Comparative Analysis of Coronary Artery Bypass: Costs of Off-Pump vs. Conventional Techniques with Variable Bonded Circuits and Drug Strategies

Michael M. Wyckoff

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COMPARATIVE ANALYSIS OF CORONARY ARTERY BYPASS
COSTS OF OFF-PUMP VS. CONVENTIONAL TECHNIQUES
WITH VARIABLE Bypass CIRCUITS AND
DRUG STRATEGIES (LABCOS)
NAME OF STUDENT: Michael M. Wyckoff, RN, BSN, CCP

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DATE OF COMPLETION: Summer 2004

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Comparative Analysis of Coronary Artery Bypass: Costs of Off-Pump vs. Conventional Techniques with Variable Bonded Circuits and Drug Strategies (CABOCS)

By

Michael M. Wyckoff

A Thesis

Submitted in fulfillment of the requirements in the course NRSG 685. Thesis
In the School of Nursing, in the Graduate School, Southern Adventist University, Collegedale, Tennessee Summer, 2004
NAME OF STUDENT: Michael M. Wyckoff, RN, BSN, CCP
CHAIRPERSON: David Gerstle, PhD, RN
TITLE: Comparative Analysis of Coronary Artery Bypass: Costs of Off-Pump vs. Conventional Techniques with Variable Bonded Circuits and Drug Strategies (CABOCS)

ABSTRACT

As baby boomers age, estimated to reach 78.8 million Americans over the age of 65 by 2050, their health care costs are skyrocketing. Increased costs in coronary artery bypass surgery have been linked to length of stay (LOS), the inflammatory response, and blood loss related to conventional coronary artery bypass (C-CAB).

Off-pump coronary artery bypass (OPCAB) has become a popular alternative to C-CAB. Utilizing proximal connector devices has truly made this option “clampless.” If detrimental outcomes can be linked to cross clamping, the use of cardiopulmonary bypass (CPB) may diminish. When the use of CPB is necessary, there are a number of circuit coatings available, along with drugs like Aprotinin, to decrease the inflammatory response, and Amicar, to decrease the amount of blood loss, all due to the exposure of the body to CPB. This study compares the cost and LOS involved with OPCAB vs. C-CAB, including a comparison of the inflammatory response and blood loss with each drug regime and circuit coating used.

Analysis of the data revealed no significant difference in several cost areas. The total
operating room (O.R.) costs showed that the C-CAB with Aprotinin group’s mean cost was $8559.13 (statistical difference [SD] of $1056.61; 95% confidence interval [CI] was reported as $8164.58 for lower bound and $8953.67 for the upper bound). The C-CAB with Amicar group’s mean cost was $9096.40 (SD of $1859.16; 95% CI was reported as $8402.17 for lower bound and $9790.62 for upper bound). The OPCAB group’s mean cost was reported as $8442.86 (SD of $1482.63; 95% CI was reported as $7621.81 for lower bound and $9263.92 for upper bound).

The O.R. supply costs showed that the C-CAB with Aprotinin group’s mean cost was $3889.66 (SD of $685.91; 95% CI was reported as $3633.54 for the lower bound and $4145.79 for the upper bound). The C-CAB with Amicar group’s mean cost was $3934.30 (SD of $1198.46; 95% CI was reported as $3486.78 for the lower bound and $4381.81 for the upper bound). The OPCAB group’s mean cost was $4014.13 (SD of $1084.77; 95% CI was reported as $3413.40 for the lower bound and $4614.86 for the upper bound).

The pharmacy costs showed that the C-CAB with Aprotinin group’s mean cost was $2553.76 (SD of $1305.61; 95% CI was reported as $2066.24 for the lower bound and $3041.29 for the upper bound). The C-CAB with Amicar group’s mean cost was $2654.33 (SD of $3502.66; 95% CI was reported as $1346.41 for the lower bound and $3962.25 for the upper bound). The OPCAB group’s cost was reported as a mean of $1710.93 (SD of $1147.01; 95% CI was reported as $1075.73 for the lower bound and $2346.13 for the upper bound).
ACKNOWLEDGMENTS

The first accolades of appreciation need to be extended the sample population that graciously allowed this research to be conducted. The facility at which the research took place is not considered a teaching institution; therefore the population utilizing the services typically does not view it in this light.

Secondly, to all the staff, from the pre-op, perfusion, and SICU areas, that tolerated my unending determination for completion of the study, I applaud you.

My committee has provided unending support and valuable opinions along with advice. Dr. David Gerstle, your patience and good humor have encouraged me beyond what I can express and has lead to the completion of this project. Drs. Barbara James and Mary Ann Roberts, your thoughtful critique of my submissions have allowed this project to progress to completion and hopefully reflects a knowledge base that was greatly influenced by your input.

Finally, Dr. James Zellner, having the confidence to allow your reputation and "stamp of approval" to be associated with a "fledgling" researcher such as I, cannot be expressed in words that are fitting for the task.

All not specifically mentioned that were "behind the scenes", your unending support was greatly appreciated!
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<td>ANCOVA</td>
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<td>ANOVA</td>
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<tr>
<td>ARDS</td>
<td>Adult Respiratory Distress Syndrome</td>
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<tr>
<td>BIOLINE ®</td>
<td>Jostra Heparin Coating System</td>
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<td>BSA</td>
<td>Body Surface Area</td>
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<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Graft</td>
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<td>CPB</td>
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<td>CRYO</td>
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<tr>
<td>FDA</td>
<td>Food &amp; Drug Administration</td>
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<tr>
<td>FFP</td>
<td>Fresh Frozen Plasma</td>
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<tr>
<td>HBC</td>
<td>Heparin-bonded Circuits</td>
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<td>HCT</td>
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<td>HGB</td>
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<td>ICU</td>
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<td>IL</td>
<td>Interleukin</td>
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<td>IRB</td>
<td>Investigational Review Board</td>
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<tr>
<td>LAD</td>
<td>Left Anterior Descending Coronary Artery</td>
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<td>LIMA</td>
<td>Left Internal Mammary Artery</td>
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# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Term</th>
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<tbody>
<tr>
<td>LOS</td>
<td>Length of Stay</td>
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<tr>
<td>LVEDF</td>
<td>Left Ventricular End Diastolic Function</td>
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<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
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<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
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<td>MMP</td>
<td>Matrix Metalloproteinases</td>
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<tr>
<td>MODS</td>
<td>Multi-Organ Dysfunction Syndrome</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>OPCAB</td>
<td>Off-Pump Coronary Artery Bypass</td>
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<tr>
<td>OR</td>
<td>Operating Room</td>
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<tr>
<td>PEMA</td>
<td>Poly (2-methoxyethylacrylate)</td>
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<td>PLATS</td>
<td>Platelets</td>
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<td>PPS</td>
<td>Post-Pump Syndrome</td>
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<td>PRBC</td>
<td>Packed Red Blood Cells</td>
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<tr>
<td>RCA</td>
<td>Right Coronary Artery</td>
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<tr>
<td>ROL</td>
<td>Review of Literature</td>
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<tr>
<td>SAU</td>
<td>Southern Adventist University</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SEM</td>
<td>Standard Error of the Mean</td>
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<td>SIRS</td>
<td>Systemic Inflammatory Response Syndrome</td>
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<td>Abbreviation</td>
<td>Full Term</td>
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<tr>
<td>STS</td>
<td>Society of Thoracic Surgeons</td>
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<td>WBC</td>
<td>White Blood Cell</td>
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CHAPTER 1
INTRODUCTION

Every year millions of people in the United States are diagnosed with some form of coronary artery disease, one of the top five leading causes of death. Of these millions, approximately 516,000 required surgical intervention in 2001 (American Heart Association, 2001). Open-heart surgery is regarded as one of the most significant medical advances in the 20th century (Lillehei, 1993). During the past 10 years, dramatic changes have occurred in the management of cardiac surgery patients (Dzavik et al., 2001). With the introduction of decreased reimbursement to providers by insurance carriers, rapid recovery programs introduced the concept that "less might be better" (Ley, 2001). Shorter intubation times and lengths of stay (LOS) have been associated with improved outcomes (Ott, Gutfnger, Steedman, Tanner, & Hlapchich, 1999), including decreased respiratory, neurological complications and blood usage (Ascione et al., 1999).

Attention shifted to lesser incisions via minimally invasive cardiac surgery through multiple thoracotomy incisions, and thus port access cardiac surgery began. The knowledge of adverse inflammatory and neurological effects of CPB (Ascione et al., 2000; Edmunds, 1998), along with the possibility of reducing costs and LOS (Lancey, Soller & Vander Salm, 2000), led to the pursuit of using a "pump-less" technique thus making OPCAB procedures the current trend in cardiac surgical care. The ability of operating on a "beating" heart has been accomplished through the use of special stabilization devices, such as the Medtronic Octopus® retractor (Jansen et al., 1998).

The introduction of the St. Jude (St. Paul, MN) Symmetry® Bypass System Aortic Connector (Eckstein et al., 2001) has led to clamp-free revascularization. The
body's response to the bypass circuit has been addressed by the use of coating these circuits (Ranucci et al., 1999; Schiel et al., 2001; Wendel, Philipp, Weber, Birnbaum, & Ziemer, 2001). In addition, the use of drugs to reduce bleeding has improved clinical outcomes of C-CAB (Lemmer, et al., 1996; Harmon, 1996).

The healthcare costs associated with the upcoming care of the “baby-boomers” are staggering and need to be addressed (Lee, Abdelhady, & Capdeville, 2000). If using the OPCAB technique, while maintaining acceptable patient outcomes, significantly reduces costs, then this arena of care needs continued investigation. As expected, newly available advanced technologies usually come with a staggering price tag. This factor may eventually render the OPCAB to be more expensive with no discernable difference in clinical outcomes, and therefore offers no advantage. By utilizing circuit coatings and differing drug regimes, in the presence of C-CAB, the possibility of maintaining effective cost and outcomes may be a possibility. Evidence is now needed in guiding the medical and healthcare community in making informed decisions based on the multiple variables involved with these new options for the care of the cardiac surgical patient.

Statement of Problem

Recent emphasis on cost containment in healthcare has focused attention on the economics of all medical procedures. Selections for the appropriate treatment of coronary artery disease are of increasing concern (Ryan, Carrier, Nugent, Mora Mangano & Magovern, 2000). Cost reduction with improved patient outcomes for C-CAB is reported to be possible through several strategies. Collaboration between healthcare providers involved in cardiac care and improved case management strategies, early
extubation, reduced intensive care unit (ICU) LOS and attempting OPCAB techniques may reduce the overall costs.

Ethically, cost containment should not be the only consideration (Bull et al., 2001). With over 1414 open-heart surgeries performed every day (American Heart Association, 2001), outcomes including morbidity, mortality, and quality must not be forgotten. Patients are the payers and deserve the satisfaction knowing that the quality of their care, rather than the cost, is the driving force (Arom et al., 2000). However, the major determinant of costs in C-CAB still remain the variable and fixed direct costs of disposable supplies, drugs and care, especially in the presence of post-operative complications (Bowles, 2001). Utilizing the technique of OPCAB could influence the factors of reducing blood loss (Mahomed & Vijay, 2000) and decreasing the inflammatory response (Joffs et al., 2001). Therefore, a further cost savings might be realized by using this surgical technique to decrease the fixed direct cost while maintaining clinical quality of care (Ascione, et al., 1999).

The length of stay and cost of nursing care required for coronary artery bypass patients are of special concern for the nurse administrator. By reducing these parameters, the amount of nursing care hours and thus costs (especially in the post-operative phase), can effectively be reduced. Expediting patients’ return to the stage of self-care and greater independence will also decrease the number of nursing care hours required. This is especially significant in the face of the national shortage of nurses currently being felt and on the expected future shortfall (Loquist, 2002).
Statement of Purpose

The purpose of this study is to compare the cost of OPCAB with C-CAB. Comparison will be made of the cost of two different circuit coatings, with two different drug regimes, and their impact on the inflammatory response along with blood loss. This study is designed to specifically measure the differences of (a) total intraoperative cost, (b) length of stay, including post-ICU hospitalization, (c) inflammatory response, (d) post-operative blood loss for each protocol, and (e) differences in post-operative nursing care hours as required for OPCAB and C-CAB.

There is no knowledge by the researcher of a previous study of this magnitude covering and comparing the stated parameters. Results of this study will add new information to the body of nursing, medical and perfusion knowledge.

Research Hypothesis

Hypotheses:

H1. The intra-operative cost of OPCAB is significantly greater than the intra-operative costs of C-CPB patients.

H2. There is no significant difference in the ICU and post ICU hospital LOS between the OPCAB and C-CPB patients.

H3. There is a significant decrease in the measured inflammatory response in the OPCAB vs. the C-CAB patients.

H4. There is no significant difference between the measured inflammatory response between the x-coated and y-coated circuits for C-CAB patients.

H5. There is a significant difference in measured compliment mediators between the pharmacological regimes, Aprotinin and Amicar.
H6. There is no significant difference in blood loss between OPCAB and C-CAB patients.

H7. There is a significant decrease in patient care hours with decreased complement mediator activation.

Framework

The framework for this study is Dorothea E. Orem's Model of Self-Care. “Orem labels her self-care deficit theory of nursing, a general theory composed of three related theories: (1) the theory of self-care (describes why and how people care for themselves), (2) the theory of self-care deficit (describes and explains why people can be helped through nursing), and (3) the theory of nursing systems (describes and explains relationships that must be brought about and maintained for nursing to be produced”; Taylor et al., 1998, p.176). Each is discussed briefly in the following text.

The theory of self-care is a human regulatory function that individuals must, with deliberation, perform for them or have performed for them to maintain life, health, development, and well-being. This research study is appropriately supported by this theory. A patient undergoing open-heart surgery does not have the ability to perform self-care. The care required is beyond what the average family can provide, thus the patient requires the expert care by nurses to achieve a satisfactory outcome. The elaboration of the concepts of self-care, self-care demand, and self-care agency provide the foundation for understanding the action requirements and action limitations of persons who may benefit from nursing care (Orem, 1991).

This model focuses on what nurses actually do when they practice nursing. Orem proposed that individuals generally know how to take care of themselves (self-care). If
they become dependent in some way such as when they need post-operative care following a coronary artery bypass (CABG) surgery, family members must take on the responsibility (dependent care; Orem, 1991). If individuals are ill or have some self-care deficit (i.e. immediate post-op care including major intravenous monitoring lines and mechanical support as is common after open-heart surgery), these individuals require special care (therapeutic care). An individual’s capacity to provide self-care is referred to as self-care agency. A self-care deficit occurs when self-care demand exceeds self-care agency (Taylor et al., 1998).

"Nursing care is provided only when there is a deficit in the self-care or dependant care that the individual and his family can provide (self-care deficit). In this case, the nurse or nurses develop a nursing system to provide the needed care” (Burns & Grove, 1997, pp.146-147). This system involves prescribing (monitoring vital signs, dynamic pressures, equipment and medications necessary to maintain homeostasis), designing (setting parameters for individualized care), and providing the described needed care. “The goal of nursing care is to facilitate resumption of self-care by the person and/or family. There are three types of nursing systems: wholly compensatory, partly compensatory, and supportive-educative” (Burns & Grove, 1997, pp.147). As the patient progresses through the different stages of post-op recovery and their self-care activities increase, they progress and return to independent self-care within the supportive-educative nursing system.


The Theory of Nursing Systems proposes that nursing is human action; nursing systems are action systems formed (designed and produced) by nurses through the
exercise of their nursing agency for persons with health-derived or health associated limitations in self-care or dependent care. Nursing agency includes concepts of deliberate action, including intentionality and operations of diagnosis, prescription and regulation. Nursing systems may be produced for individuals, for persons who constitute a dependent-care unit, for groups whose members have therapeutic self-care demands with similar components or who have similar limitations for engagement in self-care or dependent-care.

The central ideas of the Theory of Self-Care Deficit, are that the requirements of persons for nursing care are associated with the subjectivity of mature persons to health-related or health-care-related action limitations. This renders them completely or partially unable to know existence and emerging requisites for regulatory care for themselves and to engage in the continuing performance of care measures to control or in some way manage factors that are regulatory of their own functioning. "Self-care deficit is a term that expresses the relationship between the action capabilities of individuals and their demands for self-care. Self-care deficit is an abstract concept that, when expressed in terms of action limitations, provide guides for selection of methods of helping and understanding patient's roles in self-care" (Taylor, et al., 1998, pp.180-181).

Orem's theory addresses the nursing care philosophy, management, and financial concerns regarding the techniques of the two cardiac surgical procedures, and patient outcomes of this study. By implementing the patient self-care portions of Orem's theory and the ability of the nurse to recognize the stages of self-care, the nurse can further utilize the ability of patients to perform more of their own care, thus decreasing the need for additional nursing-care hours. Regarding the financial aspect, the more quickly the
patient can provide self-care, the shorter the LOS in the hospital setting, thus reducing costs. The concept, of decreased LOS and early discharge (Ott et al., 1997; Ott et al., 1999), propelled the idea of converting C-CAB into OPCAB. By eliminating the heart-lung machine and decreasing the inflammatory response, ventilator time, ICU time and blood usage (Fransen, Maessen, Dentener, Senden, & Buurman, 1999), the patient should recover more rapidly. A faster return to self-care will progressively decrease reliance on nursing care agency. In summary, Orem’s Model of Self-Care guides this study’s purpose to examine the differences in costs and its related factors, including inflammatory response, use of pharmacological agents, and blood loss during OPCAB and C-CAB.

Definitions

1. OPCAB

   Conceptual: Coronary artery bypass procedure performed on a slowed beating heart without the use of cardiopulmonary bypass, utilizing specialized retraction systems and proximal connector devices.

2. C-CAB

   Conceptual: Coronary artery bypass procedure performed on a still, motionless heart with the use of the cardiopulmonary bypass machine, providing a bloodless field.

3. Costs

   Conceptual: Amount of hospital revenue required to provide the necessary equipment, personnel, and disposable materials needed for OPACAB and C-CAB techniques and surgeon protocols, during the peri-operative period.
Operational: Actual cost, in dollars, of the operating room charges. These will include the cost of cardiac surgery overhead (room costs, staff: assistants, circulating nurses, scrub technicians, and perfusionist), equipment and disposable material charges as measured from the patient's record after discharge from the hospital.

4. Hospital LOS
   Conceptual: Number of days spent in the hospital from the time of discharge from the ICU to the time of discharge from the institution.
   Operational: Number of days as recorded in the patient record from the time of discharge from the ICU to the time of discharge from the institution.

5. ICU LOS
   Conceptual: Number of days spent in the ICU from the time of admission until time of discharge to the floor.
   Operational: Number of days recorded in the patient record from admission to discharge from the ICU.

6. Inflammatory Response
   Conceptual: Measurement of increased activity of the immune system can be performed at predetermined intervals.
   Operational: Levels of inflammatory mediators, including a combination of available cytokine (IL-6, IL-10) and matrix metalloproteinases (MMP-2, MMP-9), will be collected, tested, and recorded at specific times: pre-sternotomy, peri- and post-operatively.
7. Bypass Circuits

Conceptual: Type of coating used on the different cardiopulmonary bypass circuits. Circuits may be coated with either covalent or hydrophilic/hydrophobic heparin on the internal surface of the bypass circuit.

Operational: Exposure of the subjects according to the measurement of the actual inflammatory mediators previously explained at the appropriate time intervals.

8. Nursing Care Hours

Conceptual: The number of nursing care hours required to effectively provide the necessary care of the patient within the three stages of Orem’s Model of Self Care.

Operational: Actual number of hours calculated by the nursing managers, on the postoperative step down unit, for the amount of nursing care required for each of the protocols used.

9. Blood Usage

Conceptual: The use of blood or blood products in the care of the patient undergoing coronary artery bypass surgery.

Operational: Measurement and documentation of the amount of blood or blood products required during the operative and post-operative periods in the OPCAB and C-CAB groups being studied.

10. Drug Regimes

Conceptual: The are two different drug regimes which are as follows: Amicar 5-5-5 indicates, that 5 grams of Amicar will be administered after the loading
dose of Heparin, 5 grams in the cardiopulmonary bypass circuit prime, and 5 grams will be administered after Protamine administration; Aprotinin ½ dose indicates that 1 million units administered prior to the median sternotomy, 1 million units in the cardiopulmonary bypass circuit prime, and an infusion rate administered at 250,000 units/hour during the entire operative period.

Operational: The inflammatory mediators, IL-6, IL-10, MMP-2, MMP-9, will be collected and documented at the specified time intervals during the drug regimes.

Major Assumptions
1. Patients are more self-sufficient and require fewer nursing care hours when there is a decrease in the measured inflammatory response.

2. Patients desire to be discharged from the hospital as soon as they are self-sufficient in their care.

3. Less invasive procedures cause fewer complications and thus lead to a quicker recovery.

Major Limitations
1. The patient population examined (primary C-CAB) is non-randomized due to the need to have the cardiopulmonary bypass system prepared prior to the patients’ arrival to the operating room.

2. The convenience of not having two circuits (x-bonded and y-bonded) in use at the same time limits the randomization process.

3. Physician protocols of drugs use, due to cost factors and possible side effects, limit the researchers ability for randomization.
4. Physician caseload may affect the frequency of preferred treatment modalities and thus the type of patient population studied.

5. Patient selection is limited to a single healthcare facility, thus the anticipated type of patient enrollment might lead to limitation of generalization to other health care facilities.

6. Various certified clinical perfusion techniques might influence the results of the research.

7. Sample may be biased toward the male gender therefore may be less generalizable to the female population.

8. Physician selection criteria for techniques used may be biased toward ability to complete total revascularization.

9. Increasing public awareness of differing operative techniques currently in use has the potential to effect randomization.

Significance of Proposed Study

The significance of the study is its unique focus on the different aspects of major changes in the treatment of the cardiac surgery patient. Although the advances in surgical techniques are at first promising, all aspects of the final outcomes must be reviewed. Cost cannot be ignored, but also cannot be the sole determinant for change. Short term positive results are promising, but the long term results can and will be the finalizing factor (Puskas et al., 1999). As research focuses on determining whether on pump or off-pump is initially more cost effective (Ascione et al., 1999), the LOS and need for nursing care-hours must also be noted. If patients in the OPCAB group actually prove to be more
independent and discharged earlier at a reduced cost with acceptable long-term results (Puskas et al. 1999), then there truly is a place for the OPCAB surgical procedures.

Summary

As more and more “baby boomers” reach the age when they require additional intense medical treatment, the costs of such treatment will increase dramatically. In response to this situation, medicine and health-care providers are searching for ways to stretch the health-care dollar. One method currently being explored to expand the financial revenues available for coronary artery bypass surgery is to perform OPCAB. Benefits found with this technique are the hypothesized decrease in several treatment modalities: (a) less ventilator and ICU times, (b) decreased inflammatory response due to lack of exposure to the large surface area of the cardiopulmonary bypass machine (CPB), (c) decreased use of blood and blood products. It is proposed that these benefits will lead to faster recovery to self-care, and thus earlier discharge. Therefore, there will be reduced costs and more effective use of the health-care dollar. Negative aspects may include: (a) the inability to perform as many bypass grafts and thus result in incomplete revascularization, (b) no actual cost saving due to the cost of specialized equipment necessary for the techniques, and (c) longer operating room times and thus higher costs will produce poorer patient outcomes.

Nursing care is threatened by the expected national shortage of nurses. If patients are able to become independent sooner (decreased acuity) and thus require less nursing care hours, then the benefits would be enormous. By more quickly returning to independent self-care, patients will have improved self-worth resulting in improved quality of life. Orem’s Self-Care Model can guide the nurse as he or she identifies the
patient’s progression through the stages of self-care and thus more independence.

Knowing whether OPCAB or C-CAB is the most cost effective technique is essential information for administration when planning overall health-care costs.
CHAPTER 2
REVIEW OF LITERATURE

The review of the literature (ROL) reflected an increasing interest in the ability to safely perform coronary artery bypass surgery in the absence of the heart-lung machine while maintaining acceptable results. ROL included research studies and articles in research, medical and perfusion literature, nursing journals, and nursing texts. Only relevant articles dealing with the direct parameters of the study were reviewed. The purpose of the review, delimitations, resources, and keywords used, along with a combination of theoretical and research literature, are discussed in this chapter.

Purpose of Review

The purpose of this ROL was to gain an appreciation for the body of knowledge regarding C-CAB and OPCAB that exists today. The issues involving LOS (Rosen, Humphries &, Muhlbaier, 1999), length of nursing care hours and the projected nursing shortage (Loquist, 2002; Milstead, 2002), inflammatory response of the human body (Joffs et al., 2001), and costs (Lee, Abdelhady, & Capdeville, 2000) are all concerns and interests that guided this review. Also of interest are the different operative techniques currently used and the advantages of each (Magovern, Benckart, Landreneau, Sakert, & Magovern, 1998). Many studies involving the use of CPB and its detrimental effects have been published (Bull et al., 2001; Kirk et al., 2001; Lancey et al., 2000) but the question still remains, is it the pump or the surgical techniques that cause detrimental side effects? (Taggart, Browne, Halligan, & Wade, 1999) Are the long-term results of OPCAB better for patients than having them subjected to C-CAB? (Arom et al., 2000; Bowles, 2001; Puskas et al., 1999)
With the estimated clientele of 516,000 patients per year (American Heart Association, 2001) expected to increase with the addition of the “baby boomers” reaching their 50s and 60s (Beller, 2001), the process of providing the most cost-effective and safe method of revascularization of the heart needs to be addressed. Extensive review of the literature has failed to find a previous study that compares OPCAB with C-CAB including the variables that have been identified for this study, which indicates the need for a study of this magnitude. There are numerous previous studies which have focused on a few of the variables proposed, but to date none have been found that address the relationships of this study’s variables. The variables involved are numerous and will provide a broad scope for this study. Wholly available and commonly used surgical techniques, drug and perfusion practices will be studied and thus will provide results and information that can and will assist health care providers with informed and responsible decisions.

Delimitations

The extent of the ROL was limited to periodicals from the years 1992 to the present and books spanning seventeen years, 1986 to the present, since these authors are considered to be experts in the early years of cardiovascular surgery.

Keywords and Resources

The keywords for searching electronic databases were: (a) Aprotinin; (b) Blood; (c) Bonded Circuits; (d) Compliment Activation; (e) Cardiopulmonary Bypass (CPB); (f) Complications; (g) Off-Pump Coronary Artery Bypass (OPCAB); (h) Cardiopulmonary Bypass Grafts (CABG); (i) Cost; (j) Fast Tracking; (k) Length of Stay (LOS); (l) Proximal Connector; (m) Proximal Connector; and (n) Stabilization Devices.
The databases utilized were: (a) the Cumulative Index to Nursing and Allied Health Literature (CINAHL), (b) Medline (Medical Literature Analysis and Retrieval System Online), (c) Medscape, and (d) AMSECT Digital Interactive Library. Other resources used were the (a) McKee Library at Southern Adventist University, (b) Erlanger Medical Center Library, and (c) Memorial Hospital Medical Library. Other resources, including abstracts and numerous medical, perfusion, and nursing journals, along with texts, were referenced.

Description of Literature

In the world of ever changing medical treatments and techniques, those who are dormant will find themselves in the dust of the progressive ones. Within this context fall the present and ambitious changes in cardiovascular surgery. Whether driven by changes in reimbursement, a need to improve outcomes, or a combination of both, health care providers are once again involved in the search for better techniques. This has led to the resurgence of OPCAB. A resurgence of interest in CABG without CPB began when it was first performed by Kolessov in the former Soviet Union and by Favaloro and Garret and associates in the United States (BUFFOLO et al., 1996). Researchers in the United States and Canada later reported on the technique but abandoned it as the use of CPB, along with cardioplegic cardiac arrest, became routine.

A major advantage in using CPB during C-CAB is the ability to operate on a still heart with a relatively bloodless field. This also enables the exposure of all distal coronary arteries (Ardehali, Kessler, Formosan, & Lakes, 1999). Manipulation of the heart can allow for more accurate, secure grafts and allow for the reestablishment of blood flow to the myocardium. Numerous complications have been linked to the use of CPB.
Included in these complications are coagulopathy, inflammatory responses, edema, renal dysfunction, and neurological deficits (Kirk, et al., 2001). Kirklin (1986) stated, “the most obvious mechanisms for damage during CPB are exposure of blood to an abnormal environment, and altered arterial blood flow patterns”. It is with these changes in mind that the analysis of current techniques and trends are reviewed.

Off-Pump Coronary Artery Bypass

It has been shown that CPB initiates a cascade of inflammatory processes that may result in many complications (Lee, Abdelhady, & Capdeville, 2000). Avoidance of CPB during OPCAB has gained increased popularity in modern cardiac surgery. With the development of new mechanical stabilization devices (Jansen et al., 1998), the revascularization of the posterior wall of the heart and the distal right coronary circulation has become feasible. High-risk patients, with multiple risk factors for open-heart surgery, will especially profit from this approach due to avoidance of the negative effects associated with CPB (Tugtekin et al., 1999).

Advances in technology and commercial availability of mechanical stabilization systems have permitted wider application of OPCAB surgery. These systems strive to provide a well-exposed, immobilized target site for performance of precise vascular anastomosis. The early clinical outcome and angiographic follow-up in patients who have undergone left internal mammary artery (LIMA) anastomosis to the left anterior descending (LAD) coronary artery with the available mechanical stabilization systems have been encouraging (Puskas et al., 1999).

Since minimally invasive techniques have become increasingly common in CABG, there has been renewed interest in facilitating mechanical anastomotic devices
that may have the potential of replacing the standard suturing techniques in vascular
anastomoses. Recently, the Symmetry Aortic Connector®, which attaches the proximal
vein graft to the aorta without the use of a side-clamp, provided this option. This
technology is attractive for all CABG procedures because aortic manipulation is reduced
with resultant reduction of possible particulate emboli (Eckstein et al., 2001).

Indications are that arterial conduits, such as the LIMA, can easily be used, and
most coronary arteries can be bypassed. The mortality rates continue to show promise
with low rates, and the incidence of serious complications such as arrhythmias, pulmonary,
and neurological sequelae are lower than with C-CAB. The patency rate for the bypass
grafts is similar to the C-CAB patients.

These concerns and observations have been studied by numerous researchers and
have been reported with differing results. One such study was conducted at a large
teaching institute in the southern United States (Kirk et al., 2001). This study
retrospectively compared the performance of OPCAB versus C-CAB patients over a
period of six months. Data was collected and compared from the National Cardiac
Database of the Society of Thoracic Surgeons (STS). Variables studied included age,
gender, left ventricular ejection fraction (LVEDF), previous myocardial infarction (MI),
disease severity, number of grafts, complications, blood usage, ventilator times, operating
room (OR) times, and LOS.

There was no significant difference, as measured by the Student’s $t$-test, between
the patient groups with regard to age, gender, LVEDF, previous MI, and LOS. A $p$-value
of $< 0.05$ was considered significant. Data was presented as mean ± standard deviation.
The C-CPB patients had significantly ($p < 0.05$) more diseased vessels (2.9 vs. 2.6) and
distal grafts (4.1 vs. 2.7), as compared to the OPCAB group. The OPCAB group had a significantly lower ($p < 0.05$) mean OR time (365 min. vs. 406 min) and reduced mean ventilator times (3.4 vs. 8.3 hours) as compared to the C-CPB group. There were significantly fewer blood transfusions ($p < 0.05$) in the OPCAB group (1.1 vs. 2.4 units), and the patients transfused were significantly lower (34.9% vs. 57.3%).

The study group size was adequate ($n = 212$ patients) and the demographic data were similar. The significant differences have been given. Several studies have reported the cost savings of OPCAB over C-CAB surgeries (Ascione et al., 1999; Lee et al., 2000; Smith, Smith, & Muhlbaier, 1997) and long-term patency rates of OPCAB bypass grafts as acceptable (Puskas et al., 1999). Some concerns that are evident and deserve justification are the significantly lower number of OPCAB bypass grafts (2.7 vs. 4.1) and the possibility of incomplete revascularization (Hart, Spooner, Edgerton, & Milsteen, 1999).

Limitations of this study include: that the study was non-randomized, retrospective, and may not be applicable to prospective groups. No post-operational procedures were done to verify the anastomotic patency or bypass graft patency, and there was no long-term follow-up to verify the benefits of OPCAB. Overall, the study was thorough and gave good statistical support to verify the hypothesis.

A comparative study of a consecutive series of 8,751 patients (Buffolo, Silva de Andrade, et al.), reported that from 1981 to 1994, patients (1, 274) received CABG operations without the use of CPB. Results indicated that the operation can be performed with an acceptable mortality rate (2.5%), and that all types of arterial conduits can be used. Most commonly the LAD and right coronary arteries (RCA) were bypassed. The
incidence of pulmonary and neurological complications was significantly lower in this
group of patients compared with patients receiving CABG with CPB. Most importantly,
there was a decreased cost (approximately $3000.00) when the procedure was used,
because no extracorporeal circulation, cardioplegia sets, or cannulas were used.

Methods used were within the parameters of the other previous study, although
the sample size was significantly larger. Demographics were also consistent with other
study including age, sex, pre-operative status, the severity of coronary artery disease,
previous myocardial infarction(s), and arteries receiving bypass grafts. Number of grafts
patients received in the study (OPCAB) group was 1.7, which was not compared to the
control group. It is of interest that statistics, though no analysis, were given for the
patency rates of the internal mammary artery before hospital discharge. Both the control
and study groups had a 93.4% patency rate.

The advantages for OPCAB were as follows: (a) less mortality/morbidity, (b)
lower use of homologous blood, (c) lower cost, and (d) decreased length of stay. The
disadvantages given were: (a) technically more demanding, (b) possible in only 20% of
cases, and (c) lower reproducible results.

In summary, this study was able to provide indications for OPCABs in
approximately 20% of their population, with acceptable results and low complication
rates. Though no analysis was given, the raw numbers would indicate comparable results,
therefore the authors felt that further use of the procedures were justified.

OPCAB may seem like the trend of the future, due to elimination of problems
already mentioned, but it is not without possible complications. A couple of these
complications have been identified in current literature. These include, but are not limited
to, an increase in the incidence of acute aortic dissection due to manipulation of the heart during retraction (Chavanon et al., 2001), and a concern that a hypercoagulable status may occur after OPCAB that can potentially endanger the patency of the anastomosis (Kim et al., 2001).

Conventional Coronary Artery Bypass

The advantage of using CPB during C-CAB is the ability to operate on a still heart with a relatively bloodless field, while enabling exposure of all distal coronary anatomy. The surgeon can manipulate the heart, make accurate and secure grafts, that then allow the re-establishment of blood flow to the distal coronary circulation.

Cardiopulmonary bypass is a nonphysiological process. Deleterious effects attributed to its use include coagulopathy, inflammatory responses, edema, renal dysfunction and neurological deficits (Lillehei, 1993). Kirklin (1986) states, "the most obvious mechanisms for damage during CPB are exposure of blood to an abnormal environment, and the altered arterial blood flow patterns" which may lead to increased operative mortality and morbidity and thus effect length of stay and hospital costs (p.53-54).

Edmunds (1998) noted that a large number of vasoreactive substances are produced during CPB and open-heart surgery which cause edema, decreased myocardial function, and changes in the vascular bed resistance. Reduction in mortality associated with adverse effects is the goal of numerous researchers today.

CPB is known to activate five plasma protein systems: contact, intrinsic coagulation, extrinsic coagulation, compliment and fibrinolytic. The purpose of this section of the review was to explore studies regarding prevention of the activation of
these systems. Activation of the plasma protein systems mediates some of the complications of CPB: bleeding, fluid retention (edema), and temporary organ dysfunction. The use of the drug Amicar addresses the fibrinolytic problem, sometimes associated with bleeding. Aprotinin has been shown to decrease the detrimental effects on the platelets and to decrease the inflammatory response (Mojck & Levy, 2001). Heparin is used to prevent coagulation, but is not the ideal anti-coagulant because it inhibits coagulation at the end of the coagulation cascade rather than at the beginning. Thus many powerful proteases are produced before heparin inhibits clot formation.

Many non-blood variables affect the magnitude of the inflammatory response, including biomaterials in contact with blood, surface coatings, activation of some proteins by the operation itself, temperature, aortic cross-clamping, myocardial reperfusion, steroids, antitoxins, and the various protease inhibitors that may attenuate the response (McCann & Gatto, 1999).

**Costs**

Some institutions are reporting a cost savings with OPCAB of $3000/case due to decreased use of disposable equipment such as oxygenators, cardioplegic sets, and cannulas (Buffolo et al., 1996). Lee et al., (2000), reported a reduction in variable direct costs per case of 29%, as attributed to lack of complications such as stroke, renal failure, or sternal infections for the OPCAB group in their study.

Fast track methods have been reported (Ott et al., 1997; Ott et al., 1999) for patients utilizing both C-CAB and OPCAB techniques. The LOS varied from 5.2 days with C-CAB to 3.9 days OPCAB. It was interesting to note finding that the number of
bypass grafts was considerably lower in the OPCAB group (2.9 versus 3.6) than for the C-CAB group.

Ascione, et al. (1999) noted that the emphasis on cost containment in coronary artery bypass surgery is becoming increasingly important in modern hospital management. The sample included 200 patients undergoing primary CABG surgery, which were randomized to either the C-CAB group or OPCAB group. Variable and fixed costs were obtained for each group during the operative and postoperative periods. The data were presented as mean ± standard error of the mean (SEM). Comparison of the groups was performed using the unpaired t-test and Fisher’s exact test where appropriate, assuming equal variance. Two-tailed tests were used and differences were considered significant where \( p < 0.05 \).

The researchers found there was no statistical difference between the groups with respect to pre- and intra-operative patient variables. OPCAB surgery was significantly less costly with respect to operating materials, bed occupancy, and transfusion requirements (total mean cost per patient: C-CAB = $3731.6 +/- $1169.7 vs. OPCAB = $2615.13 +/- $953.6; \( p < 0.001 \)). Morbidity was significantly higher in the on-pump group as reflected in an increased cost (Ascione et al., 1999).

The conclusion reached was that OPCAB revascularization offers a safe, cost-effective alternative to C-CAB surgery. The samples were of adequate size, the statistical analysis was very good, and the variables were well covered in comparison to the previous studies. Demographics, including age, sex, diabetes, ejection fraction, CPB times, OR times, number of grafts (including patency rates) were analyzed and statistical significances were given. Variables for cost were identified and well described. Clinical
postoperative data included mortality, morbidity, myocardial infarctions, blood usage, intubation times, and ICU and hospital LOS. Furthermore, these cost reductions are distributed from the operative theater to post-operative management.

Lancey, Soller & Vander Salm (2000) reviewed the comparison of OPCAB and the trends demonstrated towards fewer complications, faster recoveries and lower costs compared with C-CAB surgery. All patients entered into the study were case-matched by age, sex, and risk scores according to the Society of Thoracic Surgeons. Equal numbers of participates were entered into the two groups and surgery was performed by the same surgeon.

Data were collected prospectively on all patients. Data were continuously analyzed using a paired t-test, while categorical values were analyzed using a McNemar chi-square test. Both tests were effective for patients that were matched prior to statistical analysis and had significance indicated by $p$ values < 0.05. Cost differences, as well as relationships between ages, preoperative risk score and costs were examined using a $t$-test.

Results of specific interest to this research included the difference in the average number of distal anastomoses, OPCAB: 2.8; C-CAB: 3.7; $p = 0.00001$. Although, operating room times averaged 25 minutes less for the OPCAB group, this was not statistically significant and may reflect the fewer number of distal anastomosis performed. Average time on the ventilator was significantly lower for the OPCAB group, mean (in days) of 0.26 vs. 0.77, $p = 0.007$. The mean ICU LOS was shorter for the OPCAB group (in days), 1.80 vs. 2.41 for the C-CAB group, $p = 0.144$; and mean
hospital LOS was also shorter for OPCAB (in days) with 5.17 vs. 6.24, $p = 0.112$. Both LOS means fell short of being of statistical significance.

The average number of packed red blood cells transfused was significantly lower on the first postoperative day for the OPCAB group, 0.25 vs. 0.88, $p = 0.00001$; this trend continued which showed statistical significance on postoperative day two with transfusions reported to be 0.05 (OPCAB) vs. 0.18 (C-CAB), $p = 0.040$. No statistical differences were reported for complications, including atrial fibrillation, stroke, perioperative myocardial infarction, re-operation for bleeding and mortality.

Total costs revealed a savings for OPCAB ($15041.68) vs. C-CAB ($18943.73), but was not statistically different ($p > 0.05$). The costs savings for OPCAB were reported in the following areas: (a) blood transfusions, 87.4%; (b) mechanical ventilation, 67.7%; (c) OR equipment (including CPB), 67.3%; (d) ICU, 44.2%; and (e) pharmacy, 64.2%.

The authors concluded that by reducing the need for mechanical ventilation, transfusions, ICU and hospital LOS via “fast-track” protocols, OPCAB surgery decreased the use of limited and costly resources without producing an increase in morbidity or mortality.

Length of Stay

There was also a decreased LOS in the intensive care unit and in the hospital, mean LOS of 5.2 days for OPCAB versus 9.6 days for C-CAB (Buffolo et al., 1996). Lee et al. (2000) reported the OPCAB group in their study reflected a shorter LOS (6.1 versus 7.1 days) than the C-CAB group. The management of these patients in reference to fluids, electrolyte and respiratory care is simpler. Undoubtedly, the OPCAB technique is more
demanding, and there is a learning curve, however the surgeon had the option of placing
the patient on CPB, if the need arises.

Ott et al. (1999) retrospectively reviewed a series of patients undergoing C-CAB, using a fast-track recovery method and compared this with OPCAB. Using the fast-track method, all patients were placed on a protocol emphasizing a short CPB time, early extubation, and atrial fibrillation prevention. All patients were targeted for transfer from the ICU on the first post-operative day, aggressive ambulation on the second post-operative day, and all were allowed to shower on the third post-operative day. Discharge was accomplished when there was absence of weeping wounds, dysrhythmia and fever. Follow-up appointments were arranged within 72-96 hours after discharge.

The data were presented as a mean ± SEM. Comparison of the groups was performed using the t-test, whereas categorical variables were compared using the chi-squared test. Two-tailed tests were used and differences were considered significant where \( p < 0.05 \) or \( p < 0.01 \), as indicated.

The group size for C-CAB was adequate \((n = 104)\) but the OPCAB group was small \((n = 25)\). Demographic data correlated well between the groups. However, the OPCAB group was found to be at a higher-risk with increased incidence of left-ventricular dysfunction \((29\% \text{ vs. } 6\%, p < 0.01)\), congestive heart failure \((48\% \text{ vs. } 15\%, p < 0.01)\) and symptomatic peripheral vascular disease \((29\% \text{ vs. } 8\%, p < 0.05)\). Number of bypass grafts performed was \(3.6 \pm 1.0\) for C-CAB and \(2.9 \pm 1.0\) for OPCAB, \(p < 0.01\). OR times showed no significant difference with the C-CAB at \(151 \pm 31\) minutes and the OPCAB group at \(146 \pm 35\) minutes.
Mortality, post-operative complications, and LOS had no statistical difference between the groups. Data included: C-CAB vs. OPCAB: mortality, 1.9% vs. 0%; LOS (days), $4.8 \pm 2.4$ vs. $5.2 \pm 2.3$; and bleeding, 4.9% vs. 0.0% (Ott et al., 1999).

Ott and others concluded that eliminating CPB is not as important as minimizing operative risks. OPCAB is best suited for high-risk patients requiring 3 or fewer grafts. With aggressive fast-track recovery methods, patients requiring three or more bypass grafts should undergo C-CAB with the same cost and LOS results.

*Inflammatory Response*

The pro-inflammatory cascade of the immune system plays an important role in patients who undergo cardiopulmonary bypass (Edmunds, 1998). These patients displayed a “primed” system, which opens a window of susceptibility during which any physiologic stressor can unleash a generalized auto-destructive inflammatory cascade that if unchecked, can lead to several syndromes including Adult Respiratory Distress Syndrome (ARDS), Multi-Organ Dysfunction Syndrome (MODS) and death (Goris, te Boekhorst, Nuytinck, & Gimbrere, 1985; Terregino, Lopez, Karras, Killian, & Arnold, 2000). In association with CPB, a condition called post-pump syndrome (PPS), has been well characterized in humans and animal models (McCann & Gatto, 1999).
The CPB circuit has been shown to activate the pro-inflammatory arm of the immune system, as well as the coagulation cascade (McCann & Gatto, 1999), and is commonly referred to as systemic inflammatory response syndrome (SIRS). Normally, patients recover without undue sequellae of this event. In some patients, the pro-inflammatory response becomes over activated, resulting in the previously mentioned phenomena, MODS (Baue, 1992).

Measurement of the degree of immune system activation can be performed by a combination of available cytokine and matrix metalloproteinases (MMP) assays (Dollery, McEwan & Henney, 1995; Parsons, Watson, Brown, Collins, & Steele, 1996) as well as
clinical outcome measurements (Boyle, Pohlman, Johnson, & Verrier, 1997; Meduri et al., 1995; Pinsky et al., 1993). Measurements of these mediators in plasma can provide insight into the level of their production during and after procedures involving CABG. Important clinical endpoints include indices of specific organ failure, most importantly the lungs, which through ARDS, demonstrates early and frequently irreversible consequences in MODS, contributing to increased ICU stays, hospital LOS, and other complications including mortality (Boyle, Pohlman, Johnson & Verrier, 1997).

Assays of cytokines and mediators throughout the pre-, peri-, and post-operative periods allow for the measurement of the levels during various times, differing techniques, and protocols utilized. Assessment of the clinical outcome data including assays, along with the differing protocols used, will allow for analysis and determination of statistically significant differences between the techniques, drugs and circuit bondings being studied. These intermediate and clinical analyses have not been previously characterized in a prospective fashion involving this researcher’s numerous identified variables in patients undergoing CABG.

The cytokines selected for measurement include IL-6 and IL-10. IL-6, a pro-inflammatory mediator, selected as a candidate variable as it has been previously well characterized as correlated with poor outcomes such as MODS, and can be reliably measured (Kishimoto, Akira, Narazaki, & Taga, 1995). IL-10 was selected as a variable as it has been previously well characterized as an anti-inflammatory mediator and has been studied during MODS, and the ratio of IL-6 to IL-10 correlates with SIRS severity and outcomes (Taniguchi et al., 1999).
The MMPs are a group of at least 28 enzymes that effect tissue remodeling in both normal and pathological states. In pathological states, these enzymes can exert their effects either in a chronic or acute fashion. The MMPs have been shown to act in the acute phase following cardiac stress, leading to both ventricular remodeling and multiple organ failure (Carney et al., 1999). MMP-2 and MMP-9 have also been shown to rise in a predictable fashion in association with CPB (Joffs et al., 2001).

Joffs, et al. (2001), researched the question of whether a recently discovered family of enzymes, the MMPs can degrade the extracellular matrix as expressed after cardiopulmonary bypass. As previously stated, the MMPs are a large family of proteolytic enzymes responsible for extracellular matrix degradation that may account for many of the complications noted after cardiopulmonary bypass involving the pulmonary, neurological, and renal systems.

Patients \( n = 28; \) 18 men and 10 women) with an average age of \( 63 \pm 1 \) year, undergoing elective CABG were entered into the study. Blood samples were drawn after the induction of anesthesia, just prior to initiation of CPB, and again just after termination of CPB. Additional samples were obtained at 30 min., six and 24 hours after CPB.

All data analysis was completed using analysis of variance for repeated measures, followed by a Bonferroni corrected \( t \)-test. Values were expressed as mean \( \pm \) SEM. No level of statistical significance was given.

The researchers reported findings that would indicate that there is an increased release of several classes of MMPs in the period after CPB. Also, one class of MMPs (MMP-13) increased immediately after the release of the cross-clamp and transiently after separation from CPB. Thirdly, some of these enzymes may be related to the
ischemic myocardium during revascularization. Some of these MMPs (MMP-2, MMP-9) have been demonstrated in several cardiac states including atheromatous plaques, aneurysms, and after MI's. This would lead one to believe that the release of certain MMPs is from the manipulation of the myocardium and not CPB.

Results included: MMP-8 levels rapidly increased at separation from CPB ($p < 0.001$) and returned to normal levels within 30 minutes after termination of CPB; pro-MMP-13 levels increased from baseline after cross-clamp removal ($p < 0.002$) and remained elevated after removal from CPB, then returned to normal levels within 6 hours post CPB; pro-MMP-9 levels increase significantly from baseline values at cross-clamp release ($p < 0.001$) and remained elevated until 30 minutes after CPB.

The researchers concluded that numerous MMPs are released during and after CPB. Because MMPs can degrade extracellular proteins essential for cellular maintenance, enhanced MMPs release and activation may contribute to alterations in tissue homeostasis in the early postoperative period.

The following diagram correlates several strategies reviewed in the subsequent text that have been shown to affect the inflammatory response to CPB:
Some therapeutic strategies to reduce the inflammatory response to CPB (Wan, LeCleric, & Vincent, 1997, p. 685)

**Figure 2.2**

**Circuits**

Advances in cardiopulmonary bypass circuits in recent years have addressed the subject of the inflammatory response. The contact between formed and unformed blood elements and the non-endothelialized surfaces of the cardiopulmonary bypass circuits result in an intense inflammatory reaction, thought to be responsible for much of the morbidity following artificial circulation. Advances in biomaterial-surface interactions attempt to limit such damage.
The use of heparin-bonded circuits (HBC) has been demonstrated to attenuate the activation of neutrophils, platelets, complement and release of cytokines during CPB by altering the blood-surface interface (Aldea & Shemin, 1998). A new polypeptide and active heparin coating has been developed that simulates a natural endothelium, thus decreasing the inflammatory response. These polypeptides can be absorbed on the surface of the bypass circuits, thus serving as a link system for the heparin molecules. Through both covalent bounding and ionic interaction, the heparin molecules form a stable bond with the polypeptide surface.

![Diagram of heparin molecules to the immobilized polypeptides](Bader, 2001, p. 25)

**Figure 2.3**

Wendel et al. (2001) reviewed currently available circuit coatings and whether the inflammatory response is altered between the type of coating and application techniques involved, thus decreasing the depositing of fibrin and platelets. One coating is currently in use at the participating facility (Duraflo II ®) and the second coating is the study coating, Bioline®.

An established CPB model was used to simulate an extra-corporeal circuit. Using fresh human, heparinized blood, $n = 7$ oxygenators from each of the four groups was run
at 3 L/min. flows with a mean arterial pressure of 60 mmHg for 120 minutes. At specified times, laboratory analysis of platelets, white blood cells, and B-thromboglobulin (B-TG) were analyzed and documented.

The results were expressed as mean ± SEM. Statistical analysis was performed by the statistics software SPSS. Differences between the groups were calculated by univariate analysis of variance. Level of significance was set at 0.05.

Reported results for uncoated circuits versus Bioline® coated circuits are as follows (no data given for Duraflo II ®). The number of diminished platelets was not significant in the experimental group (Bioline®) during the first 60 minutes of recirculation, 211.33 ± 7.65 X 10³ to 183.00 ± 7.28 X 10³ / ul. After 120 minutes of recirculating, a greater reduction was observed, 127.83 ± 4.46 10³ / ul. An immediate and highly significant (p<0.001) reduction of platelets was measured in the non-coated control group. After 1 minute of recirculation, the platelets fell from 213.00 ± 9.29 X 10³ / ul to 32.67 ± 13.97 X 10³ / ul (p<0.001). During 5-30 minutes of recirculation, the platelets stayed at a constant low level of 4.33 ± 1.91 X 10³ / ul to 11.83 ± 2.22 X 10³ / ul and increased to values of 82.50 ± 14.15 X 10³ / ul at the end of circulation.

The release of the platelets activation marker B-thromboglobulin developed inversely proportional to the loss of the platelets. The values of B-TG increased only at the end of recirculation in the experimental group, Bioline®. Plasma concentrations of 1257.17 ± 171.89 IU/ml were measured after 120 minutes of circulation. The non-coated circuit control group showed a highly significant (p<0.001) increase of B-TG up to 5927.32 ± 171.89 IU/ml after 120 minutes.
There were similar changes in the white blood cell counts in comparison to the platelets. The experimental group showed only a small reduction in the first 60 minutes of recirculation, $5.47 \pm 0.35 \times 1000/ul$. A greater reduction of white blood cells was found after 120 minutes of recirculation, $3.52 \pm 0.35 \times 1000/ul$. However, the white blood cell counts showed a continuous decrease during the whole recirculation in the control group (from $4.85 \pm 0.40 \times 1000/ul$ to $2.02 \pm 0.20 \times 1000/ul$). This reduction is highly significant with the results of the coated circuit ($p<0.001$).

The researchers concluded that the advantage of coated circuit is to be seen in selective adsorption of plasma proteins and will be achieved by biopassivation and bioactivation as well. With the discovery of new circuit coatings, a pathological deposit of fibrin, platelets and other blood cells on the circuit, will be reduced and thus decrease the inflammatory response.

Another new polymer-coated circuit in which the surface has been coated with poly 2-methoxyethylacrylate (PEMA) has been developed and studied to assess the inflammatory responses during CPB and indicate if there were any significant differences with the HBC (Saito, Motoyama & Sawamoto, 2000).

Saito et al. (2000) reviewed known factors that induce the inflammatory response during cardiopulmonary bypass. This inflammatory response may contribute to the development of post-operative complications such as respiratory failure, renal dysfunction, bleeding disorders, and multiple organ failure (Baue, 1992; Goris et al., 1985). In particular, pulmonary-edema-associated lung injury is a problem of considerable clinical significance (Meduri et al., 1995). HBC have been demonstrated to reducing the inflammatory response, which is known to have detrimental effects on
numerous body systems. The researcher was interested in the newer polymer bonded
circuit in which the blood-contacting circuits were coated with PEMA.

Using an animal model (swine), randomly selected groups were subjected to
bypass. Four groups were identified: 1) control \( (n = 3) \), 2) heparin-coated \( (n = 3) \),
uncoated \( (n = 5) \), or PEMA coated \( (n = 5) \). All CPB circuits consisted of the identical
components. CPB was conducted for a period of 4 hours without additional procedures
such as aortic cross-clamping, hypothermia, and heparin neutralization. Blood samples
were taken at intervals of 5, 15, 30, 60, 120, and 240 minutes after initiation of bypass.
Appropriate inflammatory mediators were tested.

Data was recorded and reported as mean \( \pm \) SEM. One-way analysis of variance
(ANOVA) followed by the Tukey test was used for comparing variables among
experimental groups. Statistical significance was assumed for values of \( p < 0.05 \).

Reported results between the four groups indicated that the uncoated groups
inflammatory mediators increased continuously throughout CPB. On the other-hand, the
percentages in the PEMA coated group decreased gradually 30 to 240 min after start of
CPB, and then the values increased slightly 15 minutes after CPB was terminated. No
mention was made of the heparin-coated circuit group. There were no actual values
reported to identify statistical differences. All reported results were comparing the
PEMA-coated circuits with the uncoated circuits, and no results were given comparing
the HBC and the PEMA-coated circuits. The conclusion made was that PEMA-coated
circuits should result in the reduction of inflammatory responses, including pulmonary
edema after CPB, compared to subjects being tested with uncoated circuits.
Decreasing the activation of surface contact between blood and the circuit surface has long been sought. HBC has been researched as a means of decreasing the risks associated with a non-coated circuit. te Velthuis, et al. (1997) compared the benefits of utilizing a HBC on compliment activation as opposed to the untreated circuit.

The sample included 30 patients, who were undergoing elective CAB surgery, randomized to two groups, one group \((n = 15)\) allocated to utilize an HBC, and the other group \((n = 15)\) to utilize a non-treated circuit. Blood samples were obtained from the radial arterial line before induction of anesthesia, ten minutes after induction of CPB, and within minutes of cessation of CPB.

Data were statistically analyzed using the paired \(t\)-test and between groups using regression. The adjusted \(R^2\) for regression analysis was given and the coefficients were expressed within a 95% confidence level. Dichotomous variable analyses were performed utilizing Fischer's exact test. In all reported data, a two-sided probability of \(< 0.05\) was considered to be significant. Data were presented as means ± 95% confidence interval.

Findings of the researchers included a 62% \((p = 0.06)\) in the measured inflammatory mediators after the onset of CPB and by 43% \((p = 0.026)\) after the cessation of CPB in the coated circuit group as compared to the uncoated circuit group. The results of the statistical analysis indicated that the use of coated circuits was felt to significantly reduce the presence of inflammatory mediators that were measured.

**Pharmacology**

Another advancement in the use of CPB is the addition of drugs to help alleviate complications associated with the inflammatory responses. Before the discovery of its hemostatic properties, Aprotinin was thought to be a potential anti-inflammatory agent.
Since its clinical introduction in 1987 to prevent blood loss during cardiac surgery, its anti-inflammatory benefits have been largely overlooked in favor of a vigorous debate centering on whether Aprotinin may be pro-thrombotic. Aprotinin has been shown to exhibit an anti-inflammatory effect by suppressing leukocyte activation and therefore can be expected to provide a significant clinical benefit. This expectation has been borne out in clinical practice, particularly in the case of high-risk patients, in which the LOS following CPB surgery was significantly reduced by Aprotinin compared to other anti-inflammatory strategies, thereby offsetting the initial cost of the drug during surgery (Harmon, 1996; Landis et. al, 2000).

Cicek, Demirkilic, Kuralay, Ozal, & Tatar (1996) studied the relevancy of using Aprotinin to reduce post-operative blood loss and the need for blood transfusions. Three groups were assigned, \( n = 25 \) per group, comparable in all demographic and operative variables and for treatment with high-dose Aprotinin, intra-operatively (group 1), postoperative Aprotinin (group 2) and a non-medicated control (group 3).

Post-operative chest tube drainage was significantly decreased in both aprotinin groups compared with those in the control group (295 mL in group 1 and 325 mL in group 2 versus 411 mL in group 3; \( p < 0.05 \)). No significant difference was seen between the two Aprotinin groups. The use of homologous blood products was significantly less in group 1 and group 2 than in group 3 (1.15 ± 1.13 units and 1.35 ± 1.30 units versus 2.55 ± 1.09 units; \( p < 0.05 \)).

All results were expressed as the mean and standard deviation. Results were compared by ANOVA with subsequent pairwise comparisons according to Duncan's multiple range test. A \( p \) value of less than 0.05 was considered statistically significant.
The conclusion reached by the researchers was, despite the small patient sample, that Aprotinin was effective in reducing blood loss, even when administered after the activation of the hemostatic system. However, the results cannot be applied universally since the population studied would be considered to be low risk for post-operative bleeding. Higher-risk patients need to be investigated regarding the comparative efficacy of post-operative Aprotinin administration.

Zabeeda et al., (2002) studied the effect of low-dose trasexamic acid (TA) on post-operative bleeding and coagulation variables after CABG. Fifty patients undergoing primary CABG were assigned to receive either a placebo (0.9% NaCl; \( n = 25 \)) or a 10 mg/kg TA loading dose followed by an infusion of TA at 1 mg/kg per hour during the operation (\( n = 25 \)). Numerous coagulation measurements were taken during and following the operation. Results were as follows: the TA group weighed less and post-operative bleeding was less (194 ± 135 mL versus 488 ± 238 mL, \( p < 0.001 \)), whereas blood requirements were higher in the control group (1.68 ± 1 versus 0.52 ± 0.9 U of packed cells per patient, \( p < 0.001 \)).

Normally distributed continuous variables were expressed as ± SEM. Abnormally distributed variables are expressed as medians. For statistical analysis, the two-tailed t-test was used for normally distributed variables and the Mann-Whitney \( U \) test for abnormal distributed variables. Non-continuous variables were compared by Fisher’s exact test as appropriate. Differences were considered significant with a \( p \) less than 0.05.

This study concluded that the use of low-dose TA during CABG significantly reduced the coagulopathy-induced post-operative bleeding and requirements of blood products. TA had no effect on platelet function during CPB.
Blood Loss

Nader, Reich, Bacon, Salerno, & Panos (1999), examined intra- and post-operative bleeding and the use of blood products during CABG using either on-pump or off-pump techniques. The charts from 126 patients undergoing CABG, 66 patients revascularized off-pump and 60 patients with CPB were reviewed.

There were no differences in preoperative platelet counts or hemoglobin concentrations between groups. More patients received preoperative heparin in the off-pump group, resulting in increased partial thromboplastin times (40.4 ± 2.9 versus 34.7 ± 3.6 seconds) and activated clotting time (150.1 ± 13.3 versus 130.5 ± 10.5 seconds) in this group as compared to the on-pump group (p < 0.05). Intra-operative blood loss was calculated by the amount of cell-saver volume returned and was found to be lower in the OPCAB patients compared with the C-CAB group (508 ± 64 versus 715 ± 50 mL). OPCAB patients had lower post-operative chest tube drainage in the first 24-hour period compared with the C-CAB patients (771 ± 66 versus 1084 ± 82 ml, p < 0.05). Finally, the OPCAB group required an average of 2.25 less units of packed red blood cells, 1.75 less units of fresh frozen plasma and 3.75 less units of platelet-rich plasma (p < 0.05). Results were express as the mean and standard deviation. All data was analyzed using unpaired t-test, x2, and Fischer’s exact test as appropriate.

The conclusion reached by the researchers was that even though the OPCAB started with higher partial thromboplastin times and activated clotting times, they received less blood products and had lower post-operative blood loss. The OPCAB procedure has recently become more standardized, simplified, and refined, leading to encouraging results. With the decrease in blood product use, OPCAB surgery may
provide a means for decreasing the risk of transmitting blood-borne pathogens, blood transfusion reactions, and the associated risks of nonautologous transfusions.

**Summary of Description of Literature**

CABG without CPB is once again gaining popularity as an alternative technique of myocardial revascularization. Although the method was described many years ago, it was abandoned with the advancements in CPB with cardioplegic arrest. With the resurgence of the need to be more cognizant of patient outcomes and the constraints of the financial aspects, major manufacturers have developed specialized retraction and anastomotic devices to assist the surgeon in these techniques.

Fast-tracking the CAB patient, whether using CPB or not, has shown a reduction in costs by decreasing LOS. The shorter amount of time spent by the patient in the hospital reduces the number of nursing hours required, which in fact, will decrease the work load on nurses and their staff.

If the surgeon chooses to utilize the CPB machine, numerous coatings and drugs are available to decrease the inflammatory response and the potential side effects. Inflammatory responses, when held in check, may decrease the side effects and thus lead to early discharge, presumably at a cost savings. Possible detrimental effects associated with CPB, has led the medical community the re-evaluate patient selection parameters for the use of CPB.

The studies that were reviewed reflect the interests of both the medical and general population. These studies highlighted better utilization of resources that are currently available to provide care for the ever-increasing number of patients with coronary artery disease (CAD) that are requiring CABG procedures. Cost containment
should not be the only consideration when choosing the type of procedure; patient outcomes and satisfaction are also of concern. In the never-ending search for acceptable outcomes, the medical community has devised ways using stabilization devices to produce acceptable cost reductions with amiable outcomes. Yet to be studied are the long-term patency rates of the grafts, which will be the determining factors for the success of the OPCAB procedure.

This review of literature was conducted to generate a picture of what is known and not known concerning multiple outcomes of CAB surgery with and without CPB. Relevant literature was reviewed to provide an in-depth knowledge concerning both techniques. Included in the review was the economic factor as well as outcome analysis. A broad background and understanding of the benefits versus the potential drawbacks of each method was reviewed. The sources were selected for quality and relationship to the problem statement.
CHAPTER 3
METHODS AND PROCEDURES

A quasi-experimental comparative research design was used for the study. Differences between OPCAB and C-CAB were examined. The variables measured were:
(a) total intraoperative cost, (b) length of stay, including post-ICU hospitalization, (c) inflammatory response, (d) post-operative blood loss for each protocol, and (e) difference in post-operative nursing care hours as required for OPCAB and C-CAB.

Studies have been previously performed pursuing information related to but not as thoroughly covered as this study (Bull et al., 2001; Kirk et al., 2001); therefore this is a partial replication study with the addition of several variables, i.e. addition of Amicar and Aprotinin and the circuit coatings of Heparin and Bioline®.

The following figures depict the research design (3.1) and major variables (3.2) involved within the proposed study:

![Research Design](image_url)

Figure 3.1
This study’s design did not change any current treatment modalities that patients would normally receive. The circuit coatings are not optional to the patient. Surgeons and perfusionist determine the selection of circuit coatings depending on what is available in the market place and what best fits the needs of the patient. All patients receiving treatment involving the cardiopulmonary circuit utilize circuits that all have the same coating, therefore interaction of selection and treatment is not a viable validity concern.

The number of patients who decline to participate was reported in order to address concerns regarding external validity. Interaction of setting and treatment was addressed by the fact that the participating institution and physicians are all concerned with providing the best alternatives to their clients while maintaining the most cost effective...
environment. Ability to identify best possible care and cost effective variables lead to the
decision to conduct the research (Denton, Luevanos, & Matloff, 1998).

Population and Sample

There were five groups to be studied: control (utilizing y-bonded circuits) with
Amicar (n = 30) and Aprotinin (n= 30); experimental (utilizing x-bonded circuits) with
Amicar (n= 30) and Aprotinin (n= 30); and finally the OPCAB group (n= 30). A minimal
sample of 30 for each group was used to ensure adequate sample size for statistical
analysis. Power analysis indicated a minimum sample size of 27 per group. Utilization of
statistical techniques addressed the question involving possible error rate problems.

The sampling criteria for the target population of this study were all elective,
primary, CAB candidates, of both genders, over the age of 18, who had not received any
thrombolytic intervention (whether in the cardiac catheterization lab or anti-platelet
therapy pre-operatively). Each group analyzed was compared as to type of data
distribution and the subject of randomization was clearly explained. All participants gave
informed written consent. Exclusion criteria included the ability to give informed written
consent, anyone under the age of 18, emergent procedures, multiple procedures (i.e. CAB
with valve replacement), exposure to thrombolytic agents, or desire to withdraw from
study. Multiple or emergent procedures, along with exposure to thrombolytic agents can
have adverse effects on variables being measured (amount of chest tube drainage, platelet
counts, number of units of blood and blood products used) therefore the presence of these
factors precluded inclusion of these subjects.

Standardization of the five groups was controlled starting with the planning phase
and continuing through the implementation phase by providing exact instructions for type
and kind of testing done and what parameters are being studied (type of case, time factors, costs, LOS). Irrelevancies of surgeon preferences and techniques was acknowledged. This was necessary so that individual surgeons continued to use the best course of treatment for their patients. The patient convenience samples were divided according to the surgical technique used (Amicar or Aprotinin) and which circuits (x-coated or y-coated) was in use at the time of testing. OPCAB data was collected as the patients are scheduled for this procedure according to the surgeon’s preference. Compensatory equalization of treatments, compensatory rivalry by respondents, along with resentful demoralization of respondents can be avoided due to the fact that the selection of therapy or treatment is solely based upon the surgeon’s preference so will not bias this research.

Selection of the sample has been addressed and its group dependency has been shown. Ambiguity on the causality is prevented due to the number of samples per group. Only using one bypass circuit at a time and maintaining the current protocols for each individual surgeon prevented imitation of treatments.

Heterogeneity is addressed because surgeon preference, of either Amicar or Aprotinin, but not the circuit, is involved. When OPCAB candidates are enrolled, care will be taken to provide equivalent demographic populations and overall pre-operative cardiac status. All groups were examined for equivalency before investigating and analyzing data variables.

Representativeness deals with the fact that the sample must be as much like the population as is possible (Burns & Grove, 1997). A limitation for generalization of the results may be a fact that this sample being studied is taken from a private, mid-sized,
urban institution that targets the mid-to-upper socioeconomic population. The care of the individuals in different socioeconomic status may differ from the sample population. “Studies conducted in private hospitals often exclude the poor” (Burns & Grove, p. 295). “Of major importance is whether the samples used to establish parameters were representative of the target population in terms of characteristics such as age, gender, ethnicity, educational level and socioeconomic status” (Burns & Grove, p. 296).

Educational and socioeconomic levels will not be factored into this study so that sample subjects will not find these questions offensive and choose not to participate in this study.

A sampling error of systematic variation is possible in this study, since the sampling process is non-random. A bias may occur since the sample may differ from the general population. Convenience sampling will choose the subjects in this study, simply by the fact they are eligible for inclusion based solely on the scheduling of the surgery.

Strengths of the sample include but are not limited to the following: (a) all candidates will have the same surgical procedure; (b) will be totally voluntary; (c) will be from the same geographical area; (d) will have the same surgical group as the primary care providers; (e) will have the same protocols as those not in the study; (f) will have the same post-operative care; and finally, (g) will receive excellent care from a recognized medical facility.

Setting

The setting for this study is a private, mid-sized, urban medical center located in the southeastern United States where approximately 5.3% of the nearly 1000 open-heart procedures performed annually are OPCAB. Understanding the possible validity problems as previously stated, proper precautions were taken to ensure applicability to
the general population by identifying and stratifying the sample population and providing all details of said sample. A possible strength of this study will be that an equal number and type of subjects available with the minimal number of participants needed.

Ethical Considerations

The principal researcher successfully completed the Human Participants Protection Education for Research Teams online course sponsored by the National Institutes of Health (NIH) and Human Research Training. This course reviewed the ethical principles and federal guidelines that should be followed, gave definitions and components necessary for informed and valid consent, and a description of the details of the Internal Review Board (IRB) in the research process when human subjects are involved. In addition, training was completed for the shipping of infectious substances (see Appendix C).

Prior to data collection, permission was first obtained from the School of Nursing at Southern Adventist University (SAU). Permission was then obtained from the Human Participants Subcommittee at SAU and the IRB at the participating medical center. In addition, written permission was obtained from all cardiac surgeons to include their patients in the study.

Excluding the surgical procedure itself, the actual study represented minimal risk to the study participants. The researcher approached each possible participant so that all questions may be answered. Inclusion in the study was completely voluntary and pressure to be included in the study was not applied. Once agreement to participate was reached, a written, informed consent was obtained. Ability to withdraw from the study was reinforced numerous times throughout the consent period, and a pager number was
attached to the patients chart so communication with the principal investigator could be maintained at all times. The informed consent precluded any chance for covert data collection, as the participants had full knowledge of the study.

"Privacy is the right an individual has to determine the time, extent, and general circumstances under which private information will be shared with or withheld from others" (Burns & Grove, 1997, p. 203). Since informed consent is required, privacy is upheld, and any identifying factors will be removed from the data collection sheets. Identification was kept confidential by the use of a coding system, known only to the principal researcher and only aggregate data was reported. Participants gave consent for presentation and possible publication of findings.

In this type of study anonymity is not guaranteed. The participants can remain anonymous only if no written consent is required. Also, during the review of records, personal information cannot be avoided. The researcher did provide complete confidentiality by the measures previously stated, and by following the guidelines outlined by the NIH. Any data that is entered into databases will be password protected and the original copies of the instrument will be under lock and key. Names were removed when the coding was completed.

Fair treatment is the right of any individual based on the ethical principal of justice. Since this study cannot have complete randomization, any patient that met the criteria was approached about possibility becoming a participant. This helped preclude any possible bias by the researcher having to do with patient selection. Surgeon protocols partially dictated the selection process of participants to the study.
This study, utilized current FDA approved techniques, equipment and pharmacological regimes, thus providing the bases for protecting the participants from undue harm and discomfort. There are no investigational products or techniques used. The researcher was simply interested in response of the participants in the areas previously noted as they are affected by different techniques and protocols in use by the surgeons.

Instrumentation

The data collection instrument developed by the researcher is located in Appendix A. Each group of participants was identified on the data collection instrument. Numerous laboratory data, inflammatory mediator measures, clinical data, intra-operative costs, and LOS was recorded. Currently, a data sheet is being used at the medical center. To avoid duplication of recording data, the principal investigator gleaned and transcribed it onto the research data collection tool. This information was basically demographic in nature.

Data Collection

Once subjects met inclusion criteria and written consent was obtained, data collection began in the preoperative area using the data tool developed by the researcher. Ensuring the following measures diminished the possibility of a threat to internal validity, any event that occurred while a patient is enrolled in the study that was not planned, automatically removed the subject from the study. In that event, no further data collection was continued and all previously gathered data was “purged” from the study. All data was collected at the same intervals as previously outlined to ensure equality and validity and prevent maturation as a threat to internal validity.
Treatments being studied were of the nature currently available to the general public, were all FDA approved, and were considered the “gold standard” for most patients undergoing coronary artery revascularization (Aldea & Shemin, 1998) which precluded the interaction of history and treatment for this study.

During the consent process, the ability to withdraw from the study was noted, as was a means of contacting the investigator. After informed consent was obtained, preoperative information was documented on the data collection instrument. Routine pre-sternotomy laboratory blood specimens were drawn, appropriate laboratory values documented, and another 8-milliliter specimen of whole blood, properly labeled (date, time and base excess (B.E.)), was obtained in a serum separator tube and stored in a blood cooler. After completion of the procedure, the second specimen was drawn, properly labeled and stored in a blood cooler, as was the final specimen at the six-hour post-operative time period. All specimens were obtained from the radial arterial line.

The blood cooler containing the three specimens was then transported by the researcher to an on site laboratory and all specimens were centrifuged at 6500 x g for 15 minutes, and 1 milliliter of the supernatant decanted into cryogenic tubes, labeled with patient sample sequential number corresponding to their study identification number and stored at −72 degrees centigrade. Once collection of all study specimens was completed, the frozen specimens were transported via a Saf-T-Pak® container to the Erlanger Research Cytokine Laboratory.

Upon arrival at the Erlanger Research Cytokine Laboratory, the specimens were thawed and enzyme-linked immunosorbent assays (ELISA’s) for IL-6 and IL-10 was performed using Pelikine® Tool Kit, Pelikine® compact Human IL-6 ELISA Kit, and
Pelikine® compact Human IL-10 ELISA Kit (Research Diagnostics, Inc., Flanders, NJ).

Assay protocols were followed according to the manufacturer's instructions. Absorbances were measured using a VersaMax® Microplate Reader (Molecular Devices Corporation Sunnyvale, CA) at a wavelength of 450nm with a reference wavelength of 405nm. MMP specimens were transported at −72 degrees centigrade to the Medical University of South Carolina (MUSC) where assays were performed and reported.

Once at MUSC, quantification of MMP species were performed with enzyme-linked immunoassay systems (Amersham Pharmacia Biotech, Buxinghamshire, United Kingdom) using two-site 'sandwich' format. For MMP-2 (RPN 2617) the antiserum used reacts against the proform of MMP-2 (proMMP-2, 72kDa) and does not react against the active form. For MMP-9 (RPN 2614), the antiserum used detects the proform of the enzyme (proMMP-9, 92kDa). The coefficient of variation for these assays systems was 4% to 6%; these systems did not cross-react with other proteases, and the sensitivity was at least 0.6ng/mL.

Absolute values for MMP-2 and MMP-9 were examined using a 2-way analysis of variance in which the treatments were Amicar, Aprotinin, and OP-CAB stratified by time. Pair-wise comparisons were performed using post hoc Bonferroni adjusted t-tests. In order to more carefully examine individual response to CPB and OP-CAB with respect to MMP profiles, computations were performed as a function of baseline values. The comparisons were made using unpaired t-tests in which the mean values will be tested against the null hypothesis of a mean value set to 0. Individual comparisons between treatments were compared utilizing an unpaired t-test. All values were considered significant when a p value of 0.05 or less was detected.
All collectors in the operative suite were perfusionist, properly trained by the principal researcher so that strict data collection protocol was maintained. Data collection continued until all groups involved have the minimal number of participants enrolled to successfully complete the statistical analysis. The follow-up data collection (post-operative data) was completed by the principal researcher, either by direct chart access or by accessing the Chart Max® system at the medical center. Again, all data was separated from patient identification factors and assigned study numbers so that individual patients could not be linked to the data. Codes were accessed by the principal researcher and secured under lock and key. Once the data had been entered into a database, the database had a security code only known to the principal researcher. Data will be stored for a minimal period of three years in a locked safe, and then will be destroyed by shredding.

Data Analysis

Sample Variables

Demographic data was analyzed to assure that groups are matched and representative of the target population. Groups are considered to be ordinal level data, x-bonded versus y-bonded, Amicar versus Aprotinin, OPCAB versus C-CAB. The design of this study allowed for identification of each group and thus the investigator has the ability to apply statistics to numerous variations of the groups for comparative analysis.

Statistical analyses proposed in this study are the t-test, ANOVA, ANCOVA, Chi-square, and descriptive statistics. The t-test was used to determine if a statistical difference exists between two groups means. ANOVA measures the difference between three or more means by comparing the variances both within and across groups. If the ANOVA shows significant results, a post hoc comparison of means will be performed to
determine the location of differences. ANCOVA measures differences among means while controlling the effects of covariate within groups. Application of the ANCOVA and Tukey's HSD test will be applied depending upon the results of the $t$-test and ANOVA. Chi-square will determine how closely observed frequencies or probabilities match expected frequencies or probabilities. Descriptive statistics will allow the researcher to organize and describe the sample and other data.

The $t$-test was used to determine if there is a statistical difference between the interval level data: age (years), left ventricular ejection fraction (LVEF), number of bypass grafts, operative time (min.), cross-clamp time (min.), conduit type and destination, hemoglobin, hematacrit, and platelet count pre- & post-procedure and at 6 hours, use of blood and blood products, intubation times (min.), blood salvaged and returned, height, weight, body surface area (BSA), number of diseased vessels, and the specified inflammatory response for each of the five groups that are to be studied.

Chi-square was used to determine differences between nominal level data: gender, operative technique, circuits, and drug regimes. The ANOVA was used to determine differences among three or more means by comparing the variances both within and across groups, control group (Amicar and Aprotinin), study group (Amicar and Aprotinin) and the OPCAB group. If there was significant, observed differences, a post hoc comparison of means, such as the Tukey HSD test was applied. If it was determined that a demographic variable, such as age or gender, was unequal between groups, the ANCOVA was used to control for the effects of that variable.
Research Variables

The following hypotheses were analyzed with the t-test and ANOVA:

H1. The intra-operative cost of OPCAB is significantly greater than the intra-operative costs of C-CPB patients.

H2. There is no significant difference in the intensive care unit and post ICU hospital length of stay between the OPCAB and C-CPB patients.

H3. There is a significant decrease in the measured inflammatory response in the OPCAB patients from the C-CAB patients.

H4. There is no significant difference between the measured inflammatory response between the x-coated and y-coated circuits for either C-CAB patients.

H5. There is a significant difference in measured compliment mediators between the pharmacological regimes, Aprotinin and Amicar.

H6. There is no significant difference in blood loss between OPCAB and C-CAB patients.

H7. There is a significant decrease in patient care hours with decreased complement mediator activation.

Depending upon the results of the t-test and ANOVA, it proved relevant to ascertain ANCOVA and Tukey's HSD test for further statistical analysis.

Communication

Once completed, this study provided direction for further research involving the techniques and protocols involved. The communication of the findings was a benefit to the nursing, medical, and health communities as well as health care consumers.
The nursing community is strategically involved due to the anticipated shortage of nurses in the near future. Presentation of the collected data, through nursing seminars and educational meetings provides an excellent way to propagate the information. Excellent methods to present and possibly publish the research findings are in conjunction with the Nursing Honor Society, Sigma Theta Tau International, American Society of Extracorporeal Technology, and The Society of Cardiovascular Surgeons. Collaborative groups, nurses, surgeons and hospital administers are other avenues for informing the medical community about the possible improvements shown to be available through the utilization of the findings.

Community informational sessions, once approved by the medical community, can encourage the general population to become more informed and better consumers of their health care dollars, since they are the consumers and will, in the end, be the recipients of improved care at a more efficient rate. Also, the overall health and well being of the general public can be affected by the methods and procedures used to treat their medical conditions.

Addendum

As unforeseen changes can happen during the course of research, this was the ill-timed dilemma that occurred during this study. In a news release, dated June 3, 2003, Jostra Corporation, the provider of the control group (y-coating) circuit, unexpectedly disclosed the intent that, “We ... do not believe that the current Bentley line which consumes a significant amount of our financial and human resource, is our future. We have not been successful in expanding that line and the margins on that business do not allow us to focus on bringing new and better products to the market to improve patient
outcomes. As a result of our focused efforts on the future of perfusion, we have decided to stop manufacturing custom tubing packs and will be closing our Anasco, Puerto-Rico facility” (See Appendix D).

With the discontinuance of the y-coating product, further comparison of the products involved in the study proposal was no longer valid. It was felt by the investigators, that with the uncertainty of product availability due to corporate changes, that it was in the best interest of the study, to terminate data collection after enrollment of enough subjects to validate a portion of the research. Therefore, it was decided to terminate the study after 30 enrollees were obtained in each of the C-CAB groups and 15 enrollees in the OPCAB group.
CHAPTER 4
RESULTS

The estimated number of individuals accessing the health care system in the United States is expected to more than double within the next few decades (Beller, 2001). Cost containment while providing excellent patient outcomes, will become a major issue. It was with this issue in mind that provides the overall basis of this study.

The first purpose of this study was to determine if the intra-operative costs involved with the OPCAB technique were significantly lower than the costs involved with the C-CAB technique. The second purpose was to determine if there was a significant difference between the ICU LOS and the post-ICU LOS between the groups. The third, to determine if there was a significant difference in the measured inflammatory response between the OPCAB and C-CAB groups. The fourth purpose was to identify if there was a significant difference in the measured inflammatory responses between the drug regimes of the C-CAB groups. The fifth purpose was to identify if there was a significant difference in blood loss between the three groups. The last purpose was to identify if there was a difference in patient care hours between the groups due to a difference in the inflammatory response. It should be noted that one of the original purposes of this study was eliminated due to the loss of the comparative portion of the different circuit coatings.

The significant statistical results are revealed in this chapter. The level of significance was set at $p < 0.05$. A 95% Confidence Interval (CI) was determined for each of the research hypothesis.
IRB approval from the university and cooperating hospital was completed in the fall of 2002. Data collection began in the spring of 2003 and was completed in the fall of 2003. The researcher approached a total of 116 eligible patients, successfully enrolling 111 (4% decline rate). Of the 111 enrollees, 75 (35% attrition rate) completed the study without incidence. Of the 36 enrollees dropped, 22 (61%) were due to surgeon requesting full dose Aprotinin, seven (20%) were originally designated as OPCAB but were converted to C-CAB by the surgeon, four (11%) had one or more lab samples with hemolysis, and finally, three (8%) did not have lab specimens drawn by the staff. Data was recorded on the form developed by the researcher.

Sample Demographics

The sample demographics comparing the three groups are displayed in Table 1:

Table 1. Patient Demographics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin $(n = 30)$</th>
<th>Amicar $(n = 30)$</th>
<th>OPCAB $(n = 15)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.2 ± 11.0</td>
<td>59.9 ± 8.4</td>
<td>60.2 ± 11.3</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>83.3%</td>
<td>63.3%</td>
<td>53.3%</td>
</tr>
<tr>
<td>BSA (m2)</td>
<td>2.02</td>
<td>2.02</td>
<td>1.88</td>
</tr>
<tr>
<td>LVEF%</td>
<td>49.33</td>
<td>51.00</td>
<td>55.33</td>
</tr>
<tr>
<td>Hypertensive %</td>
<td>46.66</td>
<td>66.66*</td>
<td>55.33</td>
</tr>
<tr>
<td>Diabetic %</td>
<td>33.33**</td>
<td>60.00**</td>
<td>33.33</td>
</tr>
<tr>
<td>Smoker %</td>
<td>33.33</td>
<td>26.66</td>
<td>20.00</td>
</tr>
</tbody>
</table>

*p < .05
**p < .05 between the C-CAB groups
Description of Findings

Research Hypotheses One

The first research hypothesis stated that the intra-operative cost of OPCAB is significantly greater than the intra-operative cost of C-CPB patients. Variables taken into consideration that can influence intra-operative costs were O.R. time (minutes), overall O.R. costs (room, equipment, personnel), O.R. supplies (disposables), number of bypass grafts performed (distal anastomosis) and number of LIMA conducted. The original intent of the study was to compare the intra-operative pharmacy costs, but the accounting system to charge for pharmacy, at the participating institution, would not permit the breakout of costs to delineate pharmacy costs specific only to the O.R. Therefore, the pharmacy costs reported reflect costs incurred during the entire hospital stay.

Comparisons of the ratio level data were performed between the aforementioned groups. The means and standard deviations were compared between the groups and significance was determined by performing an ANOVA, in combination with post hoc Bonferroni’s adjustment, allowing for the pairwise comparison between the groups.

O.R. Times

The C-CAB with Aprotinin group’s mean O.R. time was 267.66 minutes (SD of 50.45; 95% CI was reported as 248.82 for lower bound and 286.50 for upper bound). The C-CAB with Amicar group’s mean time was the highest at 277.70 minutes (SD of 59.23; 95% CI was reported as 255.58 for lower bound and 299.81 for upper bound). The OPCAB group’s mean time was lowest at 214.00 minutes (SD of 39.76; 95% CI was reported as 191.97 for the lower bound and 236.02 for the upper bound).
There was no significant statistical difference between the C-CAB groups. However, there was a significant statistical difference in mean time between the C-CAB with Aprotinin and the OPCAB group \((p < .005)\). There was a significant statistical difference between the C-CAB with Amicar group and the OPCAB group \((p < .001)\).

**O.R. Costs**

The C-CAB with Aprotinin group’s mean total O.R. cost was $8559.13 (SD of $1056.61; 95% CI was reported as $8164.58 for lower bound and $8953.67 for the upper bound). The C-CAB with Amicar group’s mean total O.R. cost was $9096.40 (SD of $1859.16; 95% CI was reported as $8402.17 for lower bound and $9790.62 for upper bound). The OPCAB group’s mean total O.R. cost was reported as $8442.86 (SD of $1482.63; 95% CI was reported as $7621.81 for lower bound and $9263.92 for upper bound). There was no significant statistical difference among any of the groups.

The C-CAB with Aprotinin group’s mean O.R. supply cost was $3889.66 (SD of $685.91; 95% CI was reported as $3633.54 for the lower bound and $4145.79 for the upper bound). The C-CAB with Amicar group’s mean O.R. supply cost was $3934.30 (SD of $1198.46; 95% CI was reported as $3486.78 for the lower bound and $4381.81 for the upper bound). The OPCAB group’s mean O.R. cost was $4014.13 (SD of $1084.77; 95% CI was reported as $3413.40 for the lower bound and $4614.86 for the upper bound). There was no significance statistical difference in supply costs among any of the groups.

**Pharmacy Costs**

The C-CAB with Aprotinin group’s mean cost was $2553.76 (SD of $1305.61; 95% CI was reported as $2066.24 for the lower bound and $3041.29 for the upper
bound). The C-CAB with Amicar group’s mean cost was $2654.33 (SD of $3502.66; 95% CI was reported as $1346.41 for the lower bound and $3962.25 for the upper bound). The OPCAB group’s mean cost was $1710.93 (SD of $1147.01; 95% CI was reported as $1075.73 for the lower bound and $2346.13 for the upper bound). There was no significant statistical difference among the groups.

Distal Anastomosis

The C-CAB with Aprotinin group had the highest mean number at 4.33 (SD of 1.21; 95% CI was reported as 3.88 for the lower bound and 4.78 as the upper bound). The C-CAB with Amicar group’s mean number was 3.90 (SD of 1.26; 95% CI was reported as 3.42 for the lower bound and 4.37 as the upper bound). The OPCAB group mean number was lowest at 2.86 (SD of 1.12; 95% CI was reported as 2.24 for the lower bound and 3.48 for the upper bound). There was a significant statistical difference among the groups, \( p < .01 \) between the C-CAB with Aprotinin group and the OPCAB group, and \( p < .05 \) between the C-CAB with Amicar group and the OPCAB group.

LIMA

The final arm of Hypothesis One is the number of LIMA conducted. The C-CAB with Aprotinin group’s mean was 0.96 (SD of 0.18, 95% CI was reported as 0.89 for the lower bound and 1.03 for the upper bound). The C-CAB with Amicar group’s mean was 0.93 (SD of 0.25; 95% CI was reported as 0.83 for the lower bound and 1.02 as the upper bound). The OPCAB group mean was reported as 0.93 (SD of 0.25; 95% CI was reported as 0.79 for the lower bound and 1.07 for the upper bound). There was no significant statistical difference among the groups.
Graphic representations of these findings are displayed in Table 2.

Table 2. Intra-Operative Cost Factors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin (n = 30)</th>
<th>Amicar (n = 30)</th>
<th>OPCAB (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O.R. Time (min.)</td>
<td>267.66 ± 50.45*</td>
<td>277.70 ± 59.13**</td>
<td>214.00 ± 39.76</td>
</tr>
<tr>
<td>Total O.R. Cost</td>
<td>$8559.13</td>
<td>$9096.40</td>
<td>$8442.86</td>
</tr>
<tr>
<td>O.R. Supply Cost</td>
<td>$3889.66</td>
<td>$3934.30</td>
<td>$4014.13</td>
</tr>
<tr>
<td>Pharmacy Cost #</td>
<td>$2553.76</td>
<td>$2654.33</td>
<td>$1710.93</td>
</tr>
<tr>
<td>Distal Anastomosis</td>
<td>4.33**</td>
<td>3.90*</td>
<td>2.86</td>
</tr>
<tr>
<td>LIMA Conducted</td>
<td>0.96</td>
<td>0.93</td>
<td>0.93</td>
</tr>
</tbody>
</table>

*p < .05
**p < .01

# Total Hospital Pharmacy Costs

Research Hypotheses Two

The second research hypothesis stated that there was no significant difference in the ICU and post ICU hospital LOS between the OPCAB and C-CPB patients. There were again three groups involved: C-CAB with Aprotinin, C-CAB with Amicar, and OPCAB. Variables that were observed were: extubation from the ventilator (minutes), LOS in ICU (days), LOS in the hospital (days) and total LOS (days). Comparisons of the ratio level data were performed among the aforementioned groups. The means and SD were compared between the groups and significance was determined by performing an ANOVA post hoc with Bonferroni’s adjustment, allowing for the pairwise comparison among the groups.
Extubation Times

The C-CAB with Aprotinin group’s mean extubation time was 462.43 minutes (SD of 188.00; 95% CI was reported as 392.23 for the lower bound and 532.63 for the upper bound). The C-CAB with Amicar group had a mean extubation time of 487.33 minutes (SD of 294.86; 95% CI was reported as 377.23 for the lower bound and 597.43 for the upper bound). The OPCAB group’s mean extubation time was 377.40 minutes (SD of 90.69; 95% CI was reported as 327.17 for the lower bound and 427.62 for the upper bound). There was no significant statistical difference among the groups.

LOS ICU

The C-CAB with Aprotinin group’s mean ICU stay was 1.56 days (SD of 1.14; 95% CI was reported as 1.14 for the lower bound and 1.99 for the upper bound). The C-CAB with Amicar group had a mean ICU stay of 2.77 days (SD of 5.42; 95% CI was reported as 0.75 for the lower bound and 4.79 for the upper bound). The OPCAB group’s mean ICU stay was 1.13 days (SD of 0.64; 95% CI was reported as 0.77 for the lower bound and 1.49 for the upper bound). There was no significant statistical difference among the groups.

LOS Hospital

The C-CAB with Aprotinin group’s mean hospital stay was 4.46 days (SD of 3.05; 95% CI was reported as 3.31 for the lower bound and 5.60 for the upper bound). The C-CAB with Amicar group had a mean hospital stay of 5.12 days (SD of 3.76; 95% CI was reported as 3.72 for the lower bound and 6.52 for the upper bound). The OPCAB group’s mean hospital stay was 4.86 days (SD of 4.30; 95% CI was reported as 2.48 for
the lower bound and 7.25 for the upper bound). There was no significant statistical difference among the groups.

Total LOS

The C-CAB with Aprotinin group’s mean total post-operative stay was 6.02 days (SD of 3.23; 95% CI was reported as 4.81 for the lower bound and 7.23 for the upper bound). The C-CAB with Amicar group had a mean total post-operative stay of 7.89 days (SD of 5.74; 95% CI was reported as 5.75 for the lower bound and 10.04 for the upper bound). The OPCAB group’s mean total post-operative stay was 6.00 days (with a SD of 4.43; 95% CI was reported as 3.55 for the lower bound and 8.45 for the upper bound). There was no significant statistical difference among the groups.

Graphic representations of these findings are displayed in Table 3.

Table 3. Length of Stay

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin (n = 30)</th>
<th>Amicar (n = 30)</th>
<th>OPCAB (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extubation (mins.)</td>
<td>462.43 ± 188.00</td>
<td>487.33 ± 294.86</td>
<td>377.40 ± 90.69</td>
</tr>
<tr>
<td>LOS ICU (days)*</td>
<td>1.56 ± 1.14</td>
<td>2.77 ± 5.42</td>
<td>1.13 ± 0.64</td>
</tr>
<tr>
<td>LOS Hosp. (days)*</td>
<td>4.46 ± 3.05</td>
<td>5.12 ± 3.76</td>
<td>4.86 ± 4.30</td>
</tr>
<tr>
<td>Total LOS (days)*</td>
<td>6.02 ± 3.23</td>
<td>7.89 ± 5.74</td>
<td>6.00 ± 4.43</td>
</tr>
</tbody>
</table>

* Post-op

Research Hypotheses Three

The third research hypothesis stated that there was a significant decrease in the measured inflammatory response in the OPCAB vs. the C-CAB patients. The groups that were observed remain the same as for the previous hypotheses. Variables that were observed were: pre-IL-6 & 10, pre-MMP-2 & 9; post-protamine IL-6 &10, post-
protamine MMP-2 & 9; and IL-6 & 10 and MMP-2 & 9 drawn six hours post-op. These results are reported in picograms/milliliter (pg/ml). All C-CAB post- and six-hour results were corrected to account for hemodilution effects. Comparisons of the ratio level data were performed among the aforementioned groups. The means and SD were compared among the groups and significance was determined by performing an ANOVA with post hoc Bonferroni’s adjustment, again allowing for the pairwise comparison among the groups.

*Pre-IL-6*

The C-CAB with Aprotinin group had a mean of 7.24 (SD of 9.45; 95% CI was reported as 3.76 for the lower bound and 10.78 for the upper bound). The C-CAB with Amicar group had the lowest mean of 3.11 (SD of 4.48; 95% CI was reported as 1.44 for the lower bound and 4.79 for the upper bound). The OPCAB group had the highest mean at 23.90 (SD of 43.61; 95% CI was reported as -.248 for the lower bound and 48.05 for the upper bound). There was significant statistical difference among the C-CAB groups and the OPCAB group (*p* < .05).

*Pre-IL-10*

The C-CAB with Aprotinin group had a mean of 77.88 (SD of 95.00; 95% CI was reported as 42.11 for the lower bound and 113.36 for the upper bound). The C-CAB w/Amicar group had a mean of 117.06 (SD of 381.00; 95% CI was reported as -25.21 for the lower bound and 259.33 for the upper bound). The OPCAB group had a mean of 41.28 (SD of 40.25; 95% CI was reported as 18.99 for the lower bound and 63.57 for the upper bound). There was no significant statistical difference among the groups.
Pre-MMP-2

The C-CAB with Aprotinin group had a mean of 1190 (SD of ±71). The C-CAB with Amicar group had a mean of 1315 (SD of ±75). The OPCAB group had a mean of 1279.00 (SD of ±131). There was no significant statistical difference among the groups.

Pre-MMP-9

The results showed that the C-CAB with Aprotinin group had a mean of 60 (SD of ±5). The C-CAB with Amicar group had a mean of 67 (SD of ±7). The OPCAB group had a mean of 68 (SD of ±5). There was no significant statistical difference among the groups.

Graphic representations of these findings are displayed in Table 4.

Table 4. Baseline Inflammatory Measurements.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin (n = 30)</th>
<th>Amicar (n = 30)</th>
<th>OPCAB (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-IL-6</td>
<td>7.24 ± 9.45</td>
<td>3.11 ± 4.48</td>
<td>23.90 ± 43.60*</td>
</tr>
<tr>
<td>Pre-IL-10</td>
<td>77.88 ± 95.00</td>
<td>117.06 ± 381.00</td>
<td>41.28 ± 40.25</td>
</tr>
<tr>
<td>Pre-MMP-2</td>
<td>1190 ± 71</td>
<td>1315 ± 75</td>
<td>1279 ± 131</td>
</tr>
<tr>
<td>Pre-MMP-9</td>
<td>60 ± 5</td>
<td>67 ± 7</td>
<td>68 ± 5</td>
</tr>
</tbody>
</table>

*p < .05 vs. C-CAB

Post-Protamine IL-6

The C-CAB with Aprotinin group had a mean of 63.17 (SD of 45.73; 95% CI was reported as 46.09 for the lower bound and 80.25 for the upper bound). The C-CAB with Amicar group had a mean of 90.19 (SD of 124.61; 95% CI was reported as 43.66 for the lower bound and 136.72 for the upper bound). The OPCAB group had a mean of 37.45
(SD of 54.42; 95% CI was reported as 7.31 for the lower bound and 67.58 for the upper bound). There was no significant statistical difference among the groups.

**Post-Protamine IL-10**

The C-CAB with Aprotinin group had a mean of 242.00 (SD of 323.46; 95% CI was reported as 121.21 for the lower bound and 362.79 for the upper bound). The C-CAB with Amicar group had a mean of 217.32 (SD of 283.48; 95% CI was reported as 111.46 for the lower bound and 323.17 for the upper bound). The OPCAB group had a mean of 75.69 (SD of 57.32; 95% CI was reported as 43.94 for the lower bound and 107.44 for the upper bound). There was no significant statistical difference among the groups.

**Post-Protamine MMP-2**

The C-CAB with Aprotinin group had a mean of 1391 (SD of ±80). The C-CAB with Amicar group had the highest mean of 1574 (SD of ±79). The OPCAB group had the lowest mean of 1178 (SD of ±67). There was significant statistical difference among the C-CAB groups and the OPCAB group ($p < .05$).

**Post-Protamine MMP-9**

The C-CAB with Aprotinin group had the lowest mean of 45 (SD of ±3). The C-CAB with Amicar group had a mean of 61 (SD of ±9). The OPCAB group had the highest mean of 75 (SD of ±7). There were significant statistical differences between the C-CAB groups and the OPCAB group ($p < .05$). Also noted a significant statistical difference between the baseline C-CAB with Aprotinin and the post-Protamine level in this group ($p < .05$).
Graphic representations of these findings are displayed in Table 5.

**Table 5. Post-Operative Inflammatory Measurement.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin ($n = 30$)</th>
<th>Amicar ($n = 30$)</th>
<th>OPCAB ($n = 15$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post IL-6</td>
<td>$63.17 \pm 45.73$</td>
<td>$90.19 \pm 124.61$</td>
<td>$37.45 \pm 54.42$</td>
</tr>
<tr>
<td>Post IL-10</td>
<td>$242.00 \pm 323.46$</td>
<td>$217.32 \pm 283.48$</td>
<td>$75.69 \pm 57.32$</td>
</tr>
<tr>
<td>Post MMP-2</td>
<td>$1391 \pm 80$</td>
<td>$1547 \pm 79$</td>
<td>$1178 \pm 67^{**}$</td>
</tr>
<tr>
<td>Post MMP-9</td>
<td>$45 \pm 3^{*}$</td>
<td>$61 \pm 9$</td>
<td>$75 \pm 7^{**}$</td>
</tr>
</tbody>
</table>

* $p < .05$ vs. baseline  
** $p < .05$ vs. C-CAB

**Six-Hour IL-6**

The C-CAB with Aprotinin group had a mean of 82.14 (SD of 48.47; 95% CI was reported as 64.04 for the lower bound and 100.24 for the upper bound). The C-CAB with Amicar group had a mean of 175.31 (SD of 241.23; 95% CI was reported as 85.23 for the lower bound and 265.39 for the upper bound). The OPCAB group had a mean of 103.15 (SD of 74.86; 95% CI was reported as 61.69 for the lower bound and 144.61 for the upper bound). There was no significant statistical difference among the groups.

**Six-Hour IL-10**

The C-CAB with Aprotinin group had a mean of 81.21 (SD of 124.84; 95% CI was reported as 34.72 for the lower bound and 127.69 for the upper bound). The C-CAB with Amicar group had a mean of 48.33 (SD of 84.38; 95% CI was reported as 16.82 for the lower bound and 79.84 for the upper bound). The OPCAB group had a mean of 71.10 (SD of 91.78; 95% CI was reported as 20.27 for the lower bound and 121.93 for the upper bound). There was no significant statistical difference among the groups.
Six-Hour MMP-2

The C-CAB with Aprotinin group had the highest mean of 1247 (SD of ±44). The C-CAB with Amicar group had a mean of 1400 (SD of ±88). The OPCAB group had the lowest mean of 1013 (SD of ±68). There were significant statistical differences among the C-CAB group and the OPCAB group ($p < .05$).

Six-Hour MMP-9

The C-CAB with Aprotinin group had a mean of 79 (SD of ±4). The C-CAB with Amicar group had a mean of 92 (SD of 10). The OPCAB group had a mean of 99 (SD of ±11). There were significant statistical difference among all groups and their respective baseline measurements ($p < .05$).

Graphic representations of these findings are displayed in Table 6.

Table 6. 6-Hour Inflammatory Measurements.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin ($n=30$)</th>
<th>Amicar ($n=30$)</th>
<th>OPCAB ($n=15$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 hr. IL-6</td>
<td>82.14 ± 48.47</td>
<td>175.31 ± 241.23</td>
<td>103.15 ± 74.86</td>
</tr>
<tr>
<td>6 hr. IL-10</td>
<td>81.21 ± 124.84</td>
<td>48.33 ± 84.38</td>
<td>71.10 ± 91.78</td>
</tr>
<tr>
<td>6 hr. MMP-2</td>
<td>1247 ± 44</td>
<td>1400 ± 88</td>
<td>1013 ± 68**</td>
</tr>
<tr>
<td>6 hr. MMP-9</td>
<td>79 ±4*#</td>
<td>92 ± 10*</td>
<td>99 ± 11*</td>
</tr>
</tbody>
</table>

* $p < .05$ vs. baseline
** $p < .05$ vs. C-CAB
# $p < .05$ vs. Post
Research Hypotheses Four

The fourth research hypothesis stated there was no significant difference in the measured inflammatory response between the x-coated and y-coated circuits for C-CAB patients. As previously noted, with the discontinuance of the y-coating product, further comparison of the products involved in the study proposal was no longer valid.

It was felt by the investigators, that with the uncertainty of product availability due to corporate changes, that it was in the best interest of the study, to terminate data collection after enrollment of enough subjects to validate the rest of the research. Therefore, the study was terminated after 30 enrollees were obtained in each of the C-CAB groups and 15 enrollees in the OPCAB group. With this change, the fourth hypothesis will not be reported.

Research Hypotheses Five

The fifth hypothesis stated there was a significant difference in measured compliment mediators between the pharmacological regimes, Aprotinin and Amicar. Variables observed and statistical analyses remain the same as utilized for Hypothesis Three.

Pre-IL-6

The C-CAB with Aprotinin group had a mean pre-IL-6 count of 7.24 (SD of 9.45; a 95% CI was reported as 3.76 for the lower bound and 10.78 for the upper bound). The C-CAB with Amicar group had a mean of 3.11 (SD of 4.48; a 95% CI was reported as 1.44 for the lower bound and 4.79 for the upper bound). There was no significant statistical difference between the groups.
Pre-IL-10

The C-CAB with Aprotinin group had a mean pre-IL-10 count of 77.88 (SD of 95.00; a 95% CI was reported as 42.11 for the lower bound and 113.36 for the upper bound). The C-CAB with Amicar group had a mean of 117.06 (SD of 381.00; a 95% CI was reported as -25.21 for the lower bound and 259.33 for the upper bound). There was no significant statistical difference between the groups.

Pre-MMP-2

The C-CAB with Aprotinin group had a mean pre-MMP-2 count of 1190 (SD of ±71). The C-CAB with Amicar group had a mean of 1315 (SD of ±75). There was no significant statistical difference between the groups.

Pre-MMP-9

The C-CAB with Aprotinin group had a mean pre-MMP-9 count of 60 (SD of ±5). The C-CAB with Amicar group had a mean of 67 (SD of ±7). There was no significant statistical difference between the groups.

Graphic representations of these findings are displayed in Table 7.

Table 7. C-CAB Baseline Inflammatory Measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin (n = 30)</th>
<th>Amicar (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-IL-6</td>
<td>7.24 ± 9.45</td>
<td>3.11 ± 4.48</td>
</tr>
<tr>
<td>Pre-IL-10</td>
<td>77.88 ± 95.00</td>
<td>117.06 ± 381.00</td>
</tr>
<tr>
<td>Pre-MMP-2</td>
<td>1190 ± 71</td>
<td>1315 ± 75</td>
</tr>
<tr>
<td>Pre-MMP-9</td>
<td>60 ± 5</td>
<td>67 ± 7</td>
</tr>
</tbody>
</table>
Post-Protamine IL-6

The C-CAB with Aprotinin group had a mean post-Protamine IL-6 count of 63.17 (SD of 45.73; a 95% CI was reported as 46.09 for the lower bound and 80.25 for the upper bound). The C-CAB with Amicar group had a mean of 90.19 (SD of 124.61; a 95% CI was reported as 43.66 for the lower bound and 136.72 for the upper bound). There was no significant statistical difference between the groups.

Post-Protamine IL-10

The C-CAB with Aprotinin group had a mean post-Protamine IL-10 count of 242.00 (SD of 323.46; a 95% CI was reported as 121.21 for the lower bound and 362.79 for the upper bound). The C-CAB with Amicar group had a mean of 217.32 (SD of 283.48; a 95% CI was reported as 111.46 for the lower bound and 323.17 for the upper bound). There was no significant statistical difference between the groups.

Post-Protamine MMP-2

The C-CAB with Aprotinin group had the lower mean post-Protamine MMP-2 count of 1391 (SD of ±80). The C-CAB with Amicar group had the higher mean of 1574 (SD of ±79). There was significant statistical difference between the groups.

Post-Protamine MMP-9

The C-CAB with Aprotinin group had a mean post-Protamine MMP-9 count of 45 (SD of ±3). The C-CAB with Amicar group had a mean of 61 (SD of ±9). There was no statistical difference between the groups, although a statistical significant difference between the baseline C-CAB with Aprotinin and the post-Protamine level in this group ($p < .05$) was noted.
Graphic representations of these findings are displayed in Table 8.

Table 8. C-CAB Post-Inflammatory Measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin (n = 30)</th>
<th>Amicar (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post IL-6</td>
<td>63.17 ± 45.73</td>
<td>90.19 ± 124.61</td>
</tr>
<tr>
<td>Post IL-10</td>
<td>242.00 ± 323.46</td>
<td>217.32 ± 283.48</td>
</tr>
<tr>
<td>Post MMP-2</td>
<td>1391 ± 80</td>
<td>1547 ± 79</td>
</tr>
<tr>
<td>Post MMP-9</td>
<td>45 ± 3*</td>
<td>61 ± 9</td>
</tr>
</tbody>
</table>

*p < .05 vs. baseline

Six-Hour IL-6

The C-CAB with Aprotinin group had a mean six-hour IL-6 count of 82.14 (SD of 48.47; a 95% CI was reported as 64.04 for the lower bound and 100.24 for the upper bound). The C-CAB with Amicar group had a mean of 175.31 (SD of 241.23; a 95% CI was reported as 85.23 for the lower bound and 265.39 for the upper bound). There was no significant statistical difference between the groups.

Six-Hour IL-10

The C-CAB with Aprotinin group had a mean six-hour IL-10 count of 81.21 (SD of 124.84; a 95% CI was reported as 34.72 for the lower bound and 127.69 for the upper bound). The C-CAB with Amicar group had a mean of 48.33 (SD of 84.38; a 95% CI was reported as 16.82 for the lower bound and 79.84 for the upper bound). There was no significant statistical difference between the groups.
Six-hour MMP-2

The C-CAB with Aprotinin group had a mean six-hour MMP-2 count of 1247 (SD of ±44). The C-CAB with Amicar group had a mean of 1400 (SD of ±88). There was no significant statistical difference between the groups.

Six-hour MMP-9

The C-CAB with Aprotinin group had a mean six-hour MMP-9 count of 79 (SD of ±4). The C-CAB with Amicar group had a mean of 92 (SD of 10). There was significant statistical difference from each group’s baseline measurements ($p < .05$).

Graphic representations of these findings are displayed in Table 9.

Table 9. C-CAB 6-Hour Post-Inflammatory Measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin ($n = 30$)</th>
<th>Amicar ($n = 30$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 hr. IL-6</td>
<td>82.14 ± 48.47</td>
<td>175.31 ± 241.23</td>
</tr>
<tr>
<td>6 hr. IL-10</td>
<td>81.21 ± 124.84</td>
<td>48.33 ± 84.38</td>
</tr>
<tr>
<td>6 hr. MMP-2</td>
<td>1247 ± 44</td>
<td>1400 ± 88</td>
</tr>
<tr>
<td>6 hr. MMP-9</td>
<td>79 ±4**</td>
<td>92 ± 10*</td>
</tr>
</tbody>
</table>

*p < .05 vs. baseline

**p < .05 vs. Post

Research Hypotheses Six

The sixth research hypothesis stated there was no significant difference in blood loss between OPCAB and C-CAB patients. There were again three groups involved: C-CAB with Aprotinin, C-CAB with Amicar, and OPCAB. Variables that were observed were pre-operative, post-protamine, and six-hour post-operative hemoglobin (Hgb.) mg/dl, hematocrit (Hct.) mg%, and platelet count (Plat.) K/dl. White blood cell counts
(WBC) K/dl was only reported in the pre-operative time frame. The amount, in units, of packed red blood cells (PRBC), platelets (Plat.), fresh frozen plasma (FFP) and cryoprecipitate (Cryo.) was reported for the intra-operative period as well as total amounts given in the first 24 hours post-operatively. The amount of cell salvage returned was reported in milliliters (ml). All cell salvage volume was returned to all subjects. The final variable reported was the 24-hour chest tube drainage (ml). Comparisons of the ratio level data were performed between the aforementioned groups and significance was determined by performing an ANOVA in combination with post hoc Bonferroni’s adjustment.

Pre-Hgb.

The C-CAB with Aprotinin group had a mean pre-Hgb. of 12.80 (SD of 1.62; a 95% CI was reported as 12.19 for the lower bound and 13.40 for the upper bound). The CAB with Amicar group had a mean of 11.96 (SD of 1.54; a 95% CI was reported as 11.39 for the lower bound and 12.54 for the upper bound). The OPCAB group had a mean of 12.34 (SD of 1.94; a 95% CI was reported as 11.26 for the lower bound and 13.41 for the upper bound). There was no significant statistical difference among the groups.

Pre-Hct.

The C-CAB with Aprotinin group had a mean pre-Hct. of 37.03 (SD of 5.03; a 95% CI was reported as 35.15 for the lower bound and 38.91 for the upper bound). The C-CAB with Amicar group had a mean of 35.03 (SD of 4.71; a 95% CI was reported as 33.27 for the lower bound and 36.79 for the upper bound). The OPCAB group had a mean of 34.74 (SD of 8.07; a 95% CI was reported as 30.27 for the lower bound and
39.21 for the upper bound). There was no significant statistical difference among the groups.

Pre-Plat.

The C-CAB with Aprotinin group had the lowest mean count of 195.73 (SD of 56.7; a 95% CI was reported as 174.55 for the lower bound and 216.91 for the upper bound). The C-CAB with Amicar group had a mean of 201.66 (SD of 58.29; a 95% CI was reported as 179.90 for the lower bound and 223.43 for the upper bound). The OPCAB group had the highest mean of 248.60 (SD of 76.86; a 95% CI was reported as 206.03 for the lower bound and 291.16 for the upper bound). There were significant statistical differences between the OPCAB and Aprotinin groups ($p < .05$).

Pre-WBC

The C-CAB with Aprotinin group had a mean of 7.79 (SD of 1.62; a 95% CI was reported as 7.18 for the lower bound and 8.40 for the upper bound). The C-CAB with Amicar group had a mean of 7.55 (SD of 1.87; a 95% CI was reported as 6.85 for the lower bound and 8.25 for the upper bound). The OPCAB group had a mean of 7.48 (SD of 2.12; a 95% CI was reported as 6.31 for the lower bound and 8.66 for the upper bound). There was no significant statistical difference among the groups.
Graphic representations of these findings are displayed in Table 10.

**Table 10. Baseline Laboratory Values**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin (n = 30)</th>
<th>Amicar (n = 30)</th>
<th>OPCAB (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Hgb.</td>
<td>12.80 ± 1.62</td>
<td>11.96 ± 1.54</td>
<td>12.34 ± 1.94</td>
</tr>
<tr>
<td>Pre-Hct.</td>
<td>37.03 ± 5.03</td>
<td>35.03 ± 4.71</td>
<td>34.74 ± 8.07</td>
</tr>
<tr>
<td>Pre-Plat.</td>
<td>195.73 ± 56.72*</td>
<td>201.66 ± 58.29</td>
<td>248.60 ± 76.86</td>
</tr>
<tr>
<td>Pre-WBC</td>
<td>7.79 ± 1.62</td>
<td>7.55 ± 1.87</td>
<td>7.48 ± 2.12</td>
</tr>
</tbody>
</table>

*p < .05 vs. OPCAB group

**Intra-Operative PRBC Usage**

The C-CAB with Aprotinin group had a mean intra-operative PRBC usage of 0.20 (SD of 0.80; a 95% CI was reported as -0.10 for the lower bound and 0.50 for the upper bound). The C-CAB with Amicar group had a mean of 0.46 (SD of 1.00; a 95% CI was reported as -1.39 for the lower bound and 0.84 for the upper bound). The OPCAB group had a mean of 0.13 (SD of 0.51; a 95% CI was reported as -0.15 for the lower bound and 0.41 for the upper bound). There was no significant statistical difference among the groups.

**Intra-Operative FFP Usage**

The C-CAB with Aprotinin and OPCAB groups had none administered. The C-CAB with Amicar group had a mean of 0.02 (SD of 0.36; a 95% CI was reported as -6.96 for the lower bound and 0.20 for the upper bound). There was no significant statistical difference among the groups.
Intra-Operative Platelet Usage

The C-CAB with Aprotinin and OPCAB groups had none given. The C-CAB with Amicar group had a mean intra-operative platelet usage of 0.20 (SD of 1.09; a 95% CI was reported as -0.20 for the lower bound and 0.60 for the upper bound). There was no significant statistical difference among the groups.

Cryoprecipitate Usage

There was none given to any of the groups during the intra-operative or post-operative periods.

Post-Protamine Hgb.

The C-CAB with Aprotinin group had a mean post-Protamine Hgb. of 9.2 (SD of 1.29; a 95% CI was reported as 8.71 for the lower bound and 9.68 for the upper bound). The C-CAB with Amicar group had the lowest mean of 9.06 (SD of 1.20; a 95% CI was reported as 8.61 for the lower bound and 9.51 for the upper bound). The OPCAB group had the highest mean of 10.6 (SD of 1.44; a 95% CI was reported as 9.86 for the lower bound and 11.46 for the upper bound). There were significant statistical differences among the OPCAB and C-CAB groups ($p < .05$).

Post-Protamine Hct.

The C-CAB with Aprotinin group had a mean’post-Protamine Hgb. of 27.0 (SD of 3.35; a 95% CI was reported as 25.74 for the lower bound and 28.25 for the upper bound). The C-CAB with Amicar group had the lowest mean of 26.46 (SD of 3.08; a 95% CI was reported as 25.31 for the lower bound and 27.61 for the upper bound). The OPCAB group had the highest mean of 31.26 (SD of 4.54; a 95% CI was reported as
28.75 for the lower bound and 33.78 for the upper bound). There were significant statistical differences among the OPCAB and C-CAB groups ($p < .01$).

Graphic representations of these findings are displayed in Table 11.

**Table 11. Intra-Operative Blood Product Usage**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin ($n = 30$)</th>
<th>Amicar ($n = 30$)</th>
<th>OPCAB ($n = 15$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-OP PRBC</td>
<td>0.20 ± 0.80</td>
<td>0.46 ± 1.00</td>
<td>0.13 ± 0.51</td>
</tr>
<tr>
<td>Intra-OP FFP</td>
<td>0.00 ± 0.00</td>
<td>0.02 ± 0.36</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>Intra-OP Plat.</td>
<td>0.00 ± 0.00</td>
<td>0.20 ± 1.09</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>Intra-OP Cryo.</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>Post-Prot. Hgb.</td>
<td>9.20 ± 1.29*</td>
<td>9.06 ± 1.20*</td>
<td>10.66 ± 1.44</td>
</tr>
<tr>
<td>Post-Prot. Hct.</td>
<td>27.00 ± 3.35**</td>
<td>26.46 ± 3.08**</td>
<td>31.26 ± 4.54</td>
</tr>
</tbody>
</table>

*p < .05 vs. OPCAB group

**p < .01 vs. OPCAB group

*Six-Hour Post-Operative Hgb.*

The C-CAB with Aprotinin group had a mean six-hour post-operative Hgb. of 11.21 (SD of 1.43; a 95% CI was reported as 10.67 for the lower bound and 11.74 for the upper bound). The C-CAB with Amicar group had the lowest mean of 10.47 (SD of 1.09; a 95% CI was reported as 10.06 for the lower bound and 10.88 for the upper bound). The OPCAB group had the highest mean of 11.46 (SD of 1.18; a 95% CI was reported as 10.81 for the lower bound and 12.12 for the upper bound). There were significant statistical differences between the OPCAB and C-CAB with Amicar groups ($p < .05$).

*Six-Hour Post-Operative Hct.*

The C-CAB with Aprotinin group had a mean six-hour post-operative Hct. of 32.39 (SD of 3.93; a 95% CI was reported as 30.92 for the lower bound and 33.85 for the
upper bound). The C-CAB with Amicar group had a mean of 30.82 (SD of 3.35; a 95% CI was reported as 29.56 for the lower bound and 32.07 for the upper bound). The OPCAB group had a mean of 33.57 (SD of 3.45; a 95% CI was reported as 31.66 for the lower bound and 35.48 for the upper bound). There was no significant statistical difference among the groups.

*Six-Hour Post-Operative Platelets*

The C-CAB with Aprotinin group had a mean six-hour post-operative platelet count of 148.23 (SD of 137.17; a 95% CI was reported as 134.35 for the lower bound and 162.11 for the upper bound). The C-CAB with Amicar group had the lowest mean of 140.86 (SD of 40.21; a 95% CI was reported as 125.85 for the lower bound and 155.88 for the upper bound). The OPCAB group had the highest mean of 184.80 (SD of 41.71; a 95% CI was reported as 161.69 for the lower bound and 207.90 for the upper bound). There were significant statistical differences among the OPCAB and C-CAB with Aprotinin ($p < .05$) and C-CAB with Amicar ($p < .01$).

Graphic representations of these findings are displayed in Table 12.

**Table 12. 6-Hour Laboratory Values**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin ($n = 30$)</th>
<th>Amicar ($n = 30$)</th>
<th>OPCAB ($n = 15$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Hr. Hgb.</td>
<td>11.21 ± 1.43</td>
<td>10.47 ± 1.09*</td>
<td>11.46 ± 1.18</td>
</tr>
<tr>
<td>6 Hr. Hct</td>
<td>32.39 ± 3.93</td>
<td>30.82 ± 3.35</td>
<td>33.57 ± 3.45</td>
</tr>
<tr>
<td>6 Hr. Plat.</td>
<td>148.23 ± 37.17*</td>
<td>140.86 ± 40.21**</td>
<td>184.80 ± 41.71</td>
</tr>
</tbody>
</table>

* $p < .05$ vs. OPCAB group
** $p < .01$ vs. OPCAB group
Twenty-Four Hour Post-Operative PRBC Usage

The C-CAB with Aprotinin group had a mean twenty-four hour post-operative PRBC usage of 0.56 (SD of 1.04; a 95% CI was reported as 0.17 for the lower bound and 0.95 for the upper bound). The C-CAB with Amicar group had the highest mean of 1.46 (SD of 2.14; a 95% CI was reported as 0.66 for the lower bound and 2.26 for the upper bound). The OPCAB group had the lowest mean of 0.26 (SD of 0.70; a 95% CI was reported as 0.12 for the lower bound and 0.65 for the upper bound). There were significant statistical differences between the OPCAB and C-CAB w/Amicar ($p < .05$).

Twenty-Four Hour Post-Operative FFP Usage

The C-CAB with Aprotinin group had a mean twenty-four hour post-operative FFP usage of 0.13 (SD of 0.73; a 95% CI was reported as −0.13 for the lower bound and 0.40 for the upper bound). The C-CAB with Amicar group had a mean of 0.16 (SD of 0.53; a 95% CI was reported as −3.14 for the lower bound and 0.36 for the upper bound). The OPCAB group had no usage. There was no significant statistical difference among the groups.

Twenty-Four Hour Post-Operative Platelet Usage

The C-CAB with Aprotinin group had a mean twenty-four hour post-operative platelet usage of 0.20 (SD of 1.09; a 95% CI was reported as −0.20 for the lower bound and 0.60 for the upper bound). The C-CAB with Amicar group had a mean of 0.60 (SD of 1.83; a 95% CI was reported as −8.36 for the lower bound and 1.28 for the upper bound). The OPCAB group had no usage. There was no significant statistical difference among the groups.
Cell Salvage Return

The C-CAB with Aprotinin group had the highest mean cell salvage return of 861.66 (SD of 145.43; a 95% CI was reported as 807.35 for the lower bound and 915.97 for the upper bound). The C-CAB with Amicar group had a mean of 776.66 (SD of 148.40; a 95% CI was reported as 721.25 for the lower bound and 832.08 for the upper bound). The OPCAB group had the lowest mean of 367.53 (SD of 389.82; a 95% CI was reported as 151.65 for the lower bound and 583.40 for the upper bound). There were significant statistical differences between the OPCAB and C-CAB groups ($p < .01$).

Twenty-four Hour Chest Tube Output

The C-CAB with Aprotinin group had a mean of 422.50 (SD of 248.85; a 95% CI was reported as 329.57 for the lower bound and 515.42 for the upper bound). The C-CAB with Amicar group had a mean of 596.43 (SD of 370.40; a 95% CI was reported as 458.12 for the lower bound and 734.74 for the upper bound). The OPCAB group had a mean of 399.00 (SD of 171.11; a 95% CI was reported as 304.24 for the lower bound and 493.76 for the upper bound). There was no significant statistical difference among the groups.
Graphic representations of these findings are displayed in Table 13.

**Table 13. Twenty-Four Hour Blood Product Usage**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin (n = 30)</th>
<th>Amicar (n = 30)</th>
<th>OPCAB (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 Hr. PRBC</td>
<td>0.56 ± 1.04</td>
<td>1.46 ± 2.14*</td>
<td>0.26 ± 0.70</td>
</tr>
<tr>
<td>24 Hr. FFP</td>
<td>0.13 ± 0.73</td>
<td>0.16 ± 0.53</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>24 Hr. Plat.</td>
<td>0.20 ± 1.09</td>
<td>0.60 ± 1.83</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>24 Hr. Cryo.</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>Cell Salvage Ret.</td>
<td>861.66 ± 145.43**</td>
<td>776.66 ± 148.40**</td>
<td>367.53 ± 389.92</td>
</tr>
<tr>
<td>24 Hr. Chest Tube</td>
<td>422.50 ± 248.58</td>
<td>596.43 ± 370.40</td>
<td>399.00 ± 171.11</td>
</tr>
</tbody>
</table>

* *p < .05 vs. OPCAB & C-CAB w/Aprotinin
** *p < .01 vs. OPCAB group

**Research Hypotheses Seven**

The final research hypothesis stated there was a significant decrease in patient care hours with decreased complement mediator activation. The participating institution does not staff on patient acuity levels, therefore, results reported for Research Hypothesis Three reflect total LOS for the three groups. There was no significant difference noted among the groups.

**Summary of Findings**

The findings of this study supported the first hypothesis. There was a significant difference in the O.R. time between the C-CAB with Aprotinin group (267.66 minutes, p < .05), the C-CAB with Amicar group (277.70 minutes, p < .01) and the OPCAB group (214.00 minutes). There was also a significant difference in the number of distal anastomosis between the C-CAB with Aprotinin (4.33, p < .01), the C-CAB with Amicar
group (3.90, \( p < .05 \)), and the OPCAB group (2.86) There was no statistical difference found for total O.R. costs, O.R. supply costs, pharmacy costs, or LIMA conducted. The second research hypothesis was not supported. There were no significant statistical differences among the extubation time, LOS ICU, LOS Hosp., and total LOS among the groups.

The findings of this study supported the third research hypothesis. There was a significant statistical difference in the OPCAB group Pre-IL-6 levels \((p < .05)\). The post-Protamine MMP-2 revealed a significant statistical difference among the C-CAB groups and the OPCAB group \((p < .05)\). The post-protamine MMP-9 results showed a significant statistical difference among the C-CAB groups and the OPCAB group \((p < .05)\). Also noted was a significant statistical difference between the baseline C-CAB with Aprotinin and the post level in this group \((p < .05)\). The 6 hr. IL-6 levels also revealed no significant statistical difference between the groups. The six-hour MMP-2 results showed there were significant statistical difference among the C-CAB groups and the OPCAB group \((p < .05)\). All three groups showed a significant statistical difference in the 6 hr. MMP-9 levels from their baselines. There were no other significant statistical differences in the other inflammatory mediators that were measured.

The fourth research hypothesis was not tested. As previous stated, with the discontinuance of the y-coating product, further comparison of the products involved in the study proposal was no longer valid. It was felt by the investigators, that with the uncertainty of product availability due to corporate changes, that it was in the best interest of the study, to terminate data collection after enrollment of enough subjects to validate a portion of the research project.
The findings of this study supported the fifth research hypothesis. There were significant differences in the measured inflammatory response between the C-CAB with Aprotinin group and the C-CAB with Amicar group. Differences occurred at the post MMP-9 level and baseline level for the C-CAB with Aprotinin and also for both groups for the six-hour MMP-9 levels versus their respective baselines. There were no other significant statistical differences found in any of the other measured inflammatory mediators.

The findings of this study supported the sixth research hypothesis. There was a significant statistical difference in the number of subjects receiving blood products among the C-CAB with Aprotinin group (30%, $p < .05$), the C-CAB with Amicar group (50%, $p < .01$), and the OPCAB group. Other differences occurred in the Pre-Plat. count between the C-CAB with Aprotinin group and the OPCAB group ($p < .05$); Post-Protamine Hgb. among the C-CAB with Aprotinin group ($p < .05$), C-CAB with Amicar group ($p < .01$), and the OPCAB group; Post-Protamine Hct. among the C-CAB with Aprotinin group ($p < .01$), C-CAB with Amicar group ($p < .01$), and the OPCAB group; 6 Hr. Hgb. in the C-CAB with Amicar group ($p < .05$) and the C-CAB with Aprotinin and OPCAB groups; 6 Hr. Plat. Count among the C-CAB with Aprotinin group, the C-CAB with Amicar group and the OPCAB group; 6 Hr. Plat. Count among the C-CAB with Aprotinin group ($p < .05$), C-CAB with Amicar group ($p < .01$), and the OPCAB group; 24 Hr. PRBC usage in the C-CAB with Amicar group ($p < .05$) and the C-CAB with Aprotinin and OPCAB groups; and finally the amount of cell salvage return among the C-CAB groups ($p < .01$) and the OPCAB group.
The study's findings did not support the seventh research hypothesis. There were no significant statistical differences in the LOS among the groups.
CHAPTER 5
DISCUSSIONS, CONCLUSIONS, AND RECOMMENDATIONS

This chapter focuses on the meaning of the statistical findings for this study. Each research hypothesis is discussed separately, with the exception of Research Hypothesis Four. The significance of each hypothesis’s findings are discussed in the anticipation that the results will increase nursing administration’s body of knowledge by revealing the most cost effective treatment regime while maintaining excellent outcomes for patients undergoing CABG.

Discussion of Findings

Research Hypothesis One

The actual O.R. times were reported in Table 2 and the significant statistical differences have already been discussed. This may be due to the difference in the number of distal anastomosis performed in each group, although there was no statistical significant reported. CABOCS results almost mirrored those reported by Hart, Spooner, Edgerton & Milsteen (1999) regarding the number of distal anastomosis found in the study groups. The total O.R. costs revealed no significant difference, which was not the case as reported by Buffolo et al. (1996) who reported a cost savings for OPCAB of $3000. It should be noted that Buffolo et al. did not have the option of utilizing a proximal connection device, which one conclusion of this study was a lower, but not statistically significant total O.R. cost for the OPCAB group, therefore not rejecting the null hypothesis.

Breaking out the O.R. supply costs from the overall O.R. costs revealed that the OPCAB group was the highest at $4014.13. It should be noted that only two out of 29
possible applications of the St. Jude Symmetry Proximal Connectors® were elected to be used. Recent literature indicates concern over possible early graft closure when using these devices (Verma et al., 2003) and these concerns may have influenced the decision of whether to use the device or not. In the event the device was used in all possible applications, there would have been a further increase in the supply cost for the OPCAB group (averaging $810 per case). It was the intent of the researcher to include the use of the connector in all OPCAB cases to truly reflect the costs of “clampless” bypass surgery (Eckstein et al., 2001).

The pharmacy costs are another area that can have tremendous impact on intra-operative costs. The intent of the researcher was to compare the intra-operative pharmacy costs between the groups. It was found that the pharmacy costs were bundled for the entire hospitalization and that it was virtually impossible to breakout the intra-operative costs. Therefore, the reported costs are for the entire hospitalization. The cost of the Aprotinin regime used during this study is $450/dose, therefore reflecting an annual cost to the institution of approximately $750,000.

Since the introduction of Aprotinin in 1987, Aprotinin has been shown to exhibit an anti-inflammatory effect by suppressing leukocyte activation and therefore can be expected to provide a significant clinical benefit. This expectation has been borne out in clinical practice in which the LOS following CPB surgery was significantly reduced by Aprotinin compared to other anti-inflammatory strategies, thereby offsetting the initial cost of the drug during surgery (Harmon, 1996; Landis et. al, 2000).

By not rejecting the null hypothesis, these findings lead this researcher to conclude that even though there was a significant difference in the O.R. times, using the
C-CAB with Aprotinin regime allowed for more distal anastomosis with no significant difference in O.R. costs (total and supply) or pharmacy costs. A major concern is the possibility of incomplete revascularization in the OPCAB group as was noted by Hart et al., 1999.

*Research Hypothesis Two*

Comparing the LOS between the groups as seen on Table 3 demonstrated no significant statistical differences. Though the hypothesis was supported, Buffolo et al. did not demonstrate this in 1996. Their study demonstrated a statistical significant difference in the total LOS for the OPCAB group. This study's mean LOS Hosp. was noted to be similar to the findings of Lee et al. in 2000 where they reported a LOS of 6.1 versus 7.1 for OPCAB and C-CAB. The similar LOS demonstrated in this study between the C-CAB with Aprotinin group and the OPCAB group (6.02 vs. 6.00) reinforces the possible positive effects of Aprotinin on the inflammatory mediators thus allowing the patient to progress through the stages of self-care more rapidly.

A useful tool in assessing LOS ICU is the time it takes to wean and extubate a patient from the ventilator. This study demonstrated a lower time for extubation of the OPCAB group than the C-CAB group though this was not statistically significant. Kirk et al. in 2001 reported similar results though they showed a statistically significant difference between the OPCAB and C-CAB groups (3.4 vs. 8.3 hours).

A difference may be that the study institution is "pseudo" fast tracking similar to what Ott et al. in 1999 reported. A major advancement is the use of a new drug not available then. All patients in the study received Precedex®, which when administered in the presence of certain anesthetic agents is likely to lead to an enhancement of effects,
giving the anesthesia personnel the ability to decrease the dose of narcotics and allowing for earlier weaning and extubation from the respirator.

Research Hypothesis Three

Tables 4, 5 & 6 report the actual results of the inflammatory mediators that were measured in this study and were corrected for hemodilution as indicated. This was important in that in the C-CAB group’s hemodilution could affect the final results. One unique aspect of this study was the measurement of the various inflammatory mediators in combination of differing drug regimes in the presence of a hemoconcentrator.

The first significant finding was that there was a significant difference in the Pre-IL-6 levels, with the OPCAB group having the difference ($p < .05$). This result could be from numerous causes. It was not the intention of the researcher to monitor what occurred pre-operatively as for how long and what incidences happened to the subjects during this period. This may have influenced these results.

The pro-inflammatory cascade of the immune system plays an important role in patients who undergo coronary artery bypass (Edmunds, 1998). These patients may display a “primed” system, which opens a window of susceptibility during which any physiologic stressor can unleash a generalized auto-destructive inflammatory cascade that if unchecked, can lead to several syndromes including Adult Respiratory Distress Syndrome (ARDS), Multi-Organ Dysfunction Syndrome (MODS) and death (Goris, te Boekhorst, Nuytinck, & Gimbrere, 1985; Terregino, Lopez, Karras, Killian, & Arnold, 2000). The population may have been representative of those seen by Ott et al. in 1999 where they reported that the study population was found to be at a higher-risk with increased incidence of left-ventricular dysfunction, congestive heart failure and
symptomatic peripheral vascular disease. This might shed light as to the lack of a significant difference in the total LOS between the groups.

The post-protamine MMP-2 revealed a statistical difference between the C-CAB groups and the OPCAB group \((p < .05)\). The MMPs have been shown to act in the acute phase following cardiac stress (Carney et al., 1999). MMP-2 and MMP-9 have also been shown to rise in a predictable fashion in association with CPB (Joffs et al., 2001). These observations are most likely associated with the methods used to arrest the heart during C-CAB and the manipulation of the myocardium associated with the additional distal anastomosis.

The post-protamine MMP-9 results showed a statistical significant difference between the C-CAB groups and the OPCAB group \((p < .05)\). Some of these enzymes may be related to the ischemic myocardium during revascularization. This would lead one to believe that the release of certain MMP’s is from the manipulation of the myocardium and not CPB as Joffs, et al. noted in 2001. Also noted a statistical significant difference between the baseline C-CAB with Aprotinin and the post level in this group \((p < .05)\). This may reflect the attenuation of MMP-9 by Aprotinin, although this has not been supported in recent literature.

All three groups showed a statistical difference in the 6 hr. MMP-9 levels from baseline. This is indicative of a generalized inflammatory response regardless of surgical modality (Spinale, 2002). It should be noted that at this time interval all salvaged blood had been returned to the subjects. This is important in that the two classifications of the MMP’s are not of the molecular weight to be sieved off by the hemoconcentrator. The molecular weight of the inflammatory mediators measured are: \(\text{IL-6} = 26\, \text{kDa}; \text{IL-10} = \)
39 kDa; MMP-2 = 72 kDa; MMP-9 = 92 kDa. The hemoconcentrator cutoff limit is 65 kDa. This fact in itself might shed light as to why the IL’s in the C-CAB groups did not reflect a significant change from baseline but it does not address the significant change from baseline in the OPCAB group. None of these findings can be supported in the recent literature. Therefore the null hypothesis was not rejected; there were no statistically significant decrease in all measured inflammatory mediators.

Research Hypothesis Four

The fourth research hypothesis was not tested. As previous stated, with the discontinuance of the y-coating product, further comparison of the products involved in the study proposal was no longer valid.

Research Hypothesis Five

The fifth research hypothesis stated that there was a statistically significant difference in the measured inflammatory responses between the C-CAB groups. These results are found on Tables 7, 8 & 9.

Landis et al., 2000, and Harmon, 1996, each reviewed the effects of Aprotinin in reducing blood loss and LOS. Both of these studies used full dose, whereas this study used ½ dose. Neither of the aforementioned studies actually measured the inflammatory mediators but did make mention of possible benefits in this area.

Englberger, Kipfer, Berdat, Nydeger & Carrel, 2002, reported that there was no statistical difference in the inflammatory process when using ½ dose Aprotinin. The only similarity of these researchers, from an inflammatory standpoint, to this study was in the measurement of IL-6. Significant differences observed in this study were post-MMP-9 and 6 hr. MMP-9 in the Aprotinin group and post-MMP-9 in the Amicar group. These
differences were from the respective groups baseline measurements and no significant
differences were found between groups, therefore the null hypothesis was not rejected.

*Research Hypothesis Six*

The sixth research hypothesis predicted that there was a statistically significant
difference in blood loss and therefore the usage of blood products between the three
groups. These findings are displayed in Tables 10, 11, 12 & 13.

Similar studies found in the literature revealed comparable results. Kirk et al.,
2001 demonstrated there were significantly fewer blood transfusions (*p* <0.05) in the
OPCAB group (1.1 vs. 2.4 units), and the patients transfused were significantly lower
(34.9% vs. 57.3%). The C-CAB group of patients in that study received the Amicar
regime. In comparison, this study’s OPCAB group received fewer blood transfusion of
0.26 vs. 1.46 units and patients transfused of 13% vs. 50%. Nader, Reich, Bacon, Salerno
&amp; Panos (1999), along with Lancey et al., 2000 reported similar results to this studies
groups.

Pre-operative lab work revealed a significant difference in the pre-Plat. level for
the C-CAB with Aprotinin group. There is no reasonable explanation for this but it is
interesting to note that although the counts were significantly lower, the use of blood and
blood products along with chest tube drainage was not statistically significant from the
OPCAB group. This reinforces the research of Cicek, Demirkilic, Kuralay, Ozal, & Tatar,
1996, when they studied the relevancy of using Aprotinin to reduce post-operative blood
loss and the need for blood transfusions.

There was also a significant difference in the post-protamine Hgb. and post-
protamine Hct. between the C-CAB with Aprotinin group (*p* < .05), the C-CAB with
Amicar group ($p < .01$) group and the OPCAB group. This can easily be attributed to the fact that when these levels are measured, there has been no salvaging of the patients' blood from the CPB circuit. It is usual and routine not to salvage the blood until the sternal wires are placed as to allow for the patient to be hemodynamically stable.

The 6 hr. Hgb. for the C-CAB with Amicar group showed a significant difference from the other two groups ($p < .05$). Several factors could have influenced this. First, the pre-Hgb. was lower than the other groups though this was not statistically significant. Secondly, the amount of cell salvage returned was less than the C-CAB with Aprotinin group. Finally, the amount of chest tube drainage was higher, though again not statistically significant.

Six-hour platelet counts showed a significant difference between the C-CAB with Aprotinin group ($p < .05$), the C-CAB with Amicar group ($p < .01$) group and the OPCAB group. Interesting to note that although the C-CAB with Aprotinin began with a statistically significant lower count from the other two groups, the platelet count in the C-CAB with Amicar group dropped to a lower level at the measured time period. This would indicate that there possible is some degree of protection of the platelets from using the $\frac{1}{2}$ dose Aprotinin regime. Aldea & Shemin, (1998), demonstrated the effects on the formed elements in the blood when exposed to the HBC of CPB. This could also explain the drop in the platelet count. Finally, there is wide spread belief that the platelets tend to sequester in the spleen and liver during bypass and the destructive nature of the “pump” portion of the CPB circuit in itself can account for the decreased counts.

Usage of PRBC's at the 24 hr. timeframe for the C-CAB with Amicar group showed a significant statistical difference than the other two groups. The pre-Hgb. was
lower in this group than the other groups though this was not significant. Secondly, the amount of cell salvage returned was again less than the C-CAB with Aprotinin group. Finally, the amount of chest tube drainage was higher, though again not statistically significant. All of these factors combined may account for the differences found.

Cell salvage return revealed a significant statistical difference between the C-CAB group and the OPCAB group \((p < .01)\). This has already been accounted for when addressing the post-Protamine Hgb. and Hct. results between the C-CAB and OPCAB groups.

Patient transfusion percentage showed a significant difference between the C-CAB group and the OPCAB group \((p < .05)\). These findings are similar to those found in the literature as was given in the beginning of this section. These results supported the hypothesis.

**Research Hypothesis Seven**

The seventh research hypothesis regarded the difference in patient care hours with a decrease in the inflammatory response. It was reported that there were no statistical differences found, therefore the null hypothesis could not be rejected. It should be noted that the C-CAB with Amicar group contained data from the only mortality observed in this study. This subject suffered a massive stroke requiring an ICU LOS of 30 days and this is reflected in the final data.

**Conclusions**

Historically, numerous studies have shown the possible detrimental effects that were associated with CPB. Techniques to attenuate these side effects have been explored and several methods to decrease these effects have been given, including coating the CPB
circuit and different drug regimes. The evolvement of the specialized retractors to accomplish CABG without the use of the CPB has lead to numerous theories felt to improve patient outcomes. This study has introduced a possible alternative to accomplishing complete revascularization while attenuating the inflammatory response.

It is well documented that changing the very method of salvaging the blood in the CPB circuit utilizing a hemoconcentrator has been effective in eliminating certain inflammatory mediators. In addition to the ability to remove Il-6 & 10, adding a platelet protector such as Aprotinin may also decrease some of the inflammatory responses while providing for platelet protection. This combination of modalities is not currently seen in recent literature.

Difference in the O.R. times was a direct result of the number of distal anastomosis performed. Addressing the concern for complete revascularization has previously been addressed in other research and thus was well supported by the ROL. The null hypothesis was not rejected due to any statistical difference in the O.R. cost between the groups even though the available proximal connector was only used in 6.8% of the possible applications.

LOS has been shown to have extreme importance in numerous aspects of the hospital organization. The efficient utilization of beds, both in ICU and on the ward and the decrease in the stress on the nursing personnel by enhancing the recovery of the patient has significant importance for administrators. The ROL indicated that fast tracking could allow the patient to recover more quickly and provide for earlier discharge thus increasing efficiency and better utilizing personnel while providing for increased independence of the patient. Dorthea Orem’s Model of Self-Care supports this concept.
There was no significance statistical difference demonstrated between the groups as for a reduction in LOS. This aspect may prove to be beneficial for the nursing administrator to realize in the staffing process. Additionally, this information has the potential to provide nursing administration with the best alternatives in patient care to pursue facing the current and future shortage of nurses.

The differing inflammatory results, especially in the MMP groups, more than likely reflect the methods used to arrest the heart during C-CAB. In the presence of severe coronary artery disease, the ability to protect the myocardium is hampered, and this could be a factor involved in the results. Even with these differences, the null hypothesis was not rejected.

Comparison of the C-CAB group related to drug regimes involved can influence the inflammatory mediators in the presence of the hemoconcentrator. The molecular weight of the IL's has been shown to be less than what is passed through the hemoconcentrator, thus potentially accounting for no significant difference in these results, therefore the null hypothesis was not rejected. The ½ dose Aprotinin regime used has been supported in the ROL.

There was a significant statistical difference in the utilization of blood products. The number of patients receiving transfusions was significant statistically different between the C-CAB groups vs. the OPCAB groups, and also between the C-CAB groups. Even though the pre-Plat. count was lower in the C-CAB with Aprotinin group; there was no significant statistical difference in the use of platelets in this group, indicating the protective properties of the drug that is well documented in the ROL. The decreased use of blood and blood products in the OPCAB group was also well supported in the ROL.
The hypothesis dealt with blood loss and the results indicate no significant difference between the groups, therefore the hypothesis was accepted.

The final hypothesis dealt with in the presence of a reduction in the inflammatory mediators there should be an accelerated advancement to self-care therefore decreasing the need of nursing care hours. It was demonstrated that this was not the case, therefore the null hypothesis was not rejected.

Recommendations

Exploring non-conventional ideas to improve patient outcomes tends to tread into territory that is often tenuous. Offering new ideas that may affect standard medical practices often is not well received. Simply employing available technology in a different way may reveal interesting outcomes. This was the unexpected result that was revealed in this research project.

With the recent concerns generated over the long-term patency of the proximal connectors, the ability to perform “clampless” CABG is in limbo. This leads this researcher to favor the “single-clamp” method utilizing CPB. Results given showed there were more distal anastomosis performed with no significant difference in costs or LOS. If the ability to provide for a more complete revascularization is available, there needs to be consideration as to the long-term benefits vs. drawbacks of the two techniques.

Addressing the inflammatory issue, results given indicated that using the C-CAB with the hemoconcentrator method showed no significant differences in the measured inflammatory mediators as compared to the OPCAB group. This supported the idea that the IL’s were being sieved off by the hemoconcentrator, as was demonstrated by the size of the molecule and what the hemoconcentrator would pass. A generalized inflammatory
response was seen in all groups at the six-hour time frame, indicating that the surgical process itself was the most likely culprit. Therefore, it is recommended to utilize the hemoconcentrator in the presence of C-CAB.

Looking at the inflammatory issue involving the two C-CAB regimes, no difference was found. Interestingly enough, the pharmacy costs were also no different even in the presence of Aprotinin. With these factors in mind, it is recommended that the potential benefits of using Aprotinin for platelet protection and possible additional inflammatory effects, at no additional cost, in the presence of C-CAB be implemented.

The next recommendation involves the use of blood products. It was shown there were significant differences noted between the C-CAB group and the OPCAB group. 30-50% of the C-CAB group received blood or blood products as compared to 13% of the OPCAB group. This was well supported in the ROL. The results for the C-CAB groups also showed significant differences, thus reinforcing the recommendation to use Aprotinin for the reasons previously stated.

The final recommendation deals with LOS. There were no differences found which could indicate a couple of reasons. First, the “psuedo” fast tracking needs to be revised and implemented as to encourage compliance from the O.R. to the ward. Secondly, the organization itself needs to rethink the process to discharge and implement ways to expedite the process and take advantage of the patient’s progression through the stages of self-care.

Additional research should be conducted that would include exploring means to sieve additional inflammatory mediators that could be removed via differing pore size hemoconcentraors. Also, refining the current study to actually measure the amount of
mediators removed could prove to be beneficial. Finally, adding another “arm” to include a C-CAB group that utilized the standard practice of blood salvage using the cell-saver, could enter an aspect to compare this studies population against that seen nationally.

Summary

This chapter reviewed the reported results and what possible implications may be available to the study population. Findings indicated the importance to explore existing and new technologies that may have an influence on patient outcomes. This might well prove to be extremely important considering the potential number of individuals that will require CABG surgery in the future. Combined with the continuing and expected nursing shortage, nursing administrators may well benefit from the expanded knowledge of this study.

A through review of the statistical findings was done and recommendations were made. Encompassing all aspects of this study, interpreting the results, and delineating out possible positive changes to provide the best outcomes, was the main purpose of this chapter.
References


American Heart Association (2001). How many open-heart surgeries are performed each year? Open-Heart Surgery Statistics.


APPENDIX A

CABOCS Instrument

Memorial Hospital Data Collection Sheet
*All participants are Primary Coronary Artery Bypass Patients*

*All participants will utilize Endoscopic Vein Harvesting*

Demographics:

Pre-Operative Data:

- Age (years): ___  - Gender: ___ Male
- LVEF %: ___  - Female
- OP-CAB: ___
- CPB: ___
- Coating:  D: ___  B: ___
  Aprotinin: ___  Amicar: ___

Baseline Laboratory Data:

- Hbg. (mg./dl): ___
- Hct. (mg. %): ___
- Plat. Count (K/dl): ___
- Inflammatory Mediator Labs Drawn (Y/N): ___
  (must be pre-sternotomy, placed in proper tube & labeled with date, time, and Base Deficit)
  - IL-6: ___  IL-10: ___  MMP-2: ___  MMP-9: ___

Blood/ Blood Product Usage (Intraoperative):

(Total amount given- anesthesia & perfusion- whether OP-CAB or CPB)

- PRBC's (units): ___
- FFP (units): ___
- Plat. (units): ___
- Cryo (units): ___
Post-Procedure Laboratory Data:

- Hbg. (mg/dl): ___  - Hct. (mg%): ___
- Inflammatory Mediator Labs Drawn (Y/N): ___  
  (must be placed in proper tube and labeled with date, time and Base deficit)
  - IL-6: ___  IL-10: ___  MMP-2: ___  MMP-9: ___
- Blood Salvaged Hemoconcentrate (ml.): ___

Post-Operative Data:

Laboratory Data:
(6 hours post-op)

- Hbg. (mg/dl): ___  - Hct. (mg%): ___
- Plat. Count (K/dl): ___  - Salvaged Blood Returned (Y/N): ___
- Inflammatory Mediator Labs:
  (must be placed in proper tube and labeled with date, time and Base deficit)
  - IL-6: ___  IL-10: ___  MMP-2: ___  MMP-9: ___

Blood/ Blood Product Usage:
(24 hour total amounts given)

- PRBC’s (units): ___  - FFP (units): ___
- Plats. (units): ___  - Cryo (units): ___

Chest Tube Drainage:
(till removed or 1st 24 hours)

- Amount (cc’s): ___

Time to Extubation:

- Time (mins.): ___

Miscellaneous Data:
Operating Room:

- Time (min.): _____
- Cost ($) : _______  (OP-CAB will include stabilizer and proximal connector(s)).

Length of Stay:

- ICU (hours): _____
- Hospital (hours): _____  (measurement begins at time of operation)

STS Data:

- Height (cm.): _____  -  Weight (kg.): _____
- BSA (M^2): _____
- Pump (min.): _____  -  Clamp (min.): _____

Coronary Cath Data (% of disease):

- RCA: _____  -  PDA: _____
- LM: _____  -  LAD: _____
- Diag: _____  -  RMI: _____
- OM1: _____  -  OM2: _____
- Cx: _____  -  Other: _____

- Number of distal anastomosis performed: _____
- Number of IMA’s performed: _____
- Was a radial artery used?  :  □ Yes  □ No  .

MEMORIAL HOSPITAL

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Cardiopulmonary Bypass and Support Data

- CPS from the Cath lab: Yes / No
- Intropes (ARRIVING OR): Yes / No
- Antiarrhythmics (ARRIVING OR): Yes / No

Cardioplegia: Yes / No
- Blood
- Crystalloid
- Oxygenated Crystalloid

Infusion Mode: Yes / No
- Antegrade
- Retrograde
- Intermittent
- Continuous

Cardioplegia Temp: Yes / No
- Warm
- Cold

Hot Shot Used?: Yes / No

IABP: Yes / No
- Proop
- Intracp
- Postop

Indication: Yes / No
- Low CO
- Shock

Infusion Dose: Yes / No
- Antegrade
- Prophylactic

VAD: Yes / No
- LVAD
- RVAD
- BAHD
- TAHD

Cardioversion: Yes / No
- No
- Low CO
- Unstable Angina
- PTCA Support
- Shock

Defibrillation: Yes / No
- No

Last SVO2 on CPB > 65%: Yes / No
- No

Lowest Hct. On CPB > 19%: Yes / No
- No

Hemoconcentrator: Yes / No
- No

Cellsaver: Yes / No
- No

Amount of Autologous Blood Recovered: ml

Weaned without homologous blood: Yes / No

Number of PRBC's used on CPB: ___

CPB Time: ___ min

Cross Clamp Time: ___ min

Lowest Core Temperature: ___ (°C)

Status:
- Elective
- Urgent
- Emergent

Operative Data

Operative Category:

- CAB
- CAB + Other
- Valve
- CAB + Valve
- Valve + Other
- Other

Operative Procedure:

- CAB + Valve + Other
- CAB + Valve
- CAB
- Other

CPS Wean: Yes / No

Number of PRSC's used on CPS: ___

CPS Time: ___ min

Cross Clamp Time: ___ min

Lowest Core Temperature: ___ (°C)

Intraoperative Pharmacologic Agents

- Beta Blocker (e.g. esmolol)
- Calcium Channel Blocker (e.g. diltiazem)
- Adenosine
- Tranbyol
- Amicar
- Other, Specify

Suture Technique

- Running
- Interrupted
- Stapler
- Other, Specify

PLEASE RETURN THIS FORM TO THE PERFUSION OFFICE
### Diabetic Management For Patients Undergoing Cardiac Procedures

1. Does the patient have a history of:
   - NIDDM
   - IDDM
   - NONE

2. 1st Peri-operative Glucose = ____________ mg/dl

3. Did glucose during CPB exceed 200 mg/dl?
   - YES
   - NO
   If so, what was the highest glucose on CPB?

1. If the glucose exceeded 200 mg/dl on CPB, which treatment was instituted to correct glucose?
   - Anesthesia notified, No treatment instituted
   - Insulin drip instituted by anesthesia
   - Insulin bolus administered

### Cardiac Surgery Data

#### Vessel Stabilization
- Yes
- No
- Suture Snare
- Suction Device
- Stabilization/Restraining Device
- Other, Specify

#### Other Cardiac Procedures
- LVA
- VSD
- ASD
- Ballo (ventricular reduction)
- Transmyocardial Laser
- Cardiac Trauma
- Cardiac Transplant
- Pacemaker
- AICD
- Other, Specify

#### Other Non-Cardiac
- Aortic Aneurysm
- Asc
- Arch
- Desc
- Thoraco/Abd
- Abd
- Carotic Endarterectomy
- Other, Specify

### Coronary Bypass Data

#### Left Main disease >50%
- Yes
- No

#### LIMA Used
- Yes
- No

#### # of Distal Anast
- # of Prox Anast

#### # of IMA Grafts
- # of IMA Distals

#### # of GEPA Grafts
- # of GEPA Distals

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### Valve Surgery Data

#### Aortic:
- Implant
- Size:
- Type:
- Explant
- Size:
- Type:

#### Mitral:
- Implant
- Size:
- Type:
- Explant
- Size:
- Type:

#### Tricuspid:
- Implant
- Size:
- Type:
- Explant
- Size:
- Type:

#### Pulmonic:
- Implant
- Size:
- Type:
- Explant
- Size:
- Type:

### Valve Size in mm

#### Type
- Mechanical
- Bioprosthetic
- Mechanical
- Stentless Porcine

#### Key for Valve Surgery Data Table

1. Replacement
2. Annuloplasty
3. Annuloplasty
4. Commissurotomy
5. Commissurotomy
6. Chordal Rupture Repair
7. Pulsatile Muscle Repair
8. Ross Switch
9. Ross Switch
10. Recipient Aortic Stenosis
11. Resection of Sub-Aortic Stenosis
12. Valve Resection
13. Valve Resection
APPENDIX B

SAU Topic Proposal
SAU Approval Form A
Signature Page Form A
SAU Approval Form B
Signature Page Form B
SAU Human Participants In Research Subcommittee Approval Form

Memorial Hospital IRB Form
Memorial Hospital IRB Approval Letter

Informed Consent Form
Surgeon Approval Form
TOPIC PROPOSAL FORM FOR THESIS OR PROJECT

Student Name: Michael M. Wyckoff

Student Address: 7625 Watercrest Drive

Harrison, Tennessee 37341

Student phone number(s): 344-6219 (Home); 495-7850 (Work); 655-4622 (Pager)

Thesis / Project option: (circle one)

- Thesis
- Project

Topic: Comparative Analysis of Coronary Artery Bypass: Costs of Off-Pump versus Conventional Techniques With Variable Bonded Circuits and Drug Strategies (CABOCS)

Brief Description of Project or Thesis: This thesis examines the operative techniques, circuit coatings and drug therapies involved with current practices of coronary artery bypass surgery.

Proposed Project Advisor or Thesis Committee Chair: David Gerstle, PhD., R.N.

Proposed Associate Advisor or other Committee Members: Mary Ann Roberts, DSN., R.N.; Barbara James, DSN, R.N.; James Zellner, M.D.

Anticipated proposal presentation date: Fall 2003

Target project/ thesis completion date: Summer 2003

Office Use Only

Research Committee Action: Approval / Denial

Comments:
Southern Adventist University
RESEARCH APPROVAL FORM
Form A

Directions: Please complete this form and submit with the following documents if used: (1) Informed Consent Form, (2) Data Collection Instrument (e.g., questionnaire) or Protocol.

Level I review: Obtain approval and signature from the course professor/student club or association sponsor. Submit Form A with signature to course professor and keep copy for self.

Level II review: Obtain approval and signature(s) from Chair/Dean. Submit copies of Form A with signatures to course professor, Chair/Dean(s), and self.

1. Identification of Project

Principal Investigators:

James Zellner, M.D., Assistant Professor, University of Tennessee College of Medicine, Chattanooga Unit; Alliance of Cardiac, Thoracic and Vascular Surgeons Chattanooga, Tennessee 37404 (423) 624-5200

Michael M. Wyckoff, R.N., C.C.P. Candidate MBA / MSN, Southern Adventist University Department of Perfusion Memorial Hospital 2525 DeSales Avenue Chattanooga, Tennessee 37404 (423) 495-7850 Pager: (423) 655-4622 E-mail: Michael_Wyckoff@Memorial.org

Title: Comparative Analysis of Coronary Artery Bypass: Costs of Off-Pump vs. Conventional Techniques with Variably Bonded Circuits and Drug Strategies. (CABOCS)

Department: School of Nursing

Faculty Supervisor: David Gerstle, PhD, RN

Starting Date: Fall, 2002

Completion Date: Summer, 2003
II. Purpose of Study

The purpose of this study is to examine and compare costs of differing treatment modalities for coronary artery bypass surgery, including off-pump coronary artery bypass (OPCAB) and conventional coronary artery bypass (C-CAB). When the use of C-CAB is indicated, there are numerous circuit coatings available, along with drugs like Aprotinin, to decrease the inflammatory response associated with the exposure of the body to the bypass circuit. Exposure of the body to the cardiopulmonary bypass circuit has been shown to activate the pro-inflammatory arm of the immune system, as well as the coagulation cascade, and this is referred to as the systemic inflammatory response system. In some patients, the pro-inflammatory response may become over activated and several squeal can occur, including adult respiratory distress syndrome (ARDS), multi-organ dysfunction (MODS), and possibly death. New innovations have led to the development of methods to perform coronary artery bypass without the use of the cardiopulmonary bypass machine, commonly referred to as OPCAB, and thus the side effects of the bypass circuit can be avoided. Several drug regimes are available to inhibit the inflammatory response and these will also be investigated. If the inflammatory response is inhibited or is not activated, it is theorized that the patient will recover quicker and thus require less nursing care hours and be discharged earlier. Therefore, costs of both surgical techniques, inflammatory responses, along with length of stay (LOS), will be the emphasis of this study.

III. Description and Source of Research Subjects (e.g., human, animals, plants documents)

The sampling criteria for the target population of this study is all elective, primary, coronary artery bypass candidates, of both genders, over the age of 18, who have not received any thrombolytic intervention (whether in the cardiac catheterization lab or anti-platelet therapy pre-operatively) currently admitted to Memorial Hospital, Chattanooga, Tennessee by local cardiac surgeons for C-CAB or OPCAB procedures. A convenience sample of the target population will be performed, as the choice of the procedure is dependant upon the surgeon’s preference. All participants will have the ability to give written, informed consent. Exclusion criteria will include inability to give written, informed consent, anyone under the age of 18 years old, emergent procedures, multiple procedures (i.e. coronary artery bypass with valve replacement), exposure to thrombolytic agents, or desire to withdraw from study. Multiple or emergent procedures, along with exposure to thrombolytic agents can have adverse effects on variables being measured (amount of chest tube drainage, platelet counts, number of units of blood and blood products used) therefore the presence of these factors must preclude utilization of these participates.

If human subjects are involved, please check any of the following that apply:

_____ Minors
_____ Prison inmates
_____ Mentally impaired
_____ Physically disabled
______ Institutionalized residents (Hospitalized patients)
_____ Vulnerable or at-risk groups, e.g., minority, poverty, pregnant women (or fetal tissue), substance abuse populations
_____ Anyone unable to make informed decisions about participation
If any of the above is checked, proposal requires Level III review. Form B must be completed in addition to Form A.

IV. Materials, Equipment, or Instruments

All equipment and supplies used are those currently in use in the investigational institution. All methods and techniques are FDA approved. The inflammatory indicator samples are to be obtained from the laboratory or directly from the operating room as soon as possible after collection. These samples, IL-6, IL-10, will be taken to the Erlanger Research Cytokine Laboratory, where they will be centrifuged at 3000 xg for thirty minutes. The specimens will be stored at −20 degrees C until analysis. Two levels, MMP-2, MMP-9, will be transported to The Medical University of South Carolina for analysis (unable to be performed locally) at −70 degrees C. All samples will have identifying numbers only, as to protect the identity of the patients.

V. Methods and Procedure

The design chosen by this researcher is a quasi-experimental, comparative research design. The differing treatments, OPCAB, C-CAB, drug regimes, coatings of circuits, inflammatory response of each and finally operative costs are examined.

There are five groups to be studied: control (utilizing y-bonded circuits) with Amicar (n = 30) and Aprotinin (n = 30); experimental (utilizing x-bonded circuits) with Amicar (n = 30) and Aprotinin (n = 30); and finally the OPCAB group (n = 30). A minimal sample of 30 for each group will be used to ensure adequate sample size for statistical analysis. Power analysis indicated appropriate minimal sample size per group. Utilization of statistical techniques will address the question involving possible error rate problems.

Selection of the sample has been addressed and its group dependency has been shown. Ambiguity on the causality is prevented due to the number of laboratory samples per participant. Imitation of treatments is prevented by only using one circuit at a time and maintaining the protocols for each individual surgeon, as is currently being the in the research institute.

The basic design of this study will not change any current treatment modalities that the patients would normally receive. The circuit coatings are not optional to the patient. All patients receiving treatment involving the cardiopulmonary circuit utilizes circuits that have the same coating, therefore interaction of selection and treatment is not a viable validity concern.

VI. Sensitivity: Psychological discomfort or harm experienced by human participants because of topic under investigation, data collection, or data dissemination.

On a scale of 0 (not sensitive) to 5 (extremely sensitive), rate the degree of sensitivity of the behavior being observed or information sought:

1 Sensitivity of behavior to be observed or information sought.

If greater than “1” proposal requires Level III review. Form B must be completed in addition to Form A.
VII. Invasiveness: *Extent to which data collected is in public domain or intrusive of privacy of human participants within context of the study and the culture.*

On a scale of 0 (not sensitive) to 5 (extremely sensitive), rate the degree of invasiveness of the behavior being observed or information sought.

1 Sensitivity of behavior to be observed or information sought.

*If greater than “1” proposal requires Level III review. Form B must be completed in addition to Form A.*

VIII. Risk: *Any potential damage or adverse consequences to researcher, participants, or environment. Includes physical, psychological, mental, social, or spiritual. May be part of protocol or may be a remote possibility.*

On scale of 0 (no risk) to 5 (extreme risk), rate the following by filling each blank.

<table>
<thead>
<tr>
<th>Extent of Risk</th>
<th>To Self</th>
<th>To Subjects</th>
<th>To Environment</th>
</tr>
</thead>
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<tr>
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<tr>
<td>Spiritual harm</td>
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</tbody>
</table>

*If any blank is greater than “1,” proposal requires level III review. Form B must be completed in addition to Form A.*

IX. Benefit-Risk Ratio (Benefits vs. Risks of this Study)

The benefit of the study is that it will provide information of costs differences between OPCAB and C-CAB, and the related factors of circuit and pharmacological agents on inflammation and blood usage. As medical therapies advance and progress, it behooves us as medical professionals to continually evaluate the current advances in therapies available. Risks involved are minimal, since the therapies are all FDA approved and the surgeon’s preferences will not be altered.

X. Confidentiality/Security Measures

Since informed consent is required, privacy is upheld, and any identifying factors will be removed from the data collection sheets. Identification will be kept confidential by the use of a coding system, known only to the principal investigators and supervisory faculty. All information will be publishable and the participants will acknowledge this in the informed consent.

With the need to review records, personal information cannot be avoided. The researcher will provide complete confidentiality by the measures previously stated and by following the guidelines outlined by the National Institutes of Health (NIH). Only aggregate data will be reported and all data that is entered into databases will be password protected, the original copies of the instrument will be under lock and key, and the names will be removed after the coding is completed. All data will be separated from the identifying factors and assigned codes so that the patient cannot be
linked to the data. Codes will be accessed only by the principal investigator(s) and secured under lock and key. Once the data has been entered into a database, the database will have a security code only known to the principal investigator(s). Data will be stored for a minimal period of three years in a locked safe, and then will be shredded and destroyed.

XI. Informed Consent Process

All participates will have the ability to give written, informed consent. Prior to data collection, permission will first be obtained from this researcher's thesis committee of the School of Nursing at Southern Adventist University (SAU). Permission will then be obtained from the Institutional Review Board at the participating institution. In addition, permission from the cardiac surgery group involved will be obtained, to include their patients in the study.

___ Potential for coercion, which is considered any pressure placed upon another to comply with demand, especially when the individual is in a superior position. Pressure may take the form of either positive or negative sanctions as perceived by the participants within the context and culture of the study.

___ Coercion or Deception involved. If so, explain.
If either checked, proposal requires Level IV Full Review.

XII. Debriefing Process

Not applicable for this study.

XIII. Dissemination of Findings

___X___ Potential for presentation or publication outside of University.
If so, proposal requires Level II Review.

XIV. Compensation to Participants

No compensation is awarded to either the participants or researchers involved in this study.
By compliance with the policies established by the Institutional Review Board of Southern Adventist University, the principal investigator(s) subscribe to the principles and standards of professional ethics in all research and related activities. The principal investigator(s) agree to the following provisions:

- Prior to instituting any changes in this research project, a written description of the changes will be submitted to the appropriate Level of Review for approval.
- Development of any unexpected risks will be immediately reported to the Institutional Review Board.
- Copies of approval for off-campus sites of data collection will be obtained from the site and submitted in triplicate to the appropriate Level of Review prior to data collection.
- Close collaboration with and supervision by faculty will be maintained by SAU student investigator.

Principal Investigator Signature ____________________ Date __ __

Co-Principal Investigator(s) Signature ____________________ Date __ __

As the supervising faculty, I have personally discussed the proposed study with the investigator(s), and I approve the study and will provide close supervision of the project.

Supervising Faculty/Sponsor Signature ____________________ Date __ __
(Required by all SAU student investigators)

As Dean/Chair, I have read the proposed study and hereby give my approval.

Chair(s)/Dean(s) Signature ____________________ Date __ __
(If Level II approval required)
Southern Adventist University

RESEARCH APPROVAL FORM

Form B

This form is required in addition to Form A because of involvement of one or more of the following factors:
1. At-risk participant populations
2. Sensitivity
3. Invasiveness
4. Risk
5. Deception

Please answer the following question(s) as appropriate to the proposed research and submit 6 copies of Form A and Form B to Subcommittee Chair. If coercion or deception is involved, submission must be made to IRB for full review.

1. Describe the at-risk participant population.

The sampling criteria for the target population of this study is all elective, primary, coronary artery bypass candidates, of both genders, over the age of 18, who have not received any thrombolytic intervention (whether in the cardiac catheterization lab or anti-platelet therapy pre-operatively). All participants will be in-patients at the participating hospital.

Measures to be used to protect the participants from harm.

All subjects will be protected from physical harm in that the specimens will be obtained from existing arterial ports and samples that are stored in the laboratory. No additional access or laboratory samples will be required from the participants.

The very bases of this study, utilizing what is already FDA approved and currently in use, along with the institutions and surgeons’ desires to provide the best possible care at the most economically feasible price provides the bases for protecting the participants from harm and discomfort. There are no investigational products in use. The researcher is simply interested in response of the participates in the areas previously noted as they are affected by the different techniques and protocols of the surgeons. None of the five categories identified by Reynolds in 1972, fit the nature of this study.

2. Describe the sensitive nature of the topic under investigation, data collection, or data dissemination.

The need to review records and personal information cannot be avoided since the records contain the research information (i.e. surgical technique, circuit used, drug regime, blood usage, etc.).
Safeguards that will minimize the sensitivity.

The researcher can and will provide complete confidentiality by the measures previously stated, and by following the guidelines outlined by the National Institutes of Health (NIH). Any data that is entered into databases will be password protected, the original copies of the instrument will be under lock and key, names will be removed when the coding is complete.

3. Describe the degree of invasiveness.

The only invasive procedure, other than the actual surgical procedure, is the collection of blood samples from an existing arterial port. No invasive procedures will be incurred that are not usual for normal C-CAB or OPCAB.

4. Describe the degree of risk.

There is no risk involved to the subjects other than is customary for patients undergoing C-CAB or OPCAB surgeries. Standardization of the five groups as for equal treatment will be controlled during the planning phase all the way through the implementation phase by providing exact instructions as for when testing is done and what parameters are being studied (type of case, time factors, costs, length of stay).

Precautions that will minimize harm.

All supplies and medication utilized are FDA approved and are in use at participating institution, with the exception of the different bypass circuit, currently under evaluation.

5. Describe the use of coercion and/or deception.

N/A

Justify its use in this project.

N/A

Safeguards that will minimize harm.

See Precautions Section.
By compliance with the policies established by the Institutional Review Board of Southern Adventist University, the principal investigator(s) subscribe to the principles and standards of professional ethics in all research and related activities. The principal investigator(s) agree to the following provisions:

- Prior to instituting any changes in this research project, a written description of the changes will be submitted with 6 copies to the appropriate Level of Review for approval.
- Development of any unexpected risks will be immediately reported to the Institutional Review Board.
- Copies of approval for off-campus sites of data collection will be obtained from the site and submitted in triplicate to the appropriate Level of Review prior to data collection.
- Close collaboration and supervision by faculty will be maintained.

Principal Investigator Signature ____________________________ Date __
Co-Principal Investigator(s) Signature ____________________________ Date __

* * * * *

The IRB Subcommitteee has reviewed the proposal and hereby grants approval to the project.

Name of IRB Subcommittee __________________________________________

Subcommittee Chair Signature ____________________________ Date __
(If Level III approval required)

* * * * *

The IRB has reviewed the proposal and hereby grants approval to the project.

IRB Chair Signature ____________________________ Date __
(If Level IV approval required)
January 27, 2003

Mr. Michael M. Wyckoff, R.N., C.C.P.
Department of Perfusion
Memorial Hospital
2525 DeSales Avenue
Chattanooga, TN 37404

Dear Michael:

The Human Participants in Research Subcommittee has approved your research application "Comparative Analysis of Coronary Artery Bypass: Costs of Off Pump vs. Conventional Techniques with Variably Bonded Circuits and Drug Strategies". Investigating the modes of treatment for post coronary bypass surgery will benefit future patients and improve recovery after surgery.

The research project is well designed and ensures confidentiality of the individuals involved in your study, and I am delighted to approve your project.

Sincerely yours,

Linda Ann Foster, Ph.D., Chair, Human Participants in Research Subcommittee
Associate Professor, Biology Department
Southern Adventist University
Title: Comparative Analysis of Coronary Artery Bypass: Costs of Off-Pump vs. Conventional Techniques with Variably Bonded Circuits and Drug Strategies. (CABOCS)

I. Identification of Project:

Principal Investigators:

James Zellner, M.D., Assistant Professor, University of Tennessee College of Medicine, Chattanooga Unit; Alliance of Cardiac, Thoracic and Vascular Surgeons Chattanooga, Tennessee 37404 (423) 624-5200

Michael M. Wyckoff, R.N., C.C.P. Candidate MBA / MSN, Southern Adventist University Pager: (423) 655-4622 E-mail: Michael_Wyckoff@Memorial.org

Department: School of Nursing

Faculty Supervisor: David Gerstle, PhD, RN

Starting Date: Fall, 2002

Completion Date: Fall, 2003

II. Purpose of Study

The purpose of this study is to examine and compare costs of differing treatment modalities for coronary artery bypass surgery, including off-pump coronary artery bypass (OPCAB) and conventional coronary artery bypass (C-CAB). When the use of C-CAB is indicated, there are numerous circuit coatings available, along with drugs like Aprotinin, to decrease the inflammatory response associated with the exposure of the body to the bypass circuit. Exposure of the body to the cardiopulmonary bypass circuit has been shown to activate the pro-
Inflammatory arm of the immune system, as well as the coagulation cascade, and this is referred to as the systemic inflammatory response system. In some patients, the pro-inflammatory response may become over activated and several sequellae can occur, including adult respiratory distress syndrome (ARDS), multi-organ dysfunction (MODS), and possibly death. New innovations have led to the development of methods to perform coronary artery bypass without the use of the cardiopulmonary bypass machine, commonly referred to as OPCAB, and thus the side effects of the bypass circuit can be avoided. Several drug regimes are available to inhibit the inflammatory response and these will also be investigated. If the inflammatory response is inhibited or is not activated, it is theorized that the patient will recover more quickly and thus require less nursing care hours and be discharged earlier. Therefore, costs of both surgical techniques, inflammatory responses, along with length of stay (LOS), will be the emphasis of this study.

In the current realm of reimbursement, cost issues lead a predominant role in patient care. The supplies used influence the costs incurred for surgical procedures. OPCAB has been widely embraced due to the “lower” costs by eliminating the cardiopulmonary bypass (~$850) piece of the puzzle. The actual hospital costs to perform the off-pump procedure may not show the actual savings once thought. The “specialized” retractor system (~$600) and the necessary connector systems (requiring 2-4 @ ~$450 each) to make the procedure truly “clampless”, may in reality incur more costs than they conserve.

Finally, by documenting the inflammatory response for each category of procedure, including drug therapies, it may reveal the inflammatory response to the actual surgical procedure, and not just exposure to the bypass circuit, as the leading culprit in initiating this response.

III. Description and Source of Research Subjects (e.g. humans, animals, plants, and documents)

The sampling criteria for the target population of this study is all elective, primary, coronary artery bypass candidates, of both genders, over the age of 18, who have not received any thrombolytic intervention (whether in the cardiac catheterization lab or anti-platelet therapy pre-operatively) currently admitted to Memorial Hospital, Chattanooga, Tennessee by local cardiac surgeons for C-CAB or OPCAB procedures. A convenience sample of the target population will be performed, as the choice of the procedure is dependant upon the surgeon’s preference. All participants will have the ability to give written, informed consent. Exclusion criteria will include inability to give written, informed consent, anyone under the age of 18 years old, emergent procedures, multiple procedures (i.e. coronary artery bypass with valve replacement), exposure to thrombolytic agents, or desire to withdraw from study. Multiple or emergent procedures, along with exposure to thrombolytic agents can have adverse effects on variables being measured (amount of chest tube drainage, platelet counts, number of units of blood and blood products used) therefore the presence of these factors must preclude utilization of these participates.
IV. Materials, Equipment, or Instruments

All equipment and supplies used are those currently in use in the investigational institution. All methods and techniques are FDA approved. The inflammatory indicator samples are to be obtained from the laboratory or directly from the operating room as soon as possible after collection. These samples, IL-6, IL-10, will be taken to the Erlanger Research Cytokine Laboratory, where they will be centrifuged at 3000 xg for thirty minutes. The specimens will be stored at −20 degrees C until analysis. Two levels, MMP-2, MMP-9, will be transported to The Medical University of South Carolina for analysis (unable to be performed locally) at −70 degrees C. All samples will have identifying numbers only, as to protect the identity of the patients and will be transported to the specific institutions via Saf-T-Pak® containers utilizing the Comprehensive Guide to Shipping Infectious Substances guidelines.

The costs incurred from the laboratory testing will be minimal as the researcher will be assisting the director of the Cytokine Laboratory and all testing in South Carolina has been volunteered without cost except shipping.

V. Methods and Procedures

The design chosen by this researcher is a quasi-experimental, comparative research design. The differing treatments, OPCAB, C-CAB, drug regimes, coatings of circuits, inflammatory response of each and finally operative costs are examined.

There are five groups to be studied: control (n= 60) utilizing y-bonded circuits, 30 subjects using Amicar and 30 subjects using Aprotinin; experimental group (n= 60) utilizing x-bonded circuits, 30 subjects using Amicar and 30 subjects using Aprotinin; and finally the OPCAB group (n= 30). A minimal sample of 30 for each group will be used to ensure adequate sample size for statistical analysis. Power analysis indicated appropriate minimal sample size per group. Utilization of statistical techniques will address the question involving possible error rate problems.

Selection of the sample has been addressed and its group dependency has been shown. Ambiguity on the causality is prevented due to the number of laboratory samples per participant. Imitation of treatments is prevented by only using one circuit at a time and maintaining the protocols for each individual surgeon, as is currently being the in the research institute. A double-blinded study is not appropriate due the near impossibility of maintaining the appropriate bypass machines available at all times for emergent procedures.

The basic design of this study will not change any current treatment modalities that the patients would normally receive. The circuit coatings are not optional to the patient. All patients receiving treatment involving the cardiopulmonary circuit utilizes circuits that have the same coating, therefore interaction of selection and treatment is not a viable validity concern.
VI. Sensitivity

There is miniscule risk of harm or discomfort by human participants because the topic under investigation, data collection and data dissemination pose minimal risks. The risks involved are only those inherent to the actual surgical procedure.

VII. Invasiveness

The extent, to which the data collection is intrusive of privacy of human participants within the context of this study, is limited to laboratory collection from an existing arterial line and minimized to information accessed from the medical record.

VIII. Benefit-Risk Ratio (Benefits vs. Risks of this Study)

The benefit of the study is that it will provide information of costs differences between OPCAB and C-CAB, and the related factors of circuit and pharmacological agents on inflammation and blood usage. As medical therapies advance and progress, it behooves us as medical professionals to continually evaluate the current advances in therapies available. Risks involved are minimal in addition to those already associated with the surgical procedure since the therapies are all FDA approved and the surgeon’s preferences will not be altered.

IX. Confidentiality/Security Measures

Since informed consent is required, privacy is upheld, and any identifying factors will be removed from the data collection sheets. Identification will be kept confidential by the use of a coding system, known only to the principal investigators and supervisory faculty. All information will be publishable and the participants will acknowledge this in the informed consent.

With the need to review records, personal information cannot be avoided. The researcher will provide complete confidentiality by the measures previously stated and by following the guidelines outlined by the National Institutes of Health (NIH).

Only aggregate data will be reported and all data that is entered in to databases will be password protected, the original copies of the instrument will be under lock and key, and the names will be removed after the coding is completed. All data will be separated from the identifying factors and assigned codes so that the patient cannot be linked to the data. Codes will be accessed only by the principal investigator(s) and secured under lock and key. Once the data has been entered into a database, the database will have a security code only known to the
principal investigator(s). Data will be stored for a minimal period of three years in a locked safe, and then will be shredded and destroyed.

X. Informed Consent Process

All participants will have the ability to give written, informed consent. Prior to data collection, permission will first be obtained from this researcher’s thesis committee of the School of Nursing at Southern Adventist University (SAU). Permission will then be obtained from the Institutional Review Board at the participating institution. In addition, permission from the cardiac surgery group involved will be obtained, to include their patients in the study.

There is no potential for coercion, which is considered any pressure placed upon another to comply with demand, especially when the individual is in a superior position. Pressure may take the form of either positive or negative sanctions as perceived by the participants within the context and culture of the study.

XI. Debriefing Process

Not applicable for this study.

XII. Dissemination of Findings

The communication of the findings of this study will provide direction for further research involving the techniques and protocols involved. All information communicated will be de-identified if published. Presentation of the collected data, through nursing seminars and educational meetings is an excellent method to propagate the information.

XIII. Compensation to Participants

No compensation is awarded to either the participants or researchers involved in this study.
Memorial Health Care System

November 13, 2002

James Zellner, MD
Alliance of Cardiac, Thoracic and Vascular Surgeons
605 Glenwood Drive, Suite 405
Chattanooga TN 37404

RE: Our Study # 02-11-02

Dear Dr. Zellner:

Protocol Title: Comparative Analysis of Coronary Artery Bypass: Costs of Off-Pump vs. Conventional Techniques with Variably Bonded Circuits and Drug Strategies (CABOCS)

Memorial Hospital Institutional Review Board (IRB) is a duly constituted IRB in accordance with the requirements of the Federal Food, Drug and Cosmetic Act as specified in regulations 21 CFR part 56, and the requirements of the ICH Guideline for Good Clinical Practice. As Chairman of the Memorial Hospital IRB, I hereby certify that this action of the Board was taken in accordance with these regulations for the protection of human subjects.

This letter is to advise you that the above referenced study was presented to the Memorial Hospital IRB on November 12, 2003. The Board approved this study for twelve months. Beverly Gordon and Margie Lawson will meet with Mr. Wycoff to help with standard consent language and decide on the best way to recruit participants to comply with HIPAA regulations.

A request for continuation with a copy of the current informed consent must be submitted to the IRB for review at least one month prior to the expiration date of 11/11/2003.

Please keep the Board apprised of any untoward effects associated with this study. If you have any questions, don't hesitate to contact me at 423-495-6375 or Margie Lawson, Human Protections Administrator at 423-495-6198.

Sincerely,

Christine W. Parker, MD
Chairman, Institutional Review Board

2525 de Sales Avenue Chattanooga, TN 37404-1102 Phone 423.495.2525
Informed Consent for:


Name

Title:

Comparative Analysis of Coronary Artery Bypass: Costs of Off-Pump vs. Conventional Techniques with Variably Bonded Circuits and Drug Strategies. (CABOCS)

Participants:

Memorial Health Care Systems
Alliance of Cardiac, Thoracic and Vascular Surgeons
Southern Adventist University

Principal Investigators:

James Zellner, M.D., Assistant Professor,
University of Tennessee College of Medicine, Chattanooga Unit;
Alliance of Cardiac, Thoracic and Vascular Surgeons
Chattanooga, Tennessee 37404
(423) 624-5200

Michael M. Wyckoff, R.N., C.C.P.
MBAc / MSNc
Southern Adventist University
Pager: (423) 655-4622
E-mail: Michael_Wyckoff@Memorial.org

Introduction:

Your surgeon is asking you to participate in a research study during your heart surgery hospitalization. Before agreeing to participate, it is important that you read and understand the information presented in this consent form. The consent form describes the purpose, procedures, benefits, risks, discomforts and precautions of this study.
It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time. **No guarantees or assurances can be made as to the results of the study.**

If you are not completely truthful with your doctor regarding your health history, you may harm yourself by participating in this study.

If you have any questions after reading this form, ask a doctor or investigator from the study to explain. **You should not sign this form until you are sure you understand all the facts.**

You may want a friend or family member to read the form and talk with the doctor with you. They have the right to discuss the research with the doctors or researchers from the study. You can also talk to your regular doctor about what you should do. Talking things over can help you make your decision. You will be given a copy of this signed and dated form.

**Background and Purpose of the Study**

You are being asked to volunteer for a research study involving different ways of performing open-heart surgery, including bypass machines and drug therapies currently used by your surgeons. Heart bypass surgery is sometimes associated with side effects, such as, chest pain, heart attacks, heart failure, or impairment of memory, language, and motor skills. The purpose of this study is to determine any differences in therapies (with or without the bypass machine), costs involved with these therapies, time spent in the hospital with each, and the possible differences between drugs chosen by your doctor. All therapies used, including the bypass machine, drugs and surgical techniques, are approved by the Food and Drug Administration.

Approximately 150 people will participate in this study at this hospital. You may be able to participate if you qualify on the bases of your medical history, your surgeons' approval, and certain medical qualifications.

This study consists of two phases. Phase One will involve the use of the current bypass machine if your doctor chooses to use it; Phase Two will involve the use of the FDA approved Minimized ExtraCorporeal Circulation System (MECC) with the Bioline Coating ®. Use of the different bypass machines is based entirely upon the phase of the study in which you are being asked to enroll.
Length of the Study

Your surgical therapy will be based entirely upon your surgeons’ protocol and will not be affected in any way or means by this study. Use of the different bypass machines is based entirely upon the time of the study in which you are being asked to enroll.

The blood work will be drawn after you are asleep in surgery from an existing arterial access line, and 6 hours after completion of the operation. Information will be collected from your medical record for the duration of your time in the hospital. The study will be closed when 150 subjects have successfully completed the protocol. After leaving the hospital, there will be no further follow-up needed, thus all participants will have completed the study.

Procedures

As a participant in this study, you will have certain procedures performed. All of these procedures are part of the usual care patients receive who has open-heart surgery. During your hospital stay, some additional things will be done to help in the study. This includes obtaining information from your medical records and taking extra blood to be studied (about 10 tablespoons) throughout the course of your hospitalization. This is not part of the usual course of treatment during your care for your heart bypass surgery. After leaving the intensive care unit, there will be no further contact with the researcher(s).

If you are a woman of child-bearing age, there is no additional risks involved with this study other than the usual risks involved with the surgical procedure as explained by your doctor.

In the event that your doctor chooses to use the bypass machine, the type of machine used is random, according to which phase the study is in reflected upon your enrollment time and the duration of the study.

Risks

- There are no added risks beyond those normally associated with open-heart surgery.
- All of the blood samples (3) will be drawn at the same time for both the study and your usual care. The blood samples will be taken from an existing line used in all open-heart procedures.

You may want to talk about the risks and benefits with your doctor and other people you trust. If you have any questions, ask a doctor or researcher from the study.
Alternate Therapy

Taking part in this study – or saying no – is up to you. If you do not participate, you may undergo your heart bypass surgery in the usual fashion. There are no other approved additional treatment therapies available at this time.

Benefits

- People who take part in studies help advance knowledge and treatment. Many people may be helped if the study shows benefits from the different therapies.
- You may or may not benefit from the study-related tests and procedures.

Withdrawal From the Study

Your participation in this study is purely voluntary. You may refuse to participate or withdraw from this study at any time without the loss of any benefits to which you are entitled or without affecting your future medical care. There will be no change in your medical care or eligibility to participate in future research studies. If you withdraw from this study, please be aware that all information about you will be removed from the study.

Responsibility for Costs

The sponsors will pay for all the costs of the procedures that are unique to this study. You and/or your insurance company are responsible for the other, regular costs of a bypass operation and care.

Confidentially:

Every effort will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

If the study results are published, steps will be taken to make sure that no one will be able to tell you participated. Records of your participation in the study will be kept in a locked file in the principal researchers' computer and possession. The confidentiality of the researchers' computer is carefully guarded. Your research records will contain portions of your medical history, reports from your surgical procedure and possible treatments and results of your blood tests. Information collected, as part of the research study may also be included in your medical records.
Organizations that may inspect and copy your research records for quality assurance and data analysis include:

- Memorial Hospital Investigational Review Board (IRB), a group of people who review the research study to protect your rights;
- Southern Adventist University School of Nursing Thesis Committee, a group of faculty who ensures the research project is conducted in an ethical and professional manner;
- The blood analysis centers, Erlanger Research Cytokine Laboratory and The Medical University of South Carolina, centers providing laboratory services;
- Government agencies including the Food and Drug Administration (FDA) and the Office of Human Research Protections (ORHP) can review the research to see that it is being conducted safely and correctly.

Authorization to Share Personal Health Information in Research:

The word "you" means both the person who takes part in the research, and the person who gives permission to be in the research. You are being asked to take part in the research described in the attached consent. To do so requires health information that identifies you that must be collected while you participate in this research study. Information from your medical record will be collected as well as results of tests as described above. Only information needed for the research will be collected. This information is described in the attached consent form. For you to be in this research, your permission to collect and share this information is required.

To do the research described in the informed consent, health information about you will be collected and shared. By law, you must be told how information will be obtained and your permission is required. The following information will be collected:

- The results of the blood work performed on you
- The results of the clinical data collected from your medical record as required in the research study

This information will be provided to CABOCS Research and The Medical University of South Carolina or investigators in above described places. It will only be given with a study number identifying you. This number will be kept confidential by the investigator(s) in charge of the research at this hospital.

Your health information may be shared with people at the hospital who help with the research, and may be shared with researchers outside the participating institution(s). Some of these people are ensuring the research is conducted properly.
The “confidentiality” portion of this form lists these people. Some of these people may share your health information with someone else. If they do so, the same laws may not protect your health information.

This authorization to release personal health information, and information in your medical records, may need to be collected or examined by:

- Persons from the Memorial Hospital Institutional Review Board (IRB) which approves and monitors research
- Persons from the Food and Drug Administration (FDA), in the event it decides to examine the way the research was done
- Persons from the Office of Human Research Protections (OHRP) if they decide to examine the conduct of research
- Persons from the Southern Adventist University if they decide to examine the conduct of research

When these outside people decide to look at your information, they are not allowed to record any information in any way that will identify you. If CABOCs Research discloses your information, the researcher(s) are obligated to follow the same laws and your information must remain confidential.

If you sign this form, your health information will be collected until the end of the research. Some information from your medical records may be collected after your direct participation in the research project ends. Some of the information will be kept for a long time, in case we need to look at it again. Information about you will be kept as confidential as possible.

Information about you will be collected until the end of the research. Information may also need to be collected from your medical record after the research tests are done. Your information may also be useful for other studies [research]. Your information can only be used again if a special committee in the hospital gives permission. This committee may require you to give your permission again before doing the research. But the committee may also allow the research to be done without talking to you again, if your health information is kept private [confidential].

If you sign this form, you are giving permission to collect, use and share your health information. This permission to use your health information does not have an expiration (ending) date. You do not need to sign this form. If you decide not to sign this form, you cannot be in the research study. You need to sign this form and the attached consent form if you want to be in the research study. Research cannot be done unless your health information can be collected, used and shared.
To be in this research, you have to sign this form, giving permission to gather and share your information. If you change your mind later and do not want your health information collected or shared, you need to send a letter to the researcher at the following address:

CABOCS Research
James Zellner, M.D.
Alliance of Cardiac, Thoracic and Vascular Surgeons
605 Glenwood Drive
Suite 405
Chattanooga, Tennessee 37405

The letter needs to say that you have changed your mind and do not want the researcher to collect and share your health information. You may also need to leave the research study if you do not want your health information collected. Health information collected before you withdrew may still be used. The research benefits from information obtained from everyone who starts a research study, not just those people who stay in it.

If you do, you may need to leave the research study if all the necessary information has not been collected. We will tell you if this is the case. We may still use the information we have already collected. We need to know what happens to everyone who starts a research study, not just those people who stay in it.

Your Name Will Not Be Made Public

If you agree to take part, your medical records will be treated confidentially accept as required by law. The representatives of this study, including the institutions performing any laboratory studies, may look at your study related records.

You agree to the collection, processing, transfer and storage of your personal data relevant to this study by the researchers and their appointed entities. Your personal data is information about you, but does not identify you by name. All reasonable steps will be taken to ensure your data is protected and that confidentiality is maintained.

You agree to authorize the Erlanger Research Cytokine Laboratory, The Medical University of South Carolina, and their representatives, to perform laboratory studies on your blood specimens as described above. Also, you agree that the principle researcher(s) can have access to, and obtain information from your medical records, that is pertinent to this study. The information obtained will be combined with other information collected from other patients enrolled in this study, and you will not be identified. Your personnel data will never be presented to anyone, either in written form or in a speech.

The results of this study will be analyzed and may then be published in the medical literature. This may take up to 1-2 years after the study is complete. You will not be identified in any report or publication.

Page 7 of 9
Revised 03-28-03
Subjects Initials ___. 
Emergency Contact / IRB Contact
This study has been reviewed by and approved of by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) of both the participating institutions. During this study, if you have any additional questions about this study, please contact Michael M. Wyckoff, R.N., C.C.P. at (423) 655-4266. If you have any questions regarding your rights as a research subject, please contact Margie Lawson at (423) 495-6168 with the Memorial Hospital Institutional Review Board.

Voluntary Participation / Withdrawal
You understand that being in this study is voluntary. If you decline to be in, or later withdraw from this study, your health care will not suffer in any way.

The study researcher(s) can stop your study for any of the following reasons:

- Your health changes in other ways
- The researchers stop the study
- Knowledge of unexpected or unexplained adverse events that affect patient safety

Your doctor, the Institutional Review Board / Independent Ethics Committee, and the researcher(s) may remove you from the study at any time without your consent. If you withdraw, or are withdrawn from this study, any and all of your information will be removed from the data bank and destroyed.

Patient Details

Patient Initials: _________ Date of Birth: _____ / _____ / _____
Day Month Year
Consent

I have been informed of the reasons for this study and:

- Had the study requirements explained to me
- Had all of my questions answered
- Have carefully read this consent form, and understand that I will receive a signed and dated copy
- Confirm that I give voluntary consent to participate in this study
- Will allow direct access to my medical records, but understand these records will be used confidentially, except as required by law

I understand that:

- The study researcher(s) / participating institutions will not receive any reimbursement for conducting this study
- My participating in the study is voluntary and that I can refuse to participate or ask to be withdrawn at any time without giving a reason, without my medical care or legal rights being affected.

I want to participate in this study, and freely agree to take part. I agree that the researcher(s) may keep, publish, or dispose of the results of this study.

_________________________ _________________________
Signature of person giving consent        Day       Month     Year     Time
(Patient or legally authorized representative)

_________________________ _________________________
Signature of Person Conducting the Consent Discussion        Day       Month     Year     Time
December 30, 2002

The Alliance of Cardiac, Thoracic & Vascular Surgeons
605 Glenwood Drive
Suite 405
Chattanooga, Tennessee 37404

Dear Sirs:

As a candidate for a MBA / MSN, I have chosen to do my thesis on a subject involving all of my professional interests, perfusion, nursing, and business. The proposed research study, Comparative Analysis of Coronary Artery Bypass: Costs of Off-Pump vs. Conventional Techniques with Variable Bonded Circuits and Drug Strategies (CABOCS), will begin data collection within the next few weeks upon your approval.

Please indicate your choice as follows to approach your patients to participate:

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Thank-you for your time and consideration,

Michael M. Wyckoff, R.N., B.S.N., C.C.P.

cc: School of Nursing, S.A.U.; Margie Lawson, CIM, Memorial Hospital I.R.B.; Jackie Jackson, R.N., Director Surgical Services; Joe Fischer, Administrator, Alliance of Cardiac, Thoracic & Vascular Surgeons.
APPENDIX C

NIH Certificate

Memorial Health System

IATA Certificate
CERTIFICATE OF SUCCESSFUL COMPLETION OF AN APPROVED CONTINUING EDUCATION ACTIVITY II

Michael Wyckoff
7625 Watercrest Drive
Harrison, TN 37341

SUCCESSFULLY COMPLETED:

HUMAN PARTICIPATION PROTECTION EDUCATION FOR RESEARCH TEAMS

Code Number ND/013-624-624

Contact Hours: 1.5
Date of Completion: 3/4/02

National Institute of Health, National Cancer Institute
Rockville, MD.

Authorized by:
Brian Mozelak 4/1/02
Director, Continuing Medical Education
Memorial Health Care System

Certificate of Completion

is hereby granted to:

Michael Wychoff

for satisfactory completion of

Research Training Modules

July 24, 2002

Date

Margie M. Lawson, CIM
Human Protections Administrator
RECORD / CERTIFICATE OF TRAINING
for the Transportation of Dangerous Goods

Michael Wyckoff

has completed the training and testing for the handling / offering for transport / transporting of dangerous goods as indicated below.

Trained As Per 49CFR 172.700 / IATA 1.5
Part 6, Chapter 1 of ICAO Technical Instructions
TDGR 9.2 Training Material Used
SaT-Pak's "The 2002 Comprehensive Guide to Shipping Infectious Substances"
Materials Covered for Class/Div 6.2 & 9
Classification and Identification
Nature and Characteristics
Packaging Requirements
Marking and Labeling requirements
Documentation Requirements
Special Precaution Requirements
Reporting Requirements
Emergency Action Requirements
Safety Requirements

[Signature]
Employer's Signature

11/3/02
Date of Training Completion

11/3/04
Date of Expiry (IATA 1.5.0.3 expires 24 months)
June 3, 2003

Dear Chief Perfusionist,

On May 22, 2003, a press release was issued announcing Getinge AB had signed an agreement to acquire 100% shares of Jostra AG contingent on the approval of the German anti-trust authorities. The acquisition is by the Surgical Systems Division.

The Getinge group is a leading global provider of equipment and systems to customers within health care, extended care and pharmaceutical industries/laboratories.

This acquisition does not include Jostra Corp. or Jostra Inc. It has been confirmed to us that the agreement includes that Jostra Corp. will continue to have access to all the products that it had been acquiring from Jostra AG and its subsidiaries. We have not been a part of Jostra AG since last year and therefore this acquisition has no affect on us.

Specifically, we will continue to be able to supply you with the heart lung machines, oxygenators, reservoirs, cannula, filters and all other products acquired from Jostra AG and were not making in our Anasco, Puerto Rico, or Woodlands, Texas facilities. Lars Sunnanvaeder, founder and owner of Jostra Corp., will visit our Woodlands facility within the next couple of weeks and will address all issues. Of course, if there would be any change to the above, you as our valued customer, would be immediately notified.

Once again, we appreciate your business. If you have any questions, please call your Customer Service Representative at 1-800-854-0567.

Sincerely,

Michael J. Sorna
President,
Jostra Corp.
Jostra Inc.
June 3, 2003

Dear Chief Perfusionist:

Jostra Corp. has made the decision to focus our development, manufacturing and marketing resources on minimized bypass systems, clinical data management, heart lung machines and other leading technologies to help you and your CV Surgical Team provide better patient outcomes. Due to current economic conditions of the marketplace, we are adapting our business to what we believe is the future of perfusion and the advancement of cardiac surgery.

This month, Jostra Corp. will launch the first version of ReadySystem® MECC™, the minimized bypass system. An early version of this has had tremendous success in Europe with currently over 4,000 successful cases. We are currently spending a great deal of our resources on the second and third generations of this product. We hope the second generation will be ready for launch within the next four to six months. We strongly feel this will be the "Future of Perfusion."

In addition to Jostra Corp's direct investment in the future, the following alliances have been formed:

- We have recently signed distribution agreements with ARMUS to provide an advanced data acquisition, data management and outcomes reporting software.
- We have also signed a distribution agreement with Surge Medical as our exclusive distributor of our cannula and sucker products.
- We are in the final process of signing a licensing agreement with Surge Medical as an R&D arm for future innovative products in that area. As most of you may or may not be aware, Surge Medical is made up of the founder and key management team of DLP which was a major market holder of these types of products.
- We have signed an exclusive distribution agreement with Termatek and will by launching IRIS IV to the US market. IRIS IV is the first intraoperative infrared imaging camera for CABG which will set a new standard of care for allowing the cardiac surgeon to noninvasively visualize flow and stenosis in coronary arteries and coronary grafts.
- We are also in final negotiations and a letter of intent has been signed to work with Somanetics.

Jostra Corp. has the most advanced products in the cardiopulmonary market. We continue to invest more resources into research and development in products such as the second and third versions of our minimized bypass system. In trying to bring innovative and creative devices to you and your CV Surgical Team, it is disappointingly clear that we cannot continue to support two manufacturing facilities in Anasco, Puerto Rico, and The Woodlands, Texas. We also do not believe that the current Bentley line which consumes a significant amounts of our financial and human resources, is our future. We have not been successful in expanding that line and the margins on that business do not allow us to focus on bringing new and better products to the market to improve patient outcomes.
June 2, 2003
Page 2

As a result of our focused efforts on the future of perfusion, we have decided to stop manufacturing custom tubing packs and will be closing our Anasco, Puerto Rico facility.

Enclosed with this letter is a listing of your current quantity of custom tubing packs that we are able to supply you, either on-the-shelf or work in progress, if applicable for you. You will be contacted by your individual Jostra sales representative to discuss your available inventory. Therefore, effectively, we are no longer in the custom tubing pack business.

By the time you receive this letter we will have notified our competitors so that we can do everything possible to help you in transitioning to another supplier. We will also presenting to our competitors options to use our Woodlands custom tubing area in case there is a need, due to non-availability in their current facilities, to handle additional manufacturing of these packs. Again, we will do everything possible to help in this transition.

Please feel free to contact your Jostra Sales Representative or your Customer Service Representative at 1-800-854-0567.

Sincerely,

[Signature]

Michael J. Sorna
President
Jostra Corp.
Jostra Inc.

Jostra Corp.
2828 N. Crescent Ridge Drive • The Woodlands, TX 77381
Phone: (800) 955-4236 • Fax: (888) 570-4009
APPENDIX E

American Heart Association Abstract Submission
Differential effects of serine protease inhibitors on MMP release in patients following cardiopulmonary bypass


**Background:** Cardiopulmonary bypass (CPB) is a requirement for a number of cardiac procedures, but can elicit an inflammatory response and the release of proteolytic enzymes, such as the matrix metalloproteinases (MMPs). The release and activation of MMPs can be initiated by a number of serine proteases, such as plasmin. Accordingly the present study examined the effects of the plasmin fibrinolytic inhibitor, epsilon-aminocaproic acid (EACA), and the serine protease inhibitor, Aprotinin (APRO), on plasma MMP profiles following CPB.

**Methods:** ProMMP-2 and proMMP-9 plasma levels were measured in CPB patients with EACA (n=30) or APRO (n=30) prior to CPB, at separation (post CPB) and 6 hours post CPB. All patients were equivalent with respect to cardiac surgery type and randomized to either treatment. All MMP levels were obtained through high sensitive and validated enzyme linked immunosorbent assays.

**Results:** Baseline proMMP-2 plasma levels (1253±52 ng/mL) were increased post CPB in EACA patients (1547±79 ng/mL, p<0.05) and returned to baseline at 6 hours post CPB (1400±88 ng/mL). In contrast proMMP2 levels remained similar to baseline in APRO patients at post CPB and 6 hours post CPB (1391±80, 1247±44 ng/mL, respectively). Baseline proMMP-9 plasma levels (63±4 ng/mL) remained unchanged post CPB in the EACA patients (61±9 ng/mL), but increased at 6 hours post CPB (92±10 ng/mL, p<0.05). However, proMMP-9 plasma levels decreased from baseline in the APRO patients at post CPB (45±3 ng/mL, p<0.05), and increased at 6 hours post CPB (79±4 ng/mL, p<0.05).

**Conclusion:** The present study demonstrated a unique and differential effect of the serine protease inhibitor, Aprotinin, on MMP release and activation following CPB. Since interstitial MMP activity can alter structure and function, the effect of Aprotinin may potentially ameliorate the tissue injury sequelae of MMP activity, which can occur following CPB.
Michael M. Wyckoff

Professional Vitae

Certifications
- Certified American Board of Cardiovascular Perfusion, #920344-1253
- Licensed Clinical Perfusionist, State of Tennessee, #CP 0000000013
- Licensed Registered Nurse, State of Tennessee, #0000056858

Honors
- Graduated from Episcopal Hospital School of Perfusion Science with cumulative GPA of 3.89

Education
- MSNc / MBAc
  - Southern Adventist University, Collegedale, Tennessee, 2000 – present
  - Bachelors of Science in Nursing, Southern College of Seventh-day Adventist, Collegedale, Tennessee, 1982
  - Associate of Science in Nursing, Southern Missionary College, Collegedale, Tennessee, 1980

Professional experience
- Perfusionist
  - 1996 – present Memorial Hospital Chattanooga, Tennessee
  - 1991-1996 Erlanger Medical Center Chattanooga, Tennessee

Registered Nurse
- 1983-1988 ICU Staff Nurse, Erlanger Medical Center, Chattanooga, Tennessee
- 1986-1989 Preceptor and staff Nurse, Intensive Care, Parkridge Medical Center, Chattanooga Tennessee
- 1984-1985 Clinical Instructor, School of Nursing, Southern Missionary College, Collegedale, Tennessee

Professional memberships
- American Society of Extracorporeal Technologists (AMSECT)
- Sigma Theta Tau International, Honor Society of Nursing