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INTRAOPERATIVE DETERMINANTS OF PULMONARY COMPLICATIONS AFTER CARDIAC SURGERY: FOCUSING ON INTRAOPERATIVE TRANSFUSION AND TIME ON PUMP IMPLICATIONS ON SHORT AND LONG-TERM OUTCOMES

by

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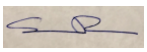
__  _____July 10, 2020_____

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AN ABSTRACT OF THE THESIS OF

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Major: Health Research

Title: Intraoperative Determinants of Pulmonary Complications after Cardiac Surgery: Focusing on Intraoperative Transfusion and Time on Pump: Implications on Short and Long Term Outcomes

Background and Introduction: Postoperative pulmonary complications remain a major contributor to morbidity in patients undergoing cardiopulmonary bypass grafting (CABG). In this study we aimed to investigate how intraoperative factors, focusing on intraoperative transfusion (iXFN) and use of cardiopulmonary bypass (CPB), affect the development PPCs. Furthermore, we aimed to explore how these factors and the development of PPCs influence survival after CABG.

Methods: This investigation is a retrospective analysis of prospectively collected clinical registries collected at two community hospitals in Ohio, USA. All patients who underwent first-time or redo, isolated CABG (N = 6,151) between Jan 1, 1994 and Dec 31, 2005, were considered for this study, and compared for two factors. The two factors are 1) use of early or intra-operative blood transfusions and 2) the role of use (on pump versus off pump) and duration of CPB in case of on pump CABG [off pump (0 minutes); short (1–59 minutes); intermediate (60-119minutes) and long (≥120minutes)]. Long-term survival data were obtained from the United States Social Security Death Index. Univariate binary logistic regression was used to calculate unadjusted odds ratios (UORs) and 95% confidence intervals (CIs) for

potential risk factors associated with pulmonary complications. Subsequently, multivariable logistic regression was applied to determine and quantify the risk-adjusted effects of independent predictors (AORs). Discrimination of logistic regression models was evaluated using the area under the receiver operating characteristic (ROC) curves. Then, the ROC curves were compared for each outcome. For the survival analysis, groups were compared by Cox proportional hazard models, Kaplan-Meier survival plots, and hazard functions to determine 1) pulmonary complications, 2) perioperative mortality and 3) intermediate and long term mortality at 1-year and 5-year follow up. Patient demographics, risk factor, operative and outcomes data were also compared for patients that did versus did not experience postoperative pulmonary complications.

Results: Analysis of preoperative and operative risk factors showed a slightly higher risk profile in patients with intraoperative transfusion, while the risk profiles were generally comparable across different CPB groups. A total of 583 (9.5%) patients developed one or more pulmonary complication. We have found both factors, intraoperative blood transfusion and CPB use, to be associated with worse pulmonary outcomes; with higher pulmonary morbidity observed in longer CPB duration. The odds of developing any PPC was 2.7 higher ($AOR_{iXFN/NoiXFN}$ = 2.7 [2.2-3.3]) in patients with intraoperative transfusion compared to those without intraoperative transfusion. As for CPB use/ duration, we noted higher odds of suffering any PPC in patients with longer CPB times compared to patients with zero CPB time (off pump); $AOR_{1\text{-}59\ mins/\ Off\ Pump}$ = 2.0 [1.1-3.8]), $AOR_{60\text{-}119mins/\ Off\ Pump}$ = 2.5 [1.4-4.5], $AOR_{\geq 120\ mins/\ Off\ Pump}$ = 3.9 [2.2-7.0]. In order to elucidate the combined effect of CPB and iXFN, a composite eight-category transfusion-CPB (2 x 4) variable based on intraoperative transfusion (Yes or No) and CPB use (off pump, 1-59 mins, 60-119 mins and ≥ 120 min) was created. Compared to patients with no iFXN and without CPB use (the reference category), the odds of developing any PPC were

consistently higher in the other categories, with greater values in patients with intraoperative transfusion and in those with longer CPB durations. Notably, the odds of developing any PPC was 10.8 times higher in the category of patients with iXFN and long CPB duration of ≥ 120 mins, compared to the reference category of patients without iXFN and without CPB use (AOR $_{iXFN\&\geq 120\ mins/\ NoiXFN\&Off\ Pump}$ = 10.8 [5.1-23]). Both factors, iXFN and CPB use/ duration, however, neither adversely affected perioperative mortality at 30-day follow up, nor intermediate and long-term 1-year and 5-year follow up. Only exception, however, is the 40% significant increase in 5-year mortality risk observed in patients who underwent surgery with long CPB time (≥ 120 mins) compared to those who underwent off pump surgery (AHR$_{\geq 120mins/Off\ Pump}$= 1.4 [1.1-2.0]). Finally, the development of postoperative pulmonary complications was generally not associated with adverse mortality outcomes at 30-day, 1-year and 5-year follow up.

Conclusion: In this study, we have identified a synergistic interaction between two widely studied intraoperative risk factors (intraoperative transfusion and cardiopulmonary bypass use/ duration), and found it to adversely affect the development of postoperative pulmonary complications in patients undergoing CABG. It is our hope that our findings will provide a knowledge base that lays the groundwork for future studies that aim to improve transfusion practices and further explore the role of CPB use/ duration.

ILLUSTRATIONS

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ABBREVIATIONS

ACSD: Adult Cardiac Surgery Database

AECC: American-European Consensus Conference

AHR: Adjusted Hazard Ratio

AUC: Area Under the Curve

AOR: Adjusted Odds Ratio

APACHE: Acute Physiology and Chronic Health Evaluation

ARDS: Acute Respiratory Syndrome

BMI: Body Mass Index

BSA: Body Surface Area

CABG: Coronary Artery Bypass Grafting

CAD: Coronary Artery Disease

CDC: Center for Disease Control

CHF: Congestive Heart Failure

CKD: Chronic Kidney Disease

CLD: Chronic Lung Disease

CI: Confidence Interval

COPD: Chronic Obstructive Pulmonary Disease

CPB: Cardiopulmonary Bypass

CVA: Cerebrovascular Accident

CVD: Cerebrovascular Disease

CVICU: Cardiovascular Intensive Care Unit

DM: Diabetes Mellitus

DVT: Deep Venous Thrombosis

ECC: Extracorporeal Circulation

HAP: Hospital Acquired Pneumonia

HR: Hazard Ratio

IRB: Institutional Review Board

ICU: Intensive Care Unit

IMA: Internal Mammary Artery

iXFN: Intraoperative Transfusion

NYHA: New York Heart Association

OR: Odds Ratio

PE: Pulmonary Embolism

PMV: Prolonged Mechanical Ventilation

PPC: Postoperative Pulmonary Complication

PRBC: Packed Red Blood Cell

RBC: Red Blood Cell

RCT: Randomized Controlled Trial

ROC: Receiver Operating Curves

SD: Standard Deviation

SIRS: Systemic Inflammatory Response Syndrome

STS: Society of Thoracic Surgeons

SAPS: Simplified Acute Physiology Score

MI: Myocardial Infection

MPM: Mortality Probability Model (MPM II)

TISS: Therapeutic Intervention Scoring System

TRALI: Transfusion Related Acute Lung Injury

TRIM: Transfusion-Associated Immunomodulation

UHR: Unadjusted Hazard Ratio

UOR: Unadjusted Odds Ratio

VAP: Ventilator Associated Pneumonia

WMD: Weight Mean Difference

CONTENTS

CHAPTER 1

THESIS PROPOSAL

1.1 Background and Problem Statement

Advances in cardiopulmonary bypass (CPB) techniques and perioperative care have resulted in lower overall complication rates and improved outcomes following cardiac surgery (Ng, Wan et al. 2002, Hulzebos, Helders et al. 2006). Postoperative pulmonary complications (PPCs), however, remain among the most frequent morbidities after surgery with significant implications on operative mortality, prolonged hospital stay and overall resource utilization (Habib, Zacharias et al. 1996, Habib, Zacharias et al. 2003, Hulzebos, Helders et al. 2006).

The unique nature of cardiac surgery which often involves median sternotomy, internal mammary artery dissection, topical cooling for myocardial protection and the use of CBP, makes some degree of pulmonary complications inevitable (Wynne and Botti 2004). These include a wide range of clinical manifestations, and range from minimal arterial hypoxemia, in 100% of patients (Taggart, El-Fiky et al. 1993), to acute lung injury in about 1% (Christenson, Aeberhard et al. 1996). Notably, previous research on pulmonary complications after cardiac surgery has been limited by small sample sizes and absence of equivocal definitions and outcomes measures (Wynne and Botti 2004).

To date, most research has focused on patient characteristics and preoperative risk factors for determining pulmonary complications after surgery, - specifically prolonged mechanical ventilation - including the risk models developed from The Society of

Thoracic surgeons National Database. Two decades ago, it was shown that duration of cardiopulmonary bypass and transfusion of blood products are associated to prolonged postoperative mechanical ventilation (Habib, Zacharias et al. 1996). Subsequently, it was also shown that the extent of hemodilution on bypass, and therefore its consequent use of transfusion, was also linked to worse pulmonary outcomes (Christenson, Aeberhard et al. 1996). Unfortunately, little research has been done since to adequately elucidate the roles, if any, of duration of cardiopulmonary bypass and the use (amount) of blood transfusions – both pro-inflammatory events - and their interaction. Furthermore, potential impact of postoperative pulmonary morbidity on intermediate and late cardiac surgery outcomes, in particular cause-specific mortality, have not been investigated.

1.2 Research Question and Objective(s)

1.2.1 Hypotheses

Surgery, per se, is a known risk factor irrespective of type with potential related complications. In case of cardiac surgery, the inflammatory hit is compounded by multiple additional risk factors such as use of cardiopulmonary bypass, hemodilutional anemia during surgery and the frequent use of transfusions. The proposed research in this thesis will, therefore, test the central hypothesis of a multi-hit model for pulmonary injury in cardiac surgery patients. Accordingly, we hypothesize:

H1: Longer durations of CPB will increase the incidence of PPCs

H2: Blood transfusion will increase the risk of PPCs

H3: There is an interaction effect between duration of CPB and transfusion leading to worse pulmonary outcomes

H4: PPCs will worsen both early and late outcomes in patients undergoing cardiac surgery

1.2.2 Specific Aims

1) To evaluate the association of PPCs (prolonged ventilation, pneumonia, acute respiratory distress syndrome, pulmonary edema, prolonged intubation (>24 hours) and reintubation) with the duration of CPB 1) in all patients who underwent cardiac surgery and 2) in subsets of patients who received PRBC transfusion during cardiac surgery and those who did not;
2) To ascertain using multivariate analysis the separate and interaction effects (multi-hit model) of CPB and transfusion on PPCs after cardiac surgery;
3) To assess the association of PPCs and early/ perioperative outcomes of cardiac surgery (30-day mortality); and
4) To investigate whether PPCs are independently linked to worse cause-specific late (1-year and 5-year) mortality after surgery.

1.3 Methods

This investigation is a retrospective analysis of prospectively collected clinical registries collected at two hospitals in Toledo, Ohio, based on the data field definitions of, , The Society of Thoracic Surgeons (STS) Adult Cardiac Surgery. The institutional review board at those institutions approved the use of this data. The need of an informed consent was waived since no additional review of the hospital records or interviewing of

patients will be done. A de-identified file was made available to us at American University of Beirut for analysis.

The primary endpoint is all-cause mortality at 30-day post op, and at 1-year and 5-year follow-up. Long-term survival data is available from the service follow-up, routine twice-annual searches of US Social Security Death Index database (2016) and will be complemented by cross-checking with the Ohio State Death Registry (January 1994 to December 2013).

Continuous variables will be expressed as mean ± SD and compared using the independent Student's *t* test or Mann-Whitney *U* test based on normality. Categorical variables will be expressed as counts and percentages and compared by the χ^2 test. Time-to-event analyses truncated at a maximum of 5 years will be calculated using the Kaplan-Meier product limit method to estimate unadjusted survival between groups (PPC versus no PCC) comparisons (log-rank test). Cox regression analysis will be used with comprehensive covariate adjustment for several known risk factors (patient and operation-related). Unadjusted hazard ratio (HR) and covariate-adjusted hazard ratio (AHR) adjusted to all factors (to be detailed later) with 95% confidence interval (CI) will be calculated using competing risk regression models.

As for the role of the two-hit hypothesis in predicting PPCs, the primary independent/exposure variables under investigation are time on CPB (minutes) and use of transfused blood. Since the time on CPB varies widely among cardiac surgery patients, we will create a composite eight-category transfusion-CPB (2 x 4) variable based on intraoperative transfusion (Yes or No) and CPB use (off pump, short, intermediate and long CPB).

A two-sided *p* value less than 0.05 will be used uniformly to indicate significance. Statistical analysis will be conducted with IBM SPSS Statistics, version 23.0 (IBM Corp, Armonk, NY).

1.4 Significance for Policy/Interventions

Several interventions to decrease postoperative pulmonary complication rates in cardiac surgery have been proposed. Yet, data is still lacking on major predictors of pulmonary complications and the associated long-term impact on outcomes. Providing solid data on both pulmonary complications risk factors and the resulting long-term survival rates will enable researchers to design better trials and evaluate more defined and targeted interventions to decrease pulmonary complications. This would improve outcomes and utilize resources in an efficient and responsible manner.

CHAPTER 2

INTRODUTION AND BACKGROUND

Coronary artery bypass grafting (CABG) is a major surgical procedure associated with postoperative mortality and significant morbidity with urgent need for improvement in order to reduce the risk of early and late adverse events (Biancari, Ruggieri et al. 2015). Previous and prospective analyses of the impact of baseline risk factors, operative techniques, perioperative treatment methods and secondary prevention strategies on the outcome of patients undergoing CABG are expected to provide valuable and reliable information to improve the safety and durability of CABG (Biancari, Ruggieri et al. 2015). In addition to the widely studied hard outcome of perioperative mortality following cardiac surgery, there is growing interest in studying other postoperative complications. The incidence of nonfatal complications after major surgery is rather high and may have a negative impact on patient's recovery and the burden of resources necessary to treat such complications. Furthermore, postoperative complications may have a significant impact also on late survival (Toumpoulis, Anagnostopoulos et al. 2005, Hansen, Gammelager et al. 2015, Phan, Ha et al. 2015). PPCs , after cardiac surgery, remain the most frequent and significant contributor to morbidity and mortality in patients undergoing coronary artery bypass grafting (CABG) (Wynne and Botti 2004, Wynne, Botti et al. 2011, Sabaté, Mazo et al. 2014). PPCs include a wide range of clinical manifestations (Wynne and Botti 2004), and range from minimal arterial hypoxemia, in 100% of patients (Taggart, El-Fiky et al. 1993), to acute lung injury in

about 1% (Christenson, Aeberhard et al. 1996). Notably, the contribution of PPCs to the morbidity and mortality in cardiac surgery has been recognized soon after the commencement of CABG (Baer and Osborn 1960, Schramel, Schmidt et al. 1963, Awad, Lemieux et al. 1966, Asada and Yamaguchi 1971). However, given the constantly changing risk profile of cardiac surgery patients which evolved over the years to include older and sicker patients (Estafanous, Loop et al. 1998, Ferguson Jr, Hammill et al. 2002, Podesser 2011), the impact of PPCs became more pronounced. Almost universally, PPCs result in increased rates of ICU admissions (Kogan, Cohen et al. 2003), hospital readmissions (Kogan, Cohen et al. 2003), prolonged postoperative hospital stays (Lawrence, Hilsenbeck et al. 1995), higher costs and vaster resource utilization (Shander, Fleisher et al. 2011).

2.1 PPCs

2.1.1 Pathophysiology, Definitions and Risk Factors

Some reviews suggest inevitability of PPCs in cardiac surgery given the numerous factors related to the underlying pathophysiology (Badenes, Lozano et al. 2015). Both general anesthesia and mechanical ventilation, and factors pertaining to cardiac surgery lead to PPCs. Alteration in the function of chest muscles and wall due to median sternotomy, systemic inflammatory response initiated by using CPB, phrenic nerve damage caused by administration of cold saline in the pericardial cavity during cardiac arrest and alveolar edema brought on by left ventricular distension and elevated pressure in the pulmonary vasculature are distinctive factors in cardiac surgery (Gravlee 2008).

First, general anesthesia results in chest wall relaxation which alters its compliance and produces a diaphragm upshift due to prolonged supine position (Hedenstierna, Strandberg et al. 1985). This affects pulmonary function and alters ventilation-perfusion mismatch and results in abnormal pulmonary shunt fraction (Hedenstierna, Strandberg et al. 1985). In addition, the majority of anesthetic agents have repercussion on pulmonary function, where inhalation anesthetics inhibit hypoxic pulmonary vasoconstriction, and narcotics reduce hypoxic and hypercapnic ventilatory response (Matthay and Wiener-Kronish 1989). This results in reduction of both the vital capacity and the lungs functional residual capacity (Hedenstierna, Strandberg et al. 1985), and a widened alveolar-arterial oxygen gradient causing hypoxemia and atelectasis (Matthay and Wiener-Kronish 1989). On the other hand, mechanical ventilation in cardiac surgery causes significant changes in lung structure and function. Both mechanical and biological trauma can result from mechanical ventilation (García-Delgado, Navarrete-Sánchez et al. 2014) and can lead to pulmonary inflammation that can spread to distant organs (Dreyfuss and Saumon 1998). Mechanical trauma involves both volutrauma and barotrauma, where lung damage is attributable to high tidal volumes in the first (Dreyfuss, Soler et al. 1988) and to the application of high airway pressure in the second (KUMAR, PONTOPPIDAN et al. 1973). The stress produced by this mechanical trauma could be strong enough to cause destruction of the anatomical lung structure with epithelial injury, loss of epithelial integrity, and edema (Badenes, Lozano et al. 2015). Biological trauma, on the other hand, is brought about by an underlying molecular mechanism that involves proinflammatory cytokines release, reactive oxygen species production, complement activation and mechanotransduction (Chen, Xia et al. 2018).

Secondly, the factors unique to cardiac surgical procedures, median sternotomy incision, dissection of the internal mammary artery, hypothermia for myocardial protection, and the use of CPB are discussed below.

The impact of median sternotomy incision on development of PPCs is not yet clear, and while some reports have described adverse outcomes (Auler Jr, Zin et al. 1987, Tulla, Takala et al. 1991), others have reported only benign findings (Barnas, Watson et al. 1994, Ranieri, Vitale et al. 1999). In principle, sternotomy leads to reduced airway pressure and increased lung compliance when the chest wall no longer impedes lung expansion (Dueck 1994). Subsequently, the hypothesis that procedures with minimal chest wall interruptions that involve smaller sternotomy incisions should result in less pulmonary complications after CABG was tested by both Lichtenberg et al (Lichtenberg, Hagl et al. 2000) and Bauer et al (Bauer, Pasic et al. 2001). While Lichtenberg and colleagues have found that a minimally invasive 8 cm incision, compared to the standard 20 cm, is associated with preservation of pulmonary function (Lichtenberg, Hagl et al. 2000), Bauer at al reported equivocal results (Bauer, Pasic et al. 2001) when comparing partial inferior midline sternotomy to the standard full midline incision.

Internal mammary artery (IMA) retrieval, which typically necessitates pleural dissection, is reported to increase pulmonary complications after cardiac surgery (Berrizbeitia, Tessler et al. 1989, Kollef 1990, Landymore and Howell 1990, Kollef, Wragge et al. 1995, Bonacchi, Prifti et al. 2001). Due to its superior patency, IMA is now accepted as the conduit of choice and is being widely used (Wynne and Botti 2004). While it remains unclear if PPCs associated with IMA are precipitated by the pleurotomy itself and the subsequent pleural effusion (Peng, Vargas et al. 1992), several

studies compared the use of unilateral IMA versus its bilateral use on PPCs (Knapik, Spyt et al. 1996, Daganou, Dimopoulou et al. 1998, Taggart 2000). Compared with unilateral IMA grafting, the use of bilateral IMA grafts during coronary artery revascularization did not increase the incidence of postoperative respiratory complications (Daganou, Dimopoulou et al. 1998, Taggart 2000), but did result in mild prolongation of postoperative respiratory support (7.6 hours versus 12 hours) (Knapik, Spyt et al. 1996).

Myocardial protection, via profound myocardial hypothermia and moderate systemic cooling of circulating blood in the CPB, is often used in cardiac surgery despite the uncertainty of its usefulness (Allen, Buckberg et al. 1992). Usually, profound myocardial hypothermia is established by either using topical iced slush (Ferguson 1999), a cooling jacket (Daily and Kinney 1991, Kinney, Daily et al. 1991) or infusion of the coronary arteries with chilled cardioplegic solution (Johnson, Dorsey et al. 1982). It is hypothesized that myocardial cooling contributes to the development of PPCs after cardiac surgery (Chandler, Rozas et al. 1984, Moat, Lamb et al. 1992, McLean, Jones et al. 1993). For example, Dimopoulou et al (Dimopoulou, Daganou et al. 1998), interested in studying postoperative phrenic nerve dysfunction after cardiac surgery, found out that the use of ice slush was the only independent risk factor significantly associated with phrenic nerve injury. Furthermore, the authors recommended against its use in cardiac surgery as it did not provide additional myocardial protection (Dimopoulou, Daganou et al. 1998). Similarly, the use of ice/slush topical hypothermia during open heart surgery was found to be associated with a high rate of diaphragm paralysis (Efthimiou, Butler et al. 1991). Wilcox et al, however, reported that topical cold cardioplegia may result in phrenic paresis after

coronary artery bypass, but cannot be solely attributable to the development of atelectasis (Wilcox, Baile et al. 1988).

Finally, pulmonary function in cardiac surgery is significantly affected by the extracorporeal circulation (ECC) in on pump surgery. When ECC initiates, the cessation of pulmonary ventilation leads to loss of surfactant and alveolar collapse resulting in retention of secretions and atelectasis (Badenes, Lozano et al. 2015). Furthermore, pulmonary ischemia, brought on by stopping the pulmonary circulation, leads to injured capillary walls and subsequent release of inflammatory mediators (UTLEY 1990), resulting in an augmented inflammatory response and higher levels of circulating neutrophils and monocytes (Ascione, Lloyd et al. 2000).

In cardiac surgery, it is very difficult to diagnose pulmonary complications with accuracy and specificity given the variability in diagnostic criteria (O'Donohue 1985). In a work aimed at improving the definition and use of outcome measures in clinical effectiveness trials in perioperative medicine, Abott et al (Abbott, Fowler et al. 2018) performed a systematic literature review looking at perioperative pulmonary outcomes definitions in both clinical trials and observational studies. The authors found out that many definitions were imprecise, or difficult to apply in large patient populations as some of these definitions required invasive diagnostic testing via bronchoscopy (Abbott, Fowler et al. 2018). Furthermore, the authors noted that the composite outcome of PPCs was widely used, and the group was particularly concerned about the lack of consensus in severity categorization given the large spectrum of underlying biological mechanisms (Abbott, Fowler et al. 2018). Theoretically a PPC is any pulmonary abnormality occurring in the postoperative period that produces identifiable disease or dysfunction

that is clinically significant and adversely affects the clinical course (O'Donohue Jr 1992). Clinically, however, a PPC may present as a singular problem or combination of pulmonary problems, and the distinction between what constitutes a clinically important pulmonary finding and a pulmonary complication is not always clear (Brooks-Brunn 1995). For example, although hypoxemia is not a diagnosis in itself, it is almost universally present in other diagnoses and results in significant clinical implications (Wynne and Botti 2004). Accordingly, there is no clear documentation of neither the severity nor the reported frequency of PPCs (Taggart, El-Fiky et al. 1993) and understandably, the overall incidence of PPCs following CABG surgery in literature varies from 5% to 90% (Brooks-Brunn 1995). In addition to the diverse definitive criteria that affect diagnostic specificity, a variety of terms are used while referring to PPCs (Wynne, Botti et al. 2011), which makes comparison across different studies very hard. Abbott et al, for example, identified the following alternative definitions of 'PPCs', 'major pulmonary complications', 'major respiratory complications', 'postoperative respiratory complications', 'postoperative respiratory outcomes', 'pulmonary complications' or 'respiratory complications' (Abbott, Fowler et al. 2018)

Many investigators have been interested in studying risk factors associated with the development of PPCs after cardiac surgery. In a review of the literature by Rochelle Wynn and Mari Botti (Wynne and Botti 2004), risk factors were categorized into preoperative and intraoperative factors. Intraoperative risk factors included Chronic Obstructive Pulmonary Disease (COPD) (Carrel, Schmid et al. 1991, Higgins, Yared et al. 1991, Wahl, Swinburne et al. 1993, Girish, Trayner Jr et al. 2001, Walthall, Robson et al. 2001), obesity (Moulton, Creswell et al. 1996, Rady, Ryan et al. 1997, Weiss, Merin et al. 2000, Walthall, Robson et al. 2001), diabetes mellitus type II (Spivack,

Shinozaki et al. 1996), history of smoking (WARNER, DIVERTIE et al. 1984, Carrel, Schmid et al. 1991, Spivack, Shinozaki et al. 1996), congestive heart failure (CHF) (Gould, Freeman et al. 1985, Higgins, Yared et al. 1991, Spivack, Shinozaki et al. 1996, Knight, Livingston et al. 1997, Engoren, Buderer et al. 1999, Weiss, Merin et al. 2000, Walthall, Robson et al. 2001), emergency surgery (Rady, Ryan et al. 1997, Suematsu, Sato et al. 2000, Weiss, Merin et al. 2000, Bezanson, Deaton et al. 2001), previous cardiac surgery (Higgins, Yared et al. 1991, Bezanson, Deaton et al. 2001), immobility (Woods, Froelicher et al. 2005) and age >60 years ((Arom, Emery et al. 1995, Bezanson, Deaton et al. 2001), >70 years (Higgins, Yared et al. 1991, Wahl, Swinburne et al. 1993, Rady, Ryan et al. 1997) and >80 years (Doering, Imperial-Perez et al. 1998, Weiss, Merin et al. 2000, Yamagishi, Ishikawa et al. 2000, Walthall, Robson et al. 2001). Intraoperative factors included respiratory depression (Matthay and Wiener-Kronish 1989), neurological injury (Roques, Nashef et al. 1999), lung deflation (Finkelmeier and Brown 1996), CPB (Weiland and Walker 1986, Matthay and Wiener-Kronish 1989), topical cooling (Goodnough 1985, Dimopoulou, Daganou et al. 1998), IMA dissection 15, 45 (Kollef, Peller et al. 1988, Berrizbeitia, Tessler et al. 1989, Matthay and Wiener-Kronish 1989, Kollef 1990, Landymore and Howell 1990, Bonacchi, Prifti et al. 2001), sternotomy incision (Tulla, Takala et al. 1991, Lichtenberg, Hagl et al. 2000), increased number of bypass grafts (Wilcox, Baile et al. 1988, Berrizbeitia, Tessler et al. 1989, Walthall, Robson et al. 2001), increased duration of CPB (Wilcox, Baile et al. 1988, Berrizbeitia, Tessler et al. 1989, Rady, Ryan et al. 1997, Engoren, Buderer et al. 1999, Rady and Ryan 1999, Suematsu, Sato et al. 2000, Weiss, Merin et al. 2000) and lower core temperature (Wilcox, Baile et al. 1988, Berrizbeitia, Tessler et al. 1989, Insler, O'Connor et al. 2000, Weiss, Merin et al. 2000).

2.1.2 ARDS

Acute respiratory distress syndrome (ARDS) after cardiac surgery was first reported in 1973 (Llamas and Forthman 1973). Following cardiac surgery, the incidence of ARDS is generally low and ranges between 0.17% (Michalopoulos, Prapas et al. 2006) and 2.5% (Kaul, Fields et al. 1998), with wide range of associated mortality between 15% (Milot, Perron et al. 2001) and 91.6% (Asimakopoulos, Taylor et al. 1999). This wide variation in both reported incidence and mortality could be explained by the underlying heterogeneity of the studied subjects and by the difference in study designs and methodologies across published data (Kogan, Preisman et al. 2014). More importantly, this is due to the diversity of the available ARDS definitions and lack of consensus on ARDS defining criteria (Fanelli, Vlachou et al. 2013). Up until the last decade, the most widely accepted definition of ARDS was that of the American-European Consensus Conference (AECC) published in 1994 (Bernard, Artigas et al. 1994). ARDS was defined as the acute onset of respiratory failure, bilateral infiltrates on chest radiograph, hypoxemia as defined by a PaO_2/FiO_2 ratio $\leq$200 mmHg, and no evidence of left atrial hypertension or a pulmonary capillary pressure <18 mmHg (if measured) to rule out cardiogenic edema. This however was challenged later by the European Society of Intensive Care Medicine with endorsement from the American Thoracic Society and the Society of Critical Care Medicine who convened an international expert panel to revise the ARDS definition. The meeting took place in 2011 in Berlin, and hence the new definition became known as the Berlin definition (Force, Ranieri et al. 2012). Developing the Berlin definition was thought to improve feasibility, reliability and predictive validity where three mutually exclusive categories of ARDS based on degree of hypoxemia were integrated; mild (200 mm

Hg < PaO_2/FIO_2 ≤ 300 mm Hg), moderate (100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg), and severe (PaO_2/FIO_2 ≤ 100 mm Hg) (Force, Ranieri et al. 2012). Another widely used definition for ARDS is Murray's Lung Injury Score (Murray, Matthay et al. 1988), which included one radiological and three physiological variables; extent of alveolar consolidations on imaging, hypoxemia, lung compliance, and applied positive end expiratory pressure (PEEP) (Murray, Matthay et al. 1988). Although published in 1988 and was later challenged by the AAEC definition, it remained widely used throughout the next two decades (Messent, Sullivan et al. 1992, Christenson, Aeberhard et al. 1996, Asimakopoulos, Taylor et al. 1999, Milot, Perron et al. 2001).

The pathophysiology of ARDS after cardiac pulmonary bypass surgery is not completely understood (Milot, Perron et al. 2001). It is postulated that during the initial stage of CBP, complement activation of the alternative pathway results in anaphylatoxins release (Chenoweth, Cooper et al. 1981, Tönz, Mihaljevic et al. 1995). This activates the neutrophils which in turn produce lysosomal granular contents resulting in diffuse injury in the pulmonary circulation (Tönz, Mihaljevic et al. 1995, Milot, Perron et al. 2001). Furthermore, postoperative low cardiac output, and subsequent splanchnic hypoperfusion and transient gastrointestinal mucosal ischemia, exacerbate the inflammatory process (Baue 1993, Ohri, Bjarnason et al. 1993, Sinclair, Haslam et al. 1995). In addition, the use of protamine, necessary for Heparin neutralization at the end of CPB, contributes to activation of the complement pathway (Cavarocchi, Schaff et al. 1985, Kirklin, Chenoweth et al. 1986). To note, genetic polymorphism in inflammatory agents, mostly the promoter of IL18, appears to further contribute to ARDS susceptibility in cardiac surgery with CPB (Chen, Xu et al. 2010, Wang, Bian et al. 2010, Rong, Di Franco et al. 2016).

Several studies have investigated the predictors of ARDS in cardiac surgery (Milot, Perron et al. 2001, Kogan, Preisman et al. 2014). No patient undergoing cardiac surgery is ARDS risk-free (Rong, Di Franco et al. 2016) and it is proposed that early identification of those at high risk could help in ARDS prevention. However, evidence about risk factors is lacking. In a retrospective analysis, Christenson et al identified hypertension, current smoking, emergency surgery, preoperative New York Heart Association (NYHA) class 3 and 4, low postoperative cardiac output and left ventricular ejection fraction < 40% as significant, independent predictors for adult respiratory distress syndrome. Combined cardiac surgery and diffuse coronary disease were also significant predictors (Christenson, Aeberhard et al. 1996). In another retrospective analysis of 6069 patients who underwent cardiac surgery, a multivariate regression analysis identified previous cardiac surgery, complex cardiac surgery, and more than three transfusions with packed red blood cells (PRBC) as independent predictors for developing ARDS (Kogan, Preisman et al. 2014). Kaul and colleagues found recent smoking, advanced chronic obstructive pulmonary disease (COPD) and emergency CABG to be associated with ARDS development after cardiac surgery (Kaul, Fields et al. 1998). Only poor cardiac contractility (low left ventricular ejection fraction) and NYHA class III–IV were identified as risk factors by (Asimakopoulos, Taylor et al. 1999). Finally, Milot and colleagues reported previous cardiac surgery, shock and multiple transfusions as predictors of ARDS (Milot, Perron et al. 2001).

2.1.3 Pneumonia

Infections post cardiac surgery, including sepsis, pneumonia, and sternal wound or harvest site infections, occur frequently in patients undergoing coronary artery

bypass grafting (CABG) (Shih, Zhang et al. 2014). In patients hospitalized for CABG, Rogers and colleagues have reported very high rates of post-operative infections in both women (16.1%) and men (9.8%) (Rogers, Langa et al. 2006). Infection in patients undergoing cardiac surgery usually requires prolonged treatment with antibiotics and, occasionally, additional surgeries, which increases morbidity, mortality and cost (Fowler Jr, O'Brien et al. 2005, LaPar, Crosby et al. 2013). This is of particular importance, given that the proportion of patients undergoing coronary artery bypass grafting is increasingly at high-risk for infection because of the aging US population, a growing number of patients undergoing "redo" procedures, and the high prevalence of conditions, like obesity and diabetes, associated with both cardiovascular and infectious risks (Fowler Jr, O'Brien et al. 2005).

Several studies have revealed that pneumonia is the most common serious infection post cardiac surgery, although, traditionally, it was thought that surgical site infection is the most common one (Gelijns, Moskowitz et al. 2014, Likosky, Wallace et al. 2015, Ailawadi, Chang et al. 2017). Pneumonia after isolated CABG is associated with greater incremental cost, even after adjusting for baseline preoperative risk factors (LaPar, Crosby et al. 2013).

Patients undergoing cardiac surgery are highly susceptible to pneumonia (Ailawadi, Chang et al. 2017). The underlying pathogenesis is multifactorial and typically starts with colonization of the aero-digestive tract and aspiration of the contaminated tract secretions in the setting of diminished host-defenses (Chughtai, Gwam et al. 2017). Furthermore, CPB, with its effect on systemic inflammatory mediators and its potential for lung injury, contributes significantly to developing pneumonia (Asimakopoulos, Smith et al. 1999). Additionally, significant fluid shifts in

the perioperative setting often lead to pulmonary edema, combined with the frequent need for transfusion of blood products, increase pneumonia risk (Banbury, Brizzio et al. 2006). Moreover, the frequent need for prolonged mechanical ventilation often places patients at increased risk for pneumonia (Allou, Bronchard et al. 2014, Fitch and Whitman 2014, Sheng, Xing et al. 2014). Finally, postoperative pain due to sternotomy or thoracotomy can affect pulmonary mechanics and invariably predispose this set of vulnerable population to pneumonia (Ailawadi, Chang et al. 2017).

As for risk factors and predictors of pneumonia post cardiac surgery, data remains largely conflicted. Fitch et al conducted a systematic review to define predictors of ventilator associated pneumonia (VAP) (Fitch and Whitman 2014) post cardiac surgery. Knowing that VAP has been used frequently in the literature and defined differently, the studies reviewed by Fitch et al defined VAP as pneumonia in patients on mechanical ventilation for greater than or equal to some set period of time, descried individually for each study. Seven studies that examined independent risk factors for development of VAP in adult cardiac surgical patients were included in the review; four were prospective cohort studies (Kollef 1993, Bouza, Pérez et al. 2003, Hortal, Giannella et al. 2009, Tamayo, Álvarez et al. 2012), one was a retrospective cohort study (Henry, Halpin et al. 2010), and two were randomized clinical trials (Bouza, Pérez et al. 2008, Poelaert, Depuydt et al. 2008). Risk factors found to be independently associated with the development of VAP ($p < 0.05$) by logistic regression modeling included perioperative transfusion of blood products, days of mechanical ventilation, reintubation, mechanical ventilation >96 hours, organ system failure index ≥3, mechanical circulatory support (intra-aortic balloon support or ventricular assistance), reintervention, ascending aorta surgery, prior central nervous system

disorder, age, ulcer disease, prior administration of antibiotics, supine head position, emergent surgery, previous cardiac surgery, intraoperative inotropic support and serum creatinine (Fitch and Whitman 2014).

2.1.4 Reintubation

Weaning from mechanical ventilation and consequent endotracheal extubation is expected to proceed straightforwardly after CABG (Engoren, Buderer et al. 1999). In rare instances, when extubation fails and reintubation becomes necessary, a complex underlying mechanism is thought to play a role. A patient's inability to tolerate extubation may reflect premature extubation or may be a marker of a sicker patient at baseline (Engoren, Buderer et al. 1999). Regardless, premature extubation often leads to hypercarbia, hypoxemia, pulmonary hypertension, right heart failure, and myocardial ischemia (Mangano, Siliciano et al. 1992). In addition, it subjects the patient to the physical risks of reintubation, including esophageal intubation, laryngeal trauma, and pulmonary aspiration (Williamson, Webb et al. 1993). After cardiac surgery, the incidence of reintubation in patients who were reweaned from mechanical ventilation is very high (Rady and Ryan 1999) and can reach up to 7.8% (Jian, Sheng et al. 2013). Reintubation is not only associated with increased duration of mechanical ventilation but also increases the length of ICU and hospital stay (Gowardman, Huntington et al. 2006). Patients who require reintubation usually have poor prognosis with a mortality rate exceeding 30%–40%, irrespective of the cause for reintubation (Rello, Diaz et al. 1999).

In a retrospective analysis, Jian et al (Jian, Sheng et al. 2013) looked into 1,244 consecutive patients who underwent isolated CABG and were extubated within 48 hours. Among them, 97 (7.8%) cases were re-intubated because of breathing problems. The most common reason for reintubation was pulmonary edema due to CHF, followed by hypoxemia due to pulmonary disease, carbon dioxide accumulation, acute respiratory tract obstruction and anaesthetic metabolic insufficiency. When determining reintubation predictive factors, the authors found that preoperative factors of COPD and CHF and postoperative ones of relative hypoxemia, AKI and total mechanical ventilation time were five independent risk factors for reintubation following CABG (Wang, Bian et al. 2010).

One of the largest retrospective analyses from the American College of Surgeons National Surgical Quality Improvement Project Database (Beverly, Brovman et al. 2016), investigated a total of 18,571 adult patients undergoing cardiac surgery. Reintubation incidence was 4.0%, with identified risk factors of older age, preoperative partial or total dependence, dyspnea, chronic kidney disease, dyspnea at rest or on exertion, chronic kidney disease, chronic obstructive pulmonary disease, previous cardiac surgery, congestive heart failure, emergency surgery, longer duration of surgery, and mitral and tricuspid valve surgery. In addition, Beverly et al found out that patients requiring reintubation after surgery had 7.5 times higher mortality (21.9% *v* 2.9%), longer hospital admissions (22.2 *v* 7.8 days), and were less likely to be discharged home within 30 days (35% *v* 80%) (Beverly, Brovman et al. 2016).

2.1.5 Prolonged Mechanical Ventilation

Prolonged mechanical ventilation (PMV) is an important complication following cardiac surgery, and universally results in increased mortality and morbidity (Gajic, Dabbagh et al. 2011). It is thought that prolonged mechanical ventilation increases the possibility of adverse effects of positive-pressure ventilation and barotrauma, maximizes associated patient discomfort, increases the risk of ventilator associated pneumonia and prevents early ambulation (Habib, Zacharias et al. 1996). Depending on its definition, as duration of prolonged mechanical ventilation has been defined differently across different studies, the incidence can range anywhere between 2.6% and 22.7% (Trouillet, Combes et al. 2009). PMV can result in increased intensive care unit (ICU) stay, increased hospital stay, decreased hospital bed availability, increased resource utilization and health care costs (Natarajan, Patil et al. 2006). In fact, one study found out that when compared to patients who have undergone early extubation, those with prolonged mechanical ventilation had 40% increase in mortality rates (within 24 hours). Needless to say, PMV increases length of hospital stay and has been reported to reach or exceed 2 to 3 weeks (Kollef, Wragge et al. 1995, Branca, Mc Gaw et al. 2001). This negatively impacts the quality of life (da Rocha Cabral, Peçanha et al. 2019) and results in a huge economic burden (Rajakaruna, Rogers et al. 2005). In one study, effective cost per survivor was 18 times higher for patients mechanically ventilated for more than 4 days than for early weaned patients (Kern, Redlich et al. 2001). Similarly, another study found that in patients with prolonged mechanical ventilation, the average hospital charge per patient was approximately $6,000 more than in the early extubation group (Arom, Emery et al. 1995). Patients who failed early extubation consumed 37% of patient-days in ICU care (Thompson, Elton et al. 1997). Therefore, the duration of

mechanical ventilation seems to be an adequate indicator of significant health complications and related health-care costs (Ghauri, Javaeed et al. 2019), with recent practice focusing on expediting early extubation (Habib, Zacharias et al. 1996).

Several studies have investigated factors associated with PMV after cardiac surgery. Serrano et al, tested the ability of the Intensive Care Unit Risk Stratification Score (ICURSS) model, which gathers both preoperative and immediately postoperative data, to predict prolonged mechanical ventilation in patients undergoing cardiac surgery (Serrano, García et al. 2005). The model performed poorly leading another group of investigators to use a more successful predictor model that consisted of different information relating to postoperative ICU admission criteria (low cardiac output, vasopressor use and pulmonary hypertension) and early postoperative complications (stroke and bacteremia) (Murthy, Arroliga et al. 2007). A similar observation was reported by Kern and colleagues who found that only the postoperative measure of severity of illness by the Simplified Acute Physiology Score (SAPS) and of the intensity of treatment and nursing care activity by the Therapeutic Intervention Scoring System (TISS) resulted in an effective model for prediction of mechanical ventilation greater than 48 hours (Kern, Redlich et al. 2001). Another simple score was developed by Trouillet and colleagues to identify patients with a strong likelihood of successful rapid weaning from mechanical ventilation, and it used postoperative day-3 physiologic parameters (Trouillet, Combes et al. 2009).

Other studies that have investigated traditional demographic and operative risk factors had different conclusions. For example, Wong et al showed that advanced age and female gender, as well as intra-aortic balloon pump, inotropes, excessive bleeding and atrial arrhythmia increase the risk of delayed extubation(Wong, Cheng et al. 1999).

In a retrospective study on 10,977 patients undergoing CABG, Saleh and colleagues showed that NYHA class of higher than II, renal dialysis, age, reduced FEV1, BMI of more than 35 kg/m2 are associated with increased risk of prolonged mechanical ventilation, with a cut-off point of 72 h for delayed extubation (Saleh, Shaw et al. 2012). In another study by London et al involving 304 patients undergoing cardiac surgery, age and inotrope use were found to be risk factors of delayed extubation defined as extubation after 10 hours (London, Shroyer et al. 1998). Arom et al, in a retrospective review of CABG patients, wherein early extubation was defined as that occurring within 12 hours, reported that age, gender, preoperative diuretic use and presence of congestive heart failure or unstable angina were associated with delayed extubation (Arom, Emery et al. 1995). In a cohort study of 3,269 CABG patients, Cislaghi et al demonstrated that redo surgery, longer CPB, intraoperative transfusion (>4 units of red blood cell or fresh frozen plasma), and LVEF of less than 30% are independent risk factors of delayed extubation (Cislaghi, Condemi et al. 2007). Finally, Totonchi et al (Totonchi, Baazm et al. 2014) were interested in studying pre-operative, intra-operative and post-operative risk factors associated with PMV. Significant pre-operative risk factors included gender, history of chronic obstructive pulmonary disease (COPD), chronic kidney disease and endocarditis; intra-operative factors included type of surgery, operation time, pump time, transfusion in operating room and postoperative variables included bleeding and inotrope-dependency.

2.1.6 Pulmonary Embolism

The incidence of pulmonary embolism after cardiac artery bypass graft surgery is thought to be very low (Canver and Fiedler 1992). It is postulated that the

administration of tens of thousands of units of heparin during CPB grafting is protective against the development of deep venous thrombus (DVT) and pulmonary embolus (PE) (Goldhaber and Schoepf 2004). In addition, the universal use of Aspirin after CABG is thought to have a measurable, although very weak, effect in reducing the frequency of postoperative DVT (White, Zhou et al. 2003). Furthermore, most patients who undergo uncomplicated CABG tend to undergo early ambulation, and are usually discharged within 4 to 5 days after surgery which further decreases the risk of DVT formation (Goldhaber and Schoepf 2004). Although uncommon, pulmonary embolism after cardiac bypass surgery carries with it very high morbidity and mortality (Shammas 2000). It is important, however, to distinguish between two entities.

In CABG patients, the clinician can understandably miss the diagnosis of symptomatic pulmonary embolism due to the overlap between reported symptoms of the postoperative course and that of PE (Shammas 2000). For example, shortness of breath is often ascribed to deconditioning, atelectasis, or preexisting left ventricular dysfunction (Shammas 2000). In addition, DVT is difficult to detect clinically because leg discomfort and swelling may be attributed to trauma from the vein harvest site, excessive hydration during CPB, or muscle cramping due to perioperative immobility (Goldhaber and Schoepf 2004). For example, a group of investigators at Rush-Presbyterian-St Luke's Medical Center in Chicago reported a low incidence of 0.7% of clinically recognized DVT in 10,638 patients who underwent cardiac surgery (DeLaria and Hunter 1991). This was further highlighted by Josa and collogues who identified DVT in one patient out of the 33 who developed PE within two weeks of CABG which translates into a recognition rate of less than 3% (Josa, Siouffi et al. 1993). To note, the true rate in both of these retrospective studies were unknown as venous duplex

ultrasound was not routinely performed in patients after CABG in either study (DeLaria and Hunter 1991, Josa, Siouffi et al. 1993). In a prospective study at Brigham and Women's Hospital, Goldhaber et al performed pre-discharge venous ultrasonography in 330 patients who had undergone CABG (Goldhaber, Hirsch et al. 1995). Out of the 67 (20%) patients who had DVT diagnosed by ultrasonography, only two had symptomatic PE and only one had symptomatic DVT, meaning the ratio of all DVT to symptomatic PE or DVT exceeded 20–to–1 (Goldhaber, Hirsch et al. 1995).

Goldhaber et al, later described an interesting extrapolation of their findings to the near half million CABG surgeries performed annually in the United States, where assuming a mortality rate of 1% among asymptomatic patients and 2% to 4% among symptomatic patients with overt DVT and PE, there would be between 1100 and 1300 deaths attributable to PE post CABG (Goldhaber and Schoepf 2004). Furthermore, it was found out that PE and DVT constituted the fifth most common cause of readmission within 30 days due to complications related directly to CABG (Hannan, Racz et al. 2003).

Very few studies have investigated thromboembolic risk factors after and predictors after cardiac bypass (Shammas 2000). Delayed recovery or immobilization, and postoperative CHF were reported as major risk factors for PE by both univariate and multivariate analysis (Gillinov, Davis et al. 1992). Data using univariate analysis without adjusting for other risk factors suggested that obesity (Josa, Siouffi et al. 1993), prior history of DVT or PE (Gillinov, Davis et al. 1992, Josa, Siouffi et al. 1993), recent myocardial infarction (Light, Rogers et al. 1999), dyslipidemia (Josa, Siouffi et al. 1993), preoperative atrial fibrillation (DeLaria and Hunter 1991), blood type A (DeLaria and Hunter 1991) and Heparin Induced Thrombocytopenia (Josa, Siouffi et al.

1993) were significant risks for development of DVT or PE. Finally, two studies that used multivariate logistic regression found out that recent cardiac catheterization and age were important risk factors for PE or DVT (Gillinov, Davis et al. 1992, Goldhaber, Hirsch et al. 1995)

2.2 Intraoperative Transfusion

Since the development of CPB, hemodilutional anemia has become a very popular and widely used technique (DeFoe, Ross et al. 2001). Hemodilutional anemia reduces blood viscosity and acheives continuous baseline blood flow during hypothermic CPB without the need for elevated arterial pressures (GUYTON and RICHARDSON 1961, Kaplan 1983). This prevents arterial hypertension and subsequent complications such as aortic dissection and collateral blood flow to the coronary arteries during cross-clamping of the aorta (DeFoe, Ross et al. 2001). Moreover, the crystalloid priming techniques used to achieve hemodilutional anemia aid in maintaining hemodynamics, and are proposed to have a potential role in reducing the need for administering blood products intraoperatively (Cooley, Beall et al. 1962). While hemodilutional anemia appears beneficial, however, it has been widely associated with worse outcomes including mortality (Carson, Duff et al. 1996, Fang, Helm et al. 1997, Hardy, Martineau et al. 1998, DeFoe, Ross et al. 2001, Habib, Zacharias et al. 2003) and resource utilization (e.g., transfusion (DeFoe, Ross et al. 2001, Habib, Zacharias et al. 2003), prolonged intensive care and hospital stays (DeFoe, Ross et al. 2001, Habib, Zacharias et al. 2003), and direct costs (Habib, Zacharias et al. 2003)). Some have linked excessive hemodilution directly to vital organ injury,

including lung dysfunction with longer mechanical ventilation requirements (Habib, Zacharias et al. 2003), increased neurologic events like stroke and transient ischemic attacks (Habib, Zacharias et al. 2003, Karkouti, Djaiani et al. 2005), cardiovascular dysfunction including heart failure ((Hardy, Martineau et al. 1998, DeFoe, Ross et al. 2001, Habib, Zacharias et al. 2003, Surgenor, DeFoe et al. 2006) and kidney injury (Swaminathan, Phillips-Bute et al. 2003, Habib, Zacharias et al. 2005).

Plausible explanations for these findings include injury related to anemia itself or the use of intraoperative red blood cell (RBC) transfusion (Surgenor, DeFoe et al. 2006). While a hematocrit level of 20% is widely accepted as "intuitively reasonable" during cardiac surgery (Kirklin 1993), values lower than that leave little doubt that red blood cell (RBC) transfusion is necessary to prevent consequent decrease in oxygen delivery and organ ischemia (Ranucci, Aronson et al. 2011). The use of blood transfusion in cardiac surgery remains very high where it is estimated that between 30% and 80% of patients receive blood products (Shapira, Aldea et al. 1998). In the United States, almost half of the patients receive at least one unit of packed red blood cells, and the probability of receiving blood is greater when procedures are more complex (Rawn 2007). This is widely driven by the accepted notion that anemia reduces oxygen supply to tissues and lead to ischemic tissue injury (Surgenor, DeFoe et al. 2006). Moreover, this practice was further augmented by studies showing worse outcomes in patients refusing transfusions for religious reasons (Carson, Duff et al. 1996). However, evidence linking transfusion during cardiac surgery to worse outcomes continue to accumulate (Leal-Noval, Rincón-Ferrari et al. 2001, Engoren, Habib et al. 2002, Koch, Li et al. 2006, Surgenor, DeFoe et al. 2006, Murphy, Reeves et al. 2008). In fact, RBC transfusions are proposed to induce a systemic inflammatory response with nonspecific

immunosuppression which result in counterproductive local tissue hypoxemia due to occlusion of local microvasculature (La Celle 1969, Simchon, Jan et al. 1987, Blumberg 2005). Prior studies have documented immunomodulation secondary to leukocytes within allogeneic blood products (Blajchman 2006) as transfusion-associated immunomodulation (TRIM), a poorly understood phenomenon. TRIM has been widely associated with worse outcomes including bacterial infection, multi-organ injury and mortality (Vamvakas and Blajchman 2001).

Yet, the recognition that blood products may do harm does not seem to be widespread (Ranucci, Aronson et al. 2011). A large survey (Rogers, Blumberg et al. 2009) of nearly 25,000 patients undergoing CABG in different hospitals in the US, with follow-up period of 30 days after discharge, found large interhospital differences of almost around 30% in transfusion practices. The survey further implied that most of these transfusions were unnecessary (Rogers, Blumberg et al. 2009). Likewise, a clinical trial that compared liberal versus restrictive transfusion practices (Hébert, Yetisir et al. 2001), showed no benefit for the liberal transfusion group. In an attempt to address this, a taskforce by the American Society of Anesthesiologists (Likosky, FitzGerald et al. 2010) developed a consensus statement supported by level B and C evidence which stated that "red blood cell transfusions should not be dictated by a single hemoglobin 'transfusion trigger' but instead should be based on the patient's risk of developing complications of inadequate oxygenation". Yet, a physician's decision to transfuse is still widely based on hemoglobin thresholds taking into account the patient's age and comorbidity (Ranucci, Aronson et al. 2011).

The effect of RBCs transfusion on PPCs is poorly understood in cardiac surgery (Koch, Li et al. 2009). Other than Transfusion Related Acute Lung Injury (TRALI),

there seems to be little information in literature on how RBC transfusion influences pulmonary outcomes. Acute lung injury is defined by acute onset, lack of left atrial hypertension, bilateral infiltrates on chest imaging, and hypoxemia with a PaO_2/FiO_2 ratio of ≤300 (Bernard, Artigas et al. 1994). TRALI is defined as an acute lung injury that occurs within 6 hours of transfusion (Kilic and Whitman 2014). Some other manifestations of TRALI include fever and mild to moderate hypotension (Silliman, Paterson et al. 1997, Popovsky 2001, Kopko, Marshall et al. 2002). TRALI constitutes a very small portion (roughly 1 per 1,000 transfusion) of the overall identified 150,000 cases of acute lung injury in the United States each year (Popovsky and Moore 1985). The incidence of TRALI, however, is reported to be higher (2.4%) in patients undergoing cardiac surgery (Vlaar, Hofstra et al. 2011), with some reports suggesting underreporting of its incidence given the poor understanding of this complication by most providers (Kilic and Whitman 2014). Diagnosis of TRALI in cardiac surgery poses unique limitations where majority of cardiac surgical patients arrive to the intensive care unit (ICU) on ventilatory support, hindering clinical symptoms of dyspnea and acute respiratory distress (Koch, Li et al. 2009). In addition, patients are usually mildly hypothermic upon arrival to the ICU, hence increases in patient temperature may not be evident (Koch, Li et al. 2009). On the contrary, some suggest that diagnosis of TRALI after cardiac surgery is overestimated as measures of pulmonary morbidity in cardiac surgery are not necessary reflective of lung injury per say, but rather cardiac events that prolong intubation support (Murthy, Arroliga et al. 2007). Furthermore, given that the 6-hour period criteria is an essential part of TRALI diagnosis, the exact timing of temporal relationships of transfusion to lung injury is often lost to providers knowing that most transfusions occur during surgery (Koch, Li et

al. 2009). Some even argue that for a definitive diagnosis of TRALI, specific lung injury risk factors such as use of CPB should be absent (Kleinman, Caulfield et al. 2004).

Universally, acute lung injury is induced by increased permeability in the pulmonary microvasculature with protein-rich edema fluid (Kilic and Whitman 2014). In TRALI, the presence of donor antibodies to recipient leukocytes is thought to be responsible for the ensuing lung damage and capillary leak (Popovsky and Moore 1985). Furthermore, neutrophil sequestration in the lungs, brought about by the general predisposing status of a cardiac surgery patient, gets activated by exposure to biologically active substances found in blood transfusions and leads to lung injury (Silliman 1999). Another proposed theory is the "two-hit model" characterized by cardiac surgery activating leukocytes as the "first hit"; and release of leukocyte cytotoxic contents with transfusion is the "second hit" occurs with transfusion which initiates release of leukocyte cytotoxic contents (Looney and Matthay 2006, Popovsky 2006, Silliman 2006). Although TRALI is thought to carry favorable short-term prognosis with complete resolution of pulmonary infiltrates and noticeable improvement in patients within 48 to 96 hours after onset, (Popovsky, Chaplin Jr et al. 1992), the mortality rate associated with TRALI remains high reaching 5% to 15% in some reports ((Popovsky, Chaplin Jr et al. 1992, Vlaar, Hofstra et al. 2011).

Although less popular than TRALI, postoperative pneumonia occurring after CABG was studied in relationship to RBC transfusion. In a large multicenter retrospective study that included a total of 16,182 consecutive patients who underwent isolated CABG surgery between 2011 and 2013 at 33 different hospitals in the state of Michigan in the United States, Dr. Likonsly et al used multivariable logistic regression

to estimate the odds of pneumonia associated with the use or number of RBC units (Likosky, Paone et al. 2015) . The authors found a significant, volume-dependent association between an increasing number of RBCs and subsequent onset of pneumonia. This remained true even after adjustment for predicted risk of mortality, pre-operative hematocrit, history of pneumonia, CPB duration and medical center (Likosky, Paone et al. 2015).

It is crucial to differentiate the real versus perceived need for transfusion of allogeneic RBCs by individualizing the risk–benefit profile for each patient (Ranucci, Aronson et al. 2011). While Hemoglobin level continues to be the primary factor in skewing the decision of transfusion, other important factors should be put in the equation, such as patient age, sex, hemodynamic profile, and signs of organ dysfunction (Shehata, Wilson et al. 2006, Sihler and Napolitano 2010). To a lesser extent, physicians should also take into consideration the risks of infectious disease transmission (Leal-Noval, Rincón-Ferrari et al. 2001), immunologic suppression (Raghavan and Marik 2005) and the cost associated with a universally diminishing blood supply (Ranucci, Aronson et al. 2011). The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists (Ferraris, Ferraris et al. 2007) tried to address this topic through its guidelines on the use of blood products in cardiac surgery. These guidelines addressed a number of valid concerns, and to some extent enabled healthcare providers to make individualized decisions. Yet, a survey among anesthesiologists (Likosky, FitzGerald et al. 2010) have pointed out that these guidelines remain widely underutilized in clinical practice. This is probably driven by an inherited culture resistant to change attributed to perceived lack of evidence, a lack

of awareness of the guidelines and logistic issues related to blood supply (Ranucci, Aronson et al. 2011).

2.3 Time on Pump

Most patients undergoing CPB inevitably experience some degree of organ dysfunction (Hall, Smith et al. 1997). This is largely attributed to the activation of the inflammatory response initiated during cardiac surgery by multiple mechanisms including blood contact with the foreign surface of the CPB apparatus (Kirklin, Westaby et al. 1983), development of ischemia and reperfusion injury (Sawa, Shimazaki et al. 1996) and finally the presence of endotoxemia (Kharazmi, Andersen et al. 1989). In fact, these mechanisms contribute concurrently to the humoral and cellular development of the processes leading to the systemic inflammatory response (Hall, Smith et al. 1997). Yet, the extent and duration of the response seems to be influenced by multiple factors, mainly the composition of the priming solution (Ellison, Behar et al. 1980, Bonser, Dave et al. 1990, Jansen, te Velthuis et al. 1996), the presence of pulsatile perfusion (Dapper, Neppl et al. 1992, Driessen, Dhaese et al. 1995), the use of mechanical filtration (Dutton, Edmunds et al. 1974, Millar, Armstrong et al. 1993, Journois, Pouard et al. 1994), the type of oxygenator (Dutton, Edmunds et al. 1974, Ferries, Marx Jr et al. 1984, Cavarocchi, Pluth et al. 1986, Dapper, Neppl et al. 1992, Videm, Svennevig et al. 1992, Gu, van Oeveren et al. 1993), the type of extracorporeal circuit (Videm, Svennevig et al. 1992, Gu, van Oeveren et al. 1993, Moen, Hogasen et al. 1997), the temperature during CPB (Ellison, Behar et al. 1980, Ferries, Marx Jr et al. 1984, Cavarocchi, Pluth et al. 1986, Bonser, Dave et al. 1990, Jansen, te Velthuis et al.

1996) and choice of pharmacological agents used to ameliorate the response (Ferries, Marx Jr et al. 1984, Cavarocchi, Pluth et al. 1986, Sawa, Shimazaki et al. 1996).

Thus, it is understandable that cardiac surgery involving CPB is often complicated by postoperative pulmonary dysfunction; sometimes necessitating prolonged mechanical ventilation (Yende and Wunderink 2002, Weissman 2004). Pulmonary dysfunction is often manifested as atelectasis, pneumonia, interstitial edema and airway obstruction and ultimately respiratory insufficiency (Bonser, Dave et al. 1990). When measured by the postoperative rise in pulmonary capillary permeability via the ^{67}Ga-transferrin pulmonary leak index, related to the duration of CPB, it is estimated that lung vascular injury occurs in 30–50% of patients (Raijmakers, Groeneveld et al. 1993, Verheij, Van Lingen et al. 2005). The injury is thought to originate from the systemic inflammatory response induced by the CPB leading to increased lung capillary permeability and interstitial fluid accumulation (Matthay and Wiener-Kronish 1989). This is caused by a rise in extravascular lung water, with transient gas exchange and mechanical abnormalities of the lungs (Weissman 2004, Staton, Williams et al. 2005). During CPB, the lungs are not ventilated, promoting atelectasis and the latter, albeit hard to recognize (Hedenstierna and Edmark 2012), may further contribute to postoperative pulmonary dysfunction and predispose to infection (Verheij, Van Lingen et al. 2005). Moreover, atelectasis may already develop prior to surgery at the induction of anesthesia (Hedenstierna and Edmark 2012). Even though biocompatibility of CPB systems have improved over decades, off pump bypass surgery has been revitalized, potentially offering less pulmonary complications as compared to on pump surgery (Sellke, DiMaio et al. 2005). Very few prospective RCTs (van Dijk,

Nierich et al. 2001, Angelini, Taylor et al. 2002, Puskas, Williams et al. 2003, Syed, Fawzy et al. 2004, Staton, Williams et al. 2005, Al-Ruzzeh, George et al. 2006) compared off pump and on pump approaches, and looked into postoperative pulmonary outcomes as either primary or secondary endpoints, including gas exchange, duration of intubation and mechanical ventilation and occurrence of pneumonia. In general, these largely favored off pump surgery (van Dijk, Nierich et al. 2001, Angelini, Taylor et al. 2002, Puskas, Williams et al. 2003, Syed, Fawzy et al. 2004, Staton, Williams et al. 2005, Al-Ruzzeh, George et al. 2006). Similarly, most non-randomized studies that looked at postoperative radiography, lung compliance and gas exchange among other pulmonary complications indicated similar (Taggart 2000, Roosens, Heerman et al. 2002, Montes, Maldonado et al. 2004) or better (Kochamba, Yun et al. 2000, Tschernko, Bambazek et al. 2002, Babik, Asztalos et al. 2003, Berson, Smith et al. 2004, Blumberg 2005) results with off pump surgery. It seems that when compared to on pump CABG, off pump CABG is associated with a reduced cytokine response, fewer circulating neutrophils and monocytes, and a significantly lower level of neutrophil elastase (Wan, Izzat et al. 1999, Ascione, Lloyd et al. 2000, Diegeler 2000).

2.4 Hypotheses and Specific Aims

2.4.1 Hypotheses

H1: Longer durations of will increase the incidence of PPCs

H2: Blood transfusion will increase the risk of PPCs

H3: There is an interaction effect between duration of CPB and transfusion leading to worse pulmonary outcomes

H4: PPCs will worsen both early and late outcomes in patients undergoing cardiac surgery

2.4.2 Specific Aims

1) To evaluate the association of PPCs (prolonged ventilation, pneumonia, acute respiratory distress syndrome, pulmonary edema, prolonged intubation (>24 hours) and reintubation) with the duration of CPB 1) in all patients who underwent cardiac surgery and 2) in subsets of patients who received PRBC transfusion during cardiac surgery and those who did not;
2) To ascertain using multivariate analysis the separate and interaction effects (multi-hit model) of CPB and transfusion on PPCs after cardiac surgery;
3) To assess the association of PPCs and early/ perioperative outcomes of cardiac surgery (30-day mortality); and

To investigate whether PPCs are independently linked to worse cause-specific late (1-year and 5-year) mortality after surgery.

CHAPTER 3

METHODS

3.1 Study Sample

This investigation is a retrospective analysis of prospectively collected clinical registries data collected at two community hospitals (Saint Vincent Mercy Medical Center, Toledo, Ohio, USA and Saint Luke's Hospital, Maumee, Ohio, USA) based on the data field definitions of The Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database (ACSD) (Clark 1994). The institutional review board approved the use of this data for retrospective analyses with waiver of informed consent based on no additional review of the hospital records or interviewing of patients. A de-identified file was made available to the American University of Beirut, Faculty of Medicine Outcomes Research Unit for analysis in collaboration with the US surgical group.

All patients who underwent first-time or redo, isolated coronary artery bypass grafting (CABG; n = 6,151) between Jan 1, 1994 and Dec 31, 2005, were considered for this study. Patients who had valvular surgery, concomitant carotid endarterectomy, or other operation performed simultaneously with their CABG procedure were excluded. Patients who underwent emergency-salvage CABG were excluded. T

3.2 Clinical Data

Clinical data for all patients were collected prospectively and entered into cardiac surgery databases at both institutions. Collected variables included demographics, medical comorbidities, operative data, and postoperative complications, and 30-day

hospital readmissions. All entries were based on definitions of the Society of Thoracic Surgeons and were regularly reported to the and quality checked by the STS ACSD data analytic center (Duke Clinical Research Institute).

3.3 Longitudinal Follow-up

Multiple sources were used to maximize outcomes follow-up after index hospital discharge. Long-term survival data was made available from the service follow-up, routine twice-annual searches of US Social Security Death Index database (last performed, November 2011), and was complemented by linkage to the Ohio State Death Registry data through December 31, 2015 as reported to the CDC National Death Index. The collected death and cause of death data as derived from death certificates of all known dead individuals were then used to update the institutional adult cardiac surgery databases from which the current study analytic dataset was derived.

3.4 Study Endpoints and Outcomes

Endpoints in this investigation included PPCs and postoperative mortality;

1. PPCs (occurring anytime perioperatively through hospital discharge), were collected and analyzed individually and as a composite pulmonary outcome of any of those complications. These included pulmonary edema, acute respiratory syndrome (ARDS), pneumonia, prolonged mechanical ventilation, reintubation, pulmonary embolism. Pulmonary complications were diagnosed on the basis of chest imaging findings and physician findings and were confirmed from hospital or physician chart notes and discharge summaries. Database quality checks for missing values and incorrect entries were performed routinely. Additionally,

complication rates and resource utilization (transfusion, cardiovascular intensive care unit [CVICU]/hospital stays) were always cross-checked for the separate CVICU and cardiac surgery databases, as well as against patients' discharge summaries and hospital medical chart attestation (or coding summary).

2. Operative mortality was defined as in-hospital death during the same hospitalization as the index surgery or out-of-hospital death occurring within 30 days of index surgery.
3. Long-term Outcomes included: 1-year and 5-years mortality estimates, with the day of surgery considered as time equal zero.

3.5 Exposure and Independent Variables

This study focused primarily on exploring the separate independent effects, and possible interaction, of two potentially modifiable intraoperative exposures on the incidence of PPCs and their short and long-term implications. These two exposures are:

1) Use of (on pump versus off pump) and duration CPB [categorized as: off pump (0 minutes); short (1–59 minutes); intermediate (60-119minutes) and long CPB (≥120minutes)];

2) early or intra-operative blood transfusions to either avoid or correct hemodilutional anemia during surgery (Figure1). Postoperative transfusions were not considered because it is not possible to determine their time relative to the onset time of the pulmonary complication per se.

Patient demographics clinical and operative characteristics as well as outcomes were also compared for patients that did versus did not experience PPCs.

3.6 Statistical Analysis

Categorical factors were summarized as counts and percentages, whereas continuous variables were reported as mean ± standard deviation. chi-square (χ_2) was used to compare categorical factors, and continuous variable were compared using unpaired *t*-test or Mann–Whitney *U* test based on normality of data.

Potential independent predictors of PPCs (PPC), and mortality) were identified via univariate comparisons of demographics, medical comorbidities and operative factors between patients experiencing PPCs versus those that did not (Table 1; unadjusted comparisons). All variables with a $P<0.10$ were considered in the multivariable risk-adjusted model for PPC (multivariable binary logistic regression). Sex was forced into the model irrespective of the level of significance due to its widely named effect on cardiac surgery outcomes.

Univariate binary logistic regression was used to calculate unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) for potential risk factors associated with pulmonary complications. Subsequently, multivariable logistic regression was used to determine and quantify the risk-adjusted effects of independent predictors, in particular use of CPB, intra-operative transfusion and their interaction, on pulmonary complications. Knowing that preoperative hematocrit is an important risk factor, and knowing that almost 20% of our patient population has no available value for preoperative hematocrit, we ran a sensitivity analysis. We excluded patients without preoperative transfusion and calculated the odds of developing PPCs in a similar fashion to what was previously explained. A $p<0.05$ level was used to indicate multivariable significance. Discrimination of logistic regression models was evaluated using the area under the receiver operating characteristic (ROC) curve.

For missing data, we assumed that data is missing completely at random, i.e. the probability that the data are missing is not related to either the specific value which is supposed to be obtained or the set of observed responses. Our approach to the missing data is to simply omit values with the missing data and analyze the remaining data. This approach is known as the complete case (or available case) analysis or listwise deletion.

Highly collinear variables were avoided.

Time-to-event analyses using the Kaplan–Meier product limit method were used to estimate unadjusted survival truncated at 5 years after surgery. Between-groups comparisons were based on the log-rank test. Univariate comparisons were performed to determine the separate effects on 5-year survival of: 1) intraoperative transfusion (iXFN; Yes versus No), 2) CPB use categories; and 3) PPC (Yes versus No). Outcomes were also compared based on the multiple stratification of the study population paradigms shown in Fig. 1. The effects of intraoperative transfusion was also explored within each CPB use category (Transfusion Effect) and within intraoperative transfusion category (CPB Effect) The studied effect was derived for each sub-stratum as the risk-adjusted intraoperative transfusion ($AHR_{iXFN/NoiXFN}$ [95% CI]) or the risk-adjusted time on pump ($AHR_{OnPump/OffPump}$ [95% CI]) hazard ratio with the corresponding 95% confidence interval. Furthermore, a separate analysis was used to elucidate the combined effect of intraoperative transfusion and time on pump. This was made possible by creating a composite eight-category transfusion-CPB (2 x 4) variable based on intraoperative transfusion (Yes or No) and CPB use (off pump, short, intermediate and long CPB). AHRs with 95% confidence interval (CI) were derived for mortality outcomes at 30 days, 1 and 5 (or maximum) year follow-up. Cox regression

analysis was used with comprehensive covariate adjustment for patient and operative factors.

Discrimination of logistic regression models was evaluated using the area under the receiver operating characteristic (ROC) curve.

Methods for dealing with multiple testing frequently call for adjusting α in some way, so that the probability of observing at least one significant result due to chance remains below the desired significance level. However, we have elected not to adjust for multiple testing.

A two-sided *p* value less than 0.05 was used uniformly, unless otherwise specified, to indicate significance. Statistical analysis was conducted with IBM SPSS Statistics, version 23.0 and 26.0 (IBM Corp, Armonk, NY).

CHAPTER 4

RESULTS

4.1 Total Study Cohort and Comparison Groups

A study participant flow diagram is presented in Figure 1. After exclusion of patients with salvage CABG or those with concomitant non-CABG cardiac surgery, 6,151 patients met all inclusion criteria and were included in this investigation. The mean age of the study population was 64.1 ± 10.6 years; 4056 (66%) were males; 5058 (82%) had hypertension; 2128 (35%) had diabetes; 1273 (22%) had chronic lung disease; 4086 (66%) were ever-smokers; 319 (5.2%) patients underwent prior CABG, and CABG was elective in 2209 (36%) patients.

A total of 1,318 CABG patients (21% of the total study population) who received intraoperative transfusion (iXFN). Several patient characteristics differed substantially among patients who received iXFN versus those who did not (Table 2). Notably, intraoperatively transfused patients were older than non-transfused patients (68 ± 11 versus 63 ± 10, $p<0.001$), and had higher prevalence of diabetes (523 (39%) versus 1605 (33%), $p<0.001$), hypertension (1131 (86%) versus 3927 (81%), $p<0.001$), chronic lung disease (943 (20%) versus 320 (25%), $p<0.001$), renal failure (124 (9.4%) versus 90 (1.9%), $p<0.001$), and CHF (272 (21%) versus 464 (10%), $p<0.001$). As for surgery related factors, patients who received iXFN had higher prevalence of previous CABG

(348 (26%) versus 921 (19%), p<0.001), and were more likely to undergo emergent CABG (172 (13%) versus 253 (5.2%), p<0.001) than those who did not.

In this cohort, the majority of patients underwent CABG with CPB , and only 352 (5.7%) underwent CABG without CBP (off pump). Perfusion time (time on pump) was less than 60 minutes in 1214 (20%) patients, between 60 and 119 minutes for 3968 (65%), and more than or equal to 120 minutes in 617 (10%) patients. For the whole cohort, the mean time on pump was 89 ± 37, with a minimum of 0 and a maximum of 503 minutes. Both preoperative and operative characteristics were roughly similar across the four groups and are illustrated in Table 3.

4.2 Preoperative and Operative Risk Factors

Results of the univariate analysis is shown in Table 1. It shows that older age, higher BMI and BSA, smoking status, presence of myocardial infarction, preoperative congestive heart failure, cerebrovascular disease, peripheral vascular disease, cerebrovascular accident, hypertension, hypercholesterolemia, diabetes, renal failure, NYHA stage, left main disease, number of diseased vessels, intraoperative transfusion, perfusion time, presence of prior CABG, surgery status (elective, urgent, emergent) and incidence of surgery (first versus repeat) were relative risk factors for PPCs. Those variables with p<0.1, obtained through the univariate analysis were then entered multivariate logistic regression analysis (PPCs or no as independent variables, variables with p<0.1 obtained through univariate analysis as dependent variables). Sex was forced into the model irrespective of p-value.

4.3 PPCs

A total of 583 (9.5%) patients developed one or more pulmonary complication; of these 138 (2.2%) had pulmonary edema, 54 (0.9%) had ARDS, 139 (2.3%) had pneumonia, 19 (0.3%) had pulmonary embolism, 181 (7.4%) needed prolonged mechanical ventilation (defined as ventilation time >24 hours) and 181 (3.0%) required reintubation. In patients who were extubated early ($\leq$ 24 hours), the mean time of intubation was 7.1±5.0.

4.3.1 Intraoperative Transfusion Effect

The incidence for both the composite outcome of PPCs and that for the individual ones differed significantly in those who received intraoperative transfusion versus those who did not (Table 4). This is illustrated in the bar chart (Figure 2); compared to patients who did not receive intraoperative transfusion, patients with intraoperative transfusion developed three times more pulmonary complications than those who did not (21% versus 6.4%) and almost four times more pneumonia (1.5% versus 5.2%).

The effect of intraoperative transfusion on the development of pulmonary complications was further explored. Table 4 shows the odds ratios ($OR_{iXFN/NoiXFN}$) for each postoperative pulmonary complication with the corresponding 95% confidence intervals (95% CI). Unadjusted odds ratios ($UOR_{iXFN/NoiXFN}$) were derived by binary logistic regression analysis. Adjusted odds ratios ($AOR_{iXFN/NoiXFN}$) were derived by multivariate

logistic regression after adjustment for the following preoperative and postoperative factors (retained from the aforementioned univariate analysis); age, BMI, sex, diabetes, hypertension, hypercholesterolemia, smoking status, chronic lung disease, peripheral vascular disease, cerebrovascular disease, cerebrovascular accident, renal failure, myocardial infarction, congestive heart failure, NYHA class, left main disease, number of diseased vessels, previous CABG, status (elective, urgent and emergent) and incidence (first versus repeat). As for the important risk factor of preoperative hematocrit, 1382 (22%) patients had no value of preoperative hematocrit and thus we chose not to include this factor among the covariates which we adjusted for. Among the 1382 patients without preoperative hematocrit value, 233 (17%) patients received iXFN. For the remaining 4769 patients with available hematocrit level, 23% received iXFN.

Intraoperative transfusion was universally associated with higher incidence of pulmonary complications (when studied as a composite outcome and separately). The odds of developing any PPC was almost four times higher in transfused patients compared to non-transfused ones ($UOR_{iXFN/NoiXFN}$ = 3.9 [3.3-4.7]). Similarly, patients with intraoperative transfusion had higher crude odds of developing pulmonary edema, ARDS, pneumonia and PE, and of undergoing prolonged mechanical ventilation and reintubation, than patients without intraoperative transfusion (Table 4, Figure 3). This remained true after adjustment, however, the association of iXFN with pulmonary complications??? was somewhat attenuated after accounting for other preoperative and operative risk factors. After adjustment, the odds of developing any PPC was 2.7 higher ($AOR_{iXFN/NoiXFN}$ = 2.7 [2.2-3.3]) in patients with intraoperative transfusion compared to those without intraoperative transfusion (Table 4, Figure 3).

Within each CPB use category (off pump, 1-59 mins, 60-119 mins and ≥ 120 min), the odds ratios depicting intraoperative transfusion effect are presented in Table 5. Notably, the effect of intraoperative transfusion was more pronounced in the sub-strata with longer perfusion times. After adjustment, and compared to non-transfused patients, patients who received iXFN had 2, 2.5 and 3.9 higher odds of developing PPCs in the 1-59 mins, 60-119 mins and ≥ 120 min categories, respectively. To note, due to the very small number of events of PPCs in the off pump category, the corresponding odds ratios could not be calculated.

4.3.2 CPB Effect

PPCs occurred more frequently in patients who had CABG with CPB compared to those who had it without CPB (off pump), with higher incidence of PPCs occurring in patients with increased CPB time (Figure 5, Table 6). In the off pump category, the incidence of any pulmonary complication was only 4%, whereas it was 6.3%, 8.4% and 13% in patients with CPB times of 1-59 mins, 60-119 mins and ≥ 120 min respectively.
The effect of intraoperative transfusion on the development of pulmonary complications was further explored by calculating the odds ratios (Figure 6, Table 6). Notably, when compared to patients with off pump surgery, those with short, intermediate and long CPB times had 1.6, 2.2 and 3.7 higher odds of suffering any PPC ($UOR_{1\text{-}59\ mins/\ Off\ Pump}$ = 1.6 [0.9-2.9]), $UOR_{60\text{-}89mins/\ Off\ Pump}$ = 2.2 [1.3-3.8], $UOR_{\geq 120\ mins/\ Off\ Pump}$ = 3.7 [2.1-6.4]) respectively. After accounting for other preoperative and operative risk factors, the effect of CPB time became more pronounced. Again noted the higher odds of suffering

any PPC in patients with longer CPB times compared to patients with zero CPB time (off pump); $AOR_{1\text{-}59\ mins/\ Off\ Pump} = 2.0$ [1.1-3.8]), $UOR_{60\text{-}119mins/\ Off\ Pump} = 2.5$ [1.4-4.5], $UOR_{\geq 120\ mins/\ Off\ Pump} = 3.9$ [2.2-7.0].

Within each iXFN use category (iXFN versus no iXFN), the effect of CPB was further explored (Table 7). In patients who did not receive iXFN, the incidence of PPCs was higher in patients with longer CPB duration; with incidence rates of 2.5%, 4.9%, 6.3% and 8.1% in the categories of off pump, 1-59 mins, 60-119 mins and ≥ 120 min respectively. A similar trend, but with higher incidence rates, was observed in patients who received iXFN; with incidence rates of 17%, 14%, 16% and 27% in off pump, 1-59 mins, 60-119 mins and ≥ 120 min categories respectively. This higher incidence of PPCs, observed in patients with iXFN compared to those without iXFN and with longer CPB durations, was not entirely reflected in the calculated odds ratios. Compared to patients without CPB, the adjusted odds of developing PPCs was 2.3 [1.1-5.3], 2.5 [1.1-5.6] and 2.9 [1.3-6.8] higher in short, intermediate and long CPB in non transfused patients; and 0.9 [0.3-25], 1.3 [0.5-3.4] and 2.6 [0.9-7.0] in transfused patients respectively.

4.3.3 Combined Intraoperative Transfusion and CPB Effect

In order to elucidate the combined effect of CPB and iXFN, a composite eight-category transfusion-CPB (2 x 4) variable based on intraoperative transfusion (Yes or No) and CPB use (off pump, 1-59 mins, 60-119 mins and ≥ 120 min) was created. Incidence of PPCs across the eight categories, with the corresponding unadjusted and adjusted odds ratios are shown in Table 8. Compared to patients with no iFXN and without CPB use (the reference category), both unadjusted and adjusted odds of developing any PPC

were consistently higher in the other categories, with greater values in patients with intraoperative transfusion and in those with longer CPB durations. This is illustrated in Figure 7 and in Figure 8. Notably, and after adjustment for preoperative and operative risk factors, the odds of developing any PPC was 10.8 times higher in the category of patients with iXFN and long CPB duration of ≥ 120 mins, compared to the reference category of patients without iXFN and without CPB use (AOR $_{\text{iXFN\&≥120 mins/ NoiXFN\&Off Pump}}$ = 10.8 [5.1-23]).

4.4.4 Receiver Operating Characteristic Analysis

Accuracy of the multivariate logistic regression model was evaluated by the area under the receiver operating characteristic (ROC) curve and 95% confidence intervals. For each pulmonary outcome, we compared two predictive models. Both models included relevant preoperative and operative risk factors (Table 2). In one of the models (model 2), we added the composite eight-category transfusion-CPB (2 x 4) variable based on intraoperative transfusion (Yes or No) and CPB use (off pump, 1-59 mins, 60-119 mins and ≥ 120 min). We then compared for each generated ROC curves, the corresponding areas under the curve (AUC) in every pulmonary outcome. We found out that the AUC for model 2 (the model with the composite variable) is consistently larger than that for model 1 (Table 9), and this difference was significant for all outcomes except for PE. Thus, including the composite outcome resulted in PPC prediction that is almost always superior or equivalent to the logistic model in terms of true and false classification rates.

4.5 Survival Analysis

4.5.1 Intraoperative Transfusion Effect

Of the total 6,151 patients, 209 (3.4%) died within thirty days of the surgery or during the index hospitalization for the surgery: 159 (3.3%) in the group of no iXFN and 50 (3.8%) in the group of iXFN (p=0.377). One-year cumulative survival was 93% and 91% for patients with no iXFN and with iXFN, respectively (log rank test, p=0.034). Five-year cumulative survival was 83% and 81% for patients with no iXFN and with iXFN, respectively (log rank test, p=0.029). The corresponding Kaplan-Meier survival curves are shown in Figure 8.

Using a multivariable Cox proportional hazards model and after adjusting for 18 preoperative and operative clinical variables (Table 2), intraoperative transfusion was found to be associated with a 20% increased risk of mortality at 30 days, 1 year and 5 years, with adjusted hazard ratios ($AHR_{iXFN/noiXFN}$ with 95% CI) of 1.2 [0.8-1.7], 1.2 [0.9-1.5] and 1.2 [0.9-1.3]), respectively (Table 10). Notably, this associated increase in mortality was not statistically significant.

Within each CPB use category (off pump, 1-59 mins, 60-119 mins and ≥ 120 min), the hazard ratios depicting intraoperative transfusion effect were also calculated (Table 10). Similar to the trend observed for the total study cohort, when calculated for each sub stratum, intraoperative transfusion was not found to have a significant adverse effect on 30-day, 1-year and 5-year mortality. In the off pump category, however, the risk of death at 5 years was found to be 2.7 times higher in patients with iXFN compared to patients without ($AHR_{iXFN/noiXFN}$ = 2.7 [1.2-6.0]).

The effect of iXFN was further explored separately for patients who suffered pulmonary complications versus those who did not. The corresponding Kaplan Meier survival curves are shown in Figure 9. Interestingly, it was found that the effect of intraoperative

transfusion on perioperative mortality at 30 days was more pronounced in the group that suffered pulmonary complications compared to the one that did not, $AHR_{iXFN/noiXFN}$ = 2.7 [0.9-7.7] and $AHR_{iXFN/noiXFN}$ = 1.1 [0.7-1.6], respectively. This effect on mortality, however, was not statistically significant in neither group. In patients with pulmonary complications, however, 5-year mortality was 1.7 times higher in patients who received intraoperative transfusion compared to those who did not ($AHR_{iXFN/noiXFN}$ = 1.7 [1.1-2.7]). Both intraoperative transfusion unadjusted and risk-adjusted hazard ratios for all patients, patients without PPCs and patients with PPCs are shown in Figure 10.

When stratified based on both CPB use and PPCs development, intraoperative transfusion was not found to have statistically significant effect on mortality across all subgroups at all follow up times (30-day, 1-year and 5-year). The only exception, however, was the significant intraoperative transfusion effect on 5-year mortality ($AHR_{iXFN/noiXFN}$ = 3.3 [1.4-7.9]) in patients who underwent off pump surgery and did not develop PPCs (Table 10).

4.5.2 CPB Effect

Among patients who died within thirty days of the surgery or during the index hospitalization for the surgery: 11 (3.1%), 36 (3.2%), 86 (3.5%) and 76 (3.5%) had off pump surgery, short, intermediate and long CPB times respectively (p=0.984). One-year cumulative survival was 93%, 92%, 93% and 93% for the groups of off pump, short, intermediate and long CPB times, respectively (log rank test, p=0.801). Five-year cumulative survival was 86%, 81%, 84% and 82% for the groups of off pump, short, intermediate and long CPB times, respectively (log rank test, p=0.048). The corresponding Kaplan-Meier survival curves are shown in Figure 11.

Compared to patients with off pump surgery, patients with CPB use generally had similar death hazard ratios at 30 days, 1 year and 5 years (Table 11). Only exception, however, is the 40% significant increase in 5-year mortality risk observed in patients who underwent surgery with long CPB time (≥ 120 mins) compared to those who underwent off pump surgery ($AHR_{\geq 120mins/Off\ Pump}$= 1.4 [1.1-2.0])

Within each iXFN use category (iXFN versus no iXFN), the effect of CPB on mortality was further explored (Table 11). Similar to the trend observed for the total cohort, mortality hazard ratios were similar among different sub-strata, indicating no adverse CPB effect on neither perioperative mortality at 30 days nor long-term mortality at 1 and 5-year follow up in patients with and without iXFN. However, in patients who did not need intraoperative transfusion, those who underwent CABG with long CPB time (≥ 120 mins) had 50% increase in death hazard at 5-year follow up compared to patients with off pump surgery ($AHR_{\geq 120mins/Off\ Pump}$ = 1.5 [1.1-2.2].

Additionally, the effect of CPB use was explored separately for patients who suffered pulmonary complications versus those who did not. The corresponding Kaplan Meier survival curves are shown in Figure 12. The effect of CPB use on mortality outcomes did not seem to be affected by the development of PPCs (Table 11). Both CPB use unadjusted and risk-adjusted hazard ratios for all patients, patients without PPCs and patients with PPCs are shown in Figure 13.

Finally, CPB mortality effect was found to be comparable at all times and among all sub-strata when patients were further stratified by iFXN status and PPCs development (Table 11).

4.5.3 Combined Intraoperative Transfusion and CPB Effect

In order to elucidate the combined effect of CPB and iXFN, the composite eight-category transfusion-CPB (2 x 4) variable based on intraoperative transfusion (Yes or No) and CPB use (off pump, 1-59 mins, 60-119 mins and ≥ 120 min), explained previously, was used again. Mortality rates across the eight categories, with the corresponding unadjusted and adjusted hazard ratios are shown in Table 12. Compared to patients with no iFXN and without CPB use (the reference category), both unadjusted and adjusted mortality hazard ratios were comparable across all other categories and at all follow-up times. Notably in patients with long CPB duration (≥ 120 mins), significant increase in 5-year mortality hazard was observed for patients without and with iXFN ($AOR_{NoiXFN\&\geq 120\ mins/\ NoiXFN\&Off\ Pump}$ = 1.5 [1.1-2.3] and $AOR_{iXFN\&\geq 120\ mins/\ NoiXFN\&Off\ Pump}$ = 1.6 [1.1-2.4]), respectively.

The combined mortality effect of iXFN and CPB use was further explored separately for patients who suffered pulmonary complications versus those who did not (Table 12). Development of PPCs did not seem to alter the combined mortality effect of iXFN and CPB use neither at perioperative follow up (30-day) nor at long follow up (1 and 5-year).

Unexpectantly, we have found similar survival rates in patients who suffered PPCs and in those who did not. We assumed that prolonged mechanical ventilation, the major deriving pulmonary complication in our study, could in fact reflect a physician's or unit's postoperative care routine rather than an underlying substantial pulmonary morbidity. Accordingly, we created a new composite outcome, termed critical PPCs (cPPCs), that excluded PMV from our original pre-defined outcome of PPCs. We also

excluded pulmonary edema, and kept only ARDS, pneumonia, reintubation and PE in the new defined outcome, cPPCs. We then derived the effect of PPCs and cPPCs on postoperative mortality, 1-Year and 5-Year mortality (Table 13). Mortality rates and trends were comparable in both patients with PPCs and cPPCs.

CHAPTER 5

DISCUSSION

This is a retrospective analysis of patients who underwent isolated first-time or redo CABG (CABG; n = 6,151) at two community hospitals in Ohio, USA, between Jan 1, 1994 and Dec 31, 2005. This study research focused primarily on exploring the separate independent, and possible interaction, effects of two potentially modifiable intraoperative variables on the incidence of PPCs and their short and long term implications on mortality. The two factors are: 1) use of early or intraoperative blood transfusions to either avoid or correct hemodilutional anemia during surgery; and 2) the role of use (on pump versus off pump) and duration CPB in case of on pump CABG [off pump (0 minutes); short CPB (1–59 minutes); intermediate (60-119minutes) and long (≥120minutes) on CPB]. Unique to our study and for the first time, we have reported the combined effect of those two factors by creating a novel composite factor. Analysis of preoperative and operative risk factors showed a slightly higher risk profile in patients with intraoperative transfusion, while the risk profiles were generally comparable across different CPB groups. We have found both factors, intraoperative blood transfusion and CPB use, to be associated with worse pulmonary outcomes; with higher pulmonary morbidity observed in longer CPB duration. Both factors, however, neither adversely affected perioperative mortality at 30-day follow up, nor intermediate and long term mortality at 1-year and 5-year follow up. Finally, the development of PPCs was generally not associated with adverse mortality outcomes at 30-day, 1-year and 5-year follow up.

5.1 PPCs

5.1.1 Incidence

Pulmonary complications following cardiac surgery with CPB are common complications. PPCs manifest early as arterial hypoxemia, during the later course as pneumonia, and in rare cases also as acute lung injury (Ji, Mei et al. 2013). The reported incidence of PPCs following CABG surgery varies from 5 to 99% (Brooks-Brunn 1995). This variation depends largely on how PPCs are defined (Huddleston 1990, Pedersen, Eliasen et al. 1990, Brooks-Brunn 1995, Wynne and Botti 2004). For example, the reported incidence of PPCs by Jensen et al, who included atelectasis in their definition, was 99.4% (Jensen and Yang 2007). Naveed et al, reported a much lower incidence of 6.2% in their studied surgical cohort (Naveed, Azam et al. 2017). In this study, 583 adult patients developed one or more postoperative pulmonary complication, accounting for 9.5% of the total population. This result was consistent with previous reports (Younossian, Adler et al. 2011, Ji, Mei et al. 2013).

As for the individual pulmonary outcomes, the incidence of ARDS in our study was 0.88%, consistent with the low incidence, that ranges between 0.17% (Michalopoulos, Prapas et al. 2006) and 2.5% (Kaul, Fields et al. 1998), reported in literature. Depending on its definition, as duration of prolonged mechanical ventilation has been defined differently across different studies, the incidence of PMV can range anywhere between 2.6% and 22.7% (Trouillet, Combes et al. 2009). In our study, PMV was defined as mechanical ventilation that lasted beyond 24 hours and occurred in 7.4% of all patients. The incidence of reintubation in our study was 2.9% and is less than that reported in

literature (Jian, Sheng et al. 2013). In a very large study of 324,085 patients undergoing CABG, pneumonia occurred in 9,175 patients (2.8%) (Brescia, Rankin et al. 2018). This is consistent with our reported incidence rate of 2.6%. Notably, however, the same multi-center study reported wide variability in pneumonia rates, with some hospitals having rates more than 6 times higher than others (10th to 90th percentile: 1.0% to 6.1%) (Brescia, Rankin et al. 2018). Finally, the incidence of pulmonary embolism in our study was very low, 0.31%, and that is consistent with the very low incidence of PE reported after cardiac artery bypass graft surgery (Canver and Fiedler 1992).

5.1.2 Intraoperative Transfusion Effect

Practice patterns and recommendations for blood transfusion have evolved over half a century (Loor, Koch et al. 2012). Once deemed safe and standard to transfuse critically ill patients liberally in an effort to enhance oxygen supply and improve outcomes, it is now believed that transfusions, although beneficial to some patients, may worsen outcomes in others. Cardiac surgical patients consume a substantial proportion of the blood products used in most hospitals. A recent investigation by Hung and colleagues (Hung, Besser et al. 2011) reported more than a 3-fold increase in the risk for perioperative RBC transfusion and higher financial costs among patients with preoperative anemia. Thus, there is a definite need for more evidence-based decision-making with respect to peri-operative RBC transfusions, and understanding the effect of blood transfusion on patients undergoing CABG is of paramount importance.

In our study, we found that intraoperative blood transfusion is associated with increased incidence of PPCs. In patients with intraoperative blood transfusion, 276 (21%) patients suffered one or more PPC, whereas 307 (6.4%) developed PPCs in patients without

blood transfusion. Koch et al , investigated pulmonary morbidity after cardiac surgery, and found that compared with CABG patients who did not receive blood transfusion, patients with blood transfusion had significantly higher rates of respiratory distress/insufficiency (1.8% versus 4.8%, $p<0.001$) and readmission to the ICU for pulmonary related reasons (1.3% versus 5.6%, $p<0.001$) (Koch, Li et al. 2009). A similar investigation (Romano, Mastroianni et al. 2010) reported that transfusion of blood products in CABG patients resulted in higher rates of suffering PPCs in those transfused when compared to those who were not transfused (5.7% versus 1.2%, $p<0.001$). In contrast to the extended definition of PPCs in our investigation, Romano and colleagues included only prolonged mechanical ventilation and the need for tracheostomy in their definition which could explain the low reported incidence of PPCs in both the transfused and the control groups. In a systematic review (Patel, Avlonitis et al. 2015) that included six randomized controlled trials (3357 patients), the authors reported no role for blood transfusion on pulmonary morbidity after cardiac surgery (OR $_{iXFN/No\ iXFN}$ = 0.9 [0.8 – 1.2]). Pulmonary morbidity included ARDS, acute lung injury, delayed extubation.

Atelectasis and pneumonia are the most common PPCs based on an analysis of 80 studies investigating PPCs post cardiac surgery (Brooks-Brunn 1995). In our analysis, 68 (5.2%) patients with iXFN developed postoperative pneumonia, while only 71(1.5%) patients developed pneumonia in the control group (with no iXFN). One of the initial groups to explore the effects of PRBCs transfusion on pneumonia, The Michigan Society of Thoracic and Cardiovascular Surgeons (Likosky, Paone et al. 2015) showed that patients who received RBC transfusions experienced an increased risk of pneumonia in a dose-dependent fashion. Among 16,182 patients, those exposed to RBC

transfusions had a significant 3.4-fold increased odds of contracting pneumonia ($AOR_{iXFN/\ No\ iXFN}$ = 3.4 [3.2–4.6]). This is comparable to our study findings where, after risk-adjustment, we found a significant 2.4-fold increased odds of developing pneumonia in patients with iXFN ($AOR_{iXFN/\ No\ iXFN}$ = 2.4 [1.6-3.5]). Likosky and colleagues further reported that the odds of pneumonia increased with the transfusion of more RBC units (p-trend< 0.001) (Likosky, Paone et al. 2015). In our definition of pneumonia, we do not make the distinction between community acquired, hospital acquired and ventilator associated pneumonia. In a case-control study aimed at identifying modifiable risk factors of nosocomial pneumonia in elderly patients post CABG, El Solh et al found transfusion ⩾4 units of PRBC to be significantly related to the development of nosocomial pneumonia by multivariate analysis (AOR 2.8 [1.2–6.3]) (El Solh, Bhora et al. 2006).

Reintubation after cardiac surgery is another widely studied postoperative pulmonary complication. In our study, reintubation occurred more frequently in patients with iXFN than in those without (6.5 versus 2.0, p<0.01). This is comparable to the findings of Likosky and colleagues where reintubation in patients with transfusion was higher than those without (5.6% versus 1.3%, p<0.001) (Likosky, FitzGerald et al. 2010). When studied as a composite respiratory complication with pneumonia, the incidence of reintubation and/ or pneumonia did not differ significantly among patients with and without transfusion (3.8% versus 2.0%, p=0.11), respectively (Crawford, Magruder et al. 2018).

Timely weaning of cardiac surgical patients may improve cardiopulmonary function, anticipate ambulation, lead to reduced ICU length of stay and save healthcare costs (Bezanson, Deaton et al. 2001, Légaré, Hirsch et al. 2001). However, patients

undergoing CABG often have multiple concurrent diseases that need to be adequately managed to reduce the risk of PMV (Branca, Mc Gaw et al. 2001). No consensus can be found in literature for the definition of PMV for cardiac surgical patients as it ranges range from 8 hours to 7–14 days (Cislaghi, Condemi et al. 2009). For the purpose of our observational prospective study, we, reasonably, considered PMV as mechanical ventilation lasting over 24 hours, occurring more frequently in patients with iXFN than no iXFN (17% versus 4.8, $p<0.001$). Crawfard and colleagues, interested in studying the effect of transfusion of one unit only of PRBCs during the combined intraoperative and postoperative periods, found out that the probability of remaining intubated beyond 24 hours did not significantly differ between transfused and non-transfused patients (Crawford, Magruder et al. 2018). In another investigation, patients with transfusion had a significantly higher incidence of PMV than those who did not receive transfusion (5.6% versus 1.2%, $p <0.001$), respectively (De Santo, Amarelli et al. 2013). Similarly, when compared to patients without transfusion, Koch and colleagues reported higher incidence of prolonged postoperative ventilation beyond 72 hours, in patients with red blood cell transfusion (1.9% versus 7.6%, $p<0.001$) (Koch, Li et al. 2009). In our investigation, and after risk adjustment, the odds of receiving PMV was 2.7 times higher in patients with iXFN than in those without ($AOR_{iXFN/\ No\ iXFN} = 2.7$ [2.1-3.3]). This is consistent with other reported odds for PMV of $AOR_{iXFN/\ No\ iXFN}$ of 1.79 [1.72-1.86] (Koch, Li et al. 2006).

In our studied population, ARDS occurred more frequently in patients with iXFN than those without iXFN (2.0% versus 0.6%, $p<0.001$), respectively. Koch and colleagues (Koch, Li et al. 2009) examined pulmonary morbidity related to transfusion both intraoperatively and postoperatively in a large cohort of patients undergoing cardiac

surgery with use of CPB (16,847 patients). Patients receiving red blood cells transfusion had more risk-adjusted ARDS (0.64% *versus* 0.21%, p=0.015). By TRALI criteria, the majority manifested "lung injury" (PaO_2/FiO_2 ratio <300) but unrelated to transfusion (65% *vs.* 64%). The authors concluded that cardiac surgical patients with poor cardiopulmonary reserve who received transfusion had more risk adjusted pulmonary morbidity after surgery. Whether increased pulmonary morbidity was related to TRALI, transfusion-associated circulatory overload or both, is uncertain in part because of current consensus-criteria for TRALI are insufficient for the selected cardiac surgical population. Of note, the current Berlin definition of ARDS (Force, Ranieri et al. 2012) was not available at the time the study was conducted.

5.1.3 CPB Effect

While the benefits of CPB pump has led to significant development in cardiac surgery, this method contributes significantly to postoperative pulmonary morbidity, mostly related to the associated systemic inflammatory response syndromes (SIRS) (Hessel II 2015, Lannemyr, Bragadottir et al. 2017). Many of the factors involved in the CPB, whether they are matter-dependent (placement of blood exposed to artificial materials) or matter-independent (surgical trauma, ischemia/ reperfusion of organs, changes in body temperature, and release of endotoxins), create multiple inflammatory responses (Mali and Haghaninejad 2019). The acute inflammatory response, brought on by activation of the complement system, increases both the number of leukocytes and leukocyte-platelet pairs. Leukocytes, located in the lungs among other organs, are affected by the duration of the aortic and CPB mutual clamping, and play a major role

in postoperative lung damage (Levy and Tanaka 2003, Evora, Bottura et al. 2016, Justus, Walker et al. 2019).

In our study, 338 (5.7%) patients underwent off pump surgery and 5799 (94%) underwent on pump surgery. The group that underwent off pump surgery developed less pulmonary complications when compared to that of the on pump surgery (4.0% versus 9.8%, p<0.001). In a study of 17, 401 isolated CABG, 7283 (42%) off pump coronary artery bypass grafts and 10,118 (58%) conventional coronary artery bypass with CPB, Mack et al matched 11,548 by propensity scoring (Mack, Pfister et al. 2004). Off pump coronary artery bypass grafting was associated with less pulmonary complications (4.1% versus 9.5%, $P < 0.001$). In another study (Naveed, Azam et al. 2017), prolonged CPB time > 120 minutes was found to be a significant predictor of postoperative pulmonary complication, defined as atelectasis, respiratory failure, pneumonia and/ or ARDS (AOR = 3.6 [1.5-8.9]). In our study, the odds of suffering any PPC were almost four times higher in patients with long CPB duration (≥ 120 mins) compared to those without CPB (AOR $_{\geq 120 \text{ mins/ Off Pump}}$ = 3.9 [2.2-7.0]). In a different analysis of 2056 adult patients undergoing cardiac surgery with CPB (Ji, Mei et al. 2013), the authors identified duration of CPB as an independent risk factor for developing PPCs (AOR=3.2 [1.6-6.2]). Similarly, Rady et al (Rady, Ryan et al. 1997) evaluated a total of 1,461 CABG patients and found that total CPB time of ≥ 140 minutes was a significant predictor of early postoperative pulmonary dysfunction (AOR = 1.54 [1.0 to 2.34]); early postoperative pulmonary dysfunction was defined by mechanical ventilation with a PaO_2/FIO_2 ratio of ≤ 20 kPa, and chest radiography on admission to the cardiovascular ICU.

In one of the largest randomized controlled trials (Staton, Williams et al. 2005) comparing off pump and on pump CABG, there was a greater decrease in postoperative respiratory static compliance seen in patients with off pump. The authors attributed this to the need to rotate the heart into the right chest to allow bypass to posterolateral vessels and the larger amounts of intravenous fluids required to maintain systemic blood pressure during the operation. Paradoxically, on pump CABG patients actually had poorer gas exchange immediately postoperatively, delaying their extubation. The explanation for these observations may lie in some aspect of CPB including release of inflammatory mediators or possible failure of replenishment of surfactant due to the lack of ventilatory cycling of the lung. To note, the authors reported no differences in readmissions to the hospital for respiratory complications between the groups (Staton, Williams et al. 2005). Another large RCT, The CABG Off or On Pump Revascularization Study (CORONARY) (Lamy, Devereaux et al. 2012), compared 30-day outcomes between off pump and on pump CABG in patients undergoing isolated CABG surgery in 79 centers in 19 countries with randomly assigned 4752 patients. Respiratory complications (defined as failure requiring reintubation and mechanical ventilation or respiratory infection) were studied as a secondary outcome and were significantly reduced in the off pump group.

In our study, pneumonia occurred less frequently in patients without pump surgery (0.3%) than it did with all the subgroups of on pump surgery (1.6% in the short CPB duration (1 – 59 mins), 1.8% in the intermediate CPB duration (60 – 119 mins) and 3.4% in the long CPB duration (≥ 120 mins)). However, this difference was not statistically significant. After adjusting for multiple preoperative and operative risk factors, we found that compared to patients with off pump surgery, the odds of

developing pneumonia is almost 8 and 15 times higher in the short and intermediate, and the long CPB groups (AOR 1-59 mins/ Off Pump = 7.8 [1.1-59.7], AOR 60-119 mins/ Off Pump = 7.9 [1.1-59.1] and AOR ≥120 mins/ Off Pump= 15 [2.0-108]), respectively. In a study aimed at comparing CABG with and without pump, Mack and colleagues stated that pneumonia was seen in 3.6% of on pump patients and only 2.0% of off pump patients, i.e. significantly lower in off pump patients (Mack, Pfister et al. 2004). A systematic review, by He at al, aimed to study risk factors and outcomes of ventilator associated pneumonia post cardiac surgery (He, Chen et al. 2014). Out of the eleven included studies, five studies with 5367 patients indicated that prolonged CPB time may increase the risk for VAP after cardiac surgery (Hortal, Giannella et al. 2009, Tang, Liu et al. 2009, Roeleveld, Guijt et al. 2011, Sheng, Chi et al. 2012, Tamayo, Álvarez et al. 2012). Staton *et al*. (Staton, Williams et al. 2005) during a study of the consequences of on pump and off pump surgery, showed that off pump surgery is accompanied by a lower incidence of postoperative pneumonia compared to on pump surgery (2.0% versus 3.6%, $p<0.001$), respectively.

In our study, less patients in the off pump surgery group were intubated for more than 24 hours than were those in the on pump surgery sub-groups (off pump: 2.6%, short on pump: 4.4%, intermediate on pump: 6.4% and long on pump: 11%). The difference, however, was not statistically significant. After controlling for several preoperative and operative risk factors, we found that CPB time longer than 120 minutes was associated with a near 5-fold risk increase in prolonged mechanical ventilation (AOR ≥120 mins/ Off Pump = 4.8 [2.4-9.9]). In an analysis of 3,269 patients by Cislaghi and colleagues (Cislaghi, Condemi et al. 2007), the authors reported that CPB time longer than 91

minutes was associated with 40% risk increase in prolonging extubation beyond 12 hours (AOR = 1.4 [1.0-1.9]).

To note, pulmonary embolism is rarely observed after CABG. In our study, we had zero incidents occurring in the reference (off pump) group, and very low incidents occurring in the on pump subgroups (0.2% in the short CPB, 0.3% in the intermediate CPB and 0.4% in the long CPB), and the difference was not statistically significant. Similarly, in the RCT by Staton and colleagues, the incidence of PE was very low (0.3%) and occurred equally in patients with on pump and off pump surgeries (Staton, Williams et al. 2005).

5.2 Mortality

5.2.1 Mortality in CABG

CABG procedure has advanced significantly over the years (Hawkes, Nowak et al. 2006) to a point where operative mortality is now much lower than reported in the early trials, at less than 3% for routine CABG (Pollick 1993, Ferguson Jr, Hammill et al. 2002, Keogh and Kinsman 2004). Increased interest in investigating long-term mortality in nation-wide study populations has yielded up to 30-year follow up data, where patients with CABG were found to have higher mortality rates than the general population, especially within 30 days of and 10 years after surgery (Adelborg, Horváth-Puhó et al. 2017).

In our study, mortality rates for the total study cohort were comparable to what is reported in literature. At 30-day, 1-year and 5-year follow up, death rates from any cause were 3.4%, 7.3% and 17%, respectively.

5.2.2 Intraoperative Transfusion Effect

It is very difficult, to determine with certainty the effect of blood transfusion on perioperative and long-term survival in CABG patients. This is due to the well-recognized confounding influence of the preoperative high-risk profiles of patients who tend to receive intraoperative and perioperative transfusion. The Michigan Society of Thoracic and Cardiovascular Surgeons explored the relationship between preoperative risk status and transfusion, and determined that the adverse effect of RBC transfusion is independent of the patient's risk profile (Paone, Brewer et al. 2012). Others have assessed the effect of RBC restriction through naturally occurring experiments; for example, the comparison of Jehovah's Witnesses to other patients undergoing cardiac operations. Pattakos and colleagues (Pattakos, Koch et al. 2012) demonstrated fewer complications, shorter lengths of stay, and better 1-year survival in Jehovah's Witnesses compared with propensity-matched patients undergoing cardiac operations.

Despite the aforementioned findings, many physicians continue to oppose a causal relationship between blood transfusions and adverse outcomes, asserting that the findings are associative or a marker of a higher-risk individual rather than an agent of harm (Crawford, Magruder et al. 2018). Certainly, several studies have demonstrated higher risk profiles among patients requiring blood transfusions after cardiac operations (Paone, Brewer et al. 2012, Crawford, Magruder et al. 2018). In our study, we have found that the group receiving intraoperative transfusion had older age, diabetes,

hypertension, chronic lung disease, renal failure, CHF, previous, emergency operative status, and previous CABG, compared with the control group.

5.2.2.1 30-Day Mortality

In our study, perioperative mortality, defined as death within thirty days of surgery or during the index hospitalization for surgery, occurred in a similar fashion among patients with and without iXFN (3.8% versus 3.3%, p=0.371). In contrast, De Santo and colleagues (De Santo, Amarelli et al. 2013) reported higher incidence of perioperative mortality in CABG patients receiving transfusion compared to those without transfusion (7.9% versus 0.5%, p<0.001). Similarly, in two investigations by Romano et al (Romano, Mastroianni et al. 2010) and Koch et al (Koch, Li et al. 2006), risk-adjusted perioperative death hazard was higher by 23% and 77% in the group of patients receiving transfusion ($AHR_{iXFN/\ No\ iXFN}$ = 1.23 [1.10-1.37 and 1.77 [1.67-1.68]), respectively. Our reported risk adjusted 30-day death hazard of $AHR_{iXFN/\ No\ iXFN}$ of 1.2 [0.8-1.7] included the *null value of 1*, indicating lack of effect of intraoperative transfusion on 30-day mortality. Other studies (Engoren, Habib et al. 2002, Kuduvalli, Oo et al. 2005, Campos, Tanganelli et al. 2017) (Michalopoulos, Tzelepis et al. 1999) have also reported worse 30-day mortality rates in CABG patients receiving transfusion. However, unlike our study which only investigated the RBC intraoperative transfusion effect, other studies have defined transfusion differently. For example, Campos et al considered transfusion of any blood product (packed red cells, packed platelets, fresh frozen plasma and cryoprecipitate), conducted between 5 days before and 10 days after CABG, to be of primary interest (Campos, Tanganelli et al. 2017). To note, several

recent randomized trials have compared restrictive versus liberal transfusion practice (Murphy, Pike et al. 2015, Mazer, Whitlock et al. 2018) and findings were mostly inconclusive. This was further illustrated in a metanalysis published last year (Shehata, Mistry et al. 2019) that investigated the effect of restrictive and liberal RBC transfusion strategies on mortality within 30 days of CABG as the primary outcome. The risk ratio (RR) of mortality derived from 4545 patients assigned to a restrictive strategy when compared with 4547 transfused according to a liberal strategy was 0.96 [95% confidence interval (CI) 0.76-1.21, I2 = 0]. The authors concluded that current evidence does not support the notion that restrictive RBC transfusion strategies are inferior to liberal RBC strategies in patients undergoing cardiac surgery. In contrast, a different meta analysis of 16 cohort observational studies in cardiac surgery showed that red blood cell transfusion compared with no transfusion was associated with substantially higher perioperative mortality at 30 days (random effects odds ratio 2·72, 95% CI 2·11–3·49; p<0·0001) (Patel, Avlonitis et al. 2015).

5.2.2.2 1-Year and 5-Year Mortality

Causes of death within the first 30 days after cardiac surgery are often a mixture of surgical challenges, reduced cardiac function, infection, sepsis and coagulopathy, which makes it difficult to extract solely the impact of transfusion (Jakobsen, Ryhammer et al. 2012), this is why it is very important to view long-term mortality outcomes.

In a large retrospective analysis by Kuduvalli and colleagues (Kuduvalli, Oo et al. 2005), patients who did not receive a peri-operative RBC transfusion (during or within 72h of surgery)

had a lower 1-year mortality. The crude and adjusted HRs for 1-year mortality in patients transfused were UHR $_{iXFN/No\ iXFN}$ = 3.0 [2.1–4.5] and AHR $_{iXFN/No\ iXFN}$ = 1.9 [1.2–3.0], respectively. In our study, the crude and risk-adjusted 1-year death hazard ratios were UHR $_{iXFN/No\ iXFN}$ = 1.2 [1.1-1.5] and AHR $_{iXFN/No\ iXFN}$ = 1.2 [0.9-1.5], respectively. It seems that the observed adverse effect of intraoperative transfusion on death was lost after after correcting for comorbidities and other risk factors.

Engoren and colleagues (Engoren, Habib et al. 2002) demonstrated survival benefit over 5 years in patients undergoing CABG who did not receive peri-operative transfusions. They reported that patients undergoing cardiac surgery who received a perioperative transfusion had twice the risk of mortality at 5 years after surgery than those who did not receive a transfusion. Even after correcting for comorbidities and other risk factors, they found that transfusion was still correlated with a 70% increase in long-term mortality. However, in the same study when intraoperative transfusion was considered solely (excluding post-operative transfusion), the risk of death at five years for patients with intraoperative transfusion compared with patients with no transfusion was no longer significant (AHR $_{iXFN/No\ iXFN}$ = 1.2 [0.6–1.7]). This is very similar to our reported 5-year mortality adjusted hazard ratio (AHR $_{iXFN/No\ iXFN}$ = 1.2 [0.9-1.3]). In another study by Surgenor and colleagues, exposure to limited RBC transfusions (1 or 2 Units) during admission for cardiac surgery was associated with a 16% increased adjusted risk of 5-yr mortality (Surgenor, Kramer et al. 2009). The impact on survival was most pronounced in the first 6 months after surgery, with a 67% increased adjusted risk. Again, this adverse impact on survival after exposure to RBC transfusion was not explained by differences among patients who received blood or by procedural characteristics. A retrospective study published by Schwann *et al*. examined the

association between transfusions and mortality among 6,947 patients who underwent CABG (Schwann, Habib et al. 2016). The overall RBC transfusion rate was 33.9%. Postoperative complications were reported in 35.2% of the patients, specifically in patients who received RBC transfusion when compared with the uncomplicated group. The group reporting complications included older females with previous comorbidities. At 30-day and 5-year follow-up survival, the incidence of death was higher in transfused versus non-transfused patients. RBC transfusion increased the risk of long-term cardiac and non-cardiac mortality after CABG. Other recently published studies have also failed to find an adverse effect of blood transfusion on mortality. In a large retrospective study by Yun and colleagues (Yun, Helm et al. 2012), RBC transfusion did not increase the risk of early (6-month) or late (3-year) death in patients 80 years or older ($AHR_{iXFN/\ no\ iXFN}$ = 1.47 [0.84, 2.56] and 0.92 [0.50-1.69]) respectively. These finding are very relevant given that octogenarians receive RBCs more often than do younger patients (Yun, Helm et al. 2012).

There is a definite need for more evidence-based decision-making with respect to peri-operative RBC transfusions in cardiac surgery. Predicting outcome in postoperative cardiac surgery patients has proved to be an extremely difficult task (Michalopoulos, Tzelepis et al. 1999). Cardiac surgery patients have even been excluded from popularly used scores, such as the Simplified Acute Physiology Score, the SAPS II (Le Gall, Lemeshow et al. 1993), Mortality Probability Model (MPM II) (Lemeshow, Teres et al. 1993) and acute physiology and chronic health evaluation, APACHE III (Knaus, Wagner et al. 1991). Likewise, the success rate in studies that have attempted to predict outcome by using preoperative risk factors in CABG surgery patients has been limited (Higgins, Estafanous et al. 1992, Quaini, Colombo et al. 1995). In some of these studies,

outcome prediction involved a large number of preoperative variables (Magovern, Sakert et al. 1996) or exponential equations (Kennedy, Kaiser et al. 1981) that made their application impractical. A common characteristic of these studies is that they have focused exclusively on preoperative variables and, in general, have not taken into account operative factors and postoperative complications that can affect patient outcome. Michalopolous and colleagues (Michalopoulos, Prapas et al. 2006) have found that the combination of the number of inotropes and the number of blood units administered in the operating room was the most important determinant of outcome in CABG surgery, with an overall positive predictive value of 91.7%.

5.2.3 CPB Effect

It seems intuitive that avoidance of the extracorporeal circulation in off pump surgery may offer a benefit early after the CABG procedure with less inflammation and embolization. However, the technique of an arrested heart, in on pump surgery, may result in a better quality of each single anastomosis and more complete revascularization, which may lead to a better short- and long-term outcomes. A huge published body of literature has attempted to explore mortality outcomes in patients undergoing off pump versus on pump CABG. Data, however, remains largely inconclusive.

5.2.3.1 30-Day Mortality

The majority of the large RCTs to date failed to show a difference in early mortality between off pump and on pump surgery (Shroyer, Grover et al. 2009, Hattler,

Messenger et al. 2012, Lamy, Devereaux et al. 2012, Diegeler, Börgermann et al. 2013, Taggart, Altman et al. 2015). One small sample size RCT by Fattouch *et al.* showed a reduced mortality in patients with ST elevation undergoing urgent/emergent off pump coronary surgery compared to on pump surgery (Fattouch, Guccione et al. 2009). Deppe *et al.* in meta-analysis of RCTs on almost 16,900 patients found no difference in 30-day mortality (Deppe, Arbash et al. 2016). All-cause-death occurred in 2.0% (1.8% in off-pump versus 2.1% in on pump, p=0.610) with OR of 0.86 [0.69 – 1.06]. Kowalewski *et al.* in meta-analysis of over 19,000 patients demonstrated no significant difference in short term mortality (Kowalewski, Pawliszak et al. 2016). Deppe *et al.* in meta-analysis of RCTs in 16,718 patients found no difference in 30-day mortality, all-cause mortality, OR = 0.88 [0.71-1.09].

As for observational studies, data is largely conflicting. For example, Mack et al reported that operative mortality in off pump coronary artery bypass grafting was significantly lower than conventional coronary artery bypass with CPB (1.9% vs 3.5%, $P < 0.001$) (Mack, Pfister et al. 2004). However, since techniques of off pump CABG have markedly improved during the past several years and many surgeons have reached a plateau on the "learning curve," older studies may not be as useful for comparison (Sellke, DiMaio et al. 2005). A retrospective study by Racz et al (Racz, Hannan et al. 2004) analyzed 9135 patients who underwent off pump CABG surgery and 59,044 who underwent on pump CABG surgery. Risk-adjusted inpatient mortality was 2.0% for off pump versus 2.2% for on pump (p = 0.390). In our analysis, mortality rates at 30 days were comparable across the different study groups (off pump: 3.1%, short CPB: 3.2%, intermediate and long CPB 3.5%). Even after adjustment for

preoperative and operative risk factors, the hazard for 30-day mortality was not increased in all on pump time categories compared to the off pump category (AHR $_{1\text{-}59\ mins/\ Off\ Pump}$ = 1.0 [0.5-2.1], AHR $_{60\text{-}119\ mins/\ Off\ Pump}$ = 1.3 [0.6-2.6] and AHR $_{>120\ mins/\ Off\ Pump}$ = 0.3 [0.6-2.9]).

5.2.3.2 1-Year and 5-Year Mortality

The group of Angelini *et al.* conducted two studies looking at all-cause mortality in off pump and on pump patients, they reported no difference in midterm (HR = 0.57 [0.17–1.96]) and long-term (HR = 0.84 [0.58–1.24]) mortality outcomes (Angelini, Taylor et al. 2002, Angelini, Culliford et al. 2009). The Veterans Affairs Randomized On/Off Bypass (ROOBY) trial randomly assigned 2,203 of patients to either off pump or on pump. It was the first trial where off patients were recruited in based on the surgeon's experience (minimum number of 20 cases) though some argue that the learning curve extends beyond this set point (Fudulu, Benedetto et al. 2016). The primary long term (1 year) composite of death, repeat revascularization, non-fatal myocardial infraction was higher (9.9% *versus* 7.4%, p=0.04) for the off pump CABG group with no significant differences between the individual composite components (Hattler, Messenger et al. 2012). A Cochrane systematic review of RCTs off pump versus on pump found an increased risk of death with off pump in the long term (>30 days) (Møller, Penninga et al. 2012). Luo *et al.* in a recent meta-analysis of RCTs found no difference in patients with over 6 months' follow-up [OR = 1.02 [0.86–1.22] (Luo and Ni 2015). The largest RCT, Coronary Artery Bypass Grafting Off- or On pump Revascularization Study (CORONARY) which primary outcome consisted of composite of death, myocardial infarction, stroke, or new renal failure requiring dialysis, reported no difference at 1-

year [HR = 0.91 [0.77 - 1.07]) and 5-year [HR = 0.98 [0.87 - 1.10]) between patients undergoing on pump and off pump CABG. There was no significant difference between the rates of the individual primary outcome components (Lamy, Devereaux et al. 2013, Lamy, Devereaux et al. 2016).

Similarly, our results revealed equivocal 1-year mortality outcomes among all groups regardless of duration of CPB. However, compared to patients with off pump surgery, patients with on pump CABG and CPB duration > 120, had better survival at 5-year follow up ($AHR_{>120\ mins/\ Off\ Pump} = 1.4\ [1.1\ -2.0]$).

5.3 Interaction between Intraoperative Blood Transfusion and CPB

Several previous studies have shown that the use of CPB was associated with increased blood transfusions (van Dijk, Nierich et al. 2001, Puskas, Williams et al. 2003, Scott, Seifert et al. 2003). Some have speculated that the observed increase in blood transfusion rate for on pump compared to off pump patients was caused by increased postoperative bleeding (Nader, Khadra et al. 1999, Ascione, Williams et al. 2001). However, data from observational analyses shows that patients undergoing CABG with CPB did not bleed more than those undergoing off pump (Puskas, Williams et al. 2003, Toraman, Evrenkaya et al. 2004, Potger, McMillan et al. 2007). In one study, intraoperative Hematocrit was lower in on pump than off pump patients undergoing CABG, and was associated with more blood transfusions (Dial, Delabays et al. 2005). In a systematic review (Deppe, Arbash et al. 2016) that compared the need for transfusion, among other outcomes, between patients undergoing on-pump versus off-pump CABG (N = 11,595 patients), the authors reported that number of patients

needing transfusion after surgery was significantly decreased in patients after off-pump CABG compared with on-pump CABG (40% versus 51%, $P < 0.001$) with a calculated $OR_{\text{off pump/ on pump}}$ of 0.60 [0.47–0.75]. Furthermore , the authors concluded that the number of units of transfused PRBCs was decreased in patients operated without the use of CPB (weight mean difference and 95% CI; WMD: −0.71 [−0.94, −0.49]). This was believed to be driven by the reduced chest tube drainage volume in off pump use (WMD = -128 [−205, −52]).

Up to our knowledge, no study has investigated how the combined/ interactive effect of intraoperative transfusion and cardiopulmonary use affects the rate of PPCs and mortality outcomes.

In order to better understand the interaction between intraoperative transfusion and CPB duration, we identified patients with no iFXN and without CPB use as a “reference” category. Risk adjusted odds of developing any PPC were consistently higher in the other categories, with greater values in patients with intraoperative transfusion and in those with longer CPB durations. Notably, the odds of developing any PPC was 10.8 times higher in the category of patients with iXFN and long CPB duration of ≥ 120 mins, compared to the reference category of patients without iXFN and without CPB use ($AOR_{\text{iXFN\&≥120 mins/ NoiXFN\&Off Pump}}$ = 10.8 [5.1-23]).

Thus, interaction between intraoperative transfusion and CPB use/ duration resulted in worsened PPCs. However, this interaction did not adversely affect mortality outcomes. This is partially explained by the fact that neither intraoperative transfusion nor CPB, when studied as independent predictive intraoperative risk factors, resulted in adverse survival outcomes; and this was true for both perioperative mortality at 30 days, and intermediate and long term mortality at one and five years respectively. Another

probable explanation is the fact that survival outcomes were not adversely affected by development of PPCs.

5.4 PPCs and Mortality

In our study, patients who developed PPCs were not found to have higher mortality rates. While this is somewhat expected for intermediate and long-term mortality outcomes at one and five-year follow-up, it was an unexpected finding for perioperative mortality.

In literature, there is a huge body of evidence linking development of PPCs to worse mortality outcomes. For example, in an observational analysis of five hundred and seventeen (517) patients, PPCs occurred in 32 (6.2%) patients (Naveed, Azam et al. 2017). The authors reported an operative mortality of 9.4% in patients with PPCs and 1.0% in patients without PPCs (p-value = 0.01). In another retrospective analysis of 18,571 adult patients undergoing cardiac surgery, reintubation incidence was 4.0%, and the authors reported that patients requiring reintubation after surgery had 7.5 times higher mortality rates (Beverly, Brovman et al. 2016). Rello and colleagues followed up two hundred fifty intubated patients during the first 48 hours after intubation, they have found that patients who require reintubation usually have poor prognosis with a mortality rate exceeding 30%–40%, irrespective of the cause for reintubation (Rello, Diaz et al. 1999).

Furthermore, several studies indicated that mortality was increased significantly in patients infected with ventilator associated pneumonia (Pawar, Mehta et al. 2003,

Hortal, Giannella et al. 2009, Hortal, Muñoz et al. 2009, Tang, Liu et al. 2009, Roeleveld, Guijt et al. 2011, Sheng, Chi et al. 2012, Tamayo, Álvarez et al. 2012).

Similar to our findings, in an analysis of 2,056 adult patients undergoing cardiac surgery with CPB by Ji and colleagues,143 (7.0%) adult patients suffered from pulmonary complications; postoperative pulmonary complication, however, was not a risk factor for hospital death (OR= 2.1 [0.9-4.3]) (Ji, Mei et al. 2013).

5.5 Limitations

A limitation of this study is its retrospective nature, which can only find associations and not show causality. However, our study reflects the experience of the entire included isolated CABG surgical population, and unlike trials, it does not suffer from selection bias. Furthermore, the present cohort includes both 'redo' and high-priority procedures (emergent and urgent) that, given their peculiar risk profile, are often excluded by other studies on this topic. Inclusion of these subsets is intended to reproduce a real-world setting and has enhanced the chances of extrapolating these findings to other experiences.

Another limitation is that we lack preoperative hematocrit levels for almost third of our selected population. This is why we have decided to exclude this very important preoperative variable from our multivariate analysis. A significant association of anemia with increased perioperative and long-term morbidity and mortality has been reported in cardiac surgery (Kulier, Levin et al. 2007). Whether anemia is a risk factor for adverse outcomes or a marker of disease remains unaddressed (De Santo, Amarelli et al. 2013),

and the present study is unable to support any further evidence. For this purpose, we conducted a separate analysis, where we only included patients with available preoperative hematocrit (N=4769). We were interested in investigating the intraoperative transfusion effect on development of PPCs in this sub-population, so we calculated both unadjusted and adjusted odds ratios (Table 13). In the adjusted analysis we adjusted for the covariate of preoperative hematocrit in addition to the previously mentioned traditional risk factors. Interestingly, the iXFN effect in this sub-analysis was similar to that observed in the main analysis, and this remained true even after adjustment (Table 14). Accordingly, we can safely assume that the absence of preoperative hematocrit did not constitute a major limitation.

Another limitation is that we lack information on the length of RBC storage and leukodepletion status of the transfused blood. There is accumulating evidence on the relationship between transfusion and adverse outcomes related to donor blood processing (Simancas-Racines, Arevalo-Rodriguez et al. 2019) and storage duration (Koch, Li et al. 2008). However, we do not have this information on all patients, and we assume that the duration of blood storage was not different among all sub-groups, causing little or no effect on our results.

A fourth limitation is that we examined all-cause mortality and were unable to determine the cause of death (cardiac or noncardiac). Although death certificates may have been helpful, they may be less than accurate in the absence of autopsies and have their own set of inherent limitations.

In general, this study focused on RBC transfusion, but other blood products, i.e. PLT and FFP, may also be associated with adverse outcomes including severe infections.

However, the results in the literature are conflicting. Most studies suggest that transfusion with PLT and FFP does not confer an increased risk of morbidity or mortality (Sreeram, Welsby et al. 2005, Vamvakas 2007, McGrath, Koch et al. 2008). Another important limitation is the fact that our patient population mostly belongs to the time era of 1900s and 2000s. A main concern is whether our findings can be generalized and applied to current practice. This concern cannot be simply addressed, as advances of coronary artery surgery are influenced by a variety of factors, including the industry, the patient, the health service, the health service purchaser, the craft of coronary surgery itself, the resident, the surgeon, the media and the cardiologist (Sergeant 2004). To examine the effect of time on outcomes of CABG, Maganti et al (Maganti, Brister et al. 2011) divided their population of CABG patients into 2 groups on the basis of year of operation: 1990–1999 and 2000–2009. The authors noted that the operative mortality of emergency coronary artery bypass grafting has remained stable over the years, despite a changing preoperative risk profile (Maganti, Brister et al. 2011). In a different study by Gao et al (Gao, Wu et al. 2006), the authors compared 22,378 patients who underwent CABG from 1968 through 2003. Long-term survival was compared between pre-stent era patients and post-stent era patients. The authors reported no difference in observed survival up to 8 years between the pre-stent and post-stent eras (Gao, Wu et al. 2006). In discussing the future of CABG, Ennker et al (Ennker and Ennker 2012) argue that coronary artery surgery in the next decade will be influenced by the further progression of minimally invasive surgical principles. Although the authors underscore several potential possible advances in the field of surgery, they argue that one of the challenges of the future will be to bring this progress in surgical technology to broad-scale application. This is mostly true in underserved areas, non-tertiary referral centers and in

third world countries. Hence, even if we are to assume that time has influenced the CABG technique per se, our studies would remain relevant in many areas and centers around the world.

A final limitation is that while we aimed to look for difference in PPCs and mortality between transfused and non-transfused patients, and between different categories of CPB use, we may have had very small number of patients and events for the 8-group analysis, insufficient to make a properly powered analysis.

CHAPTER 6

CONCLUSION

In this retrospective analysis of patients who underwent isolated first-time or redo CABG, we have found both the use of intraoperative blood transfusions and the use of CPB (on pump versus off pump), to be associated with worse pulmonary outcomes; with higher pulmonary morbidity observed in longer CPB duration. When studied together, we found out that there is a synergistic effect between intraoperative transfusion and CPB use/ duration, where pulmonary morbidity was mostly worsened by intraoperative transfusion associated with long CPB duration. Both intraoperative transfusion and CPB use/ duration, however, neither adversely affected perioperative mortality at 30-day follow up, nor intermediate and long term mortality at 1-year and 5-year follow up. Finally, the development of PPCs was generally not associated with adverse mortality outcomes at 30-day, 1-year and 5-year follow up.

PPCs, after cardiac surgery, remain the most frequent and significant contributor to morbidity in patients undergoing coronary artery bypass grafting. The mechanisms involved in the development of pulmonary dysfunction are multifactorial and are related to the activation of different inflammatory and oxidative stress pathways. Managing pulmonary dysfunction postcardiac surgery is a multistep process that starts before surgery and continues during both the operative and postoperative phases. Pulmonary protection strategies have evolved over the years with various degrees of success. Efforts should be made in order to identify those at higher risk and provide preventative strategies aimed at decreasing the likelihood of developing this ominous complication.

In this study, we have identified a synergistic interaction between two widely studied intraoperative risk factors (intraoperative transfusion and CPB use/ duration). It is our hope that our findings will provide a knowledge base that lays the groundwork for future studies that aim to improve transfusion practices and further explore the role of CPB use/ duration.

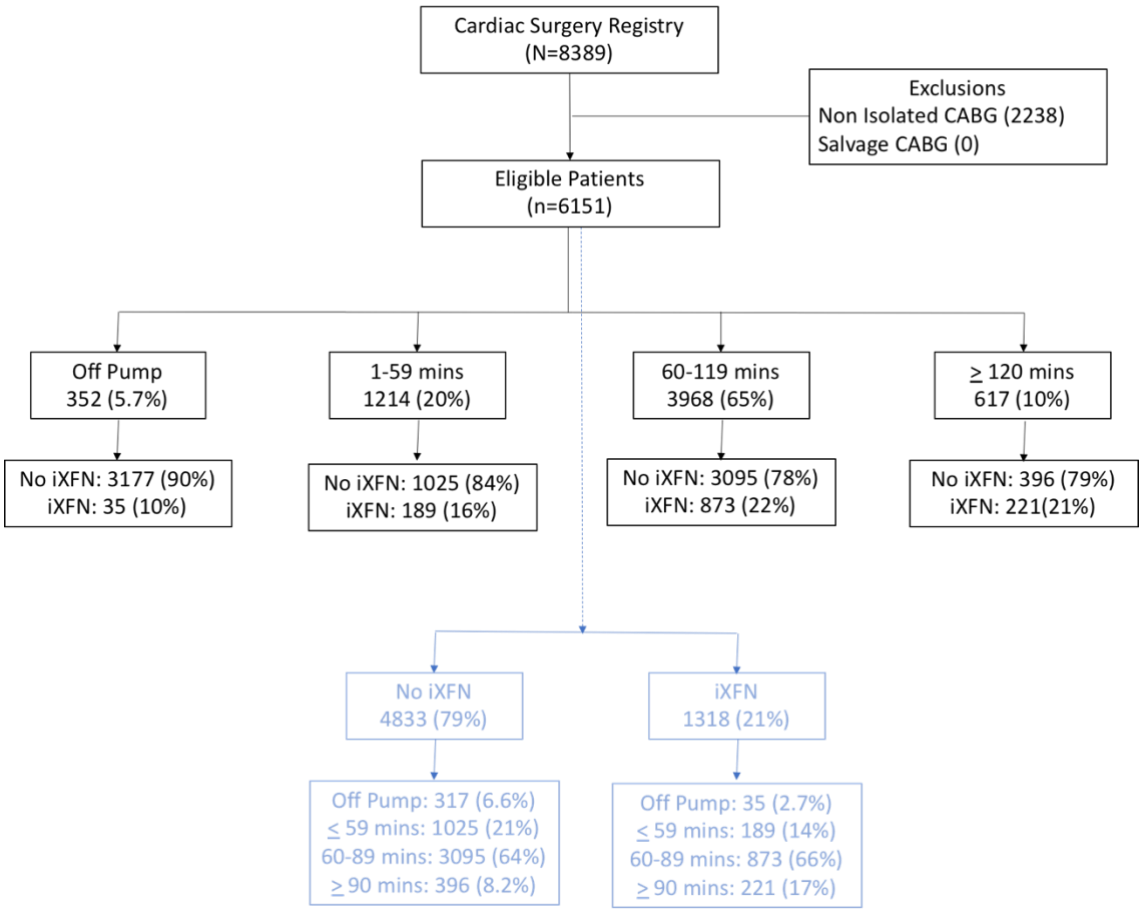

Figure 1. Flowchart depicting implemented study design and patient stratification

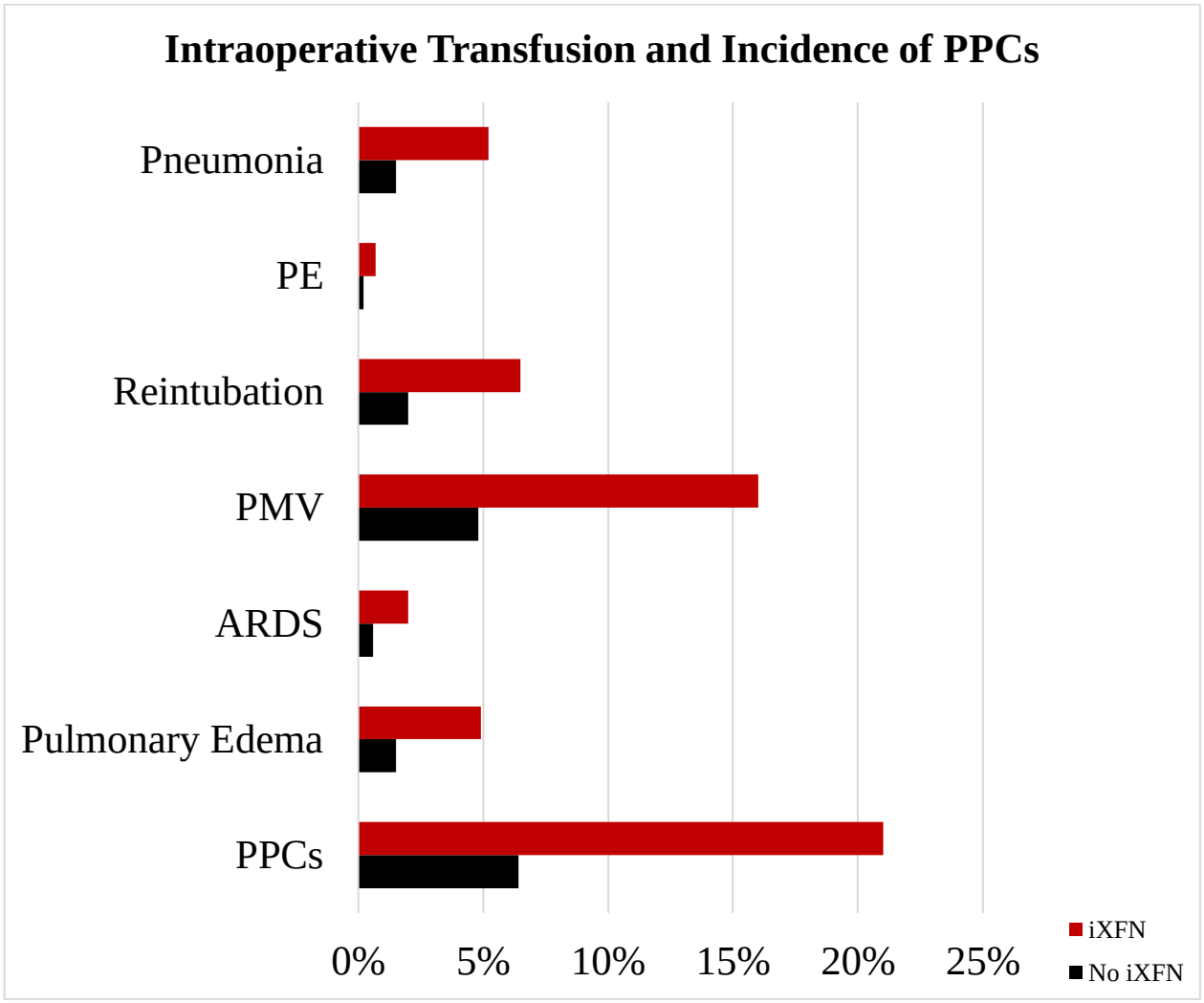

Figure 2. Rate of any pulmonary complication by intraoperative transfusion status

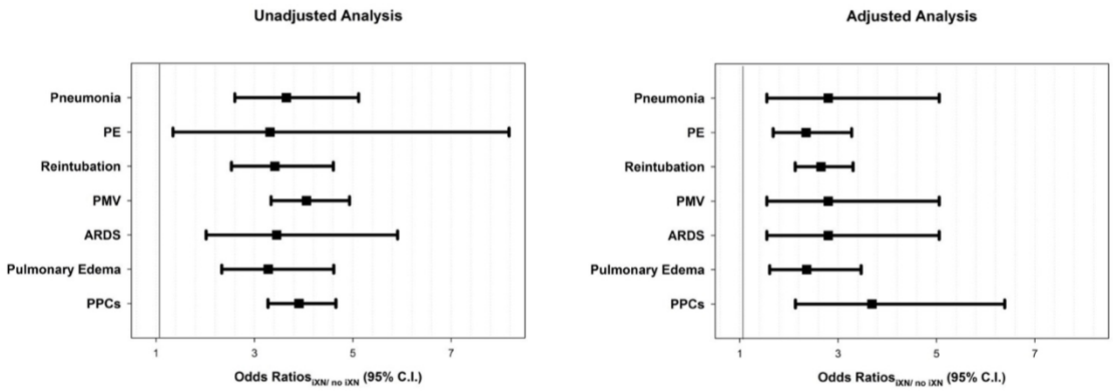

Figure 3. Forest plots of intraoperative transfusion effect on postoperative pulmonary outcomes (unadjusted and risk-adjusted odds ratios).

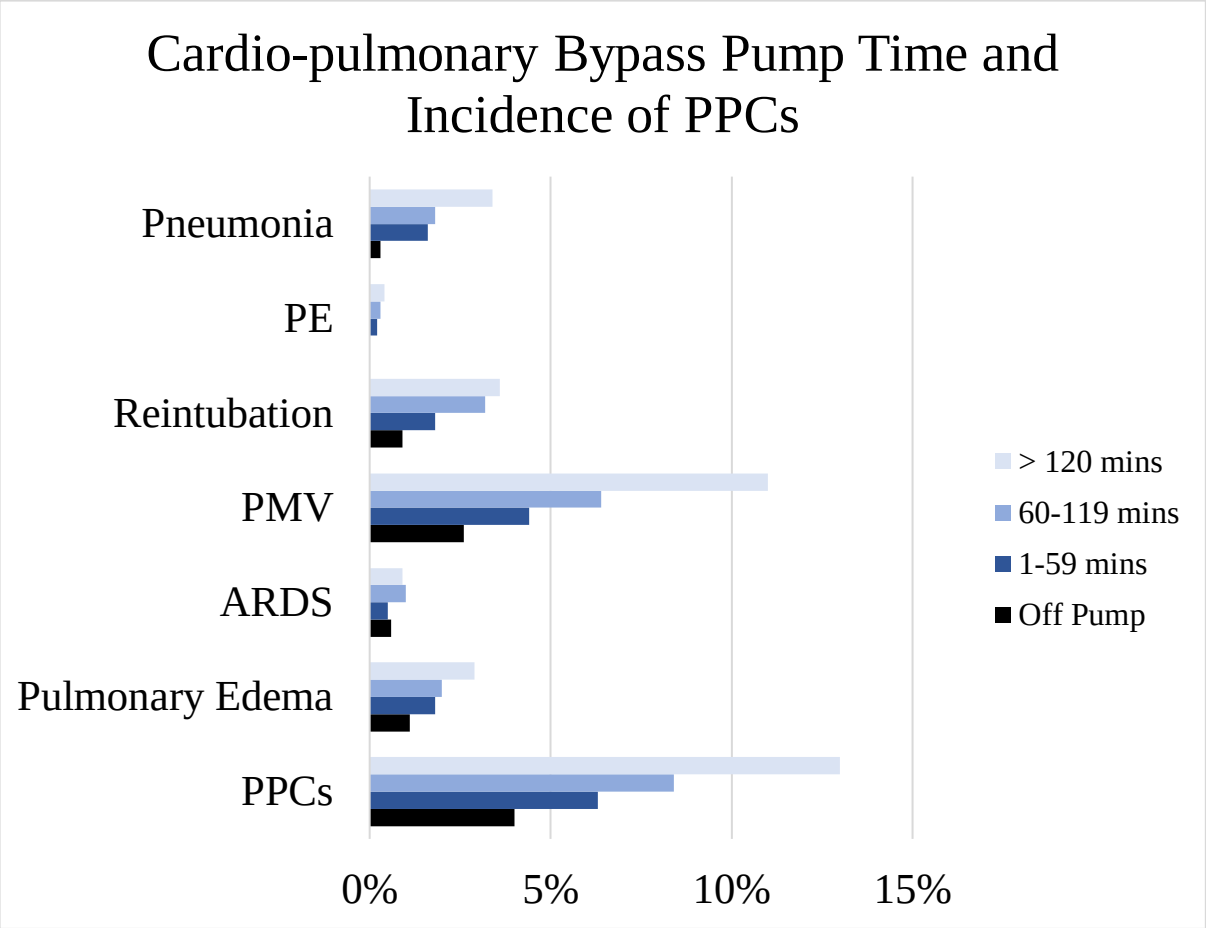

Figure 4. Rate of any pulmonary complication by cardiopulmonary bypass time

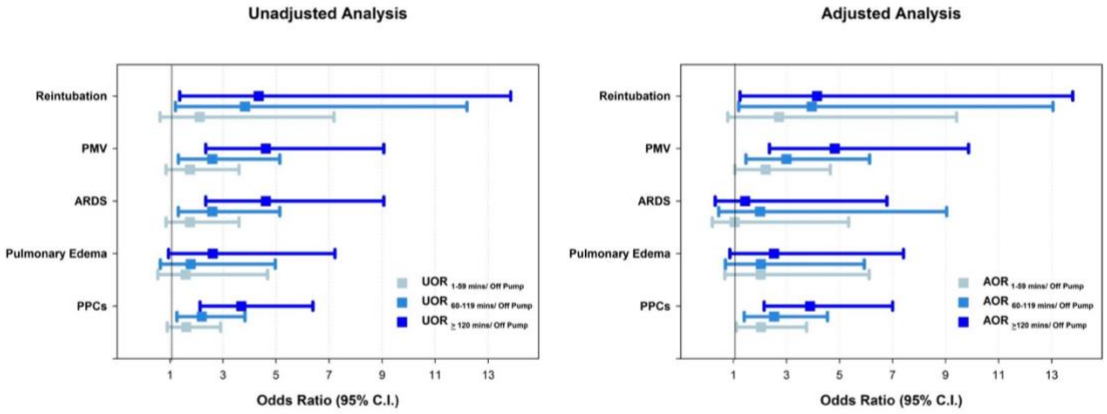

Figure 5. Forest plots of cardiopulmonary bypass effect on postoperative pulmonary outcomes (unadjusted and risk-adjusted odds ratios).

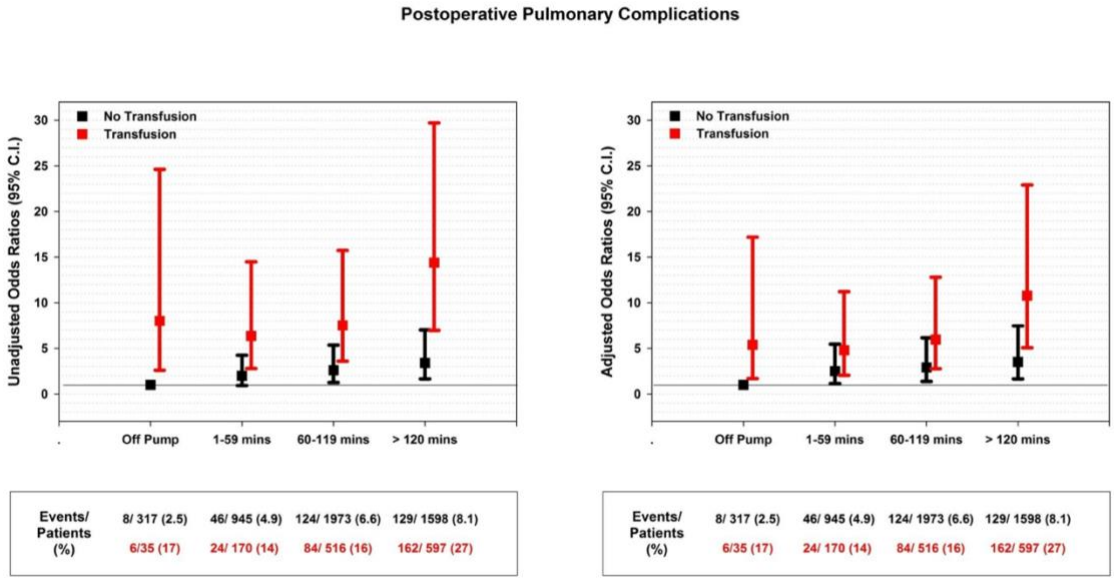

Figure 6. Illustration of the combined iXFN and CPB use effect on the development of any pulmonary complication (unadjusted and adjusted odds ratio)

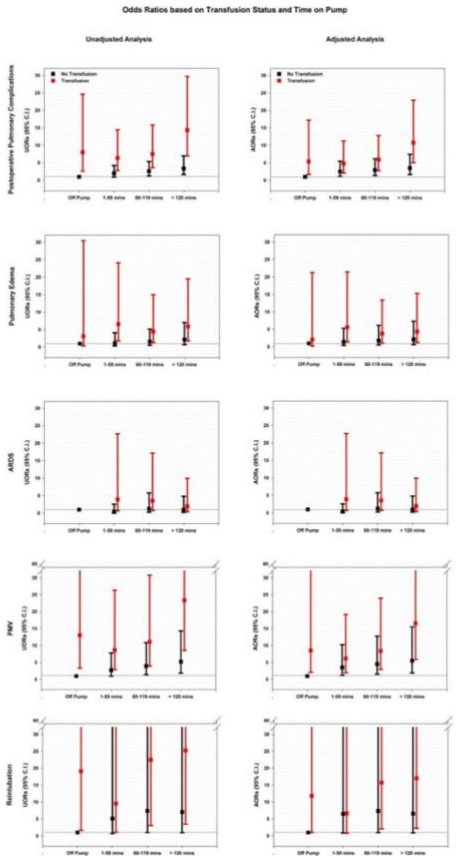

Figure 7. Illustration of the combined iXFN and CPB use effect on the development of any pulmonary complication, pulmonary edema, ARDS, PMV, reintubation, pneumonia and PE (unadjusted and adjusted odds ratio)

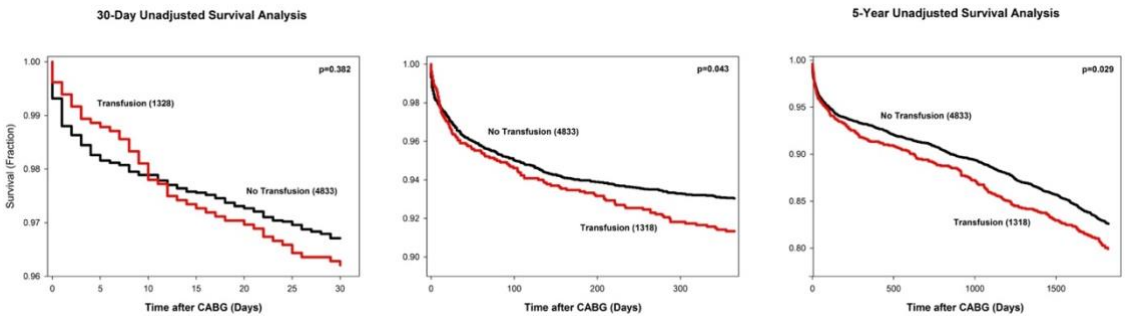

Figure 8. Unadjusted Kaplan–Meier survival analysis comparing mortality for patients with (red) and without (black) iXFN at 30 days (left), 1 year (middle) and 5 years (right)

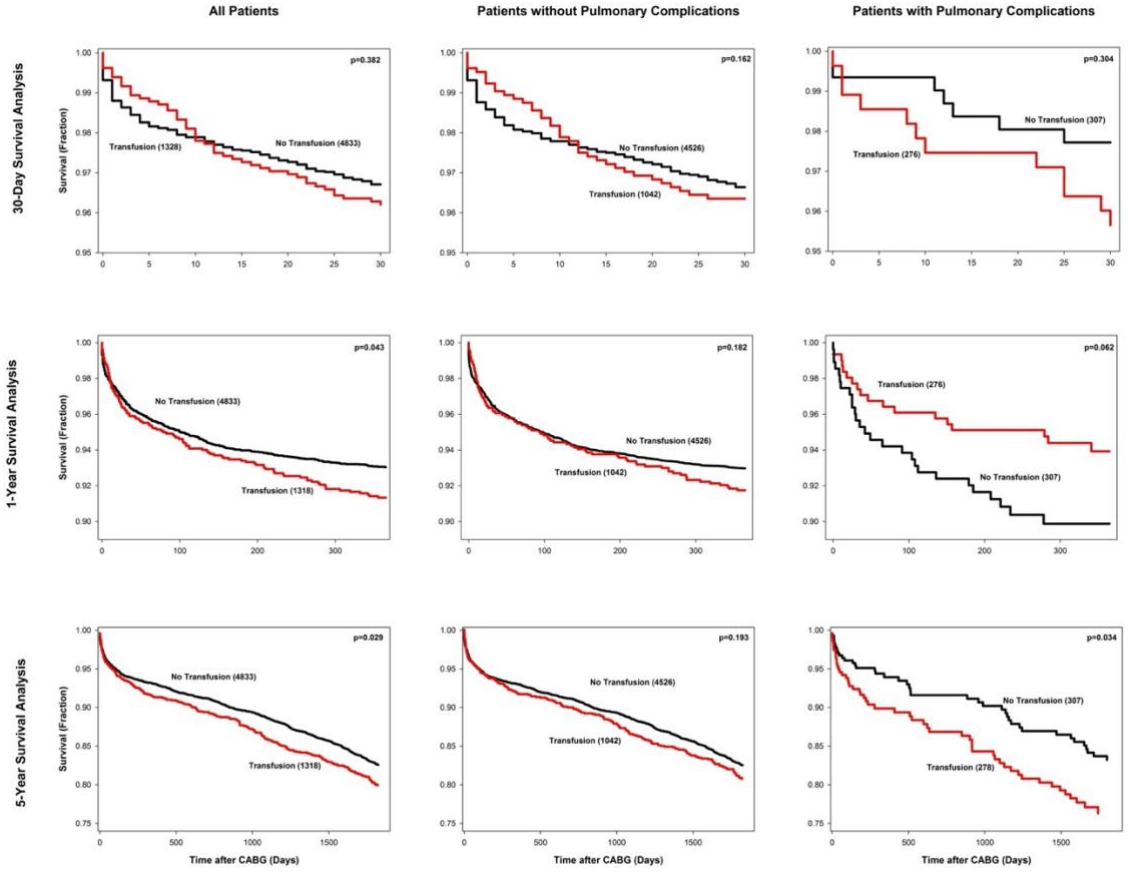

Figure 9. Unadjusted Kaplan–Meier survival analysis comparing mortality for patients with (red) and without (black) iXFN at 30 days (top), 1 year (middle) and 5 years (bottom) for the total study cohort (left), patients without PPCs (middle) and patients with PPCs (bottom)

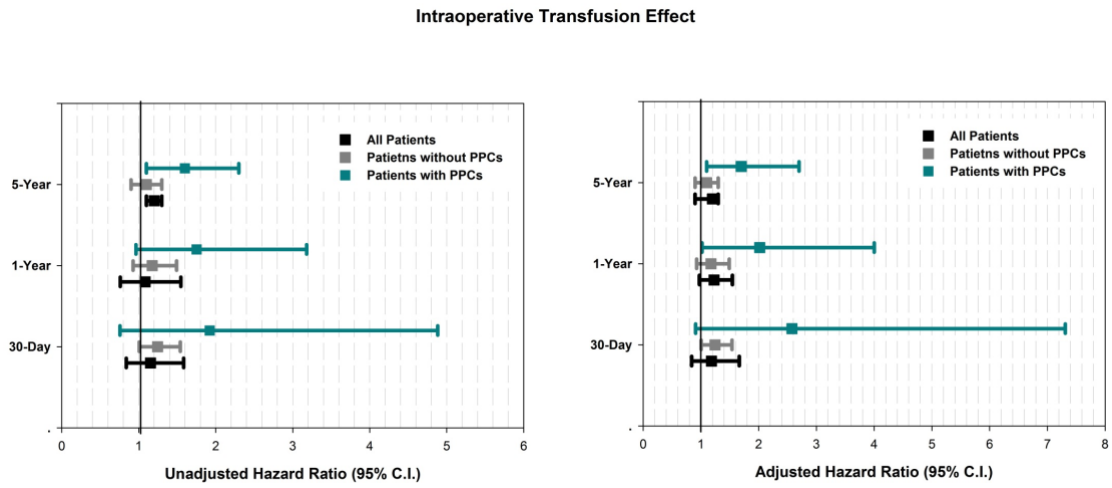

Figure 10. Forest plot of 30-day, 1-year and 5-year "iXFN Effect" or iXFN/NoiXFN unadjusted and risk-adjusted hazard ratios shown for all-cause mortality for the total study cohort (black), patients without PPCs (grey) and patients with PPCs (green)

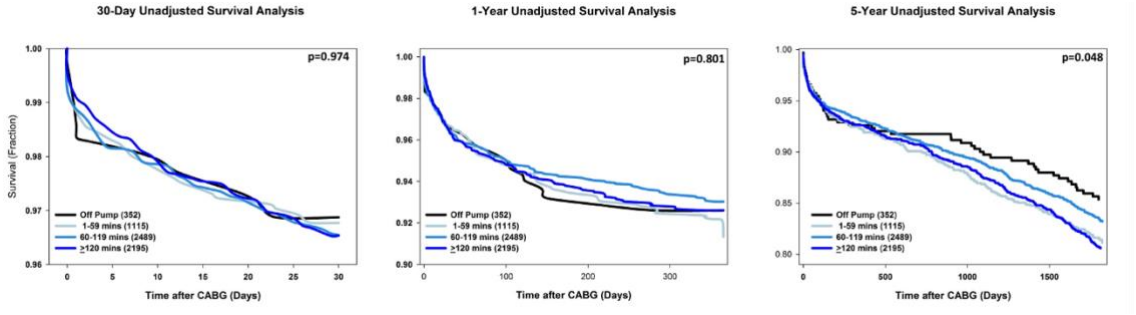

Figure 11. Unadjusted Kaplan–Meier survival analysis comparing mortality for patients as per CPB use at 30 days (left), 1 year (middle) and 5 years (right)

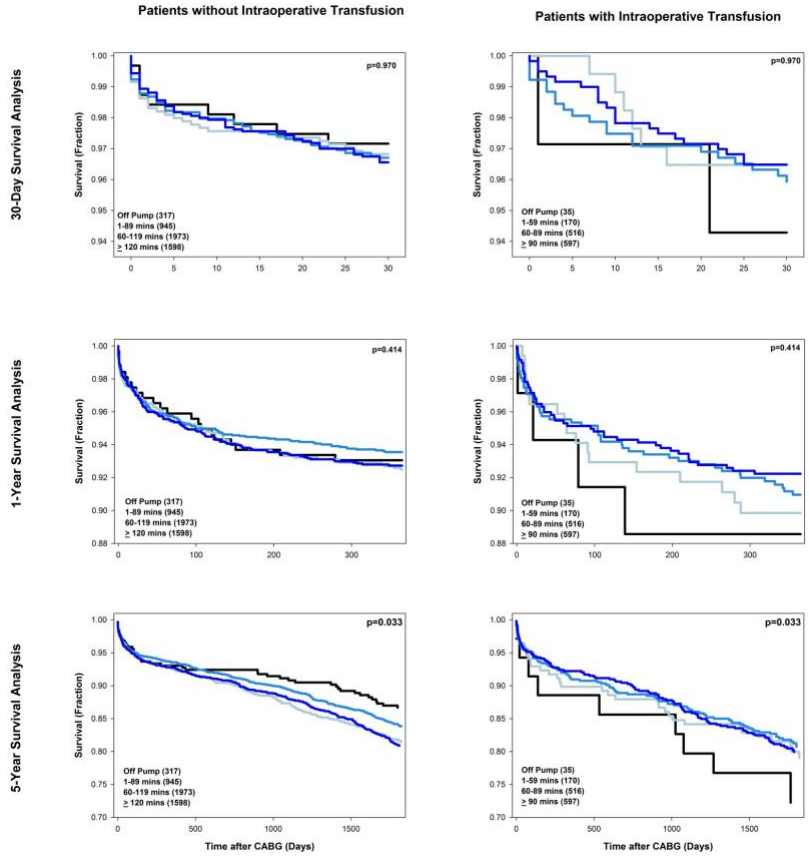

Figure 12. Unadjusted Kaplan–Meier survival analysis comparing mortality for patients as per CPB use at 30 days (top), 1 year (middle) and 5 years (bottom) for the total study cohort (left), patients without PPCs (middle) and patients with PPCs (bottom)

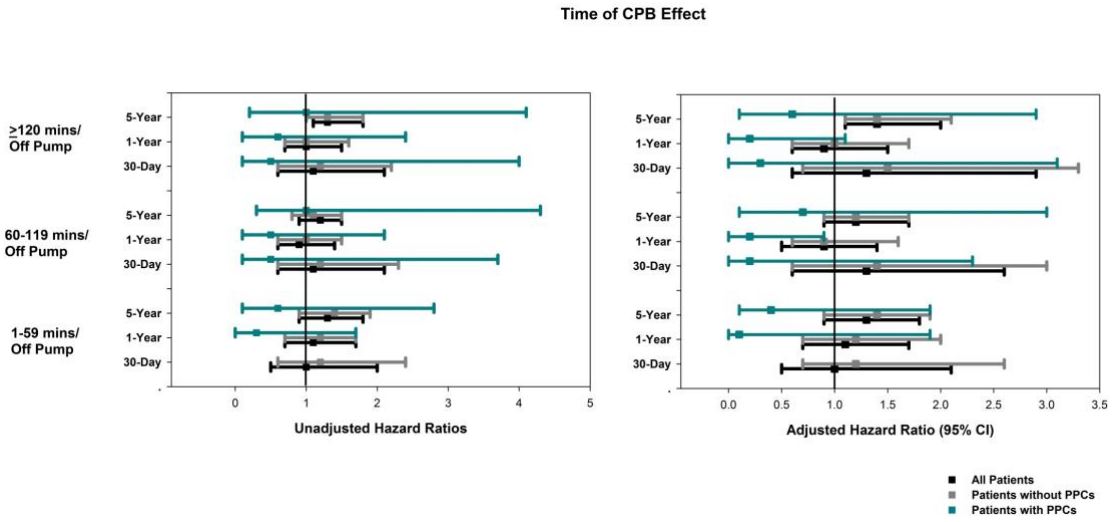

Figure 13. Forest plot of 30-day, 1-year and 5-year "CPB Effect" or CPB/NoCPB unadjusted and risk-adjusted hazard ratios shown for all-cause mortality for the total study cohort (black), patients without PPCs (grey) and patients with PPCs (green)

Table 1. Baseline demographic, clinical and surgical characteristics of patients with and without postoperative pulmonary complications.

	All Patients (N=6151)		
	Pulmonary Complications (No) (N=5568)	**Pulmonary Complications (Yes) PPCs (N=583)**	**p-value**
Continuous Variables	***Mean ± SD***	***Mean ± SD***	
Age	64 (11)	67 (11)	0.000
BMI	29 (5.5)	30 (6.3)	0.033
BSA	2.0 (0.2)	2.0 (0.3)	0.097
Categorical Variables	***n (%)***	***n (%)***	
Demographic Risk Factors			
Sex	3680 (66)	376 (65)	0.439
Smoker	3674 (66)	412 (70)	0.023
Myocardial Infarction	3163 (57)	425 (73)	0.000
Congestive Heart Failure	586 (11)	150 (26)	0.000
Cerebrovascular Disease	1281 (23)	180 (31)	0.000
peripheral Vascular Disease	856 (16)	146 (25)	0.000
Chronic Lung Disease	1073 (19)	200 (34)	0.000
Cerebrovascular Accident	414 (7.4)	63 (11)	0.000
Hypertension	4566 (82)	492 (84)	0.151
Hypercholesterolemia	3869 (70)	372 (64)	0.005
Diabetes	1888 (40)	240 (41)	0.000
Renal Failure	163 (2.9)	51 (8.7)	0.000
NYHA			
1	258 (4.6)	23 (3.9)	0.000
2	771 (14)	60 (10)	
3	2582 (46)	191 (33)	
4	1956 (35)	309 (53)	0.004
Vessel Disease			
Left Main Disease	1127 (20)	142 (24)	0.020

Number of Diseased Vessels			
2	333 (6.0)	25 (4.3)	0.000
3	1284 (23)	91 (16)	
4	3950 (71)	467 (80)	
Surgical Risk Factors			
iXFN	1042 (19)	276 (47)	0.004
Perfusion Time	338 (6.1)	14 (2.4)	0.000
Off Pump	1135 (20)	79 (14)	
1-59 mins	3592 (65)	376 (65)	
60-119 mins	503 (9.0)	114 (20)	
≥ 120 mins			
Status	2074 (37)	135 (23)	0.000
Elective	3167 (57)	350 (60)	
Urgent	327 (5.9)	98 (17)	
Emergent			
Incidence	4917 (88)	486 (83)	0.004
First	626 (11)	95 (16)	
Second	24 (0.4)	2 (0.3)	
Third	1 (0.0)	0 (0.0)	
Fourth			
Number of Grafts			
1	281 (5.0)	24 (4.1)	0.000
2	1039 (19)	88 (15)	
3	2250 (40)	246 (42)	
4	1604 (29)	188 (32)	
5	341 (6.1)	34 (5.8)	
6	50 (0.9)	3 (0.5)	
7	3 (0.1)	0 (0.0)	

NYHA: New York Heart Assocoiation, iXFN: intraoperative transfusion

Table 2. Baseline demographic, clinical and surgical characteristics of patients with and without intraoperative transfusion

	All Patients (N=6151)	
	No iXFN (N=4833)	**iXFN (N=1318)**
Continuous Variables	***Mean ± SD***	***Mean ± SD***
Age (Years)	63 ± 10	68 ± 11†
BMI (kg/ m2)	30 ± 6	28 ± 6†
Categorical Variables	***n (%)***	***n (%)***
Risk Factors		
Male	3190 (66)	866 (66)
Diabetes	1605 (33)	523 (39)†
Hypertension	3927 (81)	1131 (86)†
Hypercholesterolemia	3334 (69)	907 (69)
Smoker	3305 (68)	781 (59)†
Chronic Lung Disease	943 (20)	330 (25)†
Peripheral Vascular Disease	706 (15)	296 (23)†
Cerebrovascular Disease	1025 (21)	436 (33)†
Cerebrovascular Accident	334 (6.9)	143 (11)†
Renal Failure	90 (1.9)	124 (9.4)†
Myocardial Infarction	2721 (56)	867 (66)†
Congestive Heart Failure	464 (10)	272 (21)†
NYHA Class		
1	243 (5.0)	38 (2.9)†
2	726 (15)	105 (8.0)
3	2270 (47)	503 (38)
4	1593 (33)	672 (51)
Vessel Disease		
Left Main Disease	921 (19)	348 (26)†
Number of Diseased Vessels		
2	298 (6.2)	60 (4.6)†
3	1122 (23)	253 (19)
4	3412 (71)	1005 (76)

Surgery Details		
Previous CABG	921 (19)	348 (26)†
Status		
Elective	1874 (39)	335 (25)†
Urgent	2706 (56)	811 (62)
Emergent	253 (5.2)	172 (13)
Incidence		
First	4301 (89)	1102 (84)†
Second	515 (11)	206 (16)
Third	16 (0.3)	10 (0.8)
Fourth	1 (0.0)	0 (0.0)

SD - standard deviation, BMI - body mass index, NYHA - New York Heart Association. †Indicates statistically significant p-value ($p<0.05$).

Table 3. Baseline demographic, clinical and surgical characteristics of patients by cardiopulmonary bypass use and duration

	All Patients (N=6151)		
	Off Pump (N=352)	**0 - 59 mins (N=1214)**	**60 - 1**
Continuous Variables	***Mean ± SD***	***Mean ± SD***	
Age (Years)	64 ± 12	64 ± 11	
BMI (kg/ m2)	29 ± 6	29 ± 6	
Categorical Variables	***n (%)***	***n (%)***	
Risk Factors			
Male	231 (66)	734 (66)	
Diabetes	94 (27)	344 (31)	
Hypertension	299 (85)	915 (82)	
Hypercholesterolemia	253 (72)	758 (68)	
Smoker	232 (66)	698 (63)	
Chronic Lung Disease	93 (26)	201 (18)	
Peripheral Vascular Disease	73 (21)	161 (15)	
Cerebrovascular Disease	74 (21)	249 (23)	
Cerebrovascular Accident	30 (8.5)	84 (7.5)	
Renal Failure	33 (9.4)	44 (3.9)	
Myocardial Infarction	191 (54)	582 (52)	
Congestive Heart Failure	47 (13)	108 (9.8)	
NYHA Class			
1	24 (6.8)	57 (5.1)	
2	55 (16)	158 (14)	
3	161 (46)	515 (46)	
4	112 (32)	385 (35)	
Vessel Disease			
Left Main Disease	39 (11)	231 (21)	
Number of Diseased Vessels			
2	109 (31)	152 (14)	
3	123 (35)	507 (46)	
4	120 (34)	456 (41)	
Surgery Details			

Previous CABG	25 (7.1)	17 (1.5)	
Status			
Elective	126 (36)	409 (37)	
Urgent	216 (61)	611 (55)	
Emergent	10 (2.8)	95 (8.5)	
Incidence			
First	296 (84)	1029 (92)	
Second	54 (15)	84 (7.5)	
Third	1 (0.3)	2 (0.2)	
Fourth	1 (0.0)	0 (0.0)	

SD - standard deviation, BMI - body mass index, NYHA - New York Heart Association. †Indicates statistically significant p-value ($p<0.05$).

Table 4. Intraoperative transfusion effect of unadjusted and risk adjusted odds ratios estimated for development of postoperative pulmonary complications

	No iXFN/ iXFN n (%)	**UOR$_{iXFN/\ No\ iXFN}$ [95**
PPCs		
Any PPC	307 (6.4)/ 276 (21)†	**3.9 [3.3-4.7]**
Pulmonary Edema	74 (1.5)/ 64 (4.9)†	**3.3 [2.3-4.6]**
ARDS	28 (0.6)/ 26 (2.0)†	**3.5 [2.0-5.9]**
PMV	231 (4.8)/ 223 (17)†	**4.1 [3.3-4.9]**
Reintubation	96 (2.0)/ 85 (6.5)†	**3.4 [2.5-4.6]**
Pneumonia	71 (1.5)/ 68 (5.2)†	**3.6 [2.6-5.1]**
PE	10 (0.2)/ 9(0.7)†	**3.3 [1.3-8.2]**

†Indicates statistically significant p-value. UHR: Unadjusted Hazard Ratio, AHR: Adjusted Hazard Ratio, CI: Confidence I

mechanical ventilation, PE: pulmonary embolism

Table 5. Intraoperative transfusion effect of unadjusted and risk adjusted odds ratios estimated for development of postoperative pulmonary complications shown for each cardiopulmonary bypass category

		No iXFN/ iXFN n (%)	UOR$_{iXFN/\ No\ iXFN}$ [95% CI]	AOR$_{iXFN/\ No}$
PPCs				
Any PPC	**Off Pump**	8 (2.5)/ 6 (17)†	**8.0 [2.6 - 25]**	**15 [2.**
	1-59 mins	46 (4.9)/ 24 (14)	**3.2 [1.9 - 5.4]**	**2.1 [1**
	60 - 119 mins	124 (6.3)/ 84 (16)	**2.9 [2.2 - 3.9]**	**1.9 [1**
	≥ 120 mins	129 (8.1)/ 162 (27)	**4.2 [3.3 - 5.5]**	**3.1 [2**
Pulmonary Edema	**Off Pump**	3 (0.9)/ 1 (2.9)†	3.1 [0.3 - 30]	
	1-59 mins	10 (1.1)/ 10 (5.9)	**5.8 [2.4 - 14]**	**6.5 [2**
	60 - 119 mins	29 (1.5)/ 21 (4.1)	**2.8 [1.6 - 5.0]**	1.9 [0
	≥ 120 mins	32 (2.0)/ 32 (5.4)	**2.8 [1.7 - 4.6]**	**2.1 [1**
ARDS	**Off Pump**	2 (0.6)/ 0 (0.0)†	-	
	1-59 mins	2 (0.2)/ 4 (2.4)	**11 [2 - 63]**	
	60 - 119 mins	14 (0.7)/ 12 (2.3)	**3.3 [1.5 - 2.7]**	**2.4 [1**
	≥ 120 mins	10 (0.6)/ 10 (1.7)	**2.7 [1.1 - 6.5]**	2.6 [0
PMV	**Off Pump**	4 (1.3)/ 5 (14)†	**13 [3.3 - 51]**	
	1-59 mins	32 (3.4)/ 17 (10)	**3.1 [1.7 - 5.9]**	**1.8 [0**
	60 - 119 mins	95 (4.8)/ 64 (12)	**2.8 [2.0 - 3.9]**	**1.7 [1**

	≥ 120 mins	100 (6.3)/ 137 (23)	**4.5 [3.4 - 5.9]**	**3.1 [2**
Reintubation	**Off Pump**	1 (0.3)/ 2 (5.7)†	**19 [1.7 - 216]**	
	1-59 mins	15 (1.6)/ 5 (2.9)	1.9 [0.7 - 5.2]	0.4 [0
	60 - 119 mins	45 (2.3)/ 43 (6.7)	**3.0 [1.9 - 4.8]**	**2.1 [1**
	≥ 120 mins	35 (2.2)/ 44 (7.4)	**3.6 [2.3 - 5.6]**	**2.8 [1**
Pneumonia	**Off Pump**	0 (0.0)/ 1 (2.9)†	-	
	1-59 mins	13 (1.4)/ 5 (2.9)	2.2 [0.8 - 6.2]	1.4 [0
	60 - 119 mins	27 (1.4)/ 18 (3.5)	**2.6 [1.4 - 4.8]**	1.5 [0
	≥ 120 mins	31(1.9)/ 44 (7.4)	**4.0 [2.5 - 6.4]**	**3.2 [1**
PE	**Off Pump**	0 (0.0)/ 0 (0.0)†	-	
	1-59 mins	1 (0.1)/ 1 (0.6)	-	
	60 - 119 mins	6 (0.3)/ 2 (0.4)	1.3 [0.3 - 6.3]	0.7 [0
	≥ 120 mins	3 (0.2)/ 6 (1.0)	**5.4 [1.3 -22]**	2.3 [0

†Indicates statistically significant p-value. UHR: Unadjusted Hazard Ratio, AHR: Adjusted Hazard Ratio, CI: Confidence

Table 6. Cardiopulmonary bypass effect of unadjusted and risk adjusted odds ratios estimated for development of postoperative pulmonary complications

	Off Pump/ 1-59 mins/ 60-119 mins/ ≥ 120 mins n (%)	**UOR$_{1\text{-}59\ mins/\ Off\ Pump}$ [95% CI]**	**U**
PPCs			
Any PPC	14 (4.0)/ 70 (6.3)/ 208 (8.4)/ 291 (13)	1.6 [0.9-2.9]	
Pulmonary Edema	4 (1.1)/ 20 (1.8)/ 50 (2.0)/ 64 (2.9)	1.6 [0.5-4.7]	
ARDS	2 (0.6)/ 6 (0.5)/ 26 (1.0)/ 20 (0.9)	0.9 [0.2-4.7]	
PMV	9 (2.6)/ 49 (4.4)/ 159 (6.4)/ 237 (11)	1.8 [0.9-3.6]	
Reintubation	3 (0.9)/ 20 (1.8)/ 79 (3.2)/ 79 (3.6)	2.1 [0.6-7.2]	
Pneumonia	1 (0.3)/ 18 (1.6)/ 45 (1.8)/ 75 (3.4)	5.8 [0.8-43.3]	
PE	0 (0.0)/ 2 (0.2)/ 8 (0.3)/ 9 (0.4)	_	

†Indicates statistically significant p-value. UHR: Unadjusted Hazard Ratio, AHR: Adjusted Hazard Ratio, CI: Confidence Interval, PPCs embolism

Table 7. Cardiopulmonary bypass effect of unadjusted and risk adjusted odds ratios estimated for development of postoperative pulmonary complications shown in patients with and without intraoperative transfusion

		Off Pump/ 1-59 mins/ 60-119 mins/ ≥ 120 mins n (%)
PPCs		
Any PPC	**No iXFN**	8 (2.5)/ 46 (4.9)/ 124 (6.3)/ 129 (8.1)
	iXFN	6 (17)/ 24(14)/ 84 (16)/ 162 (27)
Pulmonary Edema	**No iXFN**	3 (0.9)/ 10 (1.1)/ 29 (1.5)/ 32 (2.0)
	iXFN	1 (2.9)/ 10 (5.9)/ 21 (4.1)/ 32 (5.4)
ARDS	**No iXFN**	2 (0.6)/ 2 (0.2)/ 14 (0.7)/ 10 (0.6)
	iXFN	0 (0.0). 4 (2.4)/ 12 (2.3)/ 10 (1.7)
PMV	**No iXFN**	4 (1.3)/ 32 (3.4)/ 95 (4.8)/ 100 (6.3)
	iXFN	5 (14.3)/ 17 (10)/ 64 (12)/ 137 (23)
Reintubation	**No iXFN**	1 (0.3)/ 15 (1.6)/ 45 (2.3)/ 35 (2.2)
	iXFN	2 (5.7)/ 5 (2.9)/ 34 (6.7)/ 44 (7.4)
Pneumonia	**No iXFN**	0 (0.0)/ 13 (1.4)/ 27 (1.4)/ 31 (1.9)
	iXFN	1 (2.9)/ 5 (2.9)/ 18 (3.5)/ 44 (7.4)
PE	**No iXFN**	0 (0.0)/ 1 (0.1)/ 6 (0.3)/ 3 (0.2)
	iXFN	0 (0.0)/ 1 (0.6)/ 2 (0.4)/ 6 (1.0)

†Indicates statistically significant p-value. UHR: Unadjusted Hazard Ratio, AHR: Adjusted Hazard Ratio, CI: Confidence Interval, iXFN

embolism

Table 8. Combined intraoperative transfusion and cardiopulmonary bypass effect unadjusted and risk adjusted odds ratios estimated for development of postoperative pulmonary complications

		no (%)	UOR [95% CI]	AOR [95% CI]	
Any PPC	No iXFN & Off Pump (Reference Category)	8 (2.5)	1	1	iXFN & No iXFN
	No iXFN & 1-59 mins/ No iXFN & Off Pump	46 (4.9)	2.0 [0.9-4.2]	**2.5 [1.1-5.4]**	iXFN & No iXFN
	No iXFN & 60-119 mins/ No iXFN & Off Pump	124 (6.3)	**2.6 [1.3-5.3]**	**2.9 [1.4-6.1]**	iXFN & 6 No iXFN
	No iXFN & > 120 mins/ No iXFN & Off Pump	129 (8.1)	**3.4 [1.6-7.0]**	**3.5 [1.6-7.4]**	iXFN & No iXFN
Pulmonary Edema	No iXFN & Off Pump (Reference Category)	3 (0.9)	1	1	iXFN & No iXFN
	No iXFN & 1-59 mins/ No iXFN & Off Pump	10 (1.1)	1.1 [0.3-4.1]	1.4 [0.4-5.3]	iXFN & No iXFN
	No iXFN & 60-119 mins/ No iXFN & Off Pump	29 (1.5)	1.6 [0.5-5.2]	1.8 [0.5-6.2]	iXFN & 6 No iXFN
	No iXFN & > 120 mins/ No iXFN & Off Pump	32 (2.0)	2.1 [0.7-7.0]	2.1 [0.6-7.3]	iXFN & No iXFN
ARDS	No iXFN & Off Pump (Reference Category)	2 (0.6)	1	1	iXFN & No iXFN
	No iXFN & 1-59 mins/ No iXFN & Off Pump	2 (0.2)	0.3 [0.0-2.4]	0.3 [0.0-2.5]	iXFN & No iXFN

	No iXFN & 60-119 mins/ No iXFN & Off Pump	14 (0.7)	1.1 [0.3-5.0]	1.2 [0.3-5.7]	iXFN & 6 No iXFN
	No iXFN & > 120 mins/ No iXFN & Off Pump	10 (0.6)	1.0 [0.2-4.5]	1.0 [0.2-4.8]	iXFN & No iXFN
PMV	No iXFN & Off Pump (Reference Category)	4 (1.3)	1	1	iXFN & No iXFN
	No iXFN & 1-59 mins/ No iXFN & Off Pump	32 (3.4)	2.7 [0.9-7.8]	**3.5 [1.2-10]**	iXFN & No iXFN
	No iXFN & 60-119 mins/ No iXFN & Off Pump	95 (4.8)	**4.0 [1.4-11]**	**4.5 [1.6-13]**	iXFN & 6 No iXFN
	No iXFN & > 120 mins/ No iXFN & Off Pump	100 (6.3)	**5.2 [1.9-14]**	**5.5 [2.0-16]**	iXFN & No iXFN
Reintubation	No iXFN & Off Pump (Reference Category)	1 (1.3)	1	1	iXFN & No iXFN
	No iXFN & 1-59 mins/ No iXFN & Off Pump	15 (1.6)	5.1 [0.7-39]	6.5 [0.9-50]	iXFN & No iXFN
	No iXFN & 60-119 mins/ No iXFN & Off Pump	45 (2.3)	**7.4 [1.1-54]**	7.3 [0.9-55]	iXFN & 6 No iXFN
	No iXFN & > 120 mins/ No iXFN & Off Pump	35 (2.2)	7.1 [0.9-52]	6.6 [0.9-50]	iXFN & No iXFN
Pneumonia	No iXFN & Off Pump (Reference Category)	0 (0.0)	1	1	iXFN & No iXFN
	No iXFN & 1-59 mins/ No iXFN & Off Pump	13 (1.4)	–	–	iXFN & No iXFN

	No iXFN & 60-119 mins/ No iXFN & Off Pump	27 (1.4)	_	_	iXFN & 6 No iXFN
	No iXFN & > 120 mins/ No iXFN & Off Pump	31 (1.9)	_	_	iXFN & No iXFN
PE	No iXFN & Off Pump (Reference Category)	0 (0.0)	1	1	iXFN & No iXFN
	No iXFN & 1-59 mins/ No iXFN & Off Pump	1 (0.1)	_	_	iXFN & No iXFN
	No iXFN & 60-119 mins/ No iXFN & Off Pump	6 (0.3)	_	_	iXFN & 6 No iXFN
	No iXFN & > 120 mins/ No iXFN & Off Pump	3 (0.2)	_	_	iXFN & No iXFN

Table 9. Areas under the curves for the two predictive models, and the corresponding comparison

	Model 1	
	AUC [95% CI]	p-v
Pulmonary Complications		
Any PPC	0.72 [0.70-0.74]	<0
Pulmonary Edema	0.71 [0.66-0.76]	0.
ARDS	0.77 [0.71-0.84]	<0
PMV	0.75 [0.72-0.77]	<0
Reintubation	0.72 [0.68-0.75]	0.
Pneumonia	0.74 [0.70-0.79]	0.
PE	0.83 [0.75-0.90]	<0

AUC: Area under the curve; ΔAUC: AUC difference; CI: confidence interval; PPC: postoperative puln

Table 10. Intraoperative transfusion effect unadjusted and adjusted hazard ratios for 30-Day, 1-Year and 5-year all-cause mortality for all study cohort and for sub-cohorts of patients with and without PPCs, and for sub-cohorts of patients by CPB use

			No iXFN/ iXFN n (%)	**UHR$_{iXFN/\ No\ iXFN}$ [9**
Total Cohort	All Patients			
		30-Day	159 (3.3)/ 50 (3.8)	1.2 [0.8-1.6
		1-Year	336 (7.0)/ 113 (8.6)†	**1.2 [1.1-1.5**
		5-Year	832 (17)/ 249 (19)†	**1.2 [1.1-1.3**
	Patients without PPCs			
		30-Day	152 (3.4)/ 38 (3.6)	1.1 [0.8-1.5
		1-Year	318 (7.0)/ 86 (8.3)	1.2 [0.9-1.5
		5-Year	791 (18)/ 196 (19)	1.1 [0.9-1.3
	Patients withPPCs	-	-	-
		30-Day	7 (2.3)/ 12 (4.3)	1.9 [0.8-4.9
		1-Year	18 (5.9)/ 27 (9.8)	1.8 [0.9-3.2
		5-Year	41 (13)/ 53 (19)†	**1.6 [1.1-2.3**
Off Pump	All Patients			
		30-Day	9 (2.8)/ 2 (5.7)	2.2 [0.4-9.4
		1-Year	22 (6.9)/ 4 (11)	1.7 [0.6-4.9
		5-Year	42 (13)/ 9 (26)†	**2.2 [1.1-4.5**
	Patients without PPCs			
		30-Day	9 (2.9)/ 1 (3.4)	1.2 [0.1-9.2
		1-Year	21 (6.8)/ 3 (10)	1.5 [0.5-5.1
		5-Year	41 (13)/ 8 (28)†	**2.3 [1.1-4.9**

	Patients withPPCs	_	_	_
		30-Day	0 (0.0)/ 1 (17)	90.4 [0-NA
		1-Year	1 (13)/ 1 (17)	1.5 [0.1-23.
		5-Year	1 (13)/ 1 (17)	1.5 [0.1-23.
1 - 59 mins	All Patients			
		30-Day	30 (3.2)/ 6 (3.5)	1.1 [0.5-2.7
		1-Year	71 (7.5)/ 17 (10)	1.4 [0.8-2.3
		5-Year	174 (18)/ 33 (19)	1.1 [0.8-1.6
	Patients without PPCs			
		30-Day	30 (3.3)/ 6 (4.1)	1.2 [0.5-2.9
		1-Year	69 (7.7)/ 16 (11)	1.4 [0.8-2.5
		5-Year	169 (19)/ 31 (21)	1.2 [0.8-1.7
	Patients withPPCs	_	_	_
		30-Day	0 (0.0)/ 0 (0.0)	_
		1-Year	2 (4.3)/ 1 (4.2)	1.2 [0.1-13
		5-Year	5 (11)/ 2 (8.3)	1.0 [0.2-5.3
60 - 119 mins	All Patients			
		30-Day	65 (3.3)/ 21 (4.1)	1.2 [0.8-2.0
		1-Year	127 (6.4)/ 46 (8.9)	1.4 [1.0-2.0
		5-Year	315 (16)/ 94 (18)	1.2 [0.9-1.5
	Patients without PPCs			
		30-Day	61 (3.0)/ 18 (4.2)	1.3 [0.7-2.1
		1-Year	120 (6.5)/ 38 (8.8)	1.4 [0.9-1.9
		5-Year	299 (16)/ 75 (17)	1.1 [0.9-1.4
	Patients withPPCs	_	_	_

		30-Day	4 (3.2)/ 3 (3.6)	1.1 [0.2-4.9
		1-Year	7 (5.6)/ 8 (9.5)	1.8 [0.6-4.8
		5-Year	16 (13)/ 19 (23)†	**2.0 [1.1-4.0**
≥ 120 min	All Patients			
		30-Day	55 (3.4)/ 21 (3.5)	1.0 [0.6-1.7
		1-Year	116 (7.3)/ 46 (7.7)	1.1 [0.8-1.5
		5-Year	301 (19)/ 113 (19)	1.1 [0.9-1.3
	Patients without PPCs			
		30-Day	52 (3.5)/ 13 (3.0)	0.8 [0.5-1.5
		1-Year	108 (7.4)/ 29 (6.7)	0.9 [0.6-1.4
		5-Year	282 (19)/ 82 (19)	1.0 [0.8-1.3
	Patients withPPCs	-	-	-
		30-Day	3 (2.3)/ 8 (4.9)	2.1 [0.6-8.0
		1-Year	8 (6.2)/ 17 (11)	1.8 [0.8-4.1
		5-Year	19 (15)/ 31 (19)	1.3 [0.8-2.4

Table 11. CPB use effect unadjusted and adjusted hazard ratios for 30-Day, 1-Year and 5-year all-cause mortality for all study cohort and for sub-cohorts of patients with and without PPCs, and for sub-cohorts of patients with and without iXFN

		Off Pump/ 1-59 mins/ 60-119mins/ ≥ 120 mins n (%)	**UHR$_{1\text{-}59\ mins/\ Off\ Pump}$ [95% CI]**	**U**
Total Cohort	All Patients			
	30-Day	11 (3.1)/ 36 (3.2)/ 86 (3.5)/ 76 (3/5)	1.0 [0.5-2.0]	
	1-Year	26 (7.4)/ 88 (7.9)/ 173 (7.0)/ 162 (7.4)	1.1 [0.7-1.7]	
	5-Year	51 (15)/ 207 (19)/ 409 (16)/ 414 (19)	1.3 [0.9-1.8]	
	Patients without PPCs			
	30-Day	10 (3.0)/ 36 (3.4)/ 79 (3.5)/ 65 (3.4)	1.2 [0.6-2.4]	
	1-Year	24 (7.1)/ 85 (8.1)/ 158 (6.9)/ 137 (7.2)	1.2 [0.7-1.8]	
	5-Year	49 (15)/ 200 (19)/ 374 (16)/ 364 (19)	1.4 [0.9-1.9]	
	Patients with PPCs	-		
	30-Day	1 (7.1)/ 0 (0.0)/ 7 (3.4)/ 11 (3.8)	_	
	1-Year	2 (14.3)/ 3 (4.3)/ 15 (7.2)/ 25 (8.6)	0.3 [0.0-1.7]	
	5-Year	2 (14)/ 7 (10)/ 35 (17)/ 50 (17)	0.6 [0.1-2.8]	
Patients without iXFN	All Patients			
	30-Day	9 (2.8)/ 30 (3.2)/ 65 (3.3)/ 55 (3.4)	1.1 [0.5-2.4]	
	1-Year	22 (6.9)/ 71 (7.5)/ 127 (6.4)/ 116 (7.3)	1.1 [0.7-1.8]	
	5-Year	42 (13)/ 174 (18)/ 315 (16)/ 301 (19)	**1.4 [1.1-2.0]**	
	Patients without PPCs			
	30-Day	9 (2.9)/ 30 (3.3)/ 61 (3.3)/ 52 (3.5)	1.1 [0.5-2.4]	
	1-Year	21 (6.8)/ 69 (7.7)/ 120 (6.5)/ 108 (7.4)	1.1 [0.7-1.8]	

	5-Year	41 (13)/ 169 (19)/ 299 (16)/ 282 (19)	**1.5 [1.1-2.1]**
	Patients with PPCs		
	30-Day	0 (0.0)/ 0 (0.0)/ 4 (3.2)/ 3 (2.3)	1.0 [0.0-NA]
	1-Year	1 (12.5)/ 2 (4.3)/ 7 (5.6)/ 8 (6.2)	0.3 [0.0-3.6]
	5-Year	1 (13)/ 5 (11)/ 16 (13)/ 19 (15)	0.6 [0.1-5.4]
Patients with iXFN	All Patients		
	30-Day	2 (5.7)/ 6 (3.5)/ 21 (4.1)/ 21 (3.5)	0.6 [0.1-3.0]
	1-Year	4 (11)/ 17 (10)/ 46 (8.9)/ 46 (7.7)	0.9 [0.3-2.6]
	5-Year	9 (26)/ 33 (19)/ 94 (18)/ 113 (19)	0.7 [0.4-1.5]
	Patients without PPCs		
	30-Day	1 (3.4)/ 6 (4.1)/ 18 (4.2)/ 13 (3.0)	1.2 [0.1-10.0]
	1-Year	3 (10)/ 16 (11)/ 38 (8.8)/ 29 (6.7)	1.1 [0.3-3.7]
	5-Year	8 (28)/ 31 (21)/ 75 (17)/ 82 (1.9)	0.7 [0.3-1.6]
	Patients with PPCs		
	30-Day	1 (16.7)/ 0 (0.0)/ 3 (3.6)/ 8 (4.9)	1.2 [0.1-10.0]
	1-Year	1 (17)/ 1 (4.2)/ 8 (9.5)/ 17 (11)	1.1 [0.3-3.7]
	5-Year	2 14)/ 7(10)/ 35 (17)/ 50 (17)	0.7 [0.3-1.6]

Table 12. Combined iXFN and CPB use effect unadjusted and adjusted hazard ratios for 30-Day, 1-Year and 5-year all-cause mortality for all study cohort and for sub-cohorts of patients with and without PPCs

		no (%)	UHR [95% CI]	AHR [95% CI]	
All Patients					
30-Day		9 (2.8)	1	1	
1-Year		22 (6.9)	1	1	
5-Year		42 (13)	1	1	
Patients without PPCs	**No iXFN &**				**iXFN &**
30-Day	**Off Pump**	9 (2.9)	1	1	**Off Pump/**
1-Year	**(Reference**	21 (6.8)	1	1	**No iXFN &**
5-Year	**Category)**	41 (13)	1	1	**Off Pump**
Patients with PPCs					
30-Day		0 (0.0)	1	1	
1-Year		1 (13)	1	1	
5-Year		1 (13)	1	1	
All Patients	**No iXFN &**				**iXFN & 1-**
30-Day	**1-59 mins/**	30 (3.2)	1.1 [0.5-2.4]	1.1 [0.5-2.3]	**59 mins/**

1-Year	**No iXFN & Off Pump**	71 (7.5)	1.1 [0.7-1.8]	1.1 [0.7-1.8]	**No iXFN & Off Pump**
5-Year		174 (18)	**1.4 [1.1-2.0]**	1.5 [1.0 - 2.1]	
Patients without PPCs					
30-Day		30 (3.3)	1.1 [0.5-2.4]	1.2 [0.5-2.6]	
1-Year		69 (7.7)	1.1 [0.7-1.8]	1.2 [0.7-2.0]	
5-Year		169 (19)	**1.5 [1.1-2.1]**	**1.5 [1.1-2.2]**	
Patients with PPCs					
30-Day		0 (0.0)	1.0 [0.0-NA]	0.3 [0.0-NA]	
1-Year		2 (4.3)	0.3 [0.0-3.7]	0.2 [0.0-2.6]	
5-Year		5 (11)	0.6 [0.1-5.5]	0.3 [0.0-3.1]	
All Patients					
30-Day		65 (3.3)	1.2 [0.6-2.3]	1.4 [0.6-3.0]	
1-Year		127 (6.4)	0.9 [0.6-1.5]	0.9 [0.5-1.4]	
5-Year		315 (16)	1.2 [0.9-1.7]	1.3 [0.9-1.8]	
Patients without PPCs	**No iXFN & 60-119 mins/ No iXFN & Off Pump**				**iXFN & 1-119 mins/ No iXFN & Off Pump**
30-Day		61 (3.3)	1.1 [0.6-2.3]	1.4 [0.6-3.1]	
1-Year		120 (6.5)	1.0 [0.6-1.5]	0.9 [0.5-1.6]	
5-Year		299 (16)	1.2 [0.9-1.7]	1.3 [0.9-1.9]	
Patients with PPCs					
30-Day		4 (3.2)			
1-Year		7 (5.6)	0.4 [0.1-3.6]	0.2 [0.0-1.6]	
5-Year		16 (13)	0.8 [0.1-6.1]	0.4 [0.0-3.2]	

All Patients					
30-Day		55 (3.4)	1.2 [0.6-2.5]	1.5 [0.7-3.4]	
1-Year		116 (7.3)	1.0 [0.7-1.7]	1.0 [0.6-1.7]	
5-Year		301 (18)	**1.5 [1.1-2.0]**	**1.5 [1.1-2.3]**	
Patients without PPCs	**No iXFN &**				**iXFN & >**
30-Day	**> 120 mins/**	52 (3.5)	1.2 [0.6-2.5]	1.6 [0.7-3.7]	**120 mins/**
1-Year	**No iXFN &**	108 (7.4)	1.1 [0.7-1.7]	1.0 [0.6-1.9]	**No iXFN &**
5-Year	**Off Pump**	282 (19)	**1.5 [1.1-2.1]**	**1.6 [1.1-2.4]**	**Off Pump**
Patients with PPCs					
30-Day		3 (2.3)	_	_	
1-Year		8 (6.2)	0.5 [0.1-3.9]	0.2 [0.0-1.6]	
5-Year		19 (15)	0.9 [0.1-6.9]	0.4 [0.0-3.4]	

Table 13. Comparison of 30-Day, 1-Year and 5-Year mortality between patients with PPCs and cPPCs

		No PPC (5568)	PPC (583)	p-Value	No Critical P (n=5,861)
Mortality Rates	**30-D**	190 (3.4%)	19 (3.3%)	0.846	196 (3.3%
	1-Year	404 (7.3%)	45 (7.7%)	0.683	429 (7.3%
	5-Year	987 (18%)	94 (16%)	0.333	1040 (18%
UHR PPC/ No PPC	**30-D**	1.0 [0.6-1.5]			
	1-Year	1.1 [0.8-1.5]			
	5-Year	1.1 [0.9-1.4]			
AHR PPC/ No PPC	**30-D**	0.9 [0.5-1.5]			
	1-Year	1.0 [0.7-1.4]			
	5-Year	1.1 [0.9-1.3]			

Table 14. Intraoperative transfusion effect of unadjusted and risk adjusted odds ratios estimated for de

	All Patients (N=6,151)	
PPCs	**UOR$_{iXFN/\ No\ iXFN}$ [95% CI]**	**AOR$_{iXFN/\ No}$**
Any PPC	**3.9 [3.3-4.7]**	**2.7 [2**
Pulmonary Edema	**3.3 [2.3-4.6]**	**2.4 [1**
ARDS	**3.5 [2.0-5.9]**	**2.8 [1**
PMV	**4.1 [3.3-4.9]**	**2.7 [2**
Reintubation	**3.4 [2.5-4.6]**	**2.3 [1**
Pneumonia	**3.6 [2.6-5.1]**	**2.4 [1**
PE	**3.3 [1.3-8.2]**	2.6 [0

†Indicates statistically significant p-value. UHR: Unadjusted Hazard Ratio, AHR: Adjusted Hazard Ratio, CI: Confidence I

ventilation, PE: pulmonary embolism

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Adelborg, K., et al. (2017). "Thirty-Year Mortality After Coronary Artery Bypass Graft Surgery: A Danish Nationwide Population-Based Cohort Study." Circ Cardiovasc Qual Outcomes **10**(5): e002708.

BACKGROUND: Data are sparse on long-term mortality after coronary artery bypass graft (CABG) surgery. We examined short-term and long-term mortality of patients undergoing CABG surgery and a general population comparison cohort. METHODS AND RESULTS: Linking data from Danish registries, we conducted a nationwide, population-based cohort study on 51 307 CABG patients and 513 070 individuals from the general population matched on age, sex, and calendar year (1980-2009). The mortality risk was higher in patients having isolated CABG surgery than in the general population, particularly during 0 to 30 days (3.2% versus 0.2%), 11 to 20 years (51.1% versus 35.6%), and 21 to 30 years (62.4% versus 44.8%), but not substantially higher during 31 to 364 days (2.9% versus 2.4%) or 1 to 10 years (30.7% versus 25.8%). The 30-day adjusted mortality rate ratio for isolated CABG surgery was 13.51 (95% confidence interval [CI], 12.59-14.49). Between 31 to 364 days and 1 to 10 years, the isolated CABG surgery cohort had a slightly higher mortality rate than the general population comparison cohort, adjusted mortality rate ratios of 1.15 (95% CI, 1.09-1.21) and 1.09 (95% CI, 1.08-1.11), respectively. Between 11 to

20 years and 21 to 30 years, the adjusted mortality rate ratios were 1.62 (95% CI, 1.58-1.66) and 1.76 (95% CI, 1.62-1.91). Within 30 days, CABG patients had a 25-fold, a 26-fold, and a 18-fold higher risk of dying from myocardial infarction, heart failure, or stroke, respectively, than members of the general population comparison cohort. We found substantial heterogeneity in absolute mortality rates according to baseline risk groups. CONCLUSIONS: The isolated CABG cohort had a higher mortality rate than the general population comparison cohort, especially within 30 days of and 10 years after surgery.

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> Many adverse events associated with the transfusion of allogeneic blood products have been shown to be related to the presence of allogeneic leukocytes in the blood product transfused. Until recently little attention has been paid to the leukocytes present in various blood components, however, over the past two decades it has been shown that the removal of such "passenger" leukocytes is

associated with improved clinical outcomes. These include: the reduction in the incidence and severity of febrile transfusion reactions; reducing the CMV transfusion transmission risk; reducing the risk of alloimmune platelet refractoriness; the possible avoidance of vCJD transmission; as well as reducing the risk of mortality and organ dysfunction in cardiac surgery patients, and possibly in other categories of patients.

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Complement activation is believed to be of importance in the development of complications arising after cardiopulmonary bypass. The effect on complement activation of priming the extracorporeal circuit with crystalloid alone, crystalloid plus albumin, or crystalloid plus the plasma expander polygeline was assessed in 36 patients undergoing coronary artery operations with cardiopulmonary bypass using a bubble oxygenator. Activation of the alternative and common complement pathways was monitored before, during, and after the bypass period by measuring concentrations of factor B and its fragment Ba and C3 and its

fragment C3d. Complement activation occurred in all three groups of patients, with no difference between the crystalloid and crystalloid-albumin groups. In contrast, Ba fragment concentrations were persistently and significantly lower during and after bypass in the polygeline group, denoting reduced complement activation. C3d levels also showed a tendency to be lower in this group. Our results indicate that addition of polygeline to the priming solution reduces complement activation. Because complement activation is associated with morbidity after cardiopulmonary bypass, addition of polygeline to the priming solution may offer an inexpensive method of reducing morbidity after cardiopulmonary bypass.

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The influence of four different membrane oxygenators (HF 4000, BOS-CM 50, CML 2, Maxima) on leucocyte count, concentrations of PMN-elastase, clotting factor XII, AT-III, C1-INH, alpha 2-antiplasmin and C3a was registered before, during and after CPB with pulsatile and nonpulsatile flow in 80 male patients aged between 36 and 67 years. With all systems tested, there was a drop in the concentrations of clotting factor XII, AT-III, C1-INH and alpha 2-antiplasmin in the early extracorporeal circulation (ECC) phase, exceeding the average hematocrit reduction accounted for by dilution. This drop was the least distinct with CML 2 systems, both with pulsatile and nonpulsatile perfusion, indicating system-inherent influences. Leucocyte cound and PMN-elastase concentration rose significantly during ECC irrespective of oxygenator tested of flow type applied. The rise in leucocyte count even continued for about 4 h after ECC. During the first 40 min of ECC, these changes were paralleled by a significant rise in C3a concentration, suggesting complement activation as a main cause for PMN activation. However, there is reason to suppose involvement of further mechanisms operating in PMN activation, since the elevated C3a-concentrations

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The present study investigated the influence of pulsatile or nonpulsatile flow delivery with a centrifugal pump for cardiopulmonary bypass (CPB) during coronary artery bypass grafting (CABG) in two randomized groups of 19 patients each. All patients received a standard anaesthetic and surgical protocol. Pulsatile perfusion during CPB was created by accelerating the baseline pump speed of the Sarns centrifugal pump at a rate of 50 cycles per minute. Measurements included perioperative systemic haemodynamics and oxygen exchange, total haemolytic complement (CH50), polymorphonuclear (neutrophil) granulocyte (PMN) count and plasma granulocyte elastase bound to alpha 1-proteinase inhibitor (E-alpha 1-PI). Laboratory measurements were corrected for haemodilution. During and after CPB there were only a few significant differences between the groups in systemic haemodynamics and oxygenation, i.e. a lower mean arterial blood pressure after the end of CPB in the nonpulsatile group (65 mmHg, SD = 11 vs 76 mmHg, SD = 11) and a lower SvO2 during rewarming on CPB in the nonpulsatile group (62%, SD = 8 vs 67%, SD = 8). The decrease in percentage of PMNs in the total white blood cell count during CPB was greater in the nonpulsatile group than in the pulsatile group (from 61 to 46% vs 63 to 53% of prebypass value). The steep increase of PMN count at the end of CPB and postoperatively was comparable in both groups. The maximal decrease of CH50 levels, occurring after surgery, was significantly higher in the nonpulsatile group (70% SD = 15 vs 79%, SD = 16, of baseline value), suggesting a greater complement activation. E-alpha 1-PI

levels increased significantly in both groups during and after CPB with higher peak levels, obtained at one hour after admission to an intensive care unit, in the nonpulsatile group (316 micrograms/l, SD = 102) than in the pulsatile group (247 micrograms/l, SD = 106). There was a partly inverse correlation between the peak postoperative elastase levels and the PaO2/FiO2 ratios at the first postoperative morning. This ratio was significantly lower in the nonpulsatile group (211, SD = 56) than in the pulsatile group (247, SD = 62). Postoperative respiratory tract infection was more frequent in the nonpulsatile group (n = 9) than in the pulsatile group (n = 2). Adding a pulsatile component to centrifugal blood pumping during CPB may have benefits with regard to the possibly detrimental whole body inflammatory response to CPB. Further studies are warranted to investigate whether these differences will affect clinical outcome.

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A directive from the Food and Drug Administration indicates that the use of plasma protein fraction (PPF) is contraindicated during cardiopulmonary bypass because of possible hypotension. Bradykinin has been implicated as the cause of this hypotension. Bradykinin levels were measured by radioimmunoassay in PPF and in 5% albumin and were found to be consistently elevated in the former and occasionally in the latter. The addition of PPF to pump primes resulted in significantly elevated levels of bradykinin, which rapidly cleared, indicating that extrapulmonary sites of bradykinin inactivation were efficient. The potential hypotensive effect of PPF was observed by determining the change in mean perfusion pressure in two groups of patients: one group with a 3,000 ml crystalloid prime and the other with a prime of 2,000 ml of crystalloid and 1,000 ml of PPF. There was no significant difference in the perfusion pressure between the two groups at any point, and the hypotensive effects seen in both groups were readily treated, suggesting that the directive against the use of PPF during cardiopulmonary bypass may be unnecessarily restrictive.

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> We have assessed the efficacy of cardiopulmonary bypass (CPB) using normal colloid oncotic pressure (COP) in a randomized, controlled study of 20 patients undergoing elective coronary artery surgery using heparin-coated circuits. For CPB, we used either crystalloid priming 1650 ml (n = 10) or colloid priming 1650 ml (2.4% modified fluid gelatin, n = 10). While COP did not change during bypass in the colloid group, a decline was observed in the crystalloid group (P = 0.005). By the end of bypass, the decrease in COP compared with baseline (delta COP) was 8.5 (S.D. 1.1) mm Hg in the crystalloid group compared with 1.5 (2.1) mm Hg in the colloid group (P = 0.0001). delta COP correlated positively with fluid balance during bypass (r2 = 0.41, P = 0.002). Similar increments in complement factors C3b/c and C4b/c, tumour necrosis factor-alpha and neutrophil elastase, but not endotoxins, were found in both groups as indicators of a systemic inflammatory response. A clinical

performance score composed of fluid balance, postoperative duration of intubation and the difference between rectal temperature and skin temperature was more favourable in patients treated with colloid priming (P = 0.03). Median postoperative hospital stay was 7 (range 5-16) days in the crystalloid group compared with 5 (4-8) days in the colloid group (P = 0.016). Regression analysis indicated that CPB time, fluid balance during operation and postoperative PO2/FlO2 ratio were independent factors that predicted postoperative hospital stay. From these preliminary results we conclude that in the absence of endotoxaemia, use of a normal COP during CPB with modified fluid gelatin in heparin-coated circuits resulted in an improved postoperative course an a reduction in hospital stay.

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In patients with coronary artery disease, infusion of very cold cardioplegic solutions at elevated pressures may facilitate homogeneous cooling and cardioplegia. This study was designed to determine if very high infusion pressures or very low temperatures of the cardioplegic solution damages normal myocardium. In a hemodynamically controlled canine right heart bypass preparation, a crystalloid solution (Plasma-Lyte 148 with 30 mEq/L potassium chloride, 0 degree to 2 degrees C) was infused with separate control of the infusion pressures in the left anterior descending and circumflex arteries. A sonomicrometer measured regional myocardial function in each area. During a 100 minute arrest period, cardioplegic solution was reinfused every 20 minutes and reduced myocardial temperatures to an average of 9.4 degrees +/- 2.2 degrees C. In a comparison of infusion pressures of 50 versus 100 mm Hg and 100 versus 150 mm Hg, postarrest regional myocardial function was unchanged from prearrest. However, in a comparison of infusion pressures of 150 to 200 mm Hg, a significant fall in regional myocardial function was noted with the higher pressures (106% and 64% recovery, respectively, p less than 0.02, n = 6). Excluding the areas perfused at 200 mm Hg, comparison of regions cooled to less than 8 degrees C and to greater than 8 degrees C demonstrated no difference in recovery of regional myocardial function. In this study, elevation of cardioplegic infusion pressures to 150 mm Hg and lowering of myocardial temperatures to less than 8 degrees C caused no impairment of regional myocardial function.

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BACKGROUND: This prospective study was intended to determine in a homogeneous population of children whether hemofiltration, performed during cardiopulmonary bypass rewarming, is able to improve hemodynamics and biologic hemostasis variables, to reduce postoperative blood loss, time to extubation, and plasma cytokines, and complement fragments. METHODS: Thirty-two children undergoing surgical correction of tetralogy of Fallot were randomly assigned to a hemofiltration or control group. Hemofiltration was performed with a polysulphone hemofilter during rewarming of cardiopulmonary bypass. Plasma clotting factors, D-dimers, antithrombin-III, complement fragments C3a and C5a, interleukin-1 beta, interleukin-6, interleukin-8, and tumor necrosis factor-alpha were measured before and after hemofiltration. Systemic mean arterial pressure, left atrial pressure, time to extubation, and postoperative blood loss were monitored. RESULTS: In the hemofiltration group, significant reductions in 24-h blood loss (250 (176-356) vs. 319 (182-500) ml/m2, median (minimum-maximum), time to extubation (15 (9-22) vs. 19 (11-24) h), plasma concentrations of C3a, C5a, interleukin-6, and tumor necrosis factor-alpha were observed compared to control. Arterial oxygen

tension on admission to the intensive care unit was significantly greater in the hemofiltration group (136 +/- 20 vs. 103 +/- 25 mmHg, mean +/- SD). Significant increases in mean arterial pressure, clotting factors, and antithrombin-III were noted for the hemofiltration group. No intergroup difference was observed in left atrial pressure, platelets count, D-dimers, interleukin-8, and duration of stay in the intensive care unit. CONCLUSIONS: Hemofiltration during cardiopulmonary bypass in children improves hemodynamics and early postoperative oxygenation and reduces postoperative blood loss and duration of mechanical ventilation. Hemofiltration is able to remove some major mediators of the inflammatory response.

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BACKGROUND: In this retrospective study, we have examined the incidence and the predictors of ARDS (adult respiratory distress syndrome), in patients undergoing coronary artery bypass (CABG) surgery on cardiopulmonary bypass (CPB). The prophylactic and therapeutic measures that were used in this series were also evaluated. METHODS: Between January 1988 and January 1995, 4318 consecutive patients undergoing an isolated and a primary CABG procedure were included. Patients with poor left ventricular function, congestive heart failure (CHF), renal failure and with an abnormal chest radiogram were excluded. RESULTS: The independent predictors of ARDS were: recent cigarette smoking, advanced COPD (chronic obstructive pulmonary disease) and emergency surgery. The overall incidence of ARDS was 2.5% and hospital mortality in patients with an established ARDS was 27.7% (30/108). The prophylactic and the therapeutic measures which have been used in this series had no significant impact on the incidence and hospital mortality. CONCLUSIONS: In view of a high perioperative mortality in patients with established ARDS, a mandate for a regular use of prophylactic and therapeutic measures that are based on its pathophysiology, clearly exists.

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BACKGROUND: Severe lung injury with the development of acute respiratory distress syndrome (ARDS) is a serious complication of cardiac surgery. The aim of this study was to determine the incidence, risk factors, and mortality of ARDS following cardiac surgery. METHODS: We retrospectively analyze data in the period between January 2005 and March 2013. RESULTS: Of 6069 patients who underwent cardiac surgery during the study period, 37 patients developed ARDS during the postoperative period. The incidence of ARDS was 0.61%, with a mortality of 40.5% (15 patients). Multivariate regression analysis identified previous cardiac surgery, complex cardiac surgery, and more than three transfusions with packed red blood cells (PRBC) were independent predictors for developing ARDS. CONCLUSIONS: ARDS remains a serious, but very rare complication associated with significant mortality. In our study, previous cardiac surgery, complex cardiac surgery, and more than three

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> Fifteen episodes of the adult respiratory distress syndrome occurred in 14 patients after cardiopulmonary bypass. The clinical course was characterized by tachypnea, hyperventilation, and progressive hypoxemia developing postoperatively after a symptom-free period. Recovery occurred after institution of respiratory support and administration of steroids, diuretics, and antibiotics. There were no deaths. Prolonged cardiopulmonary bypass time, a history of heavy cigarette smoking, and a tendency to develop cardiocirculatory failure postoperatively was present more frequently in these patients as compared to a control group of ten who experienced an uneventful recovery. Early recognition of the adult respiratory distress syndrome by serial monitoring of arterial blood gases and aggressive management of hypoxemia and bronchopulmonary infections are thought to be important factors in survival.

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> Multiorgan dysfunction still occurs after cardiopulmonary bypass and remains a major cause of morbidity and mortality, especially in the pediatric age group. This is consequent upon the so-called systemic inflammatory response to bypass with an increase in inflammatory mediators. Hemofiltration may be able to attenuate the effects of this response by elimination of some or all of these mediators. We undertook a prospective, randomized study to investigate the effect of hemofiltration on plasma levels of the cytokines tumor necrosis factor alpha, interleukin-8, and interleukin 6 in 18 infants and children undergoing deep hypothermic bypass. Serial plasma samples were taken before, during, and after bypass. Assay of the plasma samples revealed presence of the cytokines in a number of subjects in both groups, in some cases before operation. There were significant reductions in levels of tumor necrosis factor after hemofiltration, with

no reduction noted in the group not undergoing hemofiltration. A similar difference ($p < 0.05$) was detected in the levels of interleukin-6 between the two groups after bypass, although this was largely due to changes in 2 subjects. Interleukin-8 was detected in a small number of subjects insufficient for statistical analysis, but with higher values in the group undergoing hemofiltration. We conclude that hemofiltration has the potential to remove cytokines from the circulation, with consequent beneficial effects.

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BACKGROUND: The inflammatory response induced by cardiopulmonary bypass can result in severe organ dysfunction in some patients. This postperfusion response is caused mainly by contact between blood and the foreign surface of the cardiopulmonary bypass equipment and includes adhesion of leukocytes to vascular endothelium, which precedes a series of events that mediate inflammatory damage to tissues. METHODS: Low-risk patients

accepted for coronary artery bypass grafting were randomized to operation with the cardiopulmonary bypass surface either completely heparin coated (Duraflo II) or uncoated. There were 12 patients in each group. Blood plasma sampled during cardiopulmonary bypass was analyzed for complement activation (C3bc and terminal SC5b-9 complement complex) and neutrophil activation (lactoferrin and myeloperoxidase). In addition, neutrophils, monocytes, and platelets were counted, and the expression of surface markers on the neutrophils and monocytes (complement receptor [CR] 1, CR3, CR4, and L-selectin) and on the platelets (P-selectin and CD41) was quantified with flow cytometry. RESULTS: Clinical and surgical results were similar in both groups. In the group with the heparin-coated surface, the formation of the terminal SC5b-9 complement complex was significantly reduced, and the counts of circulating leukocytes and platelets were significantly less reduced initially but were higher at the end of cardiopulmonary bypass compared with baseline. Also, the expression of CR1, CR3, and CR4 was significantly less upregulated and the L-selectin, significantly less downregulated on monocytes and neutrophils. CONCLUSIONS: We conclude that heparin coating reduces complement activation and attenuates the leukocyte integrin and selectin response that occurs when uncoated circuits are used.

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> Thousands of coronary bypass operations are performed in Canada each year. Some result in longer life or improved quality of life by reducing angina, but others do not. Where the potential benefit is unknown, physicians must consider the patient's work, home life, and personality. Clinical intuition is still needed to determine which patients will benefit.

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Two hundred fifty intubated patients were followed during the first 48 h after intubation in order to identify potential risk factors for developing pneumonia within this period. Thirty-two developed pneumonia during this time. Univariate analysis established that large volume aspiration, presence of sedation, intubation caused by respiratory/cardiac arrest or decrease in the level of consciousness, emergency procedure, cardiopulmonary resuscitation (CPR), and Glasgow coma score < 9 were significantly associated with pneumonia. In contrast, prior infection and prior antimicrobial use were associated with a protective effect. Presence of subglottic secretion drainage and 15 other variables had no significant effect. Multivariate analysis selected CPR (odds ratio [OR] = 5.13, 95% confidence intervals [CI] = 2.14, 12.26) and continuous sedation (OR = 4.40, 95% CI = 1.83, 10.59) as significant risk factors for pneumonia, while antibiotic use (OR = 0.29, 95% CI = 0.12, 0.69) showed a protective effect. Our findings emphasize that risk factors for pneumonia change during the intubation period, and preventing pneumonia requires a combined approach.

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BACKGROUND: Women have higher mortality rates after coronary artery bypass graft (CABG) surgery compared with men. Explanations for this sex difference are controversial. The objective of this study was to assess whether infection contributes to the increased risk of mortality in women. METHODS: We conducted a cohort study of 9218 Michigan Medicare beneficiaries hospitalized for CABG surgery. The prevalence of infection at any site during hospitalization was determined. Patients were followed up for 100 days after surgery to assess vital status. Analyses were conducted using proportional hazards regression and population attributable risk. RESULTS: Women hospitalized for CABG surgery were more likely to have an infection than men (16.1% vs 9.8%, P<.001), regardless of age, race, type of admission, hospital volume, or presence of comorbidities. Infections of the respiratory tract, urinary tract, digestive tract, and skin and subcutaneous tissue were more common in women than in men. The risk of death in men increased 3-fold with infection, whereas the risk in women increased 1.8-fold. The interaction between infection and sex on mortality was significant after adjusting for age, type of admission, and presence of comorbidities (P = .008). The unadjusted percentage of deaths attributable to female sex was 13.9%, which decreased to 0.3% when adjusted for infection. Of the excess deaths in women, 96% could be accounted for by the differential distribution of infection between the sexes. CONCLUSION: The

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AIMS: To determine whether a restrictive strategy of red blood cell (RBC) transfusion at lower haemoglobin concentrations is inferior to a liberal strategy of RBC transfusion at higher haemoglobin concentrations in patients undergoing cardiac surgery. METHODS AND RESULTS: We conducted a systematic

review, meta-analysis, and trial sequential analysis of randomized controlled trials of the effect of restrictive and liberal RBC transfusion strategies on mortality within 30 days of surgery as the primary outcome. Secondary outcomes were those potentially resulting from anaemia-induced tissue hypoxia and transfusion outcomes. We searched the electronic databases MEDLINE, EMBASE, and the Cochrane Library until 17 November 2017. Thirteen trials were included. The risk ratio (RR) of mortality derived from 4545 patients assigned to a restrictive strategy when compared with 4547 transfused according to a liberal strategy was 0.96 [95% confidence interval (CI) 0.76-1.21, I2 = 0]. A restrictive strategy did not have a statistically significant effect on the risk of myocardial infarction (RR 1.01, 95% CI 0.81-1.26; I2=0), stroke (RR 0.93, 95% CI 0.68-1.27, I2 = 0), renal failure (RR 0.96, 95% CI 0.76-1.20, I2 = 0), or infection (RR 1.12, 95% CI 0.98-1.29, I2 = 0). Subgroup analysis of adult and paediatric trials did not show a significant interaction. At approximately 70% of the critical information size, the meta-analysis of mortality crossed the futility boundary for inferiority of the restrictive strategy. CONCLUSION: The current evidence does not support the notion that restrictive RBC transfusion strategies are inferior to liberal RBC strategies in patients undergoing cardiac surgery.

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Complement activation after cardiopulmonary bypass is correlated with postoperative organ dysfunction. Heparin coating of the entire blood-contact surface of the cardiopulmonary bypass circuit has proved to reduce complement activation in vitro. A membrane oxygenator and tubing setup coated with functionally active heparin was compared with an uncoated, otherwise identical setup in 20 patients undergoing routine coronary bypass operations. The concentrations of C3 activation products and the terminal complement complex were measured in sensitive and specific enzyme immunoassays. Peak concentrations of C3 activation products were 90.1 (74.7 to 107.4) AU/ml (medians and 95% confidence intervals) and 52.4 (35.7 to 76.4) AU/ml with the uncoated and coated setups, respectively (p = 0.02). The corresponding concentrations of the terminal complement complex were 26.2 (20.1 to 37.5) AU/ml and 13.7 (11.1 to 25.1) AU/ml (p = 0.03). Blood loss from the mediastinal drains during the first 12 postoperative hours was 533 (416 to 975) ml in patients treated with the uncoated setup and 388 (313 to 579) ml in the coated treatment group (p = 0.06) and was significantly correlated with peak

concentrations of the terminal complement complex (p = 0.01). There were no differences in neutrophil counts nor platelet numbers between the treatment groups. The approximate 45% reduction in complement activation with the heparin-coated cardiopulmonary bypass device indicates a substantial improvement of biocompatibility.

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> Postoperative pulmonary complications are the most frequent and significant contributor to morbidity, mortality, and costs associated with hospitalization. Interestingly, despite the prevalence of these complications in cardiac surgical patients, recognition, diagnosis, and management of this problem vary widely. In addition, little information is available on the continuum between routine postoperative pulmonary dysfunction and postoperative pulmonary complications. The course of events from pulmonary dysfunction associated

with surgery to discharge from the hospital in cardiac patients is largely unexplored. In the absence of evidence-based practice guidelines for the care of cardiac surgical patients with postoperative pulmonary dysfunction, an understanding of the pathophysiological basis of the development of postoperative pulmonary complications is fundamental to enable clinicians to assess the value of current management interventions. Previous research on postoperative pulmonary dysfunction in adults undergoing cardiac surgery is reviewed, with an emphasis on the pathogenesis of this problem, implications for clinical nursing practice, and possibilities for future research.

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BACKGROUND: We previously reported that transfusion of 1 to 2 units of red blood cells (RBCs) confers a 16% increased hazard of late death after cardiac surgical treatment. We explored whether a similar effect existed among octogenarians. METHODS: We enrolled 17,026 consecutive adult patients undergoing cardiac operations from 2001 to 2008 in northern New England. Patients receiving more than 2 units of RBCs or undergoing emergency operations were excluded. Early (to 6 months) and late (to 3 years, among those surviving longer than 6 months) survival was confirmed using the Social Security Death Index. We estimated the relationship between RBCs and survival, and any interaction by age (<80 years versus ≥80 years) or procedure. We calculated the adjusted hazard ratio (HR), and plotted adjusted survival curves. RESULTS: Patients receiving RBCs had more comorbidities irrespective of age. Patients 80 years of age or older underwent transfusion more often than patients younger than 80 years (51% versus 30%; p<0.001). There was no evidence of an interaction by age or procedure (p>0.05). Among patients younger than 80 years, RBCs significantly increased a patient's risk of early death [HR, 2.03; 95% confidence interval [CI], 1.47, 2.80] but not late death 1.21 (95%CI, 0.88, 1.67). RBCs did not increase the risk of early [HR, 1.47; 95% CI, 0.84, 2.56] or late (HR, 0.92 95% CI, 0.50, 1.69) death in patients 80 years or older. CONCLUSIONS: Octogenarians receive RBCs more often than do younger patients. Although transfusion of 1 to 2 units of RBCs increases the risk of early death in patients younger than 80 years, this effect was not present

among octogenarians. There was no significant effect of RBCs in late death in either age group.