this can cause changes in organ function and lengthened period of CPB (Yuh, 2014). Even with this lowered temperature, diaphragmatic function can be impaired, leading to decreased work of breathing and longer intubation times (J. W. Kirklin & Kouchoukos, 2003; Yuh, 2014). Even mild hypothermia reduces platelet aggregation and endothelial associated coagulation, which could cause increases in postoperative bleeding (J. K. Kirklin et al., 1983; J. W. Kirklin & Kouchoukos, 2003).

Neurological effects of hypothermia include a 5 to 7% reduction in cerebral metabolism for each degree Celsius reduction in the patient’s body temperature (Sirvinskas et al., 2013). This effect is actually protective against cerebral ischemic injury, since the reduced metabolic demand lessens the need for oxygen and nutrient supply (Murkin et al., 1987; Sirvinskas et al., 2013). Hypothermia also causes coagulopathy, which prevents the formation of emboli and associated embolic event related ischemia. Postoperative hyperthermia (fever) has the opposite effect in that it will increase cerebral metabolic demand 5 to 7% per degree Celsius and will increase the likelihood of cerebral ischemic injury in vulnerable patients (Yuh, 2014).

In summary, cardiopulmonary bypass has historically been a great advance in that it has saved lives through the ability to repair defects of the heart. The many mechanisms by which patients can sustain life-altering consequences of CPB mandate a thorough assessment of their functional status before and after surgery by checking basic
laboratory values as well as pulmonary function tests and mental status examination. Foremost among such consequences are neurological and neuropsychiatric sequelae which are difficult to detect at the bedside yet have potentially profound effects on quality of life and functional capacity. Several mechanisms related to the cardiopulmonary bypass machine can cause damage to the neurological system such as micro-emboli, air emboli, changes in fluid status, and hypothermia as well as hypoglycemia. The risk of bleeding and the potential for the need of blood transfusion is high since CPB changes the ability of the blood to function in addition to damaging the blood components. Other serious complications associated with CPB, such as renal and lung injury, can occur due to the changes in laminar flow as well as with the damage to blood components and changes in the way the blood flows through the CPB machine. With new cardiac surgical procedures and the ability to perform cardiac surgery off bypass, it may be possible to avoid the negative effects of the cardiopulmonary circuit in some instances.

**Organization of the Dissertation**

Each chapter of this dissertation illustrates some significant common complications associated with cardiac surgery. The purpose of Chapter Two was to determine possible predictors of the need for blood transfusion in coronary artery bypass grafting surgery using CPB using a large database of patients in one large institution in order to provide information on modifiable predictors with the long-term goal of decreasing the use of blood transfusion.

The purpose of Chapter Three was to determine whether there is an association of single occurrences versus multiple occurrences of complications of cardiac surgery using
CPB with length of stay as well as mortality. Patients had undergone valve surgery as well as open chest coronary artery bypass grafting, and aortic dissection repair.

The purpose of Chapter Four was to determine risk factors for perioperative stroke. The goal of determining risk factors for perioperative stroke is to improve preoperative planning to prevent stroke associated with CPB.

In Chapter Five, the summary and conclusions from the prior chapters are presented and clinical implications and recommendations for future research are discussed. We anticipate that the findings of these studies will contribute to the comprehensive evaluation of the cardiac surgical patient prior to surgery in elective as well as emergent surgery. Results from this dissertation will translate to improved outcomes for cardiac surgical patients and will assist healthcare providers in clinical decisions and complication management.
Figure 1: Conceptual Framework of Physiologic Effects of Cardiopulmonary Bypass and Patient Outcomes

Open Chest Cardiac Surgery with Cardiopulmonary Bypass

- Altered tissue function
  - Leaky blood brain barrier
  - Injury and Inflammation
  - Tissue hypoperfusion
- Thoracic cage dysfunction/pleural pressure changes
- Altered cardiac pre-load and after-load

Blood loss anemia
- Coagulation dysfunction
- Base deficit
- Serum glucose elevation
- Hemodynamic changes

Mortality and Morbidity Outcomes
- Infection
- Perioperative bleeding
- Neurological complications
- Renal dysfunction
- Pulmonary complications
- Myocardial complications
- Length of intensive care unit and hospital stay

Altered respiratory function
- Hypotension
- Hypovolemia
- Decreased brain tissue perfusion

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CHAPTER TWO

Background

Coronary artery bypass graft (CABG) surgery has become a common surgical procedure, with over 200,000 procedures completed annually in the United States (Linzad et al. 2018). Although CABG surgery is potentially lifesaving for individual patients, complications occur and have a reported mortality rate of about 2% (LePar et al., 2018). Because CABG is often associated with severe bleeding, due to the open-chest surgical procedure and manipulation of tissue that occurs during the procedure, there is a risk for hemorrhagic shock. Allogenic blood transfusion has been the most common intervention during cardiac surgery to manage bleeding and post-operative anemia, and cardiac surgery annually uses about 20% of the available blood supply every year in the United States (LePar, et al., 2018).

Despite the frequent use of allogenic blood transfusion with CABG, transfusion has been associated with higher morbidity and mortality postoperatively. In an isolated CABG, the most common procedure performed by cardiac surgeons, the proportion of patients receiving transfusion at different institutions varies widely, from 10-90% of use in their surgical patients. Identifying patients who are at most risk of needing a blood transfusion could help practitioners treat patients’ conditions preoperatively in order to avoid the need for transfusion. Intraoperative measures to decrease transfusion requirements during the cardiac surgical procedure have been developed, such as shorter cardiopulmonary bypass time, smaller incision sites, and minimally invasive sites (Williams, et al., 2013). Nonetheless, blood transfusion remains one of the most utilized therapies during and after CABG surgery.
Transfusion of red blood cells is intended to maintain or restore tissue oxygenation and perfusion and is used to maintain a circulating volume of blood and red blood cells. However, there is an association between red blood cell transfusion and tissue ischemia (Murphy et al., 2007). Due to increased blood cell aggregability and increased circulation of proinflammatory cytokines there is an increased risk for sepsis, stroke, and myocardial infarction association with blood transfusion (Karamnov, S. et.al., 2018).

Transfusion in cardiac surgical patients intraoperatively as well as postoperatively has been found to be associated with postoperative infectious complications such as sternal wound infection and postoperative pneumonia. Other complications associated with the use of blood transfusion include renal dysfunction, postoperative impairment of pulmonary function, and multiple organ failure. These complications may prolong length of stay. In a study completed by Crawford et. al. (2018), one unit of postoperative blood transfusion was found to be the single factor most strongly associated with the risk of postoperative mortality and with an increase in the length of hospitalization as compared with those patients who underwent the same procedure but who did not receive transfusion.

Transfusion has been associated with an increased risk for poor surgical outcomes with an increased risk for sepsis and pneumonia due to increased intubation times, as well as with the development of renal failure postoperatively (Craver, Belk, & Myers, 2018). Pattakos et al., (2012) compared a group of patients who refused blood transfusion (n=322) due to religious reasons with a larger group undergoing the same cardiac procedures (n=87,453) and found that those who did not receive transfusion had fewer acute
complications, a shorter length of stay, and better overall survival at one year. Lima et al., (2017) found that transfusion worsened postoperative outcomes significantly for patients who had comorbidities such as cirrhosis, congestive heart failure, sepsis, respiratory disease, and cancer, and blood transfusion was found to be the single factor most strongly associated with increased postoperative mortality, with an increased risk of 77% (OR 1.77, CI 1.67- 1.87) doubling the risk of renal failure (OR 2.06, CI 1.87- 2.27), and a 76% increase in the risk of serious infection (OR 1.76, CI 1.68-1.84) after surgery (Banbury, Brizzio, Rajeswaran, Lytle, & Blackstone, 2006).

Because CABG surgery has been associated with a high rate of allogenic blood transfusion, and transfusion is associated with a higher morbidity and mortality which includes a higher infection rate and longer hospital stay associated with higher cost, the risk and benefit of blood transfusion should be considered carefully (LaPar et al., 2018). Patients who are at higher risk to receive blood transfusions should be recognized so that they can be managed postoperatively to minimize the need for transfusion.

Previous investigators have shown that transfusion use varied greatly among institutions and that age, sex and presence of comorbidities were predictors for transfusion. Williams, et. al., (2013) found that lower hematocrit and lower body surface area were seen among women, and these patients had higher transfusion needs. Despite previous work in this area, questions remain about predictors of need for transfusion to better inform practice. Thus, we performed a secondary analysis of data from a large, consecutive cardiac surgery database from a large tertiary care referral center in Louisville, KY to evaluate factors associated with the need for transfusion in patients with isolated CABG. Given known gender differences in cardiac surgery outcomes, an
additional purpose of this study was to determine gender differences in predictors of need for transfusion.

**Specific Aims**

Specific Aim 1: determine predictors of need for packed red blood cell (PRBC) transfusion during or after CABG surgery with CPB.

Specific Aim 2: determine gender differences in predictors of need for packed red blood cell (PRBC) transfusion during or after CABG surgery with CPB.

**Methods**

*Design and Setting*

This study was a correlational predictive secondary analysis of data from the ongoing adult Cardiothoracic Surgery Database of the University of Louisville Department of Cardiothoracic Surgery collected at Jewish Hospital in Louisville, KY from January 1, 2011 to December 31, 2014. The database is a collaborative effort on the part of the hospital-based cardiothoracic surgical group. The database encompasses adult cardiac surgery and includes coronary bypass graft (CABG), surgery of the aortic, mitral, tricuspid, and pulmonary valves, surgery of the thoracic aorta, arrhythmia procedures, and less commonly performed procedures such as removal of tumors. These data are used to report performance on National Quality Society of Thoracic Surgeons-endorsed metrics for specific procedures. The database also is used for feedback reports, quality assessment, performance improvement initiatives, and research (Jacobs et al., 2016).

Eligible patients were those who met the following criteria: 1) a confirmed diagnosis of coronary artery disease referred to the institution for surgical treatment; 2) had undergone the procedure of primary, isolated CABG surgery of at least two coronary
artery sites; and 3) older than 18. Patients identified by these selection criteria were enrolled in the study for analysis. For this secondary data analysis, we included 2399 patients who were eligible out of a complete database of 5500.

After Institutional Review Board approval and consent waiver, our data were obtained from the adult cardiac surgery database of the University of Louisville Department of Cardiothoracic surgery collected at Jewish Hospital in Louisville, KY from January 1, 2011 to December 31, 2014. Data was collected preoperatively and postoperatively on all patients undergoing cardiac surgical procedures. Data were contemporaneously collected and stored in an electronic format at the time of operation in such manner that it could be accessed at a later point in a Health Insurance Portability and Privacy Act (HIPPA) compliant manner.

Measures

All data for the study were extracted from the database. Sociodemographic variables extracted were age and gender. These variables were originally obtained from the admission registration form.

Clinical variables extracted from the database were diagnosed comorbid conditions of heart failure confirmed by a cardiologist, hypertension, diabetes, dyslipidemia, preoperative hematocrit and body surface area. These data were originally obtained from referring cardiologists’ history and physical forms completed prior to surgery. The preoperative hematocrit used was the preoperative testing hematocrit for non-hospitalized patients and the day before or day of surgery hematocrit for hospitalized patients.
Surgical variables extracted were total perfusion time, history of prior CABG, and elective vs. emergent surgery. These data were originally obtained from the operative report. Mortality was defined as any intra- or postoperative death in the study sample. These data were extracted from the database and obtained originally from the surgical and discharge records.

**Outcome Variable**

Postoperative hematocrits were extracted and were obtained from original laboratory reports. The preoperative hematocrit used was the preoperative testing hematocrit for non-hospitalized patients and the day before or day of surgery hematocrit for hospitalized patients.

Data were entered into the database by surgical residents, nurse practitioners, fellows and the physician who managed the database. Data entry was limited to only those providers who were trained by the data manager, who was a physician. All those extracting data were trained on the method of data mining to maintain accuracy.

**Transfusion**

At this institution, the decision to transfuse packed red blood cells was based upon the patient’s clinical condition and treating practitioner’s judgement. The usual practice at the institution was to transfuse if the hemoglobin was 7 dl/l or below with clinical signs of hypovolemia such as hypotension and tachycardia. The practitioners who made the decision to transfuse were surgeons, surgical residents, or cardiothoracic nurse practitioners. All data regarding intraoperative and postoperative transfusion type and volume were extracted from the database.
Data Analysis

Demographic, clinical and surgical characteristics were presented in means with standard deviations or frequencies with percentages as appropriate to the level of measurement. These characteristics were then compared between those receiving blood transfusion and those who did not and between men and women. Independent student t-tests were used to compare normally distributed continuous variables. A Wilcoxon rank-sum test was used for non-normally distributed continuous variables, and chi square tests were used to compare proportions of categorical variables. To respond to the specific aims, we constructed a single binary multiple logistic regression model for the entire sample, and then two separate models, one for men and one for women, using binary multiple logistic regression analysis. All variables were entered into each model to determine which were independent predictors of the outcome. The assumption of independence was met as was the assumption of a linear relationship between the continuous independent variables and the logit transformation of the dependent variable, and no problems with multicollinearity were identified. All statistical analyses were performed using SSPS version 22 (Chicago, Ill.), with alpha set at .05.

Results

Characteristics of the Sample

Full sample. The characteristics of the participants are presented in Table 1. Based on the selection criteria there were 2399 patients enrolled in the study. Participants’ mean age in the sample was $62 \pm 11$ years, they were primarily male (n=1721, 72%), and 35% (n= 840) were diagnosed with heart failure prior to surgery. Most patients had a history of hypertension (n= 2135, 89.8%) and more than half had a
diagnosis of diabetes mellitus (n= 1463, 61%). The majority of patients had a history of
dyslipidemia (n= 2007, n= 83.7%). The average hematocrit prior to surgery was 38.77% (± 6%). The average body surface area was 2.01 (± .24) and bypass time 79 [62, 98] minutes. Only 160 patients in the total sample had a previous CABG surgery (6%), and 42% of patients (n=1005) had an elective rather than an emergent surgery (Table 1).

Need for transfusion. Among all patients, the rate of perioperative red blood cell transfusion was 35% (849 of 2399) and was higher in women (p <.001; Table 2). Mortality among patients who received transfusion was 4%, compared to only 0.25% in patients who did not receive a transfusion.

Sex comparison of characteristics. The following characteristics were significantly different between sexes: 1) age; 2) diabetes; 3) preoperative hematocrit; 4) body surface area; 5) bypass time; and 6) urgency of surgery. Females were older, more often had diabetes, and had lower preoperative hematocrits, lower body surface area, longer bypass times and more often required urgent surgery (Table 1). There were no significant differences between females and males with regard to history of heart failure, hypertension, diabetes mellitus, or dyslipidemia.

Characteristics of patients requiring transfusion compared to patients who did not require transfusion. The following characteristics were significantly different between those who did and did not receive perioperative transfusion (Table 3): 1) age; 2) gender; 3) heart failure; 4) diabetes; 5) preoperative hematocrit; 6) body surface area; 7) bypass time; 8) prior CABG surgery; and 9) urgency of surgery. Older patients, women, and those with a history of heart failure, hypertension, diabetes, lower preoperative hematocrit, lower body surface area, longer bypass time, prior CABG surgery and
emergent surgery more often required transfusion. There were no significant differences in need for transfusion based on history of dyslipidemia.

Multivariate Analysis

Full sample. The variables that were independently predictive of transfusion are presented in Table 4. The following variables were tested as predictors of need for transfusion based on their significance as bivariate predictors: age, gender, heart failure, hypertension, diabetes, dyslipidemia, preoperative hematocrit, body surface area, bypass time, previous CABG surgery, and elective vs. emergent surgery. Heart failure, hypertension, diabetes, and dyslipidemia did not predict need for transfusion. In the initial overall binary multiple logistic regression model, the following variables were associated with need for at least one unit of PRBC transfusion: age (OR 1.023, p<.001); female gender (OR 2.11, p<.001); preoperative hematocrit (OR 0.79, p<.0001); body surface area (OR 0.20, p<.0001); bypass time (OR 1.022, p<.0001); previous CABG surgery (OR 2.97, β=1.087, p<.001; elective vs. emergent surgery (OR 0.59, β=-0.535, p<.001). Older patients were more likely to require a transfusion, and women were about twice as likely to need transfusion. Patients with lower preoperative hematocrits were more likely to require transfusion. Patients with lower body surface area more often required transfusion. Patients who spent a longer time on cardiopulmonary bypass required transfusions more often. Patients who had been previously operated upon required transfusion three times more often than patients undergoing their first CABG. Patients undergoing elective surgery required transfusion about half as often as those requiring urgent or emergent surgery.

Female and male models. The following variables were tested as predictors of need for transfusion in both male and female models: age, heart failure, hypertension, diabetes,
dyslipidemia, preoperative hematocrit, body surface area, bypass time, previous CABG surgery, and elective vs. emergent surgery. Among males (Table 5), the independently significant variables were: age (OR 1.018 per year, $\beta=0.183$, $p=.037$); body surface area (OR 0.36, $\beta=-1.02$, $p=.021$); bypass time (OR 1.023 per minute, $\beta=0.0234$, $p<.001$); previous CABG surgery (OR 3.42, $\beta=1.22$, $p<.001$); preoperative hematocrit (OR 0.79 per unit, $\beta=-0.231$, $p<.001$) and elective vs. emergent surgery (OR 0.62, $\beta=-0.475$, $p=.009$). Older age, lower body surface area, longer bypass time, having had prior CABG surgery, and having had emergent surgery were predictive of need for transfusion (Table 5).

For females (Table 6), the independent predictive variables were: age (OR 1.034 per year, $\beta=0.0322$); body surface area (OR 0.053, $\beta=2.92$); bypass time (OR 1.027 per minute, $\beta=0.016$); preoperative hematocrit, (0.78 per unit, $\beta=0.240$) and elective surgery (OR .50 $\beta=0.69$). Previous cardiac surgery, which was one of the predictors of the need for transfusion in men, was not significant in women. As was the case for men, women with lower hematocrits, with longer total bypass times and with lower body surface areas were more likely to require transfusion. Older women were also much more likely to require transfusion, and women undergoing urgent or emergent surgery were twice as likely as women undergoing elective surgery to require transfusion.

**Discussion**

In this study we identified independent risk factors for prediction of perioperative blood transfusion in 2399 consecutive patients undergoing CABG surgery, as well as gender-specific differences in factors associated with the need for transfusion. The strengths of this study are that these data were collected systematically and prospectively.
in a large sample size over an extended period of time, which lessens the likelihood of institutional or individual surgeon practice adversely biasing results.

In our sample, the rate of perioperative transfusion was 35%. Transfusion rates have been reported with varying rates in the literature depending on the type or location of institution (LePar, 2018). Patients undergoing cardiac surgery have a higher rate of transfusion than other surgical patients due to blood loss anemia (Brouwers et. al., 2017). There are several reasons for the high rates of transfusion in cardiac surgery, which include the use of bypass requiring an open chest. Using bypass in surgery causes a dilutional anemia due to the use of fluids within the bypass system as well as the use of heparin to prevent blood coagulation on the surface of the bypass tubing and raw surfaces (Williams et.al., 2011).

The single most clinically significant finding in this study was that women were over twice as likely to require a transfusion as men. Specifically, 58% of women required a transfusion whereas only 27% of men required transfusion. Williams et. al. (2012) found a similar result in their analysis. This observation suggests that successful efforts to reduce the need for transfusion in cardiac surgical patients would likely result in a substantially proportionately greater public health benefit to women.

Independent predictors of perioperative transfusion in this study in the full sample were age, female gender, smaller body surface area, bypass time, previous CABG surgery, preoperative hematocrit and elective vs. emergent surgery. Lopes et. al. (2019) found results consistent with our study showing that body surface area as well as preoperative hematocrit were predictors of transfusion. Further studies are needed in a multicenter sample as this study was a single institution sample. Amongst the independent variables
predicting need for transfusion, previous CABG surgery had the highest odds ratio, almost tripling the odds of receiving transfusion, and female gender had the second highest odds ratio and slightly doubled the odds of transfusion. However, given that female gender occurred in a much more substantial proportion of the total sample than did persons with prior cardiac surgery, the multivariate analysis reinforces the primary finding of the study and the importance of focusing potential system-based outcome improvement measures on women.

Previous cardiac surgery was the only multivariate predictor of transfusion unique to one gender, significantly predicting the need for transfusion in men but not in women. It is possible that this difference is due to inadequate sample size in women, since more than twice as many men as women underwent CABG surgery, and because this was an infrequently observed variable overall. There is not any literature suggesting that men undergoing cardiac surgery scar more or less than women or that men are more prone to bleeding than women. In fact, our study suggests the opposite is true since women required transfusion more often than men. Although the other independent multivariable predictors of transfusion were shared by both genders, review of the data discloses that smaller body surface area is a stronger predictor in women than men. All other gender-shared multivariate predictors are comparable.

A limitation of this study is that the data are from a single-institution patient population, which may degrade its external validity and the generalizability of our results to the general population.
Conclusions

Women, especially smaller women, require blood transfusion after cardiac surgery much more often than men. Future studies seeking to reduce the rate of blood transfusion during and after cardiac surgery should focus on why this subpopulation requires transfusion so frequently, and whether any alterations in surgical technique or postoperative management may reduce this need.
Table 2.1: Characteristics of the Total Sample and Comparison of Characteristics between Males and Females

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Sample N= 2399</th>
<th>Females N= 678</th>
<th>Males N= 1721</th>
<th>P Value Men vs. women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD or n (%) or median [25th and 75th percentiles]</td>
<td>Mean ± SD or n (%) or median [25th and 75th percentiles]</td>
<td>Mean ± SD or n (%) or median [25th and 75th percentiles]</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>63 ±11</td>
<td>64 ± 11</td>
<td>62 ± 10</td>
<td>&lt; 0.001(^1)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>840(35%)</td>
<td>887(37%)</td>
<td>816(34%)</td>
<td>.27(^3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2135(89.8%)</td>
<td>2190(91.3%)</td>
<td>2137(89.1%)</td>
<td>0.12(^3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1463(61%)</td>
<td>1367(57%)</td>
<td>1487(62%)</td>
<td>0.026(^3)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2007(83.7%)</td>
<td>2077(86.6%)</td>
<td>1982(82.6%)</td>
<td>.14(^3)</td>
</tr>
<tr>
<td>Hematocrit prior to surgery, %</td>
<td>38.77 ± 6</td>
<td>36 ± 5</td>
<td>37 ± 7</td>
<td>&lt; 0.01(^3)</td>
</tr>
<tr>
<td>Body surface area, meters(^2)</td>
<td>2.01 ± .24</td>
<td>1.81 ± .21</td>
<td>2.09 ± .21</td>
<td>&lt;0.01(^1)</td>
</tr>
<tr>
<td>Bypass time, minutes</td>
<td>77[62, 96]</td>
<td>82 [63, 102]</td>
<td>74 [58, 91]</td>
<td>&lt;.001(^2)</td>
</tr>
<tr>
<td>Prior CABG surgery</td>
<td>160 (6.7%)</td>
<td>33 (5%)</td>
<td>120 (7%)</td>
<td>.063(^3)</td>
</tr>
<tr>
<td>Elective vs. emergent surgery</td>
<td>1005(41.9%)</td>
<td>240(10%)</td>
<td>816(34%)</td>
<td>.036(^3)</td>
</tr>
</tbody>
</table>

CABG= coronary artery bypass graft; \(^1\)unpaired T test; \(^2\) Wilcoxon Rank Sum test; \(^3\) Chi square test
Table 2.2: Comparison of Transfusion Outcomes Between Males and Females

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Sample</th>
<th>Females</th>
<th>Males</th>
<th>P Value Men vs. women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 2399 Mean ± SD or n (%)</td>
<td>N= 678 Mean ± SD or n (%)</td>
<td>N= 1721 Mean ± SD or n (%)</td>
<td></td>
</tr>
<tr>
<td>Received one or more perioperative red blood cell units</td>
<td>751 (31%)</td>
<td>390 (58%)</td>
<td>361 (21%)</td>
<td>&lt; 0.001(^1)</td>
</tr>
</tbody>
</table>

\(^1\)Wilcoxon Rank Sum test
Table 2.3: Characteristics of Patients Who Received Transfusion Compared to Patients who did not Receive Transfusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transfusion Means ± SD or n (%) or median [25th, 75th percentile]</th>
<th>No Transfusion Means ± SD or n (%) or median [25th, 75th percentile]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>60.9 ± 10.1</td>
<td>66.0 ± 10.0</td>
<td>&lt;.001¹</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>42% (285)</td>
<td>58% (393)</td>
<td>&lt;.001³</td>
</tr>
<tr>
<td>Male</td>
<td>21% (361)</td>
<td>79% (1360)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>23% (305)</td>
<td>77% (1020)</td>
<td>&lt;.001³</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24% (512)</td>
<td>76% (1623)</td>
<td>.034³</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22% (322)</td>
<td>78% (1141)</td>
<td>.025³</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>31% (622)</td>
<td>69% (1385)</td>
<td>0.12³</td>
</tr>
<tr>
<td>Pre-operative hematocrit, mg/dl</td>
<td>36 [32, 39]</td>
<td>41 [38, 44]</td>
<td>&lt;.001²</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.92 ± 0.25</td>
<td>2.06 ± 0.22</td>
<td>&lt;.001¹</td>
</tr>
<tr>
<td>Bypass time, min</td>
<td>83 [65, 103]</td>
<td>74 [59, 92]</td>
<td>&lt;.001²</td>
</tr>
<tr>
<td>Prior CABG surgery</td>
<td>10.1%</td>
<td>4.8%</td>
<td>&lt;.001³</td>
</tr>
<tr>
<td>Elective vs emergent surgery</td>
<td>55%</td>
<td>45%</td>
<td>&lt;.001³</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass graft; ¹unpaired T test; ²Wilcoxon Rank Sum test; ³Chi square test
Table 2.4: Multivariable Predictors of Perioperative Red Blood Cell Transfusion in the Full Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>Odds Ratio and 95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.233</td>
<td>1.023(1.013-1.040)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1.2</td>
<td>2.11(1.69-2.96)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4.23</td>
<td>.269(0.265-4.682)</td>
<td>.680</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.66</td>
<td>1.414(0.801-2.499)</td>
<td>0.232</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.363</td>
<td>1.363(0.916-1.904)</td>
<td>0.069</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.93</td>
<td>.804 (0.519-1.245)</td>
<td>0.325</td>
</tr>
<tr>
<td>Preoperative hematocrit</td>
<td>0.23</td>
<td>0.79 (0.76-2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body surface area</td>
<td>.021</td>
<td>0.2(1.81-2.087)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bypass time</td>
<td>.021</td>
<td>1.022(0.861-2.087)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous coronary artery bypass graft surgery</td>
<td>1.087</td>
<td>2.97(1.81-4.86)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Elective vs. emergent surgery</td>
<td>0.535</td>
<td>0.59(0.44-0.67)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Table 2.5: Multivariable Predictors of Perioperative Red Blood Cell Transfusion in Men

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>Odds Ratio and 95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.183</td>
<td>1.018 (1.01-1.05)</td>
<td>0.037</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1.2</td>
<td>2.11(1.69-2.96)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4.1</td>
<td>0.27(0.265-4.3)</td>
<td>.62</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.5</td>
<td>1.2(0.801-2.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.65</td>
<td>1.36(0.916-1.904)</td>
<td>0.069</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.7</td>
<td>0.504 (0.434- 1.245)</td>
<td>0.23</td>
</tr>
<tr>
<td>Preoperative hematocrit</td>
<td>0.231</td>
<td>0.79(0.74-0.83)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Body surface area</td>
<td>1.02</td>
<td>0.36 (.2-.65)</td>
<td>0.021</td>
</tr>
<tr>
<td>Bypass time</td>
<td>0.0234</td>
<td>1.023 (1.012-1.036)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous coronary artery bypass graft surgery</td>
<td>1.22</td>
<td>3.42( 2.32-4.64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Elective vs. Emergent surgery</td>
<td>0.475</td>
<td>0.62(0.48-0.71)</td>
<td>0.009</td>
</tr>
<tr>
<td>Variable</td>
<td>B</td>
<td>Odds Ratio and 95% Confidence Interval</td>
<td>P value</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-------</td>
<td>----------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Age</td>
<td>.0322</td>
<td>1.034(0.53-1.0662)</td>
<td>0.007</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1.2</td>
<td>2.11(1.69-2.96)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.23</td>
<td>.269(0.365-4.682)</td>
<td>.680</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.6</td>
<td>1.414(0.801-2.499)</td>
<td>0.32</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.22</td>
<td>1.363(0.9-1.87)</td>
<td>0.069</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.93</td>
<td>.804 (0.519- 1.245)</td>
<td>0.325</td>
</tr>
<tr>
<td>Preoperative HCT</td>
<td>0.240</td>
<td>0.79 (0.72-0.85)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Body surface area</td>
<td>-2.92</td>
<td>0.053(0.15-.66)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bypass time</td>
<td>0.0161</td>
<td>1.027( 0.52-1.043)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pervious coronary artery bypass graft surgery</td>
<td>0.40</td>
<td>1.48 (1.018-1.041)</td>
<td>0.53</td>
</tr>
<tr>
<td>Elective vs. Emergent surgery</td>
<td>-0.69</td>
<td>0.50 (0.23-0.73)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
CHAPTER THREE

Open chest cardiac surgery has been historically associated with several known complications, and these complications could occur at any point in the perioperative period. In recent years, the systematic tracking of postoperative complications by the operative team has assisted in the early identification and treatment of these complications (Goldfarb et al., 2015). One important measure that is directly tied to complications is patient length of stay in the hospital, more specifically the intensive care unit (ICU) length of stay as well as overall length of stay in the hospital. Certain major complications of surgery may directly increase a patient’s length of ICU stay and overall length of stay. The four most common major complications are pulmonary, neurological, cardiac and renal complications (Crawford et al., 2017).

Complications that are common to cardiac surgery can lengthen a patient’s ICU stay as well as prolong their overall length of stay, leading to a further risk for additional complications as well as increased cost (McLaughlin, Hardt, Canavan, & Donnelly, 2009). Hospitals with high volume cardiac surgical services commonly collect data on complications and length of stay in order to determine how their metrics compare with certain benchmarks (Siregar et al., 2017). At the University of Louisville Jewish Hospital in Louisville, Kentucky, one of the highest volume cardiac surgical centers in the United States, such data have been collected but never analyzed. Therefore, we sought to identify how major complications were associated with ICU and total postoperative hospital length of stay in this institution in the large population of patients who underwent open chest cardiac surgery.
Specific Aim

Specific Aim 1: To determine the relationship between occurrence of one or more major cardiac surgery complications (i.e., pulmonary, neurological renal and cardiac complications) and length of stay in the ICU, perioperative length of stay as well as overall hospital length of stay in a large sample of 2350 patients undergoing cardiothoracic surgery with cardiopulmonary bypass (CPB).

Methods

Design and Database

This study was a secondary analysis of data from the ongoing database of the University of Louisville Department of Cardiothoracic Surgery in Louisville, Kentucky. These data were used after Institutional Review Board approval and consent waiver. We used data collected January 1, 2014 through December 31, 2018. The cardiothoracic surgical group collects data continuously based upon the guidelines set forth by the Society of Thoracic Surgeons (STS). Data are collected and stored in an electronic format at the time of operation in such manner that it can be accessed at a later point in a Health Insurance Portability and Privacy Act (HIPPA) compliant manner. Data are collected by the nurse practitioners and physicians caring for the patients. Data are entered into the database by surgical residents, nurse practitioners, fellows, and the physician who manages the database. Data entry is limited to only those providers who are trained by the data manager. All those extracting data are trained on the method of data mining to maintain accuracy.

The database encompasses all adult cardiac surgery and includes coronary bypass graft (CABG), surgery of the aortic, mitral, tricuspid, and pulmonary valves, surgery of
the thoracic aorta, arrhythmia procedures, and less commonly performed procedures such as removal of tumors. Data are used to report performance on National Quality STS endorsed metrics for specific procedures and are included in the STS database for use in national benchmarks. The database is used for feedback reports, quality assessment, performance improvement initiatives, and research (Jacobs et al., 2016).

**Sample**

Eligible patients were those who met the following criteria: 1) undergoing CABG; 2) undergoing cardiac valve replacement or repair with CPB; 3) undergoing CABG with cardiac valve replacement or repair and CPB; and 4) older than 18. Patients identified by these selection criteria were enrolled in the current study for analysis. Patients who underwent heart transplantation or mechanical heart implantation were excluded from the study.

**Measures**

Sociodemographic data extracted from the database included age and sex along with the surgical variables of type of procedure, the urgency of the operation (emergent or elective), length of full hospital stay (from day of admission to discharge), perioperative length of stay (from time of surgery to discharge from hospital) and length of ICU stay (from admission to the ICU from the operating room (OR) to time of transfer to the lower level of care) body mass index (BMI), and comorbid conditions of diabetes mellitus, heart failure, hypertension and previous stroke. The specific major perioperative complications tracked were pulmonary (i.e., respiratory failure), neurological (i.e., stroke), cardiac (i.e., myocardial infarction, cardiogenic shock, bleeding requiring
reoperation, arrhythmias, and sternal wound infection), and renal (i.e., acute renal failure) complications.

*Data Analysis*

Independent student t-tests were used to compare continuous variables that were normally distributed, Wilcoxon rank Sum test was used for non-normally distributed continuous variables, and chi-square tests were used to compare proportions of categorical variables. The assumptions of independence and randomness in non-parametric data were met. All statistical analyses were performed using SPSS version 27 (Chicago, Ill.), with a two tailed alpha set at .05.

**Results**

*Patient Demographic, Clinical and Perioperative Characteristics*

Out of the 2350 patients who underwent cardiac surgery between December 31, 2014 and January 1, 2018, the majority of patients were male (n= 1442; Table 3.1) and were primarily Caucasian (77.1%). The majority of patients were between ages 66-80 (40.1%). Most patients (n= 1364) did not have a history of lung disease, however there were 321 (13.9%) with mild lung disease prior to surgery, 211 (10%) with moderate lung disease, and 190 (8%) with severe lung disease. There were 913 patients in the sample who were diagnosed with diabetes mellitus (40%) where 82 patients (3.6%) were controlled with diet, 351 (15.2%) were prescribed insulin, and 372 (16.1%) were taking an oral hypoglycemic medication. There were 266 (11.4%) patients who had a previous stroke and 846 (36%) who had a previous myocardial infarction. Only patients with heart failure received a New York Heart Association (NYHA) classification; 77 (3.3%) were class I, 274 (11.9%) were class II, 678 (29.4%) were class III, and 296 (12.8%) were
class IV. Eighteen percent of the sample were actively smoking tobacco (n= 414) and 22% (n=507) had a history of smoking but had stopped smoking more than 30 days prior to surgery. Over half of the sample had been diagnosed with hypertension (n= 1175) (50%) (Table 3.1).

Comparison of Patient Demographic, Clinical and Perioperative Characteristics between Those with and without Complication

Out of the 2530 cases, 445 patients had a complication for an overall rate of 19%. Patients had at least one comorbid pre-existing condition including hypertension (51.4%), chronic lung disease (26%), and renal insufficiency (12%). Almost two thirds of patients experiencing a complication had a diagnosis of heart failure (66%) as compared to the group without complications having 21%. Patients with a history of diabetes mellitus, whether insulin dependent or non-insulin dependent, were found to have a higher incidence of complication perioperatively than those who were not diagnosed as having diabetes mellitus (with complication 47% vs. no complication 27%).

Complications

Most patients in the sample did not have a major complication (n=1860, 80%). We looked at four major categories of complication which included cardiac complication, specifically perioperative myocardial infarction (MI) and perioperative bleeding; major neurological event, specifically stroke; pulmonary complication, specifically pneumonia; and renal failure. Of those patients who had a complication, 19 experienced a perioperative MI and 63 had postoperative bleeding. 102 experienced a perioperative stroke, 165 had pneumonia postoperatively, and 25 had renal failure (Table 3.3).
**Association of Total Number of Complications with Length of Stay**

Of the patients who did not experience a complication, the ICU length of stay in hours averaged 40 hours, perioperative length of stay (POLOS) was 5.26, and total length of stay (LOS) averaged 6.93 days. Of those patients who had just one major complication (any complication), the ICU length of stay increased to an average of 171 hours with an overall POLOS of 13.5 days and total LOS of 20.6 days.

When a patient had any two major complications, there was an increase in all lengths of stay with ICU length of stay increasing to an average of 434 hours, POLOS to 25.9 days, and a total LOS of 44.0 days (Table 3.2) When the patients in our sample had three major complications, we saw the highest average hourly length of ICU stay at 534 hours and an average POLOS at 28.5 days and average overall LOS of 50.8 days. All of these increases in length of stay were statistically and clinically significant. In our sample we had only one patient with 4 major complications with an ICU stay of 279 hours with the end point of mortality (Table 3.2).

**Association of Individual Major Complications with Increased Length of Stay**

The complication of perioperative MI in the population resulted in a median POLOS of 5 days and did not differ significantly from those patients who did not have a perioperative MI (Median = 5; p= 0.335). Those patients who had a perioperative stroke did significantly increase their length of stay with a median length of stay of 7 days (median 7.66) compared to those patients who did not have a stroke with a median length of stay of 5 days (p= < .000). Patients who needed to have a reoperation perioperatively for bleeding increased their length of stay to a median of 15.79 days compared to those who did not have this complication (p< .000). Having a complication of pneumonia also
increased the POLOS with a median of 7.7 days compared with those patients who did not have pneumonia with a median length of stay of 5 days (p = < .001). Renal failure, which is a common complication after cardiac surgery, was not a significant factor in prolonging a patient’s POLOS (Median 6.7 days; p = 0.483).

Discussion

The results of the study showed that perioperative and postoperative complications significantly added to the length of stay of cardiac surgical patients, with a doubling of length of stay when a patient experiences one major complication, and additional incremental significant increases in length of ICU stay if a second complication occurred (which more than quadrupled length of stay) or a third major complication occurred (an over five -fold increase in LOS). Thus, even in patients with a single major complication, efforts to prevent the addition of a second or third additional complication could provide very substantial opportunities to lessen lengths of ICU and overall stay, and subsequently mitigate overall cost of care.

We found that certain specific complications were more likely to prolong the lengths of stay, and in our population the complication that most prolonged length of stay was reoperation for bleeding, which tripled median length of stay followed by pneumonia and stroke, which equally increased LOS. Because the number of complications can significantly prolong ICU stay and total postoperative length of stay, it is imperative to optimize the patient’s presurgical condition to whatever extent is practically feasible in order to avoid significant complications.

McCann et. al (2019) refer to this emerging important risk mitigation strategy as “cardiac prehabilitation” where patients undergoing elective surgery are optimized with
specific attention to prevention of neurological complication though checking
preoperative carotid dopplers, increasing respiratory muscle strength through
preoperative incentive spirometry and treatment of lung illness such as asthma, attention
to preoperative smoking cessation, increasing muscle mass with adequate diet and protein
intake, and improving nutritional status as well as controlling hyperglycemia and weight
(Litton et al., 2018). This strategy is more feasible with elective procedures but not with
an emergent procedure. Postoperatively, early extubation as well as early mobility may
help decrease any major complication (Ahmed et al., 2014). Traditionally, cardiac
surgical programs have looked toward morbidity and mortality to evaluate their
programs. Our study has shown that one or more major complications as specifically
defined and categorized in this study can significantly add to the both the ICU length of
stay and overall length of stay, and this can add greatly to the cost of the patient’s care

Limitations

The current study has a number of potentially important implications. Our study
has revealed, using a large sample, that one or more complication of cardiac surgery
significantly increased a patient’s length of stay. However, even though it is a large
sample, it may be more significant with a larger sample across many institutions.
Ongoing data collection into the registry, and/or combining our data with that of other
comparable registries could create a pooled database and meta-analysis could be
performed to identify additional data regarding length of stay.

Conclusion

The occurrence of one or more complications substantially and exponentially
increases lengths of stay in patients undergoing CPB. These data support the notion of
“cardiac pre-habilitation” or optimization of patients’ physical health before cardiac surgery.
### Table 3.1: Baseline Clinical Characteristics of Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (n) (%) (n=2305)</th>
<th>With Complication (n=445) Mean ± SD or n (%)</th>
<th>No Complication (n=1860) Mean ± SD or n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-50</td>
<td>407(18)</td>
<td>66±12</td>
<td>58.3±13</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>51-65</td>
<td>677(29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66-80</td>
<td>934(40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>287(13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1442(62.6)</td>
<td>273(61)</td>
<td>1169(63)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Female</td>
<td>863(37.4)</td>
<td>172(39)</td>
<td>691(37)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1175(51.4)</td>
<td>396(88)</td>
<td>1667(89)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>27(.1)</td>
<td>15(14.7)</td>
<td>12(05)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>490(20)</td>
<td>100(22)</td>
<td>369(20)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet control</td>
<td>82(34)</td>
<td>16(14)</td>
<td>66(35)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Insulin</td>
<td>351(15)</td>
<td>75(36)</td>
<td>276(15)</td>
<td></td>
</tr>
<tr>
<td>Oral agent</td>
<td>90(35)</td>
<td>17(15)</td>
<td>297(34)</td>
<td></td>
</tr>
<tr>
<td>No diabetes control</td>
<td>372(16)</td>
<td>16(15)</td>
<td>69(16)</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>77(3.3)</td>
<td>0(0)</td>
<td>77</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Class II</td>
<td>274(11.9)</td>
<td>8(7)</td>
<td>266</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>678(29.4)</td>
<td>8(8)</td>
<td>670</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>296(12.8)</td>
<td>11(11)</td>
<td>285</td>
<td></td>
</tr>
<tr>
<td>Lung disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lung disease</td>
<td>1364(59)</td>
<td>33(32)</td>
<td>1331(60)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mild</td>
<td>321(13.9)</td>
<td>6(6)</td>
<td>315(14)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>211(10)</td>
<td>4(4)</td>
<td>207(9)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>190(8)</td>
<td>3(3)</td>
<td>187(8)</td>
<td></td>
</tr>
<tr>
<td>All major complications</td>
<td>Number of patients in sample</td>
<td>Variable</td>
<td>Mean (SD)</td>
<td>Median (25&lt;sup&gt;th&lt;/sup&gt; and 75&lt;sup&gt;th&lt;/sup&gt; percentile)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>-----------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>0</td>
<td>1860 (80%)</td>
<td>Postoperative length of stay in days</td>
<td>5.26 (3.59)</td>
<td>5 (4,6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial hours in the ICU</td>
<td>40.35 (33.22)</td>
<td>27.15(23,48)</td>
</tr>
<tr>
<td>1</td>
<td>301(13%)</td>
<td>Postoperative length of stay</td>
<td>13.5 (9.5)</td>
<td>11(7,16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial hours in the ICU</td>
<td>171.5 (182.77)</td>
<td>118(70.5,175.4)</td>
</tr>
<tr>
<td>2</td>
<td>129 (5%)</td>
<td>Postoperative length of stay</td>
<td>25.9 (21.84)</td>
<td>20(11,33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial hours in the ICU</td>
<td>434.06 (480.62)</td>
<td>33 (135.5,505.7)</td>
</tr>
<tr>
<td>3</td>
<td>14 (1%)</td>
<td>Postoperative length of stay</td>
<td>32.15 (28.84)</td>
<td>23(20,38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial hours in the ICU</td>
<td>534.37 (413.44)</td>
<td>468.0 (155.5,722.75)</td>
</tr>
<tr>
<td>4</td>
<td>1(0.4%)</td>
<td>Postoperative length of stay</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial hours in the ICU</td>
<td>279.2</td>
<td>279.2</td>
</tr>
</tbody>
</table>
Table 3.3: Comparison of Lengths of Stay Between Those with and without a Specific Complication

<table>
<thead>
<tr>
<th>Variable</th>
<th>Perioperative Length of Stay (POLOS)</th>
<th>Intensive Care Unit (ICU) Initial Hours</th>
<th>Intensive Care Unit (ICU) Total Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complication present</td>
<td>Complication absent</td>
<td>Complication present</td>
</tr>
<tr>
<td></td>
<td>Median days (range)</td>
<td>Median days (range) (range)</td>
<td>Median days (range)</td>
</tr>
<tr>
<td></td>
<td>Complication present</td>
<td>Complication absent</td>
<td>Complication present</td>
</tr>
<tr>
<td></td>
<td>Median days (range)</td>
<td>Median days (range) (range)</td>
<td>Median days (range)</td>
</tr>
<tr>
<td></td>
<td>p- value</td>
<td>p- value</td>
<td>p- value</td>
</tr>
<tr>
<td>Perioperative myocardial</td>
<td>5 (0-140)</td>
<td>88 (1.2-3330)</td>
<td>57.61(0-3365)</td>
</tr>
<tr>
<td>infarction</td>
<td>n= 19</td>
<td>n=19</td>
<td>n=19</td>
</tr>
<tr>
<td>Stroke</td>
<td>7.66 (0-140)</td>
<td>85.679(1.3-3365)</td>
<td>58 (0-3330)</td>
</tr>
<tr>
<td></td>
<td>n= 49</td>
<td>n=49</td>
<td>n=49</td>
</tr>
<tr>
<td>Re-operative bleeding</td>
<td>15.79 (0-116)</td>
<td>87.6 (1.0-3332)</td>
<td>55.6 (0-3500)</td>
</tr>
<tr>
<td></td>
<td>n= 63</td>
<td>n=63</td>
<td>n=63</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7.7 (0-140)</td>
<td>85.67(1.3-178)</td>
<td>57.61(0-3365)</td>
</tr>
<tr>
<td></td>
<td>n=165</td>
<td>n=165</td>
<td>n=165</td>
</tr>
<tr>
<td>Renal failure</td>
<td>6.7 (1-26)</td>
<td>86 (1.3-180)</td>
<td>57.60(0-3365)</td>
</tr>
<tr>
<td></td>
<td>n= 25</td>
<td>n=25</td>
<td>n=25</td>
</tr>
</tbody>
</table>

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CHAPTER FOUR

Cardiac surgery can be lifesaving, although it can be associated with several life-threatening complications, including neurological complications. Stroke is one of the leading causes of death and can result in permanent damage to neurological function and increased cost of care in the United States (Mozaffarian et al., 2015). In particular, ischemic stroke is one of the most feared of all complications of cardiac surgery, particularly with valve surgery. As such, ischemic stroke is one of the most common complications of valve and cardiothoracic procedures, and the most common neurological complication, occurring in 6% of those undergoing cardiac surgery in a small sample of 36 patients (Weinmar & Knipp, 2016).

The risk of ischemic stroke increases to 12% when patients have co-morbid carotid disease, are aged over 75, are female, and/or have hypertension (Howard et al., 2019; Weinmar & Knipp, 2016). Other identified risk factors for stroke after surgery include atrial fibrillation, presence of carotid stenosis, use of cardiopulmonary bypass, diabetes mellitus, kidney failure, tobacco use, chronic obstructive pulmonary disease and perioperative blood transfusion (Howard et al., 2019; Whitlock et al., 2014; DeCosta et al., 2015; Noh et al., 2015; Omar et al., 2016; Whitlock et al., 2014; Messe et al., 2014).

Strokes and impairment of cognitive function of patients following surgery can be responsible for significant morbidity and mortality. Furthermore, the morbidity and cognitive function impairments associated with stroke may lengthen hospital stay and lead to increased cost (Cropsey et al., 2015; Giovannetti et al., 2017). Cropsey et al. (2015) studied this topic and explored cognitive dysfunction among cardiac surgery
The authors noted that neurologic injury commonly occurs after cardiac surgery and persists as one of the most common complications following cardiac surgery. It can be in the form of cognitive decline, delirium, and stroke, and can lead to persistent functional impairment despite decreased overall mortality rates due to improved surgical and anesthetic techniques (Cropsey et al., 2015). A major predictor of cognitive decline after surgery was baseline cognitive function (Cropsey et al., 2015; Giovannetti et al., 2017).

It may be possible to modify risk factors prior to surgery (Giovannetti et al., 2017; Jacobs et al., 2016; Waldron et al., 2018). Carotid artery disease can be evaluated through carotid doppler preoperatively in order to identify carotid stenosis before undergoing anesthesia (DeCosta et al., 2015; Udes et al., 2017). Other precautions can include the early detection and expeditious treatment of arrhythmias, avoidance of the manipulation and cannulation of the aorta, and avoiding hyperglycemia (Masrur et al., 2015; Turakhia et al., 2015). Identifying predictors of stroke in cardiac surgery could potentially lead to the prevention and mitigation of these neurological complications and their associated debility.

We conducted the current study using a larger sample size than previously cited studies and had sufficient sample size and power.

**Specific Aim**

Specific Aim: To define predictors (i.e. gender, type of surgical procedure, mortality, last creatinine level, diabetes control, hypertension going into surgery, cerebrovascular disease prior to surgery, previous cardiac procedure, post-surgery
complication, and reoperation because of bleeding) of stroke in patients who have undergone cardiothoracic surgery with CPB.

Methodology

This study was a retrospective analysis of data from the ongoing prospectively and contemporaneously compiled database of the University of Louisville Department of Cardiothoracic Surgery. The database is a collaborative effort on the part of the hospital based cardiothoracic surgical group. The database encompasses all adult cardiac surgery and includes coronary bypass graft (CABG), surgery of the aortic, mitral, tricuspid, and pulmonary valves, surgery of the thoracic aorta, arrhythmia procedures, surgical arrhythmia ablation procedures and less commonly performed procedures such as removal of tumors. This data are used to report performance on National Quality STS endorsed metrics for specific procedures. The database is used for feedback reports, quality assessment, performance improvement initiatives, and research (Jacobs et al., 2016).

After obtaining Institutional Review Board approval and consent waiver, we gathered data from the database.

Based upon the specific aims, eligible patients were those who met the following criteria: 1) those patients admitted to the cardiothoracic surgical surgery service who underwent cardiothoracic surgery at Jewish Hospital in Louisville, Kentucky from January 1, 2014 through December 31, 2018 inclusive; and 2) age greater than 18. Patients identified by these selection criteria were enrolled in the study for analysis.

In this study, stroke was defined as the occurrence of either ischemic or hemorrhagic stroke. Ischemic stroke was defined as any new focal neurological deficit due to new cerebral infarction visualized on brain CT or MRI. Hemorrhagic stroke was
defined as any new intracranial hemorrhage (subdural, subarachnoid, or intraparenchymal) visualized on brain computed tomography (CT) or magnetic resonance imaging (MRI). Sociodemographic data extracted from the database included age and sex. Clinical variables extracted from the database included diagnosed comorbid conditions of body mass index (BMI), last creatinine level, chronic lung disease, diabetes control, history of stroke in the past, history of myocardial infarction (MI) in the past, taking medication, oral or insulin, for diabetes, class of heart failure, hypertension, and cerebrovascular disease prior to surgery. Surgical variables included surgical procedure, number of grafts used, perioperative complications, number of major complications, body surface area (BSA) and re-operation for bleeding.

**Data Analysis**

Demographic and preoperative characteristics were compared for those patients who underwent cardiac surgery during the years January 1, 2014 through December 31, 2018 between the entire group (n= 2350) and those who had the complication of stroke (n= 102). Independent student t tests were used to compare normally distributed continuous variables, Wilcoxon rank Sum test was used for non-normally distributed continuous variables, and a chi-square test was used to compare proportions of categorical variables. All statistical analyses were performed using SPSS version 25 (Chicago, Ill.), with alpha set at .05.

A binary logistic regression analysis was conducted to determine the independent multivariate predictors of stroke in patients who had undergone cardiothoracic surgery with CPB. The candidate independent variables or predictors included gender, age, surgical procedure, BMI, last creatinine level, chronic lung disease, number of grafts
used, taking oral medications or insulin for diabetes, history of stroke in the past, history of MI in the past, class of heart failure, hypertension going into surgery, cerebrovascular disease prior to surgery, previous cardiac procedure, post-surgery complication, reoperation because of bleeding, and number of major complications. A two tailed level of significance of 0.05 was used in the binary logistic regression analysis. An independent variable significantly predicts the dependent variable if $p$-value of the *Wald* statistic was less than or equal to the level of the significance value of 0.05. In addition, it should be noted that dummy codes were created for categorically or nominally measured independent variables which include gender, surgical procedure, chronic lung disease, taking oral medications or insulin for diabetes, history of stroke in the past, history of MI in the past, class of heart failure, hypertension going into surgery, cerebrovascular disease prior to surgery, previous cardiac procedure, post-surgery complication, and reoperation because of bleeding.

The required assumptions for a binary logistic regression include that the dependent variable should be dichotomous in nature; and independent variables should be measured as continuous, discrete, or dichotomous or a mix; and should have independence of observations wherein the dependent variable should have mutually exclusive and exhaustive categories. All of these required assumptions were satisfied by the characteristics of the data.

**Results**

A total of 2350 patients were identified, and their demographic characteristics are presented in Table 4.1. The participants of this study were primarily male (56%) with an average overall age of $66 \pm 12$, BMI of $29.8 \pm 6.2$, and BSA of $2.1 \pm 1.1$. 
Out of the 2530 cases, 102 patients had a stroke for an overall rate of 4.34%. Fifteen percent of the patients who had a stroke perioperatively had a prior history of a neurological event prior to surgery, compared to 11% of those who did not have a stroke (p>0.05). Most patients had at least one comorbid pre-existing condition including hypertension (51.4%), chronic lung disease (26%) and renal insufficiency (12%). Almost two thirds of patients experiencing a stroke had a diagnosis of heart failure (66%) as compared to the non-stroke group having 21%. Patients who underwent CABG received 3.2 ± 1.0 grafts during their operation and 35% of patients required transfusion (table 4.1). Patients with a history of diabetes mellitus, whether insulin dependent or non-insulin dependent, were found to have a significantly higher risk of stroke perioperatively than those who were not diagnosed as having diabetes mellitus (stroke 47% vs. no stroke 27%). Cardiopulmonary bypass time was associated with in an increased incidence of stroke with prolonged time being associated with a higher prevalence of stroke (283.8 minutes ± 133) vs 235 ± 58 minutes in the non-stroke group.

**Multivariate Analysis**

A binary logistic regression was conducted to determine the independent multivariate predictors of stroke in patients who had undergone cardiothoracic surgery. Result of the omnibus test of model coefficients test showed that the binary logistic regression had a significant model fit ($\chi^2(27) = 3339.89, p < 0.001$). This means that the overall combined impact of all the predictors significantly predicted post-surgery stroke.

There were three significant predictors of post-surgery stroke. These were BMI ($Wald(1) = 6.21, p = 0.01$), having chronic lung disease ($Wald(1) = 5.37, p = 0.02$), and taking oral medications or insulin for diabetes ($Wald(1) = 4.82, p = 0.03$). These means
that individuals who had lower BMI, did not have chronic lung disease, or who were taking medication to control diabetes had lower odds of experiencing stroke.

For BMI, the Exp(B) coefficient (odds ratio) was 0.91 which indicated that having higher BMI decreased the odds of patients experiencing post-surgery stroke. A one unit increase in BMI of the patients decreased the odds that they will experience post-surgery stroke by 0.09 or 9%. For chronic lung disease, the Exp(B) coefficient (odds ratio) was 2.96 which indicated that having chronic lung disease increased the odds 2.96 times that of a patient experiencing post-surgery stroke compared to those who did not have chronic lung disease. For taking oral medications or insulin for diabetes, the Exp(B) coefficient was 0.31, which indicated that taking oral medications or insulin for diabetes decreased the odds of patients experiencing post-surgery stroke by 0.69 or 69%.

Discussion

The overall purpose of this study was to identify predictors of ischemic and hemorrhagic stroke in patients who have undergone cardiothoracic surgery. Despite our large sample size, we found only three predictors among a large number of candidate predictors.

When looking at the impact of each independent variable, we found that there were three significant predictors of post-surgery stroke: lower BMI, having chronic lung disease, and not being on medications to control diabetes. Paradoxically, having a higher BMI decreased the odds of patients experiencing a post-surgery stroke with a one unit increase in BMI decreasing the odds of experiencing post-surgery stroke by 9.1%.

Having chronic lung disease nearly tripled the odds of patients experiencing post-surgery stroke in our study. Charlesworth et. al. (2003) found that chronic lung disease was
a predictor of stroke in coronary artery bypass grafting. Most recent studies do not include chronic lung disease in their prediction models (Sultan, et. al. 2020). Impaired lung function is known to be associated with stroke due to systemic inflammation with progressive airflow limitation leading to cerebral vascular dysfunction (Austin, et. al., 2016).

Importantly, taking oral medications or insulin for diabetes decreased the odds of patients experiencing post-surgery stroke by 69%. This is the most significant finding of the study. Preoperative BMI and pre-existing COPD are not easily modifiable risk factors, whereas controlling diabetes, by contrast, is a very actionable finding which can be quickly achieved. This is consistent with the literature on uncontrolled diabetes mellitus as a risk factor for ischemic stroke, because hyperglycemia has been associated with both an increased risk of stroke and a poorer stroke outcome (Howard, et.al., 2019).

Perioperative strokes are typically excluded from analyses of stroke outcomes and stroke registries because the cause of perioperative stroke is automatically causally attributed to the procedure itself (Farcoq, et.al., 2008). This type of automatic categorization impedes our ability to identify whether other non-procedural pre-existing co-morbidities could be identified that may reduce the risk of postoperative stroke. Our study’s finding that taking oral medications or insulin for diabetes preoperatively substantially reduced the risk of a postoperative stroke creates an opportunity for future randomized interventional studies investigating whether or not delaying non-emergent cardiac surgery until diabetes is controlled reduces the risk of postoperative stroke and could improve overall outcome. (Sultan et al., 2020) found similar results where diabetes mellitus as well as advanced age were predictors of stroke in cardiac surgical patients.
Amassi et al. (1999) reported again that diabetes mellitus was a predictor of stroke in their cardiac surgical population.

Limitations

The current study has a number of potentially important implications. Despite our study having a larger sample size than its predecessors, we still only have identified three significant predictors or postoperative stroke, and these three variables explained only 14% of the variance of postoperative stroke, and this may indicate that other variables may have been more significant. This may have been underpowered due to variable selection or sample size. Ongoing data collection into the registry, and/or combining our data with that of other comparable registries could create a pooled database, and meta-analysis could be performed to identify additional important predictors, and also potentially allow for stratified analyses by specific surgical procedure and/or specific type of stroke (ischemic versus hemorrhagic). Furthermore, because our database was not created for the purpose of researching postoperative stroke risk, it may have lacked all variables that one would ideally preferred to enter into predictive models and analyses. Our study furthermore did not collect data on whether specific measures of pulmonary function optimization preoperatively or postoperatively for that matter affected postoperative stroke risk or not. However, the association we identified between preoperative COPD and experiencing a postoperative stroke suggests that incorporating the consistent collection of such data measures into future databases should be strongly considered, since this is a potentially modifiable risk factor.
Conclusion

These findings may be useful for practitioners as they provide information on what type of patients in particular may be prone to post-cardiac surgery stroke. Such interventions should be investigated in future randomized clinical intervention trials. Communication of the results of this study to cardiothoracic surgeons and other practitioners, including which variables actually predicted stroke as opposed to which variables they have traditionally assumed would predict stroke such as age, may also reduce risk perception biases on their part and allow for more patients to benefit from these procedures by including reasonable risk candidates who are presently being excluded.
Table 4.1: Baseline Clinical Characteristics of Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (n) (%) (n=2305)</th>
<th>Stroke (n=102)</th>
<th>No Stroke (n=2203)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-50</td>
<td>407(18.1)</td>
<td>66±12</td>
<td>58.3±13</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>51-65</td>
<td>677(29.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66-80</td>
<td>934(40.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>287(12.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1442(62.6)</td>
<td>68(5)</td>
<td>1374(95)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Female</td>
<td>863(37.4)</td>
<td>34(4)</td>
<td>829(96)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>1175(51.4)</td>
<td>46(4)</td>
<td>56(3)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>Previous stroke</strong></td>
<td>27(.1)</td>
<td>15(14.7)</td>
<td>12(05)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>Previous myocardial infarction</strong></td>
<td>48(2)</td>
<td>1(0.09)</td>
<td>47(46)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>351(15.2)</td>
<td>10(.98)</td>
<td>341(15)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Oral agent</td>
<td>90(3.9)</td>
<td>11(10.7)</td>
<td>79(34)</td>
<td></td>
</tr>
<tr>
<td>No diabetes control</td>
<td>372(16.1)</td>
<td>16(16)</td>
<td>356(15)</td>
<td></td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>77(3.3)</td>
<td>0(0)</td>
<td>77</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Class II</td>
<td>274(11.9)</td>
<td>8(7)</td>
<td>266</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>678(29.4)</td>
<td>8(8)</td>
<td>670</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>296(12.8)</td>
<td>11(11)</td>
<td>285</td>
<td></td>
</tr>
<tr>
<td><strong>Lung disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lung disease</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mild</td>
<td>1364(59)</td>
<td>33(32)</td>
<td>1331(60)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>321(13.9)</td>
<td>6(6)</td>
<td>315(14)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>211(10)</td>
<td>4(4)</td>
<td>207(9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>190(8)</td>
<td>3(3)</td>
<td>187(8)</td>
<td></td>
</tr>
</tbody>
</table>
Table 4.2: Binary Logistic Regression Results of Significant Predictors of Post-Surgery Stroke

<table>
<thead>
<tr>
<th>Predictors</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>p-value</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>0.66</td>
<td>0.52</td>
<td>1.62</td>
<td>1</td>
<td>0.20</td>
<td>1.94</td>
</tr>
<tr>
<td>Age</td>
<td>0.02</td>
<td>0.02</td>
<td>1.10</td>
<td>1</td>
<td>0.30</td>
<td>1.02</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical procedure (AVR)</td>
<td>1.05</td>
<td>1.01</td>
<td>1.10</td>
<td>1</td>
<td>0.30</td>
<td>2.87</td>
</tr>
<tr>
<td>Surgical procedure (CAB)</td>
<td>-0.60</td>
<td>0.97</td>
<td>0.38</td>
<td>1</td>
<td>0.54</td>
<td>0.55</td>
</tr>
<tr>
<td>Surgical procedure (MV Repair)</td>
<td>0.65</td>
<td>1.62</td>
<td>0.16</td>
<td>1</td>
<td>0.69</td>
<td>1.91</td>
</tr>
<tr>
<td>Surgical procedure (MV Replace)</td>
<td>-2.06</td>
<td>1.34</td>
<td>2.35</td>
<td>1</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>Surgical procedure (AVR + CAB)</td>
<td>0.17</td>
<td>0.98</td>
<td>0.03</td>
<td>1</td>
<td>0.87</td>
<td>1.18</td>
</tr>
<tr>
<td>Surgical procedure (AVR + MV Replace)</td>
<td>0.40</td>
<td>10844.07</td>
<td>0.00</td>
<td>1</td>
<td>1.00</td>
<td>1.49</td>
</tr>
<tr>
<td>Surgical procedure (MV Repair + CAB)</td>
<td>0.85</td>
<td>1.44</td>
<td>0.35</td>
<td>1</td>
<td>0.56</td>
<td>2.34</td>
</tr>
<tr>
<td>Surgical procedure (MV Replace + CAB)</td>
<td>-16.94</td>
<td>10061.85</td>
<td>0.00</td>
<td>1</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.10</td>
<td>0.04</td>
<td>6.21</td>
<td>1</td>
<td>0.01*</td>
<td>0.91</td>
</tr>
<tr>
<td>Last Creatinine Level</td>
<td>-0.36</td>
<td>0.24</td>
<td>2.37</td>
<td>1</td>
<td>0.12</td>
<td>0.70</td>
</tr>
<tr>
<td>Chronic Lung Disease (Yes)</td>
<td>1.09</td>
<td>0.47</td>
<td>5.37</td>
<td>1</td>
<td>0.02*</td>
<td>2.96</td>
</tr>
<tr>
<td>Number of IMA Grafts Used</td>
<td>0.42</td>
<td>0.75</td>
<td>0.32</td>
<td>1</td>
<td>0.57</td>
<td>1.52</td>
</tr>
<tr>
<td>Diabetes control (Yes)</td>
<td>-1.17</td>
<td>0.54</td>
<td>4.82</td>
<td>1</td>
<td>0.03*</td>
<td>0.31</td>
</tr>
<tr>
<td>History of stroke in the past (Yes)</td>
<td>-0.05</td>
<td>0.92</td>
<td>0.00</td>
<td>1</td>
<td>0.96</td>
<td>0.95</td>
</tr>
<tr>
<td>History of MI (Yes)</td>
<td>-0.40</td>
<td>0.59</td>
<td>0.45</td>
<td>1</td>
<td>0.50</td>
<td>0.67</td>
</tr>
</tbody>
</table>
Table 4.2 (continued)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>p-value</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class of heart failure</td>
<td>5.44</td>
<td></td>
<td>4</td>
<td></td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Class of heart failure (Class I)</td>
<td>1.20</td>
<td>0.69</td>
<td>3.03</td>
<td>1</td>
<td>0.08</td>
<td>3.32</td>
</tr>
<tr>
<td>Class of heart failure (Class II)</td>
<td>-14.71</td>
<td>3636.85</td>
<td>0.00</td>
<td>1</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Class of heart failure (Class III)</td>
<td>0.71</td>
<td>0.79</td>
<td>0.80</td>
<td>1</td>
<td>0.37</td>
<td>2.03</td>
</tr>
<tr>
<td>Class of heart failure (Class IV)</td>
<td>-0.51</td>
<td>0.78</td>
<td>0.43</td>
<td>1</td>
<td>0.51</td>
<td>0.60</td>
</tr>
<tr>
<td>Hypertension going into surgery (Yes)</td>
<td>0.09</td>
<td>0.78</td>
<td>0.01</td>
<td>1</td>
<td>0.91</td>
<td>1.10</td>
</tr>
<tr>
<td>Cerebrovascular disease prior to surgery (Yes)</td>
<td>0.45</td>
<td>0.76</td>
<td>0.35</td>
<td>1</td>
<td>0.55</td>
<td>1.57</td>
</tr>
<tr>
<td>Previous cardiac procedure (Yes)</td>
<td>-0.15</td>
<td>0.52</td>
<td>0.08</td>
<td>1</td>
<td>0.78</td>
<td>0.86</td>
</tr>
<tr>
<td>Constant</td>
<td>-67.51</td>
<td>2381.82</td>
<td>0.00</td>
<td>1</td>
<td>0.98</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Note: Cox and Snell $R^2 = 0.14$, $\chi^2(27) = 3339.89, p < 0.001$

a. Predictors: Gender, Age, Surgical procedure, BMI, Last Creatinine Level, Chronic Lung Disease, Number of Grafts Used, Diabetes control (diet, medication or insulin) History of stroke in the past, MI(Myocardial infarction) New York Heart Association Class of heart failure (NYHA), Hypertension going into surgery, Cerebrovascular disease prior to surgery, Previous cardiac procedure, Post surgery complication (Hours in vent), Reoperation because of bleeding, Number of major complications.

B. Dependent Variable: Post surgery stroke

*Significant at level of significance of 0.05
CHAPTER FIVE

Chapter One highlighted the basic physiology of cardiopulmonary bypass and what a patient may undergo when they have traditional open chest cardiac surgical procedures. Cardiopulmonary bypass (CPB) was developed in the early 1950’s in order to repair life threatening problems of the heart by stopping the heart and emptying it of blood. It is a simple concept based upon the fact that the heart is really two blood pumps, the right and the left heart, working to continuously supply oxygenated blood to the body. The lungs just provide a surface through which oxygen and carbon dioxide can be exchanged, where the primary function of the heart is to deliver this oxygenated and decarboxylated blood to all other organs in the body (Cohn, 2012). Cardiopulmonary bypass totally replaces the function of the heart and lungs during cardiac surgery. Because of the circuit and the way the blood bypasses the heart and lungs during surgery the patient faces several potential complications that can contribute to greater morbidity and mortality.

In Chapter Two, the results of the study revealed a relationship between gender and transfusion requirement in coronary artery bypass graft surgery, as well as those patients with a lower body surface area to require higher amounts of transfusion. Increasing age was also a predictor for higher transfusion requirements as well as longer cardiopulmonary bypass times, preoperative anemia, and reoperation. In the initial overall binary multiple logistic regression model, the following variables were (in order of most to least statistically significant) associated with need for at least one unit PRBC transfusion: pre-operative hematocrit, (OR 0.79 per unit, β=-0.23, p<. 0001); body surface area (OR 0.20, β = .021, p<. 0001); female gender (OR 2.11, β=0.750, p<. 001); perfusion time (OR 1.022 per minute, β=. 021, p<. 0001); re-operation (OR 2.97, β=1.087, p<. 001; elective surgery
(OR 0.59, β=-0.535, p<.001) and age (OR 1.023 per year, β=0.233, p<.001). Thus, patients with higher preoperative hematocrits were less likely to require transfusion, as expected. Women were about twice as likely to need a transfusion, which approximates the data observed on the descriptive analysis of the sample. Patients who had been previously operated upon required transfusion three times more often than patients undergoing their first CABG, most likely due to bleeding from adhesions and scar tissue, which are both highly vascular. Patients undergoing elective surgery required transfusion about half as often as those requiring urgent or emergent surgery. Patients who spent a longer time on cardiopulmonary bypass bled more and required transfusions more often. Finally, the older patients were on average more likely to require a transfusion. Gender was an independently significant predictor of transfusion needs; therefore, we proceeded with creating two gender specific multiple logistic regression models to explore what variables were most strongly predictive of need for transfusion in men as compared to women.

For the male model, the independently significant variables in order of decreasing statistical significance were: perioperative hematocrit (OR 0.79 per unit, β=-0.231, p<.0001); perfusion time (OR 1.023 per minute, β=0.0234, p<.0001); re-operation (OR 3.42, β=1.22, p<.0001); elective surgery (OR 0.62, β=-0.475, p=.009); body surface area (OR 0.36, β=-1.02, p=.021); and age (OR 1.018 per year, β=0.183, p=.037). Thus, the single most important factor in predicting risk of transfusion was how high the preoperative hematocrit was, with men with higher hematocrits being much less likely to require transfusion as compared to relatively anemic men. Total bypass time and having had a prior CABG were also strongly associated with need for transfusion, whereas body surface area and age were weaker, only marginally significant predictors of transfusion.
We found that most predictors of transfusion during coronary artery bypass grafting surgery were not modifiable, however, the evaluation of preoperative patients for modifiable predictors of transfusion need may produce superior outcomes.

In Chapter Three we identified how complication of surgery may contribute to the length of stay in the intensive care unit. Length of stay can be a significant marker for outcomes in cardiac surgery. We aimed to identify how 1-4 major complications could contribute to the length of stay within the intensive care unit (ICU). Major complication was considered to be neurological complications, specifically stroke; renal insufficiency and failure, respiratory failure, myocardial infarction, heart failure, and bleeding which led to reoperation. We showed that one complication did increase the length of stay in the ICU but when there were two or more complications the length of stay increased significantly, revealing that it is imperative to optimize the patient as much as possible before surgery to avoid any potential complications. Patients’ length of stay was increased significantly (p<0.05) with the complications of stroke, pneumonia, and reoperation for bleeding. Patients’ intensive care unit length of stay did not differ by gender, type of surgical procedure, last creatinine level, diabetes control, hypertension going into surgery, cerebrovascular disease prior to surgery, previous cardiac procedure, and sternal wound infection.

The overall purpose of the study in Chapter Four was to define predictors of ischemic and hemorrhagic stroke in patients who have undergone cardiothoracic surgery. In this respect, ischemic stroke should be understood as any new focal neurological deficit due to cerebral infarction visualized on brain CT or MRI, and hemorrhagic stroke should be interpreted as any new intracranial hemorrhage (subdural, subarachnoid, or intraparenchymal) occurring during the identified perioperative period. Cardiac surgery is
used to bypass occluded vessels as well as repair or replace valves in the heart that are not opening or closing properly, resulting in decreased cardiac output. We know from previous studies that cardiac bypass comes with an increased risk of stroke as well as organ failure due to changes in blood flow and coagulation, blood loss and hypoperfusion (Fanari et al., 2015; O’Brien et al., 2018). Additionally, recent studies have demonstrated that traditional valve procedures have a potentially higher risk of stroke, which may be due to the manipulation of the valve during this procedure (Decosta, Gauera, Gomes, & Schafranski, 2015; Devgun et al., 2018; Nicolini et al., 2016). This is worrisome as stroke has been documented as a potential devastating consequence of cardiac surgery, possibly resulting in decreased physical functioning as well as pain, depression, and anxiety (Galligan et al., 2016). Kishimoto et al. (2016) further added that stroke history decreases overall quality of life, increasing bodily pain, sleep disturbance, and depression symptoms. The aforementioned clearly illustrates the potential danger of post-surgery stroke and signifies a need for knowledge on how to prevent the risk of stroke in cardiac surgery patients. In alignment with this, the current study therefore seeks to explore and make an attempt to identify possible predictors of stroke patients undergoing cardiac valve surgery.

Obtaining such information may result in controlling risk factors with the goal of reducing the prevalence of stroke in this type of surgery, hence the importance of this study. More specifically, the current study looked at the following variables as possible predictors: gender, type of surgical procedure, mortality, last creatinine level, diabetes control, hypertension going into surgery, cerebrovascular disease prior to surgery, previous cardiac procedure, post-surgery complication, and reoperation because of bleeding. To determine the role of these factors, the study used secondary data which was obtained from
the ongoing database of the University of Louisville Department of Cardiothoracic Surgery. This database is a collaborative effort on the part of the hospital based cardiothoracic surgical group, and encompasses data on adult cardiac grafting surgery, including coronary bypass graft (CABG), surgery of the aortic, mitral, tricuspid, and pulmonary valves, surgery of the thoracic aorta, arrhythmia procedures, and less commonly performed procedures such as removal of tumors. The participants of this study were primarily male (56%) with an average overall age of 66 ± 12. To analyze the data and address the research aims, the research carried out a binary logistic regression and tests of differences. The results showed that the overall combined impact of all the predictors significantly predicted post-surgery stroke and accounted for 14% of the variance in predicting post-surgery stroke. When looking at the individual impact of each independent variable, the results suggested that there were three significant predictors of post-surgery stroke: BMI ($Wald(1) = 6.21, p = 0.01$), having chronic lung disease ($Wald(1) = 5.37, p = 0.02$), and having diabetes control ($Wald(1) = 4.82, p = 0.03$). More specifically, the results indicated that (1) having a higher BMI decreased the odds of patients experiencing post-surgery stroke with a one unit increase in BMI decreasing the odds of experiencing post-surgery stroke by 9%, (2) having chronic lung disease increased the odds of patients experiencing post-surgery stroke by 2.96 times, compared to a patient without chronic lung disease, and (3) taking oral medications or insulin for diabetes decreased the odds of patients experiencing post-surgery stroke by 0.69 or 69%.

Previous studies have demonstrated that early and delayed stroke after cardiac surgery have different risk factors and impacts on operative mortality as well as on long-term survival (Galligan et al., 2016; Kishimoto et al., 2016). More specifically — as was
found by this study — (1) having a higher BMI decreased the odds of patients experiencing post-surgery stroke, (2) having chronic lung disease increased the odds of patients experiencing post-surgery stroke, and (3) taking oral medications or insulin for diabetes decreased the odds of patients experiencing post-surgery stroke. These findings may be useful for medical experts as they provide information on what type of patients in particular may be more prone to post-cardiac surgery stroke. Such knowledge is valuable as it makes it possible for medical experts to identify high-risk patients and improve the monitoring of such patients, as well as potentially suggest other options for such individuals to avoid negative outcomes and decrease the likelihood of post-surgery stroke. We also found a relationship between gender and transfusion requirement in coronary artery bypass graft surgery, as well as between patients with a lower body surface area and requiring higher amounts of transfusion. Increasing age was also a predictor for higher transfusion requirements as well as longer cardiopulmonary bypass times, preoperative anemia, and reoperation. Complications of cardiac surgery were highlighted in this dissertation, and we showed that two or more major complications can significantly increase ICU length of stay, which can have a negative effect on morbidity and mortality, as well as increase the cost of surgery.

**Recommendations**

To further investigate the trustworthiness of these results, we recommend a substantial increase in the sample size and possibly a trans-national study. The average overall age of participants was 66 ± 12, and including younger individuals may make the results more authentic and increase generalizability for the sample. It may be possible to repeat the studies using databases from several institutions and different areas of the
country. We have found that the general optimization of health is the overall goal when a patient is facing elective cardiac surgery. We also found specifically that in terms of the predictors for transfusion, management of preoperative anemia with iron supplementation or recombinant erythropoietin, and weight management prior to elective surgery could reduce transfusion need and improve surgical outcomes. The optimization of major organs prior to surgery has shown to decrease the risk of complication. These studies have found significant results that can be implemented in most cardiac surgical programs throughout the country.


Iijima, K., Hashimoto, H., Hashimoto, M., Son, B. K., Ota, H., Ogawa, S., et al. (2010). Aortic arch calcification detectable on chest X-ray is a strong independent predictor of cardiovascular events beyond traditional risk factors. *Atherosclerosis, 210*(1), 137-144.


VITA
Christine A. Williamitis, DNP, APRN

Education

<table>
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<tr>
<th>Institution</th>
<th>Degree</th>
<th>Date Conferred</th>
<th>Field(s) of Study</th>
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<tr>
<td>Brandman University</td>
<td>BA</td>
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<td>Child Psychology</td>
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<tr>
<td>University of Tennessee</td>
<td>DNP</td>
<td>2011, June</td>
<td>Psychiatric Mental Health Nurse Practitioner</td>
</tr>
<tr>
<td>University of Louisville</td>
<td>Post Master’s</td>
<td>2008, July</td>
<td>Family Nurse Practitioner</td>
</tr>
<tr>
<td>University of Cincinnati</td>
<td>MSN</td>
<td>1997, June</td>
<td>Acute Care Nurse Practitioner</td>
</tr>
<tr>
<td>Columbia Union College</td>
<td>BSN</td>
<td>1985, June</td>
<td>Nursing</td>
</tr>
<tr>
<td>Kettering College of Medical Arts</td>
<td>ADN</td>
<td>1982, July</td>
<td>Nursing</td>
</tr>
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</table>

Certifications and Licensure
1989-present ACLS
1997-present Acute Care Nurse Practitioner, ANCC
2008-present Family Nurse Practitioner, AANP
2012-present Family Psychiatric Mental Health Nurse Practitioner
2005-present ARNP Kentucky 3004608
1997-present ARNP Ohio

Awards and Honors
1980 Recipient of the Koch Scholarship from Otterbein Home
1996 Big Sister of the Year, Big Brother’s and Big Sister’s organization
1997 Sigma Theta Tau International Honor Society of Nursing
2011 University of Tennessee, Graduate with Highest Honors
2011 Janssen Student Scholar, American Psychiatric Nurse’s Association
2012 Recipient of the New Horizons Scholarship- University of Kentucky
2014 Induction into Omicron Delta Kappa Honor Society
2018 Faculty of the Year, Brandman University-Chapman University
### Professional Experience Teaching and Clinical Practice

<table>
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<tr>
<th>Dates</th>
<th>Institution and Location</th>
<th>Academic Position</th>
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<tbody>
<tr>
<td>1/2014- present</td>
<td>Brandman University-Chapman University System (Now the University of Massachusetts since 5/2021)</td>
<td>Assistant Professor/Director of the Psychiatric Mental Health Nurse Practitioner Program</td>
</tr>
<tr>
<td>12/2011- 1/2014</td>
<td>Frontier Nursing University</td>
<td>Course Faculty /Adjunct</td>
</tr>
<tr>
<td>August 2009 to June 2011</td>
<td>University of Cincinnati</td>
<td>Instructor</td>
</tr>
<tr>
<td>May 2019- present</td>
<td>U.S. Psychiatry</td>
<td>Psychiatric Nurse Practitioner/ Director of Mental Health clinic for VAD patients</td>
</tr>
<tr>
<td>June 2015- October 2018</td>
<td>The Emily Program Center for Eating Disorders</td>
<td>Psychiatric Nurse Practitioner</td>
</tr>
<tr>
<td>August 2008- 2014</td>
<td>University of Louisville Physicians</td>
<td>Nurse Practitioner</td>
</tr>
<tr>
<td>August 2000- April 2005</td>
<td>United States Air Force</td>
<td>Flight Nurse</td>
</tr>
<tr>
<td>August 1993-March 1998</td>
<td>The Christ Hospital Mobile Care Unit</td>
<td>RN Staff Nurse</td>
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<tr>
<td>August 1993-March 1998</td>
<td>University of Cincinnati Hospital</td>
<td>RN/CCU and ED</td>
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<td>March 1988-August 1993</td>
<td>VA Medical Center</td>
<td>RN/MICU</td>
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<tr>
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### Publications