RELATIONSHIP OF PERIOPERATIVE HYPERGLYCEMIA AND MAJOR INFECTIONS IN CARDIAC SURGERY PATIENTS

by

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TABLE OF CONTENTS

TABLE OF CONTENTS - *Continued*

TABLE OF CONTENTS - *Continued*

LIST OF TABLES

LIST OF TABLES - *Continued*

LIST OF TABLES - *Continued*

LIST OF FIGURES

ABSTRACT

Two of the major infectious complications of cardiac surgery are pneumonia and surgical site infections of the sternum and graft harvest site. These postoperative adverse events significantly increase patient morbidity, mortality and cost associated with coronary artery bypass graft operations. Pre-existing diabetes mellitus is commonly considered one of the primary risk factors for development of these major infections. However, most of the previous cardiac surgery risk factor studies have not considered the role perioperative stress hyperglycemia may play in initiating these complications.

The primary hypothesis of this retrospective descriptive cohort study was that perioperative stress hyperglycemia (defined as either perioperative serum glucose threshold ≥250 mg/dL or perioperative serum glucose change ≥50 mg/dL) is an independent risk factor for the composite outcome of postoperative infections, including pneumonia and surgical site infections of the sternum and harvest site. The relationship of stress hyperglycemia to the individual infection outcomes was also examined. The secondary study hypothesis was that stress hyperglycemia increases resource utilization as excess days of care. The setting was a tertiary care federal medical facility in the southwestern United States, and the study cohort involved 1285 male military veterans.

Univariate regression analysis of major known risk factors and multivariate logistic regression analysis of significant predictors were used to model the relationship of perioperative hyperglycemia and major postoperative infections.

The multivariate logistic modeling showed that stress hyperglycemia was not an independent risk factor for major infection. However, in interaction with other commonly occurring risk factors such as prior heart surgery and operation time greater than 240 minutes, it became highly significant. In addition, stress hyperglycemia, as either a threshold variable or baseline change variable, consumed significant postoperative excess intensive care as well as acute unit days of care amounting to an average of $3600.00 in unreimbursed costs per patient episode.

CHAPTER ONE

INTRODUCTION

This chapter present an overview of the proposed dissertation project, statement of the problem to be investigated, the theoretical framework supporting this investigation and the statement of the purpose for this project. In addition, the research questions that were proposed will be presented, along with the potential significance of this work.

1.1 Overview of Dissertation

Pre-existing diabetes mellitus (DM) is reported to be the leading cause of morbidity following coronary artery bypass graft (CABG) surgery, being implicated in increased risk of developing postoperative infections [1-11]. These complications may occur in greater than 20% of all CABG patients and in greater than 30% of those patients with pre-existing diabetes [12-14]. However, it is known that most patients, both non-diabetic and diabetic alike, who undergo CABG surgery experience acute perioperative stress hyperglycemia with serum glucose levels significantly exceeding the normal threshold of 110 mg/dL [15]. This project examined the relationship of short-term surgical stress-induced glucose elevation to the post-operative occurrence of major infection, including pneumonia and surgical site infection, in a historical cohort of diabetic and non-diabetic veteran patients who had undergone CABG surgery. Additionally, the impact of stress hyperglycemia on excess resource utilization, as measured by length of stay, was also investigated.

1.2 Statement Of The Problem

Coronary artery bypass graft surgery is the most commonly performed major surgery in the United States with over 571,000 operations reported in 1999 and over 800,000 annual cases world-wide [16,17]. Post-operative morbid events such as surgical site infection and pneumonia significantly increase the cost of an already expensive operation, and affect the quality of life for patients that experience these recovery setbacks. The U.S. healthcare dollars associated with cardiac surgery complications exceed $500 million dollars annually, with much of the costs for these post-procedural events being uncompensated under the current fee-capitated system. Hollenbeck, et al., reviewed the skyrocketing costs of cardiac surgery surgical site infections (SSIs), noting that the average cardiac surgery SSI was reported to cost $886 in 1975 dollars compared with over $20,000 in 2000 [18]. They found that the economic toll for cardiac surgery SSI patients that died could be as high as $80,000.

In the current reimbursement setting there is strong incentive to reduce adverse patient outcomes. However, one of the frustrations observed by researchers in this field is that few intrinsic patient risk factors are readily amenable to intervention. Weight loss and smoking cessation have proven difficult to accomplish for many patients, but perioperative hyperglycemia may be managed with relative ease [19]. Early perioperative stress hyperglycemia afflicts the majority of patients that undergo cardiac surgery, regardless of their pre-existing diabetic status and in addition to chronic hyperglycemic levels [15,20].

However, most of the published studies either attempting to identify relevant risk factors or reporting on efforts to control perioperative hyperglycemia have only focused on those patients with pre-existing diabetes [10,21], even though at least half of the adverse postoperative events occur in non-diabetics.

This dissertation project performed a retrospective study on a historical cohort of U.S. veteran CABG patients for the purpose of examining the relationships between perioperative stress hyperglycemia and major post-operative morbid events. If perioperative hyperglycemia, regardless of diabetes status, were found to be a critical risk factor for post-CABG infectious complications, then strict control of blood glucose in all CABG patients during the early perioperative period would be considered to prevent or minimize these potential adverse outcomes.

1.3 Theoretical Framework

The stress of cardiac surgery may induce a temporary state of acute hyperglycemia in both diabetic and non-diabetic patients during the early perioperative phase, which in turn may increase their intrinsic or baseline risks for major infectious events including surgical site infection and/or pneumonia. Acute hyperglycemia affects autonomic nerve function in healthy as well as diabetic individuals, initiating widespread systemic responses [22]. Sharmoon, Hendler and Sherwin noted in 1980 that in the non-diabetic "a transient form of overt diabetes occurs during periods of severe surgical or medical stress" as a result of the combined secretion of endogenous epinephrine, glucagons and

cortisol in a setting of hyper secretion of multiple anti-insulin hormones" [23] .

See Table 1.1 for an outline of this process.

TABLE 1.1 Risk factors and metabolic mechanisms implicated in the development of perioperative stress hyperglycemia in the cardiac surgery patient

RISK FACTORS	MAJOR METABOLIC MECHANISMS		PHYSIOLOGICAL EFFECTS
Acute surgical stress	Systemic inflammatory response syndrome (SIRS)	Whole body proteolysis; lipolysis; gluconeogenesis	Perioperative stress hyperglycemia in the non-diabetic patient
Fast-track anesthesia; Glucocorticoid therapy; Excessive dextrose administration	Autonomic Nerve System dysfunction; Counter-regulatory hormones release: cortisol, glucagon, epinephrine; anti-insulin hormones release	Insulin resistance; Insulin deficiency	
Preexisting diabetes mellitus			Perioperative hyperglycemia + chronic hyperglycemia

Khaodhiar, McCowen and Bistrian characterize this cascade of events as the systemic inflammatory response syndrome (SIRS) which may occur either after a major complicated surgery such as CABG or as the result of a serious, untreated infection [24]. Simultaneous elevation of these hormones rapidly results in a diabetic-like state, characterized by overproduction of glucose, impaired glucose utilization and plasma glucose levels exceeding 200 mg/dL. As outlined in Table 1.2, an extensive review of stress-induced hyperglycemia by McCowen, Malhotra and Bistrian notes that the metabolic milieu of these excessive counterregulatory hormones results in failure of insulin to suppress hepatic gluconeogenesis despite hyperglycemia [20]. Additionally, the insulin-mediated

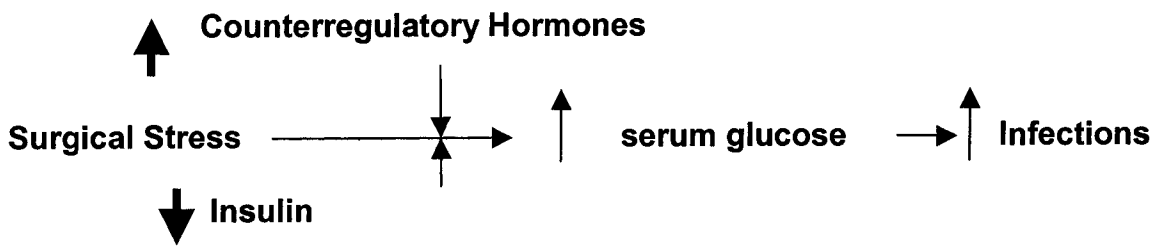
ability of skeletal muscle to take up glucose is also impaired, in the condition known as insulin resistance.

TABLE 1.2 Physiological effects and adverse outcomes associated with perioperative stress hyperglycemia in the cardiac surgery patient

PHYSIOLOGICAL EFFECTS OF STRESS HYPERGLYCEMIA		
Functional Disturbance	Physiological Effect	Adverse Outcome
Decreased vascular circulation; Decreased cellular-level functions	Reduced tissue perfusion; Reduced chemotaxis, phagocytosis, killing of PMNs	Surgical Site Infection
Alterations in esophageal peristalsis & gastrointestinal motility; Antral hypomotility; Gastric dysrhythmia; Gastro- & small intestine paresis; Decreased gall-bladder contraction; Decreased gastric acid secretion	Increased risk of reflux and aspiration; Increased bacterial colonization of stomach contents	Pneumonia
Altered composition of cell receptor sites	Amplified adherence of microorganisms to cells; Increased microorganism virulence	Infection

Both type 1 and type 2 diabetes mellitus patients also experience perioperative stress hyperglycemia during cardiac surgery over and above their baseline glycemic state, which in turn exacerbates their intrinsic increased risk for postoperative complications [(25)]. It is this stress hyperglycemia that is posited to be a major influence on the development of post-CABG morbidity, as noted in FIGURE 1.1.

FIGURE 1.1 Relationship of surgical stress to development of postoperative infections



The explicit mechanisms which support the hypotheses of this study will be elaborated upon in CHAPTER TWO.

1.4 Statement Of Purpose

The primary purpose of this research project was to distinguish the role that perioperative stress hyperglycemia (SH) plays in the induction of CABG patients' major types of infectious morbidity from that attributed to diabetes mellitus per se. Using established statistical techniques, the association between SH and subsequent development of major post-operative infections was measured. If perioperative stress hyperglycemia is found to be a significant predictor of these post-CABG adverse events in both non-diabetic and diabetic patients, then it would lead to the subsequent hypothesis that aggressive control of serum glucose in all CABG patients with elevated levels during and after surgery may improve patient outcomes. A follow-up interventional study could then be developed to study the effects of aggressive control of perioperative hyperglycemia on adverse outcomes.

1.5 Research Questions

The primary hypothesis was that perioperative stress hyperglycemia is a significant, independent predictor of the major post-CABG infections in both non-diabetic and diabetic patients. The secondary hypothesis was that perioperative stress hyperglycemia increases resource utilization in CABG patients.

Primary Research Question 1: In relation to other intrinsic patient variables and extrinsic process variables, is perioperative stress hyperglycemia a significant, independent predictor of the composite outcome variable of major post-CABG infections, which includes surgical site infection and/or pneumonia, in both non-diabetic and diabetic patients?

Primary Research Question 2: In relation to other intrinsic patient variables and extrinsic process variables, is perioperative stress hyperglycemia a significant, independent predictor of the individual adverse outcomes of sternal SSI, leg SSI, and pneumonia in non-diabetic and diabetic patients?

Secondary Research Question: Does perioperative stress hyperglycemia significantly increase resource utilization as measured by excess postoperative length of stay including intensive care unit stay, readmission to hospital within 60 days of discharge or extended care length of stay?

1.6 Significance

The Veterans Health Administration (VHA), a division within the Department of Veterans Affairs (DVA), has been a leader in the battle to minimize adverse outcomes associated with CABG surgery. Since 1988 the Continuous Improvement in Cardiac Surgery Program (CICSP), based at the Denver Veterans Affairs Medical Center (VAMC), has performed on-going data collection and surveillance on cardiac surgery outcomes with the result of significantly standardizing and improving CABG surgery programs within the VHA. Although the CICSP has collected and evaluated patient risk factor data including diabetes status, it does not routinely collect perioperative serum glucose data on CABG patients and has not evaluated the relationship of perioperative stress hyperglycemia and post-CABG infections in the veteran population. The significance of this study is the potential for major reduction in post-operative morbidity and mortality in the veteran CABG patient and attendant resource savings for the VHA. If this study identifies perioperative stress hyperglycemia as a significant risk factor in the high risk, high co-morbid veteran population as found within the VHA, this may prove generalizable to other high risk populations, e.g., Medicare patients, as well as other less problem-prone populations.

1.7 Summary

The majority of CABG patients, including non-diabetics, experience perioperative stress hyperglycemia during the early perioperative period. Perioperative stress hyperglycemia may be a significant, independent risk factor for post-CABG infections in both diabetic and non-diabetic patients. Investigation of these hypotheses may lead to an intervention, such as controlling perioperative hyperglycemia in all CABG patients, which may ultimately improve patient care and post-CABG outcomes.

CHAPTER TWO

REVIEW OF LITERATURE

This chapter presents a thorough review of the pertinent evidence-base surrounding the relationship of perioperative stress hyperglycemia, chronic diabetes mellitus, coronary artery bypass graft surgery and the development of major postoperative infections. The known risk factors for these adverse outcomes also will be discussed.

2.1 Literature Review

Coronary artery bypass graft surgery has been the object of considerable research and debate since this surgical treatment for coronary artery disease (CAD) was first attempted in the late 1960s. Although diabetes mellitus (DM) as a risk factor has been explicitly investigated in many epidemiological cardiac surgery studies, perioperative stress hyperglycemia is rarely mentioned or investigated in this context. Review of the Medline database from 1966 through March 2003 (limit human and English language) noted that there were 338 papers that correlated CABG surgery with DM, while only 15 studies related CABG surgery and hyperglycemia. As shown in TABLE 2.1, no papers were identified which focused primarily on stress hyperglycemia in the non-diabetic patient undergoing CABG surgery.

TABLE 2.1: Citations found in Medline 1966 – March 2003

Keywords	CABG	CABG + HG	CABG + SHG	CABG + DM
1. Coronary Artery Bypass Graft (CABG)	*	*	*	338
2. Hyperglycemia (HG)	15	*	*	5
3. Stress or perioperative hyperglycemia (SHG)	0	*	*	0
4. Diabetes mellitus (DM)	391	5	0	*
5. Wound infection/SSI	31	1	0	17
6. Pneumonia (PNA)	68	0	0	4

2.1.1 Coronary Artery Bypass Graft Surgery

The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for Coronary Artery Bypass Graft Surgery [26], last revised in 1999, note that CABG surgery offers significant advantages to an important subset of patients with CAD compared with either medical or interventional cardiology (percutaneous transluminal coronary angioplasty – PTCA), especially in those patients with severe multiple-vessel disease. Although an increasing number of patients are being treated with PTCA for emergent and urgent CAD, the annual number of CABG procedures performed does not appear to have decreased markedly. This may to due to the fact that in addition to offering survival benefits for patients with advanced CAD, CABG has been found to improve these patients' quality of life by consistently relieving angina pectoris as well as allowing resumption of many normal activities of daily living. Additionally, the

past 30-plus years' experience with CAGB surgery has provided insight into identifying two other high-risk populations of patients who may benefit from the historical expertise of this most common major operation: geriatric patients and patients with prior CABG surgery [27,28].

It is becoming increasingly common to perform CABG surgery on patients 70 or more years of age, as well as "re-do" on patients who have experienced cardiac revascularization surgery five or more years previously. The relevant implications of applying this surgical technique to progressively older and/or sicker patients are that they are more likely to have other comorbidities as well as being at increased risk for major morbid events after surgery. This in turn requires careful patient and procedure selection, a skilled surgeon, and excellent postoperative care to minimize the incidence of adverse outcomes associated with this cardiac revascularization procedure [28].

2.1.2 Major Post-CABG Infections

As noted by Eagle and Guyton, "one of every $10 spent on coronary disease is related to a complication", amounting annually to at least 1 billion excess health care dollars in the United States [26]. Aside from mortality, the major morbid events that occur after CABG surgery may be classified as either infection or vascular related. The major infections that occur after CABG surgery include pneumonia, sternal surgical site infection or mediastinitis, and infection of the distal graft harvest site (most often the saphenous vein leg incision). This

study focused on the relationship of perioperative stress hyperglycemia with the subsequent development of these major infections.

2.1.2.1 Sternal surgical site infection

Sternal SSI, including mediastinitis, is a relatively uncommon but dreaded event following CABG surgery, with reported rates ranging from 0.5%-5% [29-31]. Reported incidence of this and other post-CABG infections varies considerably depending on case definition, as well as comprehensiveness and duration of surveillance for these events, since greater than 60% of cardiac surgery-related SSIs occur after patients leave the hospital [32-34]. The consequences of deep chest infection include extended hospital stay and/or readmission, prolonged treatment with multiple antibiotics, re-operation for debridement, flap closure of the chest and death. Attributable in-hospital or early mortality reports range from 10%-20% and long-term mortality can be as high as 50% [35-37]. In 2000, Hollenbeck et al., noted that, on average, patients with deep chest SSI were hospitalized for 20 additional days and had a 22% 1-year mortality rate vs. 0.6% for non-infected patients. The average additional 1-year hospital cost for surviving infected patients was $20,927 compared to $81,474 for infected patients who died and $11,002 for surviving non-infected patients.

As noted by Roy, "host, surgical and microbiological risk factors are intertwined in a complex way for an SSI to develop" [30]. The most commonly reported intrinsic patient or host risk factors associated with development of sternal SSI include diabetes mellitus (DM), obesity, chronic obstructive

pulmonary disease (COPD), peripheral vascular disease (PVD), renal insufficiency, advanced age, male gender, female with pendulous breasts, use of steroids, and current smoking [18,36,38,39]. The list of common extrinsic perioperative process factors noted to increase risk of sternal SSI is even more extensive. The preoperative factors include length of stay greater than 5 days before surgery, skin preparation with razors, and antibiotic prophylaxis administration greater than 60 minutes prior to first operative incision. Intraoperative factors include use of bilateral internal mammary artery grafts, perfusion and total operation time, use of an intra-aortic balloon pump, extensive electrocautery, and excessive use of bone wax. Postoperative factors include bleeding and re-operation, sternal re-wiring, mechanical ventilation for greater than 48 hours, and pneumonia.

Although there are a few of these risk factors that are identified consistently as significant, independent risk factors in most CABG risk factor studies, i.e., diabetes mellitus and total operation time, there essentially is no consensus for most of the other risk factors mentioned. This is partly because there is variation among studies in the variables examined. It also may be due to institutional process variations that are present or absent within some of the studies. For example, if all prophylactic antibiotics were given within the prescribed timeframe, then antibiotic timing would not identified be a risk factor at the institution where the study was performed. Additionally, perioperative serum glucose in non-diabetics was not routinely investigated or mentioned as a host

risk factor in these papers. An exception is the study by Trick and colleagues from the Hospital Infections Program at the Centers for Disease Control and Prevention (CDC), which found that a preoperative serum glucose of ≥200 mg/dL in known diabetics was a modifiable risk factor associated with deep sternal site infection after CABG [21]. They also looked at postoperative serum glucose, but as a seven-day average, which would not be sensitive to the 24 to 48 hour peak of early postoperative stress hyperglycemia in non-diabetics.

2.1.2.2 Leg harvest site infection

Saphenous vein leg harvest site infections, although usually less devastating than those affecting the sternum, may afflict as many as 25% of patients following CABG surgery, impede recovery and consume considerable health care resources [40,41]. As noted by Mullen, studies of factors associated with leg SSIs "have varied in their findings" [42]. Intrinsic host factors commonly associated with leg SSI include diabetes, increased age, PVD, female gender, and obesity. Extrinsic process factors related to development of leg SSI include wound length, especially extension into the groin, wound depth, use of staples rather than sutures, time wound open and duration of surgery. Use of registered nurse first assistants (RNFAs), rather than less skilled residents or cardiothoracic fellows, has also been found to markedly reduce the incidence of leg SSIs. The premise for this finding is that early, consistent closure of the harvest site leg wound minimizes the risk of infection [43].

2.1.2.3 Pneumonia

Pneumonia is a relatively common and uniformly dreaded post-operative infectious complication of CABG surgery, with an reported incidence in the range of 4%-10% and a mortality rate approaching 25% [44,45]. It may also be the most over- or under-diagnosed of the infections as it is often confused with or clouded by congestive heart failure (CHF), adult respiratory distress syndrome (ARDS) or pleural effusion. As reported by Light, most CABG patients have postoperative evidence of a small pleural effusion, with approximately 10% displaying a large, persistent effusion [46]. An excellent case-control study reported by Gaynes et al., noted that pneumonia occurred approximately 4 days after CABG surgery with an accompanying 26.6% mortality [47]. The independent risk factors identified were COPD, mechanical ventilation greater than 48 hours and receipt of antacids or H2-blockers for gastric acid inhibition.

2.1.3 Primary Risk Factors for Post-CABG Infections

Because of the significant patient morbidity and mortality that may accompany the development of post-CABG infections such as pneumonia or surgical site infection, a large number of studies have been conducted to better understand the epidemiology of these events, with often-conflicting results. This study focused on investigating the relationship between the major patient and process risk factors and perioperative stress hyperglycemia and the occurrence of these morbid occurrences.

2.1.3.1 Diabetes mellitus as a risk factor for infection

Diabetes mellitus, a known major risk factor for CABG surgery, afflicts up to 25% of adults in this country [48]. DM is not only a well-recognized risk factor for CABG surgery, with 25%-30% of patients undergoing CABG surgery having pre-existing diabetes, but it is also one of the major predictors of post-CABG morbidity and mortality with approximately 35%-50% of complications occurring to patients with that co-morbidity [49-52]. As noted in the first section of this chapter, since 1966 there have been numerous studies and reviews that have related CABG surgery and diabetes. Post-CABG adverse outcomes are believed to be related to the pre-existing complications of chronic hyperglycemia, which include vascular atherosclerotic disease, and peripheral and autonomic neuropathies.

2.1.3.2 Perioperative hyperglycemia as a risk factor for infection

Unlike DM, scientists continue to question whether perioperative hyperglycemia is a significant risk factor for post-CABG adverse events. Perioperative hyperglycemia in non-diabetics has infrequently been acknowledged as a potential risk factor for adverse outcomes following serious health events such as major surgery, myocardial infarction or stroke [53,54]. However, it appears unclear in these studies whether those persons, classified as non-diabetic who exhibit perioperative hyperglycemia, are undiagnosed diabetics, or showing evidence of long-standing insulin resistance exacerbated by the health event, or simply responding to the stress of the acute medical or

surgical state. It is also unclear whether hyperglycemia is causally associated with a worse outcome or simply reflects a more severe adverse event, since serum glucose is often measured only after the fact. One study attempted to clarify the situation. A review performed by Khaodhiar, McCowen and Bistrian looked specifically at the infection outcomes of perioperative hyperglycemia and noted that the timing of elevated perioperative serum glucose indicated whether it was a risk factor for nosocomial postoperative infection or a harbinger of an infection [24]. The authors observed that the early post-operative period, when the patient is at greatest physiological stress, holds the highest risk for development of SSI. This is also the time when serum glucose is highest in both diabetic and non-diabetic patients and when it is unlikely that patients would have pre-existing, untreated infections. They concluded that when hyperglycemia occurs during the first two post-operative days, the rates of nosocomial infection are higher.

A meta-analysis of 32 studies conducted by Capes et al., noted that non-diabetic patients who were admitted after stroke with serum glucose levels > 108 to 144 mg/dL had a 3.07 increased relative risk of in-hospital or 30-day mortality compared with 1.30 for diabetic patients with comparable serum glucose levels [55]. Non-diabetic patients with elevated serum glucose levels also had a greater risk of poor functional recovery.

2.1.3.3 Perioperative hyperglycemia and surgical site infection

There are two primary mechanisms that place patients experiencing acute perioperative hyperglycemia at increased risk for SSI. The first mechanism is the decreased vascular circulation that occurs, reducing tissue perfusion and impairing cellular-level functions. A recent study by Akbari et al., noted that when healthy, non-diabetic subjects ingested a glucose load, the endothelial-dependent vasodilatation in both the micro and macro-circulations were impaired similar to that seen in diabetic patients [56]. The second affected mechanism is the reduced activity of the cellular immunity functions of chemotaxis, phagocytosis and killing of polymorphonuclear cells as well as monocytes/macrophages which have been shown to occur in the hyperglycemic state [57]. These two impairments of natural host defenses combine to increase the risk of tissue infection in both diabetic and non-diabetic CABG patients.

The rationale for this research study can be found in three recently published studies. DeCherney, et al., identified that although 30% of CABG patients were previously identified diabetics, 48% of CABG patients exhibited postoperative glucose values greater than 250 mg/dL (13.9 mmol/L) within the first 24 hours postoperatively [19]. Both Furnary, et al., and Van den Berghe, et al., found that it is possible to safely control acute perioperative hyperglycemia to within normal limits of 80 mg/dL-110 mg/dL in both diabetic and non-diabetic patients with resultant improvement of outcomes in both groups [15,58]. This study examined whether stress hyperglycemia is an independent risk factor for

major infection in veteran CABG patients and whether there is a resultant increase in length of stay related to this perioperative development.

2.1.3.4 Perioperative hyperglycemia and pneumonia

The posited mechanisms that may place patients experiencing acute hyperglycemia at increased risk for pneumonia are the attendant reduction in esophageal peristalsis and sphincter pressure as well as delayed gastrointestinal motility and emptying which accompany serum glucose elevation [59,60]. This constellation of impaired digestive processes may in turn increase the likelihood of gastric reflux and aspiration, predisposing these patients to post-operative pneumonia. These alterations are believed to be the result of autonomic neuropathy leading to vagal-cholinergic inhibition during the hyperglycemic state, which occurs in both healthy and diabetic subjects alike [61,62].

2.1.4 Secondary Risk Factors for Post-CABG Infections

In addition to DM, a number of risk factors have been noted in previous studies to adversely affect post-CABG infectious outcomes. A few studies have noted that the risk factors for sternal SSI compared with leg harvest site SSI may be very different. These infections were examined separately in order to clarify the possible differences in host and process factors.

2.1.4.1 Predictors of sternal surgical site infection

Many of the studies that have investigated sternal wound SSI have noted common as well as contradictory findings. In looking at intrinsic patient risk factors, males have been noted to be at increased risk for sternal wound infection, thought to be related to the removal or shaving of chest hair prior to the operation [39,63,64]. However, other studies have either found women, especially those with pendulous breasts, to be at greater risk of sternal wound infection [3,65], or else did not find that gender played a role in this negative outcome [4,66]. Due to the fact that 2% of the subjects in the cohort were women, the contribution of gender to CABG-associated SSI by site was not evaluated in the logistic modeling in this study.

One of the reasons for the lack of definitive findings related to age might be that age is probably the most common matching variable used for most of the case-control studies initiated to study these infections. Since this was a cohort study and patients were not be matched on specific variables, the effect of age was examined in this study. Two other host factors which have been inconsistently associated with sternal wound infection are age and obesity (body mass index (BMI) ≥30) [67,68]. In one study that compared overweight subjects with obese ones, obesity was associated with almost a four-fold increase in risk of sternal wound SSI. Another study noted that there is some indication that residual confounding may exist when obesity and diabetes are

both present [3]. These variables as well as their interactions were investigated in this study and the results are reviewed in CHAPTER FOUR.

Diabetes mellitus (DM) has been by far the host factor most commonly associated with sternal wound infection, with approximately 35% of cases being diabetic [39,69-71]. Not surprisingly, it is also the most common pre-existing co-morbid condition in patients undergoing CABG surgery, with approximately 10-20% of CABG patients diagnosed with DM. Interestingly, in-depth scrutiny has identified evidence to support the notion that the risk for sternal wound SSI may be higher for insulin dependent diabetics (IDDM) compared with patients on oral hypoglycemic medication, although most studies do not differentiate between insulin-dependent and non-insulin dependent diabetics (NIDDM). The data on whether or not CT patients have IDDM, or are controlled on oral hypoglycemics, are available within the database, and this association was evaluated. Another intrinsic risk factor that was evaluated is the presence of chronic obstructive pulmonary disease (COPD), which along with steroid use, which is very common among patients with this comorbid disease [70,72]. Patients with COPD are believed to carry a higher bioburden of pathogenic organisms than normal subjects, while steroid use is known to have a deleterious effect on the immune system's ability to effectively respond to inflammation and infection.

Cigarette smoking has been associated with inhibited wound healing and decreased circulation to the skin due to microvascular obstruction from platelet aggregation and increased nonfunctioning hemoglobin [63]. In addition, it has

been found to compromise the immune system and respiratory system. Cigarette smoking may also be one of the few pre-existing patient factors amenable to intervention, especially with the relatively new smoking cessation supports now available, such as the nicotine patch or welbutrin. Cigarette smoking is another host risk factor with variable findings, and that may be partly due to the fact that some studies that evaluate this factor consider only current smoking to increase risk of SSI [4]. A percentage of patients quit smoking immediately after the initial heart attack or diagnosis of heart disease, and may signify themselves as non-smokers at the time of CABG surgery, which may be performed within days or weeks of smoking cessation. The results may be dependent on how distant prior smoking must be before there is a significant difference in the groups. Recent and current smokers have been found to require extended ventilatory support compared with non-smokers and former smokers. The data used in this study classified patients as current smokers if they were still smoking or had quit smoking less than 3 months prior to surgery.

Malnutrition has been identified as a risk for nosocomial infections, including SSI, among patients undergoing any type of surgery, and CABG surgery is no exception [73]. Patients who are malnourished have been found to have less competent immune response to infection. Serum albumin level is the surrogate marker most commonly used to classify nutritional status. Not unexpectedly, malnutrition and cigarette smoking have shown evidence of

interaction. These variables and their interactions with each other were evaluated in this study.

Staphylococcus aureus nasal carriage also predisposes patients to have higher risk of sternal wound SSI. Having an endogenous source for the bacterium that may be responsible for as many as 70% of sternal wounds can increase the likelihood of infection 10-fold [74,75]. However, patients were not routinely screened for colonizing organisms, so that variable was not evaluated at this time.

Extrinsic perioperative risk factors that have been investigated in the literature include those variables, processes, conditions or situations that have been associated with surgical outcome and which occur during the period of time immediately before, during or within 30 days after surgery. The important point to note about extrinsic surgical process variables is that they often are more amenable to intervention than intrinsic patient risk factors.

One of the major extrinsic risk factors for development of sternal wound infection is dissection/ mobilization of one or both of the internal mammary arteries (IMA) for coronary artery bypass grafting because of the significant subsequent reduction in blood flow to the sternum [63]. Bilateral IMA has been noted to increase a patient's risk of infection as high as 10.5%. However, IMA grafts have the greatest likelihood of prolonged patency, as well as reduced operative and long-term mortality, and so are used preferentially whenever possible [76].

Two other perioperative risk factors most commonly and consistently associated with sternal wound SSI include extended preoperative length of stay and prolonged operative time [47,66,69,77]. Both of these factors are complex variables that are difficult to completely understand and explicate. Extended preoperative length of stay may be linked to intrinsic host factors that predispose to adverse outcomes such as pre-existing chronic diseases or co-morbidities, and recent colonization with nosocomial bacteria to which the patient has not developed resistance [78]. One study noted a 1-day preoperative stay infection rate of 1.2%, a 1-week preoperative stay infection rate of 2.1%, and a 2-week preoperative stay infection risk of 3.4% [63]. Prolonged operative time, for the purposes of this study, was primarily classified as greater than 4 hours or 240 minutes. This is not accordance with the CDC's SSI risk indicator that CABG surgeries that extend past the 75th percentile for that operation's time are at increased risk, which for CABG is 5 hours. The 4-hour threshold is based on pilot study data that is discussed in section 2.2.2 of this chapter. Clean wound infection rate approximately doubles with each hour of operative time. Prolonged operative time may also have multiple contributing and interacting factors including number and type of cardiac vessels bypassed and grafted as well as cardiothoracic team members' expertise [79,80]. It has also been hypothesized that an open chest allows opportunity for organisms to access the chest incision. Prolonged chest wall retraction increases the likelihood of cell damage by compression, drying and exposure to air. Longer procedures may also be

associated with blood loss and shock, reducing the general resistance of the patient. One large prospective study reported by the DVA Cardiac Surgery Risk Assessment Program was unable to identify pre-operative risk factors for the development of mediastinitis, and concluded that this outcome was more likely due to technical factors rather than pre-existing patient-related factors [81]. The development of hemorrhage and the subsequent need for re-operation to control bleeding and/or blood products and volume expanders may also be related to the skill of the cardiothoracic team [6].

2.1.4.2 Predictors of leg harvest site infection

Most CABG surgeries involve grafting an average of three coronary arteries, which essentially mandates harvesting additional vessels such as the saphenous vein or radial artery. This study limited the evaluation of harvest site infections to saphenous vein graft leg wound SSIs because other peripheral sites are used so infrequently there were insufficient cases to power such an effort.

The intrinsic host risk factors for leg wound SSI note both similarities and contradictions with those intrinsic host factors for sternal wound SSI. Gender is also noted to increase the risk of infection at the site where the saphenous vein graft has been harvested, but almost uniformly it is the female who has been found to be at greatest risk, along with those persons with higher body mass index (BMI) [39,72,82]. One hypothesis related to increased risk of leg wound SSIs among females is the common practice of leg shaving. Shaving may cause skin abrasions that in turn may lead to increased presence of microorganisms. As

noted above, gender was not evaluated at this time due to the low number of women in the study and the lack of power to detect a true difference.

Diabetes mellitus again plays an important role in the prediction of leg wound infections, with at least one study reporting an association among those patients with non-insulin dependent diabetes mellitus being at greatest risk. Not surprisingly, peripheral vascular disease (PVD) is a well-described risk for leg wound SSI and is not uncommonly associated with a history of DM.

Extrinsic perioperative factors associated with leg wound SSI include the technical skill of the cardiothoracic surgical team, which has been found to be strongly associated with the development of leg wound SSI [82]. At least one study noted that the task of harvesting the saphenous vein graft is often relegated to the least experienced members of the surgical team [34]. Skill, or its lack may be directly associated with operation time, with less skilled surgeons taking longer to perform CABG surgery. This, in turn, may affect the development of post-operative lymph leak and edema, which are related recognized risk factors. Technical skill may also be related to the postoperative need for and use of blood products.

2.1.5 Perioperative Hyperglycemia and Excess Resource Utilization

Post-CABG excess resource utilization, as measured by extended hospital length of stay and/or hospital readmission within 60 days of discharge is a matter of concern because it indicates adverse events for patients and increased costs for healthcare institutions. As noted earlier, excess costs of care associated with CABG morbidity and mortality can approach $80,000 with an average of $20,000

per major occurrence [18]. Hannan et al., looked at complications following CABG surgery, noting that readmission with 30 days following discharge was an important indicator of adverse events, with infection being the most common problem identified [83]. A recent study by Fish and colleagues which studied perioperative blood glucose noted that patients with levels >250 mg/dL had a 10-fold increased risk of postoperative complications following CABG surgery [84]. In addition, they found that every 30 mg/dL increase in glucose was associated with a 1-day increase in total length of hospital stay. Researchers at East Carolina University reported similar findings - that CABG patients experiencing 50 mg/dL increases in perioperative serum glucose had longer postoperative hospital stays and higher hospitalization costs [85].

2.2 Relevant Preliminary and Pilot Research

Prior to the development of this proposal, four related projects were completed that helped provide some of the theoretical, factual and methodological underpinnings used in this study. These projects have evolved as a natural consequence of our attempts to expand our understanding of the epidemiology of cardiac surgery SSIs and assist in local prevention efforts.

2.2.1 Antibiotic Use In Cardiac Surgery

This study was embarked upon after reviewing the CDC's "Recommendations for preventing the spread of vancomycin resistance" and identifying that more than 30% of the vancomycin prescribed at our institution was used for cardiac surgery antibiotic prophylaxis [86]. This initial study

examined whether there was any difference in SSI outcome when surgeons restricted their use of prophylactic vancomycin antibiotic [87]. The major findings of this study were two-fold. One was that cardiac surgeons voluntarily and significantly reduced the use of vancomycin prophylaxis for coronary artery bypass graft surgery in patients without prosthetic valve implantation from 94% to 18% in our medical center. The other important result noted was median hospital stay (10 vs. 9 days, P = .30) and number of postoperative infections (17.0% vs. 14.3%, P = .60) did not differ among patients who received vancomycin and those who did not. The study identified that cardiac surgeons could comply with the CDC's recommendations on reducing the use of vancomycin without adversely affecting patient outcomes. It also generated interest in further study of cardiac surgery outcomes.

2.2.2 Coronary Artery Bypass Graft Surgery SSI Case-Control Pilot Study

This pilot project was an outbreak investigation case-control study using a two-year data subset of 60 case CABG patients who were compared 1:2 to patients undergoing similar surgery but who had not developed SSI [88]. The initial investigation prompting the study had noted a significant increase in harvest site infections. Using conditional logistic regression, univariate analysis identified thirteen risk factors significant at $P \leq 0.1$ for infections of either the sternum or leg. The intrinsic host factors included age >70, diabetes mellitus, oral-controlled DM or insulin-controlled DM, and peripheral vascular disease. The extrinsic process factors included mortality estimate, operation time > 240

minutes, cardio-pulmonary bypass time (CPB), low cardiac output > 6 hours, on ventilator > 48 hours, and registered nurse first assistant. The multivariate model that best fit the data included only the extrinsic factors of operation time, low cardiac output, and RNFA, with RNFA being protective for SSI. This was in keeping with one of the working hypotheses for the study, that the predominant risk factors during an outbreak of SSIs are the extrinsic process factors, which are out of control or exceeding normal variation. For sternal SSI, the univariately significant intrinsic host factors were DM and PVD; the extrinsic process factors were ventilator > 48 hours and RNFA. The multivariate model noted only the intrinsic host factors of oral DM and PVD as independently significant for sternal SSI. For development of leg harvest site SSI, univariate analysis identified age >70, DM and PVD as significant intrinsic factors. The significant extrinsic factors included mortality estimate, surgical priority, operation time >240 minutes, low cardiac output, and RNFA as significant. The multivariate logistic models that best fit the data for leg SSI included operation time >240, low cardiac output for greater than 6 hours and RNFA. Having a RNFA as either first or second assistant on the case was extremely protective, reducing the risk of leg SSI as much as 89%. The findings from this study were used to support increased utilization of RNFAs as first and second assistants in CABG surgeries at our institution.

2.2.3 Random Early Perioperative Serum Glucose Levels in Cardiac Surgery Patients

A two-year cohort of cardiac surgery patients classified as non-diabetic or diet-controlled diabetic, diabetic on oral medications or diabetic on insulin were noted to have mean serum glucose levels of 173, 220 and 193 mg/dL respectively, during the first 72 hours from the start of surgery. Mean serum glucose levels were found to increase 60, 62 and 36 mg/dL respectively, with some patients recording levels exceeding 400 mg/dL[89]. Although 37% of patients were classified as having DM, 87% of early perioperative serum glucose values were greater than the high normal value of 110 mg/dL. In the non-diabetic subset, 83% of the glucose values were above normal. These results support the hypothesis that stress hyperglycemia occurs in most cardiac surgery patients. It is also noteworthy that insulin-controlled diabetes exhibited the smallest variation in perioperative serum glucose levels. This correlates with the multivariate regression findings that oral hypoglycemia-controlled diabetics, who had the largest increase in stress hyperglycemia, were at greatest risk of sternal SSI compared with non-diabetics and insulin controlled diabetics. This would be contrary to the prevailing wisdom that insulin DM patients are more seriously affected by diabetes and therefore at higher risk for adverse outcomes.

2.2.4 Excess Resource Utilization of CABG SSI Patients

The impetus to investigate and calculate the cost of CABG SSIs was to provide supporting information about the impact of sternal and leg SSIs on the

health care system resources [90]. A six-month subset of CABG surgery patients with SSI were identified along with their subsequent health care interactions, including initial post-operative length of stay, readmission to acute care or extended care within 60 days. The mean cost for each acute care readmission for sternal surgical site infection was $35,910. Extended or subacute care readmission cost for sternal SSI averaged $17,431 per stay. The cost for leg SSI acute care readmission was $4,990, while for extended care the excess unreimbursed cost was $11,352 per patient. The six month total excess days of care for cardiac surgery SSI at our medical center were 528 days and the excess attributable costs were in excess of $415,000. These findings were helpful in supporting the belief that these infections were very expensive to the health care system and that expenditure of modest resources, such as increased use of RNFA first and second assistants, could substantially reduce costs as well as benefit patients.

2.3 Summary

Most of the literature involving adverse post-CABG post surgical outcomes has noted an association with diabetes mellitus as a major risk predictor. Few studies have attempted to distinguish between the risks of the chronic hyperglycemia of DM compared with those associated with acute hyperglycemia of the stressful perioperative period. The theoretical and clinical evidence supporting the hypothesis, that perioperative stress hyperglycemia may play a major role as an independent predictor of adverse postoperative infectious

complications following cardiac surgery, was reviewed in this chapter. Additional, secondary risk factors for CABG SSI were discussed including the site-specific factors for sternal and harvest site infections. Lastly, the preliminary research projects, which provided pilot data as well as research direction, were discussed.

CHAPTER THREE

METHODOLOGY

This chapter presents a description of the research design, setting, study subjects and data collection methods that are used in this project. Human subject protections as well as data analysis strategy, study assumptions and limitations are also discussed.

3.1 Research Design

This is a retrospective study using an historical cohort of patients who underwent coronary artery bypass graft surgery between January 1,1995 and June 30, 2003. The primary purpose of this study is to measure the association between perioperative hyperglycemia and the major infections, which may occur after CABG surgery, controlling for other known risk factors.

3.2 Setting And Subjects

The setting for this study was a 225-bed tertiary care, university-affiliated, Department of Veterans Affairs Medical Center (DVAMC) located in the southwestern United States. It is one of 43 medical centers within the Veterans Health Administration where cardiac surgeries are performed, serving as a cardiac surgery referral center for veterans living in Arizona, southern New Mexico and eastern Texas, and performing a minimum of 150 CABG surgeries annually.

The subjects in this study are 1,285 veteran male patients who experienced either primary or prior heart surgery ("re-do") CABG surgery with or

without heart valve replacement since January 1995 at the DVAMC. These "re-do" patients may differ from primary heart surgery patients in that they may be older and may have more advanced disease and comorbidities. However, they were kept in the study cohort because they may comprise an increasing subset of future CABG patients, and the information provided to this study may be pertinent. Also, patients are not excluded because of age, urgency of surgery, clinical state of health or concomitant heart valve replacement surgery. There are only four criteria for study exclusion. Patients within the cohort who had more than one cardiac surgery performed during the study timeframe at the study center only had the first surgery included. Subsequent surgeries were excluded. Women are excluded because there are insufficient numbers to analyze them separately, and they may be different enough to affect the overall findings. Patients dying within 72 hours of surgery are excluded because 72 hours is the minimum time that serum glucose is monitored perioperatively. There is insufficient data from these patients to evaluate the effect of glucose on outcome. The final exclusion criterion is having a surgical wound classification which is less than clean, i.e., clean-contaminated, contaminated or infected, meaning that for some pre-existing reason the intrinsic risk of surgical site infection would be higher than normal.

3.3 Data Collection Methods

This study takes advantage of a large body of data collected previously and prospectively for the Department of Veterans Affairs' system-wide

Continuous Improvement in Cardiac Surgery Program (CICSP) [91]. Since its inception in 1988, the CICSP has maintained a locally inputted national database of all cardiac surgeries performed at DVA Medical Centers. Most of the pertinent patient and process variable data reside within the Veterans Health Information Systems & Technology Architecture (VISTA) mainframe computer database in a primary data set called Cardiac Surgery Risk Assessment (CSRA). The VISTA database contains patient demographics and intrinsic risk factors as well as the perioperative extrinsic and non-infection outcome data required for the study. A single registered nurse, who has performed this task for the past 10 years, conforming to the variable definitions provided by the CICSP, prospectively collected the CSRA data at the study center.

The infection outcome data, which includes pneumonia and surgical site infections, including sternal and leg SSI, that occurred after CABG surgery in the study cohort, were collected prospectively by this researcher and a co-investigator, two registered nurses trained in applying the Centers for Disease Control and Prevention (CDC) definitions for nosocomial infections [92]. Prompted by the need to investigate an epidemic of harvest site infections, since 1995 all cardiac surgery patients who had undergone CABG surgery, with or without heart valve replacement, at the study medical center have been prospectively followed for a minimum of 30 postoperative days. The outcome data reside within the study medical center Infection Control Program nosocomial infections Microsoft® Access 2002©database. The 8.5-year study time-period

benefits from the increasing computerization of the patient medical record, including clinical laboratory data and post-discharge outpatient clinic encounter information.

3.4 Risk Factor and Outcome Variables

The CICSP CSRA prospectively collected data include four data subset categories: clinical data, operative risk summary data, operative data, and resource data. See TABLES 3.1 through 3.6 for a listing of the pertinent collected variables.

All of the risk factor and outcome variables collected had to meet established criteria or definitions such as contained in the CDC Guidelines for Nosocomial Infections [92]. The clinical data set shown in TABLE 3.1 include demographic variables such as age and gender, pre-existing intrinsic patient co-morbid concerns such as diabetes or peripheral vascular disease, and other know risk factors such as smoking and prior heart surgery.

TABLE 3.1 Intrinsic patient variables to be extracted from VISTA Cardiac Surgery Risk Assessment Clinical Dataset

Demographic and Intrinsic Patient Variables	Units of Measure and Categories
Name	First Name, Middle Initial, Last Name
Social Security Number	9 digit social security number
Surgery Date	month, day, year
Gender	Male, Female
Age	years; <73, ≥73
Height	inches
Weight:	pounds
BMI	<30, ≥30
Diabetes:	No, Yes; No, Oral, Insulin
COPD:	No, Yes
Current Smoker:	Yes, Current Smoker; Quit within 2 weeks of Surgery; Quit <3 months prior to Surgery; Quit >3 months prior to surgery; Never Smoker, No
Prior Heart Surgery	No, Yes
Peripheral Vascular Disease (PVD)	No, Yes
Cerebral Vascular Disease (CVD)	No, Yes
Hypertension:	No, Yes

TABLE 3.2 contains operative risk summary data that summarize the patient's pre-existing preoperative risk for adverse outcomes which have been assessed by the cardiac surgeon and the anesthesiologist. Included are such variables as the physician's preoperative estimate of operative mortality and the

Anesthesia Society of America (ASA) classification of surgical risk.

TABLE 3.2 Estimates of intrinsic patient adverse outcome risk to be extracted from VISTA Cardiac Surgery Risk Assessment Operative Risk Summary Dataset

Operative Risk Summary Variables	Units of Measure and Categories
Physician's Preoperative Estimate of Operative Mortality	NS (Not Significant), %
ASA Classification:	1-Normal, 2-Mild systemic disease, 3-Severe systemic disease, 4-Severe systemic disease that is a constant threat to life, 5-Moribund; <3, 3-4, 5
Surgical Wound Classification	Clean; Clean-Contaminated; Contaminated Infected

TABLE 3.3 contains the relevant extrinsic process and outcome variables extracted from the CSRA Operative Dataset. These are the risk factors for infection that occur during the perioperative period and include the type of operative procedure, the duration of surgery (total operation time), and some intervening outcomes such as low cardiac output greater than or equal to 6 hours and ventilator greater than or equal to 48 hours.

TABLE 3.3 Extrinsic process and outcome variables to be extracted from VISTA Cardiac Surgery Risk Assessment Operative Dataset

Extrinsic Process and Outcome Operative Dataset Variables	Units of Measure and Categories
Cardiac procedures requiring cardiopulmonary bypass	
Number with Saphenous Vein	Number
Number with Internal Mammary Artery (IMA)	Number
Total Ischemic Time	minutes;
Total Cardiopulmonary Bypass (CPB) Time	minutes; <60, ≥60
Total Operation Time	minutes; <240, ≥240;<270, ≥270
Operative Death	No, Yes
Date of Death:	Date
Low cardiac output (LCO) ≥6 hours	No, Yes
Cardiac arrest requiring CPR	No, Yes
Reoperation for bleeding	No, Yes
On Ventilator ≥48 Hours	No, Yes

The CSRA resource data set, specified in TABLE 3.4, provides data on patient length of stay (LOS) in the operating room (OR time), intensive care unit (ICU) and total hospital LOS. These are the data elements that are used to calculate the cost of care for patients with infections compared to patients without infections.

TABLE 3.4 Extrinsic process and outcome variables to be extracted from VISTA Cardiac Surgery Risk Assessment Resource Dataset

Extrinsic Process and Outcome Resource Dataset Variables	Units of Measure and Categories
Time Operation Started	Date & Time
Time Operation Ended:	Date & Time
Operation time ≥240 minutes	No, Yes
Patient Extubated	Date & Time
Patient Discharged from ICU	Date & Time
Hospital Admission Date	Date
Hospital Discharge Date	Date
Postoperative Length of Stay	Days
Total Hospital Length of Stay	Days
Readmission within 30 days	No, Yes
Readmission Length of Stay	Days

A number of data elements essential to this project reside outside of the CSRA database. These include the perioperative serum glucose values and other pertinent lab values, as noted in TABLE 3.5, which are stored within the Clinical Laboratory Database. Two categorical variables for stress hyperglycemia were derived from the Clinical Laboratory data based on the 75th percentile or highest quartile of the values. One is a postoperative threshold value of serum glucose < or ≥250 mg/dL and the other is a baseline increase value of serum glucose < or ≥50 mg/dL from preoperative maximum value.

TABLE 3.5 Intrinsic Patient Variables extracted from the Clinical Laboratory Database

Clinical Laboratory Variables	Units of Measure and Categories
Serum Glucose (1)	mg/dL; 1)preoperative and postoperative mean & maximum
Stress Hyperglycemia (2 & 3)	2) perioperative increase 50mg/dL; 3) maximum ≥250 mg/dL;
Serum Creatinine	<4.0, ≥4.0
Serum Albumin	g/dL; <3.5, ≥3.5
HbA1c	<7%, ≥7%

The infections outcome data elements stored within the Infection Control database, and which are utilized to answer the research questions of interest, are noted in TABLE 3.6. This prospective outcome data, collected over the past 8.5 years, include the site of surgical infection (SSI) and date identified, as well as incidence and date of pneumonia.

TABLE 3.6 Outcome variables to be extracted from the Infection Control Program database

Extrinsic Process and Outcome Variables	Units of Measure and Categories
SSI	No, Yes;
Date identified	Date
Chest SSI	No, Yes;
Date identified	Date
Leg SSI	No, Yes;
Date identified	Date
Pneumonia	No, Yes;
Date identified	Date

3.5 Data Analysis Plan

The data analysis plan consists of two phases. During the first phase, the data are examined for missing or erroneous values and preliminarily examined using descriptive and summary statistics. During the second phase of data analysis, univariate and multivariate logistic regression statistical techniques are applied in order to answer the proposed research questions.

3.5.1. Missing, Erroneous and Misclassified Data

Missing data and extreme data values that appeared erroneous are evaluated as to whether they occurred randomly throughout the data set, systematically, or time-clustered. Missing data are left absent and erroneous data are replaced with the reference value, which is imputed from the non-missing correlated data, when possible. If the variable data are continuous, the reference value used is the mean. If the variable data are categorical, then it is either 0 for binomial data (condition absent), the lowest value if stratified in two or more categories, or the category with the lowest risk for infection [93].

Misclassification of the data is not a major concern for most variables in this study because of the rigorous application of the definitions and the limited number of data collectors for most of the study data. However, it is a significant concern with regard to patients classified as non-diabetics, who may actually be undiagnosed diabetics. This variable is evaluated in relation to the patient's preoperative serum glucose levels. In the event that non-diabetic patients had at least one preoperative serum glucose level ≥200 mg/dL, they are then classified

as either undiagnosed diabetics (stratified variable) or diabetics (dichotomous variable) in order to limit the effect of this potential bias.

3.5.2 Preliminary Statistical Analyses

Independent demographic and intrinsic patient variables, as well as extrinsic process variables for cohort cases (subjects with the outcome) and non-cases initially are compared and analyzed using descriptive statistics including means, standard deviations, ranges and percentages. All continuous variables are examined for normality, outliers and influential data points, with transformation for subsequent parametric statistical tests performed as indicated. Certain continuous variables such as age, serum glucose, albumin and creatinine are categorized along clinically relevant cut-points to facilitate the development of useful models. Comparisons of independent continuous variables are made using the nonparametric Mann-Whitney *U* test. Frequency tables are constructed for independent categorical variables, with comparisons of proportions between cases and non-cases made using chi square analysis.

Initial standard univariate diagnostics for skewness and outliers are performed, as well as variable transformation, where necessary to provide the best fit. The predictor variables of interest are evaluated for optimum performance by inspection of univariate *p*-values. Using STATA 8.0 statistical software package and univariate logistic regression analysis, serum glucose levels and diabetes status are regressed on the composite endpoint of major infection (SSI, pneumonia) as well as the individual outcomes [(94)]. Diabetes

mellitus and its treatment are categorized and tested as either "No" or "Yes", or into "Non-Diabetic or Diet-Controlled", "Diabetic on Oral Medication" or "Diabetic on Insulin". Those patients who used both oral hypoglycemic medication and insulin are categorized as insulin users. Patients with pre-operative random blood glucose ≥200 mg/dL or glycosylated Hemoglobin A1c ≥7 mg are classified as diabetic in this study regardless of their prior diabetes classification. Operation Time (OT) is evaluated initially as a continuous variable, and is also categorized and examined as a dichotomous variable (<240 minutes, ≥240 minutes and <270 minutes, ≥270 minutes). Other continuous variables, such as age, serum glucose, HbA1c, etc., also undergo similar, clinically relevant transformations based on distribution characteristics. See TABLES 3.1through 3.5 for utilized examples. Variables are considered significant and eligible for multivariate model inclusion if they achieve a *p*-value of ≤0.1. Variable interactions, as supported by the clinical literature, are also investigated, such as age x smoking, DM x PVD or Operation Time x On Ventilator >48 hours.

3.5.3 Multivariate Analyses

Independent predictors of adverse outcomes are identified by multivariate logistic regression analysis with the final models being selected by the likelihood ratio test using a p-value of 0.05. Logistic regression allows the modeling of the log-odds of a dichotomous (yes/no) dependent event's occurrence, in this case adverse post-operative events.

Conditional probability that the outcome (infection) is present is noted by $P(Y=1|x) = \pi(x)$. The multiple logistic regression model is given by the equation

$$g(x) = \beta_0 + \beta_1 \chi_1 + \beta_2 \chi_2 + \beta_3 \chi_3 + \ldots + \beta_p \chi_p$$

where g (x) = logarithm of the odds = $\log [\pi(x) / (1 - \pi(x))]$ (95)

and $\pi(x)$ is the probability that the Composite Endpoint=1, given a subject's set of predictor values. The coefficients β_J estimate the change in log odds of the adverse outcome for a one-unit change in independent variables χ_j.

Primary Research Question 1: After adjusting for the potential effects of other intrinsic patient variables and extrinsic process variables, is perioperative stress hyperglycemia a significant, independent predictor of the composite outcome variable of major post-CABG infections, which includes pneumonia and surgical site infections, in both non-diabetic and diabetic patients?

An example of the primary models tested for Question 1:

Major Infection = Stress Hyperglycemia (SH) + Diabetes + Age + OR Time + On Ventilator >48 hours + Low Cardiac Output>6 hours (LCO) + SH*LCO

Primary Research Question 2: After adjusting for the potential effects of other intrinsic patient variables and extrinsic process variables, is perioperative stress hyperglycemia a significant, independent predictor of the individual adverse outcomes of pneumonia, SSI, sternal SSI or leg SSI in non-diabetic and diabetic patients?

An example of the primary models to be tested for Question 2:

SSI = Stress Hyperglycemia (SH) + Age + Diabetes Mellitus + COPD+ OR Time + On Ventilator >48 hours + SH*OR Time

3.5.3.1 Sample size and power estimates

Sample size calculations for the primary research question are performed based on the planned univariate and multivariate logistic regression strategies. The primary univariate analyses compare the composite infection endpoint in CABG patients and analyze whether stress hyperglycemia as variable Glucose Maximum ≥250 mg/dL is a significant predictor for this composite outcome. For the univariate analysis of CABG patients, the study has a power of .95 to find a significant difference in the 257 subjects who experience perioperative stress hyperglycemia as Glucose Maximum ≥250 mg/dL and a resultant 23% composite infection rate, compared to the 1028 subjects who did not experience stress hyperglycemia and have a 13% composite infection rate [90, 96]. The study power would be reduced to .16 if the composite infection rate in those subjects experiencing stress hyperglycemia as the Glucose Change ≥50 variable is 18% compared to 15% in those subjects not experiencing stress hyperglycemia.

The multivariate analyses utilized the statistical convention of the "rule of ten", meaning that the number of modeled predictor variables are limited to 10% of the number of events, or in this case, 20 variables for the composite model of major infection, 13 for SSI and 5 for pneumonia [97]. The total number

of subjects in the study cohort is 1285 with a composite outcome incidence rate of 16% (13% SSI, 4% pneumonia).

There are at least two reasons to believe that 11 or fewer predictor variables are sufficient to develop a model strong enough to test the study hypothesis regarding perioperative stress hyperglycemia. The first is that previous work by this researcher, utilizing a data subset and case-control methodology, identified that only five out of 49 similar intrinsic and extrinsic variables were significant predictors for SSI [88]. This preliminary study identified that patients with SSIs had significantly more diabetes, peripheral vascular disease, low cardiac output, prolonged ventilatory support, and longer operative time. The other reason is that two published studies on CABG-associated outcomes both noted that "a relatively small number of clinical variables", seven or less, "provide a large amount of prognostic information in patients undergoing CABG" [98,99]. Patient variables such as age, surgical priority, previous cardiac surgery, etc. provided between 45% to 85% of the models' predictive information, and the authors believe that complex models provide only "marginal predictive benefits" prone to the statistical problem of "overfitting" where a more complex model performs poorer than a simpler one.

Secondary Research Question: Is perioperative stress hyperglycemia an independent predictor of increased resource utilization as measured by excess postoperative length of stay including intensive care unit stay, readmission to hospital within 60 days of discharge or extended care length of stay? The

resource utilization of the two glucose exposure variable groups, those in the cohort with a postoperative Glucose ≥250 mg/dL and those in the cohort with postoperative Glucose Change ≥50 mg/dL are compared with patients whose values fall below these cut-points using the Mann-Whitney *U* test. Differences are considered significant at the 0.05 level.

3.6 Protection of Human Subjects

The Institutional Review Board of the University of Arizona and the Department of Veterans Affairs Medical Center's Research and Development Committee approved this study prior to its commencement. This study was granted expedited administrative approval because there was no risk of physical injury to the human subjects and no planned experimental interventions. The primary concern or risk to patients involved confidentiality of their protected medical information. Although patient identifiers remained initially linked with patient records in order to merge the different databases, only the investigator had access to the complete records. To protect patient confidentiality, all unmerged database files were placed on computer CD-Read-Writable discs and kept in a locked file when not actively in use. All merged files had Health Information Portability and Privacy Act (HIPPA)-specified patient identifiers stripped. Only merged files without patient identifiers pertaining to this project were stored on the investigator's PC hard drives. All files with patient identifiers were destroyed at the completion of the data merger. Only aggregated data results are reported in this study.

3.7 Assumptions

Three preliminary assumptions have been identified. Due to the historical, descriptive nature of the study, patients are not at risk for physical or emotional harm. The data were collected prior to this study's inception, which limits misclassification bias. Three trained registered nurses collected the data prospectively, which improves quality and accuracy of the data.

3.8 Summary

This chapter reviewed the study methodology including setting and subject selection, study variables and data collection plans. In addition, data analysis strategies were discussed as well as sample size adequacy relative to modeling techniques. Human subjects concerns as well as study assumptions and potential limitations were assessed.

CHAPTER FOUR

RESULTS

This chapter reports the results of the data analysis, including the descriptive statistics, the univariate and multivariate logistic regression modeling findings and the resource utilization comparisons. Descriptive statistics for continuous and categorical explanatory variables are reported in TABLES 4.1 through 4.11. Univariate analyses are shown in TABLES 4.12 through 4.19. Logistic regression findings are synthesized in TABLES 4.20 through 4.31 and resource utilization results are reported in TABLES 4.32 and 4.33.

4.1 Descriptive Data Analysis

Initial data collection identified 1418 subjects who had undergone CABG surgery with or without heart valve replacement from January 1, 1995 through June 30, 2003. Subjects were removed from analysis who had more than one cardiac surgery during the study timeframe at the study institution (n=7; 0.5%), were either female (n=29; 2%), had died within 72 hours of surgery (n=58; 4%), or whose surgery wound classification was not clean (n=46; 3%). The resultant number of subjects in the dataset for analysis was 1285. TABLE 4.1 describes the dataset continuous variables and TABLES 4.2 through 4.10 describe the categorical variables included in the dataset.

Four of the eleven continuous variables had data missing, ranging from 1%-79%. Only 21% of subjects had glycosylated Hemoglobin A1c (HbA1c)

measurements recorded within 6 months prior to surgery. Since HbA1c is usually only performed on known diabetics, this low degree of data availability was not unexpected. Fifty-two percent of diabetic subjects controlled with insulin had recorded HbA1c values, as did 45% of diabetic patients controlled with oral hypoglycemic medication . Missing values were not imputed for any of these variables.

TABLE 4.1 Dataset Continuous Variables Including Number and Percent of Data Completeness, Median, Mean and Standard Deviation

Continuous Variables	n (%)	Median	Mean	SD
Age, years	1285 (100)	66	65.1	9.2
HbA1c, %	266 (21)	7	7.4	2.1
Body Mass Index	1285 (100)	27	27.5	4.9
Creatinine, mg/dL	1272 (99)	1	1.2	0.73
Albumin, g/dL	657 (51)	3.9	3.8	0.46
Glucose, Pre-op Average, mg/dL	1285 (100)	135	147.5	47.2
Glucose, Pre-op Maximum, mg/dL	1285 (100)	180	201.2	80.8
Operation Time, minutes	1285 (100)	230	239.4	71.3
Ventilator Hours	1212 (94)	14	19.6	30.5
Glucose, Post-op Avg. mg/dL	1285 (100)	163	174.8	44.8
Glucose, Post-op Max., mg/dL	1285 (100)	193.0	214.3	73.1

n = number of subjects with data available SD = standard deviation

TABLE 4.2 displays the dichotomous categorical variables contained in the Cardiac Surgery Risk Assessment database, which notes that 31% of the subjects had a history of chronic obstructive pulmonary disease (COPD), 7% had undergone prior heart surgery (PHS), 10% developed low cardiac output (LCO) during surgery and 3% died within 30 days of surgery (operative death).

TABLE 4.2 Initial Dataset Dichotomous Categorical Variables Showing Breakdown of No/Yes Categories

Categorical Variables	No (%)	Yes (%)
Chronic Obstructive Pulmonary Disease (COPD)	882 (69)	403 (31)
Prior Heart Surgery (PHS)	1198 (93)	87 (7)
Peripheral Vascular Disease (PVD)	1082 (84)	203 (16)
Cerebral Vascular Disease (CVD)	1036 (81)	249 (19)
Hypertension	88 (7)	1197 (93)
Low Cardiac Output (LCO)	1163 (90)	122(10)
Cardiac Arrest requiring CPR	1246 (97)	39 (3)
Reoperation for Bleeding	1263 (98)	22 (2)
Cardiothoracic (CT) Fellow Surgeon	796 (62)	489 (38)
Registered Nurse First Assistant (RNFA)	693 (54)	592 (46)

Of the categorical variables, only race contained missing data elements, with 24% of the entries either noted as missing or unknown, as shown in TABLE 4.3. Because of the reported racial homogeneity of the subject population and the high percentage of missing data, race was not included in any of the subsequent analyses.

TABLE 4.3 Racial Composition of Subject Population

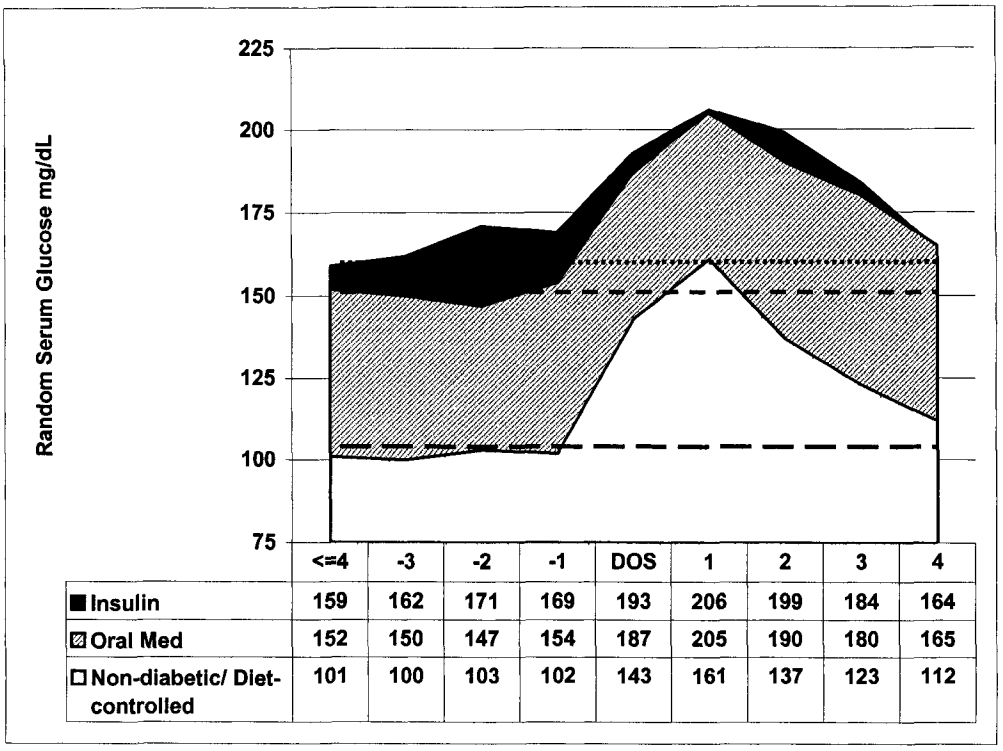
Race	n	%
White	931	72
Unknown or Missing	302	24
American Indian	21	2
Black	30	2
Asian	1	0.1

4.1.1.1 Perioperative Serum Glucose Values

Review of the perioperative serum glucose values by day of surgery and VA diabetes classification notes that the median preoperative glucose value for non-diabetics or diet-controlled diabetics (ND) was 101 mg/dL while those for controlled on oral medications (NIDDM) and insulin-dependent diabetics (IDDM) were 149 and 165, respectively. For the day of surgery and first two postoperative days (72 hours) the median serum glucose values were 151, 199

and 203 for the same groups. FIGURE 4.1 displays the perioperative glucose value excursion by VA diabetic status classification and day of surgery, with the median preoperative glucose values noted by the dashed lines and the daily median glucose values noted below in the attached table.

FIGURE 4.1 Perioperative Serum Glucose Values by VA Diabetic Classification and Day of CABG Surgery



	<=4	-3	-2	-1	DOS	1	2	3	4
■ Insulin	159	162	171	169	193	206	199	184	164
▨ Oral Med	152	150	147	154	187	205	190	180	165
□ Non-diabetic/ Diet-controlled	101	100	103	102	143	161	137	123	112

Predictably, the average number of glucose values obtained per patient differed by diabetic classification as well as operative status. Within the two weeks before surgery, non-diabetics or diet-controlled diabetics had an average of 2 serum glucose levels drawn, while patients on oral hypoglycemic medication (Oral Med) or under insulin control (Insulin) had 5 and 9 values each. During the day of surgery and first four postoperative days, non-diabetics and diet-controlled diabetics had 9 serum glucose values taken per patient,

while patients on oral medications or insulin had an average of 15 and 18 glucose levels recorded for the same time period.

4.1.2 Undiagnosed Diabetes Mellitus

As noted in CHAPTER THREE, the Veterans Affairs (VA) Cardiac Surgery Risk Assessment database classified patients as being non-diabetic or diet-controlled diabetic, having non-insulin dependent (oral medication-controlled) diabetes mellitus or insulin dependent diabetes mellitus. To minimize possible misclassification, non-diabetic patients or unknown diet-controlled diabetics with preoperative random blood glucose levels ≥200 mg/dL or HbA1c levels ≥ 7% were re-classified as undiagnosed diabetics. See TABLE 4.4 for this comparison. Using this method, an additional 202 patients (16%), were identified as having diabetes, which meant that a total of 568 subjects (44%) were considered to have diabetes as a pre-existing condition.

TABLE 4.4 Comparison of Veterans Affairs Diabetes Classification with Classification to Identify Potentially Undiagnosed Diabetics

Diabetes Mellitus (DM)	Non-Diabetic or Diet-controlled (%)	Undiagnosed DM (%)	NIDDM (%)	IDDM (%)
VA Classification	919 (71)		193 (15)	173 (13)
Preoperative Glucose Classification	717 (56)	202 (16)	193 (15)	173 (13)

DM = diabetes mellitus
NIDDM = non-insulin DM
VA = Veterans Affairs
IDDM = insulin dependent DM

Also using random blood sugar ≥200 mg/dL as the defining threshold for undiagnosed diabetes mellitus postoperatively, an additional 138 of the 717 non-diabetic subjects (19%) could be classified as undiagnosed diabetics, making 55% of the CABG cohort possibly diabetic, either by prior diagnosis or elevated random blood glucose levels, as shown in TABLE 4.5. However, these patients with postoperatively elevated serum glucose were not considered diabetic in the analyses. Postoperatively, the percentage of diabetics with maximum serum glucose values ≥200 mg/dL only changed from 23% to 25% of the total cohort; however, 85% of diabetics on oral hypoglycemic medication and 89% of insulin-controlled diabetics had at least one perioperative serum glucose value ≥200 mg/dL.

TABLE 4.5 Comparison of Preoperative and Postoperative Non-Diabetic and Diabetic Classification using Serum Glucose ≥200 mg/dL as the Threshold Value

Diabetes Mellitus (DM)	Non-Diabetic <200 (%)	Undiagnosed DM ≥200 (%)	DM <200 (%)	DM ≥200 (%)
Preoperative DM Classification	719 (56)	200 (16)	63 (5)	303 (23)
Postoperative DM Classification	579 (45)	340 (26)	47 (4)	319 (25)

4.1.3 Stress Hyperglycemia Variables

In addition to the two main diabetes classification variables, three other dichotomous variables related to glucose exposure were constructed, as shown in TABLE 4.6. The variable "Diabetes Mellitus" combined patients classified preoperatively with undiagnosed diabetes, diabetic on oral medication or diabetic on insulin as diabetics. The stress hyperglycemia threshold variable labeled "Postoperative Glucose ≥250 mg/dL" identified those highest quartile subjects with at least one postoperative glucose value greater than or equal to 250 mg/dL. Only 5.7% of non-diabetics exhibited postoperative serum glucose ≥250 mg/dL, while 53.2% of diagnosed and undiagnosed diabetics had such elevated values. Within the diabetic classification, 33.7% of undiagnosed diabetics had postoperative random serum glucose levels ≥250 mg/dL, while 58.5% of non-insulin dependent diabetics had similarly high glucose values, as did 69.9% of insulin-dependent diabetics.

The stress hyperglycemia baseline change variable "Glucose Change ≥ 50 mg/dL" identified the highest quartile of patients whose maximum postoperative glucose value was at least 50 mg/dL higher than the highest preoperative value. Within this grouping, 25% of those classified pre-operatively as non-diabetic had at least a 50 mg/dL increase, while 11% of undiagnosed diabetics, 27% of oral medication-controlled and 29% of Insulin-controlled diabetics increased their serum glucose by at least that much as well. These two variables were developed from the initial analysis of blood

glucose values and became the primary exposure variables representing stress hyperglycemia used in univariate and multivariate logistic regressions analyses to test whether a high glucose threshold value or the change in glucose from preoperative baseline increased risk of infection outcomes or resource utilization.

TABLE 4.6 Dichotomous Glucose Exposure Variables

Glucose Exposure Variables	No (%)	Yes (%)
Diabetes Mellitus	717 (56)	568 (44)
Glucose Change ≥50 mg/dL	964 (75)	321 (25)
Postoperative Glucose ≥250 mg/dL	942 (73)	343 (27)

It is also interesting to note, as shown in TABLE 4.7, the perioperative changes in serum glucose levels according to the probable diabetes status. Patients with insulin-controlled diabetes increased their serum glucose levels less perioperatively compared to non-diabetic/diet-controlled diabetics or diabetics on oral medication, while patients with undiagnosed diabetes (with preoperative serum glucose values ≥200 mg/dL) had a reduced incidence of serum glucose ≥200 mg/dL (100% vs. 68%) and serum glucose ≥250 mg/dL (38% vs. 34%) postoperatively. These findings may indicate that insulin-controlled diabetics have better glycemic control and patients classified as undiagnosed diabetics may have less labile glycemia as well.

TABLE 4.7 Comparison of Perioperative Serum Glucose Changes by Diabetes Status

Diabetes Status	Preoperative Glucose Values			Postoperative Glucose Values		
	>110	≥200	≥250	>110	≥200	≥250
Non-diabetic or Diet-controlled	91%	0%	0%	100%	19%	6%
Undiagnosed DM	100%	100%	38%	100%	63%	34%
NIDDM	99%	78%	46%	100%	85%	59%
IDDM	100%	88%	65%	100%	89%	70%

DM = diabetes mellitus NIDDM = Non-insulin dependent DM
IDDM = insulin dependent DM

4.1.4 Additional Variable Construction

Review of the variables in the databases noted that additional variables needed to be constructed to facilitate model development and hypothesis testing. Smoking history provided a challenge in classification because the method of documenting this exposure changed during the study timeframe. Initially, patients had been classified as either non-smokers or smokers (No or Yes), but within the past 4 years the classification scheme became more complex, with subjects classified as Never Smokers, Remote Smokers (quit > 3 months ago), quit within 2 weeks-3months, or Smoking/quit within 2 weeks. The Smoking History variable, shown in TABLE 4.8 placed No or Never Smoker into one category and collapsed Yes, Current Smokers and those who had quit smoking within 2 weeks of surgery into another category. To minimize possible misclassification bias, a dichotomous variable of Smoker – Yes/No was also created, with smokers being those who were identified as either current or recent smokers (n=350; 27%) and non-smokers being either never smokers or had quit more than 3 months prior to surgery (n=935; 73%).

However there was little real difference between the two extreme categories of Yes/Current Smoker and No/Never Smoker and the dichotomous Smoker variable, so that the later became the variable used to investigate the effect of smoking on infections.

TABLE 4.8 Smoking History Variable Combining Changes in Smoking Classification

Smoking History	n	%
Yes / Current Smoker or quit within 2 weeks	340	26
Recent Smoker / Quit within 2 – 12 weeks.	10	1
Quit >3 months / Remote Smoker	307	24
No or Never Smoker	628	49

After evaluating the continuous variables in TABLE 4.1, additional dichotomous variables were developed based on clinically relevant considerations as noted in TABLE 4.9. Operationally, the variable categorization facilitated model development, particularly inclusion of interaction variables and resultant interpretation. Age was dichotomized using the 75th percentile, body mass index was dichotomized using the definition of obesity, HbA1c was dichotomized using the definition of diabetes and albumin was dichotomized using the abnormal threshold value. Dichotomizing operation time ≥240 minutes placed almost half (42%) of the cohort in the upper category, while only 6% of subjects experienced ventilator ≥48 hours.

TABLE 4.9 Additional dichotomized variables developed from initial continuous variables

Dichotomized Continuous Variables	No (%)	Yes (%)
Age ≥73 years old	975 (76)	310 (24)
Body Mass Index ≥30	1240 (96)	45 (4)
HbA1c ≥7%	140 (53%)	126 (47%)
Albumin <3.5 g/dL	1246 (97)	39 (3)
Operation ≥240 minutes	744 (58)	541 (42)
Ventilator ≥48 hours	1204 (94)	81 (6)

Outcome variables were retrieved from the Infection Control database and consisted of a number of dichotomous categories, including a composite variable of "major infection" which was the identification of either pneumonia or surgical site infection or both (see TABLE 4.10). Separate variables were also developed for pneumonia and surgical site infection (SSI), as well as the site-specific sternal infection and leg infection.

TABLE 4.10 Infection Outcome Variables

Infection Outcomes	No (%)	Yes (%)
Major Infection	1080 (84)	205 (16)
Pneumonia	1240 (96)	45 (4)
Surgical Site Infection (SSI)	1121 (87)	164 (13)
Sternal SSI	1211 (94)	74 (6)
Leg SSI	1179 (92)	106 (8)

SSI = Surgical Site Infection

A number of patients developed more than one infection. As shown in TABLE 4.11, 16 patients (1.2% of the cohort, 7.3% with infection) had both a sternal and leg infection. Seven patients with pneumonia were also identified with a surgical site infection. One patient not only developed pneumonia but also sustained sternal and leg infections.

TABLE 4.11 Type, frequency and percent of infections occurring to cohort subjects

Infection Types	Frequency	Percent
No Infection	1081	84.1
Sternal SSI	58	4.5
Leg SSI	90	7.0
Sternal & Leg SSI	16	1.2
Pneumonia	38	3.0
Pneumonia + SSI	7	0.5

SSI = Surgical Site Infection

4.2 Univariate Data Analysis

Model development and hypothesis testing required initial univariate analysis of the composite outcome variables of major infection, pneumonia and surgical site infection with the glucose exposure variables, the potential confounders as well as the possible explanatory variables. This was accomplished primarily by using either the Mann-Whitney *U* test for continuous variables or the Pearson Chi-Square test for categorical variables. TABLE 4.12 shows the six initial continuous glucose variables developed to explore and compare serum glucose changes in CABG patients with and without infections. This information was used to create the two categorical glucose variables shown in TABLE 4.13 - Postoperative Glucose ≥250 mg/dL and Glucose Change ≥50 mg/dL. Explanatory variables with a significance level of 0.1 or lower were subsequently used for multivariate logistic model hypothesis testing, with one exception. Of the two primary glucose exposure variables that were analyzed, Postoperative Glucose ≥250 mg/dL and Glucose Change ≥50 mg/dL, only the threshold exposure variable of postoperative glucose ≥250 mg/dL

achieved statistical significance, although both were used for hypothesis testing and measurement of interaction effects to allow for comparison.

TABLE 4.12 Univariate Analysis of Major Infection and Continuous Explanatory Variables

	No Infection		Infection		*p*
	Median	Mean	Median	Mean	Mann-Whitney *U*
Age, years	65	65.0	67	65.8	0.192
Body Mass Index	27	27.4	27	27.9	**0.080**
Creatinine, mg/dL	1.1	1.2	1.1	1.3	0.513
Albumin, g/dL	3.9	3.8	3.8	3.75	0.164
Pre-Op Glucose Avg., mg/dL	133	145.6	144	157.4	**<0.001**
Pre-op Glucose Max., mg/dL	178	197.7	198	223.9	**<0.001**
HbA1c, %	6.9	7.4	6.8	7.4	0.626
Post-op Glucose Avg.,mg/dL	161	172.8	172	184.0	**<0.001**
Post-op Glucose Max.,mg/dL	188	210.2	220	232.5	**<0.001**
Glucose Avg Change, mg/dL	27	27.8	25	25.7	0.620
Glucose Max Change, mg/dL	10	13.4	11	11.6	0.942
Total CPB time, minutes	86	90.3	90	104.1	0.341
Total Ischemic time, minutes	51	52.7	53.5	58.6	0.252
Operation time, minutes	225	235.3	250	261.5	**<0.001**
Ventilator hours	14	17.6	14	28.5	0.763

Pre-op = Preoperative Post-op = Postoperative
CPB = Cardiopulmonary Bypass Avg = Average Max = Maximum

4.2.1 Univariate Analysis of Major Infection

Initially significant confounders and explanatory variables for major infection, in stratified analysis by DM status, are noted in TABLE 4.13. These include four diabetes-related continuous variables, preoperative and postoperative glucose average and maximum values, as well as the average and maximum changes in those values. Also identified as significant were

body mass index (BMI), operation time, chronic obstructive pulmonary disease (COPD), prior heart surgery (PHS), peripheral vascular disease (PVD), low cardiac output >6 hours (LCO), cardiac arrest, and reoperation for bleeding. Additional analysis of major infection with the four-category diabetes variable also noted significant findings. Subjects classified as non-diabetic had a 12.7% rate of major infection and those identified as undiagnosed diabetic has a similar rate of infection (14.4%). Subjects with non-insulin dependent diabetes had the highest rate of major infection (24.9%), while patients with insulin dependent diabetes had a comparable rate of 21.4% (p <0.001).

TABLE 4.13 Univariate Analysis of Major Infection and Categorical Variables

	No Infection n (%)				Infection n (%)				X^2 p
Diabetes by VA Classification	**No or Diet-Controlled** 799 (87)	**NIDDM / Oral Med** 145 (75)	**Insulin-controlled** 136 (79)		**No or Diet-Controlled** 120 (13)	**NIDDM/ Oral Med** 48 (25)		**Insulin-controlled** 37 (21)	<0.001
Diabetes	**No** 626 (87)	**Undiag.** 173 (86)	**NIDDM** 145 (75)	**IDDM** 136 (79)	**No** 91 (13)	**Undiag.** 29 (14)	**NIDDM** 48 (25)	**IDDM** 43(21)	<0.001
Diabetes by VA, Glucose & HbA1c	**No** 626 (87)		**Yes** 454 (80)		**No** 91 (13)		**Yes** 114 (20)		<0.001
Postoperative Glucose ≥250 mg/dL	**No** 816 (87)		**Yes** 264 (77)		**No** 126 (13)		**Yes** 79 (23)		<0.001
Glucose Change ≥ 50 mg/dL	**No** 831 (85)		**Yes** 249 (82)		**No** 152 (15)		**Yes** 53 (18)		0.390
Age ≥ 73 years	**No** 829 (85)		**Yes** 251 (81)		**No** 146 (15)		**Yes** 59 (19)		0.090
Albumin <3.5 g/dL	**No** 1047 (84)		**Yes** 33 (85)		**No** 199 (16)		**Yes** 6 (15)		0.920
Body Mass Index ≥ 30	**No** 788 (85)		**Yes** 292 (83)		**No** 144 (15)		**Yes** 61 (17)		0.420
Cerebral Vascular Disease	**No** 879 (85)		**Yes** 201 (81)		**No** 157 (15)		**Yes** 48 (19)		0.111
Chronic Obstructive Pulmonary Disease	**No** 753 (85)		**Yes** 327 (81)		**No** 129 (15)		**Yes** 76 (19)		0.032
Peripheral Vascular Disease	**No** 930 (86)		**Yes** 150 (74)		**No** 152 (14)		**Yes** 53 (26)		<0.001
Prior Heart Surgery	**No** 1014 (85)		**Yes** 66 (76)		**No** 184 (15)		**Yes** 21 (24)		0.031
Smoker	**No** 781 (84)		**Yes** 299 (85)		**No** 154 (16)		**Yes** 52 (15)		0.410
Cardiothoracic Fellow Surgeon	**No** 664 (83)		**Yes** 416 (85)		**No** 132 (17)		**Yes** 73 (15)		0.432
Registered Nurse First Assistant	**No** 572 (83)		**Yes** 508 (86)		**No** 121 (17)		**Yes** 84 (14)		0.110

TABLE 4.13 Univariate Analysis of Major Infection and Categorical Variables – Continued

	No Infection n (%)		Infection n (%)		X^2 p
Operation >240 minutes	No 646 (87)	Yes 434 (80)	No 98 (13)	Yes 107 (20)	0.001
Low Cardiac Output > 6 hours	**No 997 (86)**	**Yes 83 (68)**	**No 166 (14)**	**Yes 39 (32)**	<0.001
Ventilator >48 hours	**No** 1043 (87)	**Yes** 37 (46)	**No** 161 (13)	**Yes** 44 (54)	<0.001
Cardiac Arrest	**No** 1057 (85)	**Yes** 23 (59)	**No** 189 (15)	**Yes** 16 (41)	<0.001
Reoperation for Bleeding	**No** 1065 (84)	**Yes** 15 (68)	**No** 198 (16)	**Yes** 7 (32)	0.040

4.2.2 Univariate Analysis Of Pneumonia

TABLES 4.14 and 4.15 show the continuous and categorical variable univariate results for pneumonia, with significant variables being age, preoperative maximum glucose, postoperative average and maximum glucose, total cardiopulmonary bypass time, total ischemic time, operation time and ventilator hours.

TABLE 4.14 Univariate Analysis of Pneumonia and Continuous Variables

	No Pneumonia		Pneumonia		*p*
	Median	Mean	Median	Mean	Mann-Whitney *U*
Age	65	65.0	68	68.2	0.017
Body Mass Index	27	27.5	27	26.7	0.937
Creatinine	1.1	1.2	1.1	1.1	0.855
Albumin	3.9	3.8	3.8	3.8	0.977
Pre-Op Glucose Avg	135	147.4	145.5	155.4	0.120
Pre-op Glucose Max	180	201.1	211.5	226.6	0.011
HbA1c, %	6.9	7.4	6.9	7.1	0.882
Post-op Glucose Avg	162	174.1	171.5	189.4	0.039
Post-op Glucose Max	192	212.6	231.5	249.0	0.003
Glucose Avg Change	27	26.8	32.5	34.0	0.261
Glucose Max Change	10	11.4	14.5	22.4	0.544
Total CPB time, min	86.5	91.3	95	129.2	0.003
Total Ischemic time	51	53.1	58	70.7	<0.001
Operation time	225	238.3	296	296.2	<0.001
Ventilator Hours	14	19.5	22.5	63.7	0.027

TABLE 4.14 Abbreviations

Pre-op = Preoperative Post-op = Postoperative min = minutes
Avg = Average Max = Maximum ICU = Intensive Care Unit
CPB = Cardiopulmonary Bypass LOS = length of stay

The categorical variables noted to be significantly associated with pneumonia included "diabetes by VA, glucose & HbA1c classification", postoperative glucose ≥250 mg/dL, age > 73 years, prior heart surgery, peripheral vascular disease, low cardiac output, cardiac arrest,

TABLE 4.15 Univariate Analysis of Pneumonia and Categorical Variables

	No Pneumonia n (%)				Pneumonia n (%)				X^2 p
Diabetes by VA Classification	**No or Diet-Controlled** 890 (97)	**NIDDM / Oral Med** 185 (96)		**IDDM / Insulin** 165 (95)	**No or Diet-Controlled** 29 (3)	**NIDDM / Oral Med** 8 (4%)		**IDDM / Insulin** 8 (5%)	0.547
Diabetes	**No or Diet-Controlled** 699 (97)	**Undiag.** 191 (95)	**NIDDM** 185 (96)	**IDDM** 165 (95)	**No or Diet-Controlled** 18 (3%)	**Undiag.** 11 (5%)	**NIDDM** 8 (4%)	**IDDM** 8 (5%)	0.156
Diabetes by VA, Glucose & HbA1c	**No** 699 (97)		**Yes** 541 (95)		**No** 18 (3)		**Yes** 27 (5)		0.030
Postoperative Glucose ≥ 250 mg/dL	**No** 918 (97)		**Yes** 322 (94)		**No** 24 (3)		**Yes** 21 (6)		0.002
Glucose Change ≥ 50 mg/dL	**No** 950 (97)		**Yes** 290 (96)		**No** 33 (3)		**Yes** 12 (4)		0.610
Age ≥ 73 years	**No** 946 (97)		**Yes** 294 (95)		**No** 29 (3)		**Yes** 16 (5)		0.068
Albumin <3.5 g/dL	**No** 1201 (96)		**Yes** 39 (100)		**No** 45 (4)		**Yes** 0 (0)		0.227
BMI ≥ 30	**No** 900 (97)		**Yes** 340 (96)		**No** 32 (3)		**Yes** 13 (4)		0.828
Cerebral Vascular Disease	**No** 1002 (97)		**Yes** 238 (96)		**No** 34 (3)		**Yes** 11 (4)		0.381
COPD	**No** 856 (97)		**Yes** 384 (95)		**No** 26 (3)		**Yes** 19 (5)		0.110
Peripheral Vascular Disease	**No** 1048 (97)		**Yes** 192 (95)		**No** 34 (3)		**Yes** 11 (5)		0.105
Prior Heart Surgery	**No** 1161 (97)		**Yes** 79 (91)		**No** 37 (3)		**Yes** 8 (9)		0.003
Smoker	**No** 901 (96)		**Yes** 339 (97)		**No** 34 (4)		**Yes** 11 (3)		0.668
CT Fellow Surgeon	**No** 770 (97%)		**Yes** 470 (96%)		**No** 26 (3%)		**Yes** 19 (4%)		0.432
RNFA	**No** 673 (97%)		**Yes** 567 (96%)		**No** 20 (3%)		**Yes** 25 (4%)		0.194

TABLE 4.15 Univariate Analysis of Pneumonia and Categorical Variables – Continued

	No Pneumonia n (%)		Pneumonia n (%)		X^2 p
Operation Time ≥ 240 minutes	**No** 727 (98%)	**Yes** 513 (95%)	**No** 17 (2%)	**Yes** 28 (5%)	0.005
Ventilator > 48 hours	**No** 1188 (99%)	**Yes** 52 (64%)	**No** 16 (1%)	**Yes** 29 (36%)	<0.001
Low Cardiac Output > 6 hours	**No** 1136 (98)	**Yes** 104 (85)	**No** 27 (2)	**Yes** 18 (15)	<0.001
Cardiac Arrest	**No** 1210 (97)	**Yes** 30 (77)	**No** 36 (3)	**Yes** 9 (23)	<0.001
Reoperation for Bleeding	**No** 1222 (97%)	**Yes** 18 (82%)	**No** 41 (3%)	**Yes** 4 (18%)	<0.001

Undiag. = undiagnosed
COPD = Chronic Obstructive Pulmonary Disease
BMI = Body Mass Index
CT Fellow = Cardiothoracic Fellow
RNFA = Registered Nurse First Assistant

reoperation for bleeding, ventilator ≥48 hours, and operation time ≥240 minutes. These are noted in TABLE 4.15.

4.2.3 Univariate Analysis Of Surgical Site Infection

The continuous variables noted to be significantly related ($p<0.10$) to surgical site infection during initial univariate analysis, as noted in TABLE 4.16, include body mass index, pre- and postoperative glucose average and maximum values as well as operation time. The categorical variables, shown in TABLE 4.17 and identified as significant by univariate analysis, were the three diabetes variables, postoperative glucose ≥250 mg/dL, peripheral vascular disease, low cardiac output, ventilator >48 hours, registered nurse first assistant and operation time ≥240 minutes.

Univariate analysis of variables related to development of sternal surgical site infections (SSI) and leg infections was also performed to ascertain whether there were any notable differences between them. These results are summarized in TABLES 4.18 and 4.19. For sternal SSI the significant variables ($p<0.10$) were preoperative and postoperative average and maximum glucose levels, body mass index, diabetes (Y/N), age >73 years, COPD, PVD, CVD, ventilator >48 hours, maximum postoperative glucose ≥250 mg/dL, and operation time >240 minutes. Leg SSI significant variables included preoperative glucose average and maximum, postoperative glucose maximum, diabetes (Y/N), albumin, operation time, operative time >240 minutes, PVD, LCO, and RNFA.

TABLE 4.16 Univariate Analysis of Surgical Site Infections and Continuous Variables

	No Surgical Site Infection		Surgical Site Infection		*p*
	Median	Mean	Median	Mean	Mann-Whitney *U*
Age, years	65	65.1	67	65.2	0.689
Body Mass Index	27	27.4	27	28.3	0.092
Creatinine, mg/dL	1.1	1.2	1.1	1.3	0.749
Albumin, g/dL	3.9	3.8	3.8	3.7	0.118
Pre-Op Glucose Avg	134	145.9	145	159.4	0.005
Pre-op Glucose Max	179	198.6	198	224.8	0.003
HbA1c, %	6.9	7.4	6.9	7.5	0.977
Post-op Glucose Avg	162	173.3	172	183.6	0.012
Post-op Glucose Max	190	211.6	214	229.2	0.002
Glucose Avg Change	27	27.5	23	24.1	0.322
Glucose Max Change	11	13.9	11.5	7.8	0.805
Total CPB time, min	87	91.9	83	94.0	0.848
Total Ischemic time	51	53.5	50	55.6	0.901
Operation time	225	237.4	246.5	253.6	0.007
Ventilator hours	14	19.5	14	20.1	0.659

BMI = Body Mass Index
Avg = Average
Max = Maximum
CPB = Cardiopulmonary Bypass
min = minutes
LOS = Length of Stay

4.17 Univariate Analysis of Surgical Site Infections and Categorical Variables

	No Surgical Site Infection n (%)				Surgical Site Infection n (%)				X^2 p
Diabetes by VA Classification	**No** 826 (90)	**NIDDM / Oral Med** 155 (80)		**IDDM / Insulin** 140 (81)	**No** 93 (10)	**NIDDM / Oral Med** 38 (20)		**IDDM / insulin** 33 (19)	<0.001
Diabetes by VA, Glucose & HbA1c	**No** 642 (90)	**Undiag.** 184 (91)	**NIDDM** 155 (80)	**IDDM** 140 (81)	**No** 75 (10)	**Undiag.** 18 (9)	**NIDDM** 38 (20)	**IDDM** 33 (19)	<0.001
Diabetes	**No** 642 (90)		**Yes** 479 (84)		**No** 75 (10)		**Yes** 89 (16)		0.005
Postoperative Glucose ≥ 250 mg/dL	**No** 837 (89)		**Yes** 284 (83)		**No** 105 (11)		**Yes** 59 (17)		0.002
Glucose Change ≥ 50 mg/dL	**No** 861 (88)		**Yes** 260 (86)		**No** 122 (12)		**Yes** 42 (14)		0.495
Age ≥ 73 years	**No** 856 (88)		**Yes** 265 (85)		**No** 119 (12)		**Yes** 45 (15)		0.288
Albumin <3.5 g/dL	**No** 1088 (87)		**Yes** 33 (85)		**No** 158 (13)		**Yes** 6 (15)		0.618
BMI ≥ 30	**No** 816 (88)		**Yes** 305 (86)		**No** 116 (12)		**Yes** 48 (14)		0.581
Cerebral Vascular Disease	**No** 911 (88)		**Yes** 210 (84)		**No** 125 (12)		**Yes** 39 (16)		0.127
COPD	**No** 777 (88)		**Yes** 344 (85)		**No** 105 (12)		**Yes** 59 (15)		0.173
Peripheral Vascular Disease	**No** 961 (89)		**Yes** 160 (79)		**No** 121 (11)		**Yes** 43 (21)		<0.001
Prior Heart Surgery	**No** 1049 (88)		**Yes** 72 (83)		**No** 149 (12)		**Yes** 15 (17)		0.195
Smoker	**No** 813 (87)		**Yes** 308 (88)		**No** 122 (13)		**Yes** 42 (12)		0.616
Cardiothoracic Fellow Surgeon	**No** 688 (86%)		**Yes** 433 (89%)		**No** 108 (14%)		**Yes** 56 (11%)		0.270
Registered Nurse First Assistant	**No** 590 (85%)		**Yes** 531 (90%)		**No** 103 (15%)		**Yes** 61 (10%)		0.015

4.17 Univariate Analysis of Surgical Site Infections and Categorical Variables - Continued

	No Surgical Site Infection n (%)		Surgical Site Infection n (%)		p X^2
Operation Time ≥240 minutes	**No 664 (89%)**	**Yes 457 (84%)**	**No 80 (11%)**	**Yes 84 (16%)**	0.001
Low Cardiac Output > 6 hours	**No** 1022 (88)	**Yes** 99 (81)	**No** 141 (12)	**Yes** 23 (19)	0.034
Ventilator > 48 hours	**No** 1058 (88%)	**Yes** 63 (78%)	**No** 146 (12%)	**Yes** 18 (22%)	0.008
Cardiac Arrest	**No** 1088 (87)	**Yes** 33 (85)	**No** 158 (13)	**Yes** 6 (15)	0.618
Reoperation for Bleeding	**No** 1103 (87%)	**Yes** 18 (82%)	**No** 160 (13%)	**Yes** 4 (18%)	0.442

NIDDM = Non-Insulin Dependent Diabetes Mellitus
IDDM = Insulin Dependent Diabetes Mellitus
Undiag. = Undiagnosed
BMI = Body Mass Index
COPD = Chronic Obstructive Pulmonary Disease

TABLE 4.18 summarizes the results of the continuous variable univariate analysis by infection type. Preoperative and postoperative maximum glucose, as well as operation time were significant for all infection types. Age, total cardiopulmonary bypass time, total ischemic time and ventilator hours were significant only for pneumonia. Preoperative and postoperative average glucose and body mass index were significant for sternal SSI, while albumin was significant only for leg SSI.

TABLE 4.18 Summary Table of Significant Continuous Variables by Infection Type

	Major Infection	Pneumonia	Surgical Site Infection	Sternal SSI	Leg SSI
Age		X			
Body Mass Index	X		X	X	
Creatinine					
Albumin					X
Pre-Op Glucose Avg	X		X	X	X
Pre-op Glucose Max	X	X	X	X	X
HbA1c					
Post-op Glucose Avg	X	X	X	X	
Post-op Glucose Max	X	X	X	X	X
Glucose Avg Change					
Glucose Max Change					
Total CPB time, min		X			
Total Ischemic time		X			
Operation time	X	X	X	X	X
Ventilator hours		X			

X = p $\leq$0.1

BMI = Body Mass Index **Avg = Average**

Max = Maximum **CPB = Cardiopulmonary Bypass**

min = minutes

TABLE 4.19 summarizes the results of the categorical variable univariate analysis. Postoperative glucose ≥250 mg/dL, diabetes, peripheral vascular disease, and operation time > 240 minutes were significant for all infection types. Age ≥73 years was significant for major infection, pneumonia and sternal SSI.

TABLE 4.19 Summary Table of Significant Categorical Variables by Infection Type

	Major Infection	Pneumonia	Surgical Site Infection	Sternal SSI	Leg SSI
Postoperative Glucose ≥250 mg/dL	X	X	X	X	X
Glucose Change ≥50 mg/dL					
Diabetes	X	X	X	X	X
Age ≥73 years	X	X		X	
Albumin <3.5					
Body Mass Index ≥30					
Cerebral Vascular Disease	X			X	
Chronic Obstructive Pulmonary Disease	X	X		X	
Peripheral Vascular Disease	X	X	X	X	X
Prior Heart Surgery	X	X			
Smoker					
CardioThoracic Fellow Surgeon					
Registered Nurse First Assistant	X		X		X
Operation Time ≥240 minutes	X	X	X	X	X
Low Cardiac Output > 6 hours	X	X	X		X
Ventilator > 48 hours	X	X	X	X	
Cardiac Arrest	X	X			
Reoperation for Bleeding	X	X			

X = p <0.1 SSI = Surgical Site Infection

4.3 Logistic Regression Modeling

Logistic regression modeling was the statistical technique used to answer the primary research questions as to whether (1) perioperative stress hyperglycemia is a significant, independent predictor of the composite outcome variable of major post-CABG infections, which includes pneumonia and/or surgical site infection, in both non-diabetic and diabetic patients and whether (2) perioperative stress hyperglycemia is a significant, independent predictor of pneumonia or the individual adverse wound outcomes of sternal SSI or leg SSI in non-diabetic and diabetic patients. Both assumed control of other significant variables. Logistic regression modeling used two dichotomous stress hyperglycemia exposure variables, postoperative glucose ≥250 mg/dL and postoperative glucose change ≥50 mg/dL. Postoperative glucose ≥250 mg/dL is a threshold value, whereas postoperative glucose change ≥50 mg/dL is a baseline increase value, measuring a minimum of 50 mg/dL glucose baseline increase from preoperative highest value to postoperative highest value regardless of the starting value. The logistic modeling of the two stress hyperglycemia exposure variables along with the five infection outcome variables, the control variables, the explanatory variables and the interaction variables, was performed using the methods outlined by Kleinbaum and Klein [100]. The results are noted in TABLES 4.20 through 4.29 and include log likelihood, log likelihood ratio χ^2, Hosmer-Lemeshow Goodness -of-Fit and LROC values. The models were formed using the findings from the univariate analysis

as a basis, with the dichotomous variables of age ≥73 years and diabetes (no/yes) kept in all models to control for these two essential factors. Two variable interactions were developed between each variable and models were tested for significance using the likelihood ratio test. Only one model - Surgical Site Infection with postoperative glucose ≥250 mg/dL - as noted in TABLE 4.24, exhibited a significant goodness-of-fit value, meaning that the model did not fit the data. All LROC values were satisfactory.

The results of the logistic modeling were that neither of the two stress hyperglycemia exposure variables were significant ($p<0.05$), independent predictors of major infection, pneumonia, surgical site infection, sternal SSI or leg SSI. Glucose change ≥ 50 achieved borderline significance ($0.05 < p < 0.10$) and significance ($p<0.05$) as a protective factor for major infection, pneumonia and sternal surgical site infection and may be indicative of the fact that a large percentage of the patients who achieved a perioperative glucose change ≥ 50 mg/dL are not diabetics. This is supported by the findings that the stress hyperglycemia variables did consistently and significantly ($p<0.05$) predict infection as interaction effects. Postoperative glucose ≥250 mg/dL interacted with prior heart surgery, which 7% of the cohort had experienced, to increase the risk of major infection and surgical site infection almost five-fold and interacted with low cardiac output, which 10% of the cohort developed perioperatively, to increase the risk of pneumonia almost seven-fold. Postoperative glucose change ≥50 mg/dL interacted with operation time >240 minutes, which 42% of

surgeries exceeded, to increase the risk of major infection almost five-fold, to increase the risk of pneumonia over six-fold and to increase the risk of surgical site infection almost three-fold. Interaction with operation time >240 minutes for increased risk of leg surgical site infection did not achieve significance, but operation time >270 minutes did. By themselves the stress hyperglycemia variables did not indicate an increased risk of infection, but in conjunction with other commonly occurring risk factors, increased the risks significantly.

Neither glucose variable interacted with another variable to increase the risk of sternal surgical site infection, but the variable resident/cardiac fellow surgeon interacted with age ≥73 years old in both models to increase the risk of sternal SSI over three-fold. Peripheral vascular disease interacted with prior heart surgery within both glucose variable models to increase risk of major infection and surgical site infection four-to-five-fold and increase risk of sternal surgical site infection ten-to-eleven-fold.

TABLE 4.20 Logistic Regression Model for Major Infection with Postoperative Glucose ≥250 mg/dL, Control, Explanatory and Interaction Variables

Variable	Estimate	Standard Error	Odds Ratio	p-value
glucose 250	.2039	.2103	1.2262	0.332
dm	.1786	.1941	1.1955	0.357
age ≥73	.1755	.1821	1.1918	0.335
pvd	.5920	.2020	1.8077	0.003
phs	-.7732	.5128	.4615	0.132
vent48	1.7804	.2548	5.9322	<0.001
lco	.5629	.2451	1.7558	0.022
lglucose250Xphs	1.5833	.6701	4.8710	0.018
lpvdXphs	1.7184	.8347	5.5754	0.040

Log Likelihood = -509.28594 Likelihood Ratio X^2 = 109.39, p-value <0.001
Hosmer-Lemeshow Goodness of Fit p-value = 0.9376 LROC = 0.6844

glucose 250 = Postoperative Glucose ≥250 mg/dL
dm = Diabetes Mellitus age ≥73= age ≥73 years old
pvd = Peripheral Vascular Disease phs = Prior Heart Surgery
vent48 = Ventilator ≥48 hours lco = Low Cardiac Output >6 hours
Interaction Terms: lgluXphs = glucose 250 *phs
lpvdXphs = pvd * phs

TABLE 4.21 Logistic Regression Model for Major Infection with Postoperative Glucose Change ≥50 mg/dL, Control, Explanatory and Interaction Variables

Variable	Estimate	Standard Error	Odds Ratio	p-value
glucose 50	-.4919	.2732	.6114	0.072
dm	.3651	.1650	1.4407	0.027
age ≥73	.1939	.1826	1.2140	0.288
pvd	.6101	.2040	1.8407	0.003
phs	-.1762	.3514	.8384	0.616
optime240	-.0904	.1960	.9135	0.645
vent48	1.7819	.2585	5.9410	<0.001
lco	.5931	.2482	1.8095	0.017
lglucose50 X opt	1.1430	.3860	3.1362	0.003
lpvdXphs	1.5281	.7799	4.6092	0.050

Log Likelihood = -508.45558 Likelihood Ratio X^2 = 111.05, p-value <0.001
Hosmer-Lemeshow Goodness of Fit p-value = 0.6381 LROC = 0.702

glucose 50 = Postoperative Glucose Change ≥50 mg/dL dm = Diabetes Mellitus
age ≥73 = age ≥73 years old pvd = Peripheral Vascular Disease
phs = Prior Heart Surgery optime240 = operation time ≥240 minutes
vent48 = Ventilator ≥48 hours lco = Low Cardiac Output >6 hours
Interaction Terms: lgluXopt = glucose 50 * optime240
lpvdXphs = pvd * phs

TABLE 4.22 Logistic Regression Model for Pneumonia with Postoperative Glucose ≥250 mg/dL, Control, Explanatory and Interaction Variables

Variable	Estimate	Standard Error	Odds Ratio	p-value
glucose 250	-.4076	.5377	.6652	0.448
dm	.0028	.4302	1.0028	0.995
age ≥73	.5677	.3715	1.7642	0.126
vent48	3.4096	.3670	30.2544	<0.001
lco	.2034	.6683	1.2256	0.761
lglucose250Xlco	1.8973	.8799	6.6677	<0.001

Log Likelihood = -129.92291 Likelihood Ratio X^2 = 130.23, p-value <0.001
Hosmer-Lemeshow Goodness of Fit p-value = 0.5827 LROC = 0.888

glucose 250 = Postoperative Glucose ≥250 mg/dL
dm = Diabetes Mellitus
age ≥73 = age ≥73 years old
vent48 = Ventilator ≥48 hours
lco = Low Cardiac Output >6 hours
Interaction Terms: lgluose250Xlco = glucose 250 * lco

TABLE 4.23 Logistic Regression Model for Pneumonia with Postoperative Glucose Change ≥50 mg/dL, Control, Explanatory and Interaction Variables

Variable	Estimate	Standard Error	Odds Ratio	p-value
glucose 50	-1.4956	.7279	.2241	0.040
dm	-.0945	.3821	.9098	0.805
age ≥73	.4880	.3723	1.6291	0.190
optime240	-.7335	.4617	.4802	0.112
vent48	3.6656	.4035	39.0818	<0.001
lco	1.4027	.4268	4.0663	0.001
lglucose50Xopt	1.8241	.8900	6.1970	<0.001

Log Likelihood = -129.79188 Likelihood Ratio X^2 = 130.49, p-value <0.001
Hosmer-Lemeshow Goodness of Fit p-value = 0.7627 LROC = 0.891

glucose 50 = Postoperative Glucose Change ≥50 mg/dL
dm = Diabetes Mellitus
age ≥73 = age ≥73 years old
optime240 = operation time ≥240 minutes
vent48 = Ventilator ≥48 hours
lco = Low Cardiac Output >6 hours
lgluXopt = Interaction Term glucose 50 * optime240

TABLE 4.24 Logistic Regression Model for Surgical Site Infection with Postoperative Glucose ≥250 mg/dL, Control, Explanatory and Interaction Variables

Variable	Estimate	Standard Error	Odds Ratio	p-value
glucose 250	,1690	.2220	1.1893	0.434
dm	.2818	.2027	1.3409	0.149
age ≥73	.1945	.1931	1.2322	0.281
pvd	.7319	.3935	1.2321	0.004
phs	-.3940	.4553	.4293	0.134
rnfa	-.5421	.1779	.5925	0.003
optime240	.4540	.1789	1.5511	0.014
lpvdXphs	1.6274	.8054	5.0908	0.043
lglucose250Xphs	1.4267	.6988	4.1649	0.041

Log Likelihood = -467.65862 Likelihood Ratio X^2 = 46.04, p-value <0.001
Hosmer-Lemeshow Goodness of Fit p-value = 0.0453 LROC = 0.657

Glucose 250 = Postoperative Glucose ≥250 mg/dL
dm = Diabetes Mellitus age ≥73 = age ≥73 years old
pvd = Peripheral Vascular Disease phs = Prior Heart Surgery
rnfa = Registered Nurse First Assistant
optime240 = operation time ≥240 minutes
lpvdXphs = Interaction Term pvd * phs
lgluXphs = Interaction Term glucose 50 * phs

TABLE 4.25 Logistic Regression Model for Surgical Site Infection with Postoperative Glucose Change ≥50 mg/dL, Control, Explanatory and Interaction Variables

Variable	Estimate	Standard Error	Odds Ratio	p-value
glucose 50	-.4072	.2923	.6655	0.160
dm	.4681	.1734	1.5970	0.007
age ≥73	.2257	.2429	1.2532	0.244
pvd	.6267	.2143	1.8715	0.003
phs	-.2178	.3832	.8043	0.570
rnfa	-.5288	.1793	.5893	0.003
optime240	.2049	.2027	1.2274	0.312
lpvdXphs	1.4497	.7419	4.2417	0.051
lglucose50Xopt	1.0368	.4020	2.8203	0.010

Log Likelihood = -467.26986 Likelihood Ratio X^2 = 46.81, p-value <0.001
Hosmer-Lemeshow Goodness of Fit p-value = 0.6064 LROC = 0.660

glucose 50 = Postoperative Glucose Change ≥50 mg/dL
dm = Diabetes Mellitus age ≥73 = age ≥73 years old
pvd = Peripheral Vascular Disease phs = Prior Heart Surgery
rnfa = Registered Nurse First Assistant
optime240 = operation time ≥240 minutes
lpvdXphs = Interaction Term pvd * phs
lgluXopt = Interaction Term glucose 50 * optime240

TABLE 4.26 Logistic Regression Model for Sternal Surgical Site Infection with Postoperative Glucose ≥250 mg/dL, Control, Explanatory and Interaction Variables

Variable	Estimate	Standard Error	Odds Ratio	p-value
glucose 250	.3041	.2982	1.3554	0.308
dm	.3377	.2119	1.4017	0.247
age ≥73	-.0093	.3457	1.4017	0.247
pvd	.5700	.2953	1.7683	0.054
phs	-.3986	.6197	.6712	0.;520
CT Fellow	-.5555	.3467	.5738	0.109
vent48	.8296	.3758	2.2924	0.027
IpvdXphs	2.4036	.9112	11.0632	0.008
ICTfellowXage	1.2680	.5501	3.5537	0.021

Log Likelihood = -263.50259 Likelihood Ratio X^2 = 30.11, p-value <0.001
Hosmer-Lemeshow Goodness of Fit p-value = 0.9651 LROC = 0.674

glucose 250 = Postoperative Glucose ≥250 mg/dL
dm = Diabetes Mellitus age ≥73= age ≥73 years old
pvd = Peripheral Vascular Disease phs = Prior Heart Surgery
CT Fellow = CT Fellow as Primary Surgeon
vent48 = Ventilator ≥48 hours
IpvdXphs = Interaction Term pvd * phs
ICT FellowXage = Interaction Term CT Fellow as Primary Surgeon* age ≥73

TABLE 4.27 Logistic Regression Model for Sternal Surgical Site Infection with Postoperative Glucose Change ≥50 mg/dL, Control, Explanatory and Interaction Variables

Variable	Estimate	Standard Error	Odds Ratio	p-value
glucose 50	-.8600	.4989	.4231	0.085
dm	.5f382	.2536	1.7129	0.034
age ≥73	.0387	.3497	1.0394	0.912
pvd	.6348	.2978	1.8866	0.033
phs	-.4435	.6341	.6418	0.484
CT Fellow	-.5535	.3483	.5749	0.112
optime240	.0533	.2960	1.0547	0.112
IpvdXphs	2.3461	.9220	10.4450	0.011
ICT fellowXage	1.3083	.5550	3.6699	0.018

Log Likelihood = -264.02127 Likelihood Ratio X^2 = 38,07, p-value <0.001
Hosmer-Lemeshow Goodness of Fit p-value = 0.3999 LROC = 0.669

glucose 50 = Postoperative Glucose Change ≥50 mg/dL
dm = Diabetes Mellitus age≥73 = age ≥73 years old
pvd = Peripheral Vascular Disease phs = Prior Heart Surgery
CT Fellow = CT Fellow as Primary Surgeon
optime240 = operation time ≥240 minutes
IpvdXphs = Interaction Term pvd * phs
ICT FellowXage = Interaction Term CT Fellow as Primary Surgeon* age ≥73

TABLE 4.28 Logistic Regression Model for Leg Surgical Site Infection with Postoperative Glucose ≥250 mg/dL, Control and Explanatory Variables

Variable	Estimate	Standard Error	Odds Ratio	p-value
glucose 250	*			
dm	.3299	.2080	1.3868	0.116
age ≥73	-.1950	.2490	.8228	0.434
pvd	,4592	.2505	1.5829	0.067
RN first assistant	-.5197	.2138	.5947	0.015
lco	.5786	.2899	1.7642	0.051

Log Likelihood = -346.51575 Likelihood Ratio X^2 = 39.05, p-value <0.001
Hosmer-Lemeshow Goodness of Fit p-value = 0.8192 LROC = 0.621

glucose 250 = Postoperative Glucose ≥250 mg/dL * dropped due to colinearilty
dm = Diabetes Mellitus
age ≥73= age ≥73 years old
pvd = Peripheral Vascular Disease
RN first assistant = Registered Nurse First Assistant
lco = Low Cardiac Output >6 hours

TABLE 4.29 Logistic Regression Model for Leg Surgical Site Infection with Postoperative Glucose Change ≥50 mg/dL, Control, Explanatory and Interaction Variables

Variable	Estimate	Standard Error	Odds Ratio	p-value
glucose 50	-.2755	.3030	.7592	0.363
dm	.4266	.2058	1.5320	0.038
age ≥73	-.1015	.2473	.9034	0.681
RN first assistant	-.5670	.2161	.5672	0.009
optime270	.0319	.2649	1.0325	0.904
lglucose 50 X optime 270	1.0445	.4932	2.8420	0.034

Log Likelihood = -346.45432 Likelihood Ratio X^2 = 39.05, p-value <0.001
Hosmer-Lemeshow Goodness of Fit p-value = 0.3904 LROC = 0.607

glucose 50 = Postoperative Glucose Change ≥50 mg/dL
dm = Diabetes Mellitus
age≥73 = age ≥73 years old
RN first assistant = Registered Nurse First Assistant
optime270 = Operation time ≥ 270 minutes
lglucose50Xoptime270 = Interaction Term glucose 50 * optime270

TABLE 4.30 Summary Table of Postoperative Glucose ≥250 mg/dL Models with Significant Odds Ratios

	Major Infection	Pneumonia	Surgical Site Infection	Sternal SSI	Leg SSI
Postoperative Glucose ≥250 mg/dL					dropped due to collinearity
Diabetes					
Age ≥73 years					
Peripheral Vascular Disease	1.8		1.2	1.8	
Prior Heart Surgery					
CardioThoracic Fellow Surgeon					
Registered Nurse First Assistant			.59		.59
Operation Time ≥240 minutes			1.5		
Low Cardiac Output > 6 hours	1.7				1.8
Ventilator > 48 hours	5.9	30.2		2.3	
Iglucose 250X phs	4.9		4.2		
Ipvd X phs	5.6		5.1	11.1	
Iglucose 250X lco		6.7			
ICT Fellow X age≥73				3.5	

TABLE 4.31 Summary Table of Glucose Change ≥50 mg/dL Models with Significant Odds Ratios

	Major Infection	Pneumonia	Surgical Site Infection	Sternal SSI	Leg SSI
Glucose Change ≥50 mg/dL		.22			
Diabetes	1.4		1.6	1.7	1.5
Age ≥73 years					
Peripheral Vascular Disease (PVD)	1.8		1.9	1.9	
Prior Heart Surgery (PHS)					
CardioThoracic Fellow Surgeon					
Registered Nurse First Assistant			.59		.57
Operation Time ≥240 minutes					
Low Cardiac Output > 6 hours	1.8	4.1			
Ventilator > 48 hours	5.9	39.1			
Iglucose50 Xoptime240/270	3.1	6.2	2.8		2.8
IpvdXphs	4.6		4.2	10.4	
ICT Fellow Xage≥73				3.7	

4.4 Excess Resource Utilization Analyses

4.4.1 Excess Days Of Care

To answer the secondary research question: "Is perioperative stress hyperglycemia an independent predictor of increased resource utilization as measured by excess postoperative length of stay including intensive care unit stay, readmission to hospital within 60 days of discharge or extended care length of stay? ", the Mann-Whitney *U* test was used to compare various lengths of stay (LOS) of the stress hyperglycemia and diabetes exposure variable groups within the cohort. As noted in TABLES 4.30 and 4.31, the stress hyperglycemia threshold variable postoperative glucose ≥250 mg/dL was examined with 27% (n=343) of the cohort having at least one postoperative glucose value ≥250 mg/dL. This high glucose group was noted to have significantly longer median intensive care unit (ICU), postoperative, hospital, and mean acute care readmit lengths of stay (LOS) than those cohort subjects with lower serum glucose levels. The cohort was next examined in terms of pre-existing diabetes mellitus with the diabetic group (n=566; 44%) being anyone either classified by the Veterans Affairs (VA) as having either non-insulin dependent diabetes mellitus (NIDDM) or insulin dependent diabetes mellitus (IDDM), or having random preoperative glucose >200 mg/dL or HbA1c >7% (undiagnosed diabetics). This diabetic group was more likely to have longer median ICU, postoperative, hospital and mean acute care readmit LOS than the non-diabetic subset. The stress hyperglycemia baseline change variable - postoperative glucose ≥50 mg/dL -was examined

three ways. First, using the entire cohort of 1285 subjects, the subset of 302 subjects whose postoperative glucose increased at least 50 mg/dL compared to preoperative levels (24%) was noted to have significantly longer ICU, postoperative, and readmission LOS. Next, the same analysis was performed after removing those subjects preoperatively classified by the VA as having either NIDDM or IDDM (n=366). Again the group with postoperative glucose ≥50 mg/dL (n=200) had significantly longer ICU and postoperative as well as hospital and total LOS. The third comparison of the postoperative glucose change ≥50 mg/dL group removed not only the subjects classified by the VA as diabetic, but also the undiagnosed diabetics (n=202), in an effort to remove the effect of diabetes from the analysis. Again the high glucose change group had significantly longer ICU, postoperative, hospital and total LOS. It is noteworthy that the total LOS median and mean of 2 days and 3 days respectively in this group was the longest for any of the comparisons.

4.4.2 Costs Associated With Excess Days Of Care

Within the past few years the Department of Veterans Affairs has endeavored to associate financial resource utilization with episodes of care. The cost data was obtained for specific CABG patient hospitalizations, and from that data the Surgery episode, ICU, Medical-Surgical Unit and Extended Care Unit average daily costs were extrapolated. The findings showed that for the majority of uncomplicated CABG surgeries, ICU care accounts for 73% of the initial bed days of care costs, with each ICU day of care costing

approximately $2500.00, including ancillary services fees. Medical-surgical bed days cost an additional $1100.00 each, including ancillary services, while each surgery episode costs add an average additional $6100.00 to the total bill. Extended Care Days of Care add $485.00 per day, but those days of care do not appear to be significantly protracted as a result of stress hyperglycemia. From this data it appears that each episode of stress hyperglycemia, defined as postoperative glucose ≥250 mg/dL or postoperative glucose change ≥50 mg/dL, can increase the ICU LOS cost by at least $2500.00, and the medical-surgical LOS by $1100.00, for a minimum total of $3600.00 for at least 25% of the CABG surgery patients. Considering that each of the 42 DVAMCs that perform cardiac surgery must complete at least 150 CABG surgeries annually to maintain competency credentials, this amounts to a minimum of $135,000 in excess costs annually attributed to perioperative stress hyperglycemia at each center.

4.5 Summary

This chapter reported on the results of the data analysis for this dissertation research project including the descriptive data results, the univariate and multivariate logistic modeling as well as the resource utilization comparisons. The research questions were answered using two main glucose exposure variables; postoperative glucose ≥250 mg/dL and postoperative glucose change ≥50 mg/dL.

TABLE 4.32 Comparison of preoperative and postoperative glucose factors for excess ization in length of stay days - median (mean)

	n (%)	Preoperative LOS	ICU LOS	Postoperative LOS	Hospital LOS	Acute Care Readmit LOS	Extended Care LOS	Total LOS
Total Cohort	1285	days	days	days	days	days	days	days
Non-Diabetic	719 (56)	1 (3.1)	2 (3.1)	6 (8.1)	10 (12.2)	5 (7.7)	18 (26.4)	12 (16.3)
Diabetic (VA or Pre-op Glucose >200 mg/dL or HbA1c >7%)	566 (44)	1 (3.1)	3 (4.3)	7 (9.2)	10 (13.4)	5 (8.6)	20 (24.6)	12 (16.1)
LOS difference		0 (0)	1 (1.2)	1 (1.1)	0 (1.2)	0 (0.9)	2 (-1.8)	0 (-0.2)
p value		0.78	0.001	0.01	0.05	0.77(0.001)	0.72	0.8
Total Cohort	1285							
Postop Glucose <250 mg/dL	942 (73)	1 (3.1)	2 (3.1)	6 (8.0)	12.1	5 (7.9)	20 (26.2)	12 (15.9)
Postop Glucose ≥250 mg/dL	343 (27)	1 (3.1)	3 (5.0)	7 (10.1)	14.2	5 (8.8)	21 (24.3)	12 (17.1)
LOS difference		0 (0)	1 (1.9)	1 (2.1)	2.1	0 (0.9)	1 (-1.9)	0 (1.2)
p value		0.46	0.001	0.001	0.05	0.43 (0.01)	0.69	0.14

ICU = intensive care unit
postop = postoperative
w/o = without
DM = diabetes mellitus
LOS = length of stay
VA = Veterans Affairs
undiag. = undiagnosed

TABLE 4.32 Comparison of preoperative and postoperative glucose factors for excess resource utilization in length of stay days - median (mean) - continued

	n (%)	Preoperative LOS	ICU LOS	Postoperative LOS	Hospital LOS	Acute Care Readmit LOS	Extended Care LOS	Total LOS
Total Cohort	1285	days	days	days	days	days	days	days
Postop Glucose Change <50 mg/dL	983 (76)	1 (3.3)	2 (3.4)	6 (8.3)	10 (12.6)	5 (8.0)	21 (26.3)	11 (15.9)
Postop Glucose Change ≥50 mg/dL	302 (24)	1 (2.6)	3 (4.3)	7 (9.5)	10 (13.1)	5 (8.9)	17 (24.4)	12 (17.5)
LOS difference		0 (-0.7)	1 (0.9)	1 (1.2)	0 (0.5)	0 (0.9)	-4 (-1.9)	1 (2.5)
p value (Mann-Whitney)		0.01	0.01	0.001	0.18	0.74	0.41	0.05
Cohort w/o DM or Major Infection	626							
Postop Glucose Change <50 mg/dL w/o DM or Major Infection	472 (75)	1 (3.1)	2 (2.6)	6 (7.0)	9 (11.2)	4 (6.4)	22 (27.9)	11 (15.0)
Postop Glucose Change ≥50 mg/dL w/o DM or Major Infection	154 (25)	1 (2.7)	2.5 (3.2)	7 (8.7)	10 (12.4)	7 (8.7)	16 (25.1)	13 (18.3)
LOS difference		-0.4	.5 (0.6)	1 (1.7)	1 (1.2)	3 (2.2)	-6 (-2.8)	2 (3.3)
p value		0.39	0.001	0.001	0.01	0.01	0.34	0.001

TABLE 4.33 Summary comparison of resource utilization as length of stay and length of stay difference by glucose or diabetes variables - median (mean)

Length of Stay (LOS)	n (%)	Preoperative LOS	ICU LOS	Postoperative LOS	Hospital LOS	Acute Care Readmit LOS	Extended Care LOS	Total LOS
		days	days	days	days	days	days	days
Diabetic (VA or Pre-op Glucose >200 mg/dL or HbA1c >7%)	566 (44)	1 (3.1)	3 (4.3)	7 (9.2)	10 (13.4)	5 (8.6)	20 (24.6)	12 (16.1)
Postop Glucose ≥250 mg/dL	343 (27)	1 (3.1)	2 (3.1)	6 (8.0)	12.1	5 (7.9)	20 (26.2)	12 (15.9)
Postop Glucose Change ≥50 mg/dL	302 (24)	1 (2.6)	3 (4.3)	7 (9.5)	10 (13.1)	5 (8.9)	17 (24.4)	12 (17.5)
Postop Glucose Change ≥50 mg/dL w/o DM or Major Infection	154 (25)	1 (2.7)	2.5 (3.2)	7 (8.7)	10 (12.4)	7 (8.7)	16 (25.1)	13 (18.3)
Length of Stay Differences	n (%)	Preoperative LOS	ICU LOS	Postoperative LOS	Hospital LOS	Acute Care Readmit LOS	Extended Care LOS	Total LOS
		days	days	days	days	days	days	days
Diabetic (VA or Pre-op Glucose >200 mg/dL or HbA1c >7%)	566 (44)	0 (0)	1 (1.2)	1 (1.1)	0 (1.2)	0 (0.9)	2 (-1.8)	0 (-0.2)
Postop Glucose ≥250 mg/dL	343 (27)	0 (0)	1 (1.9)	1 (2.1)	2.1	0 (0.9)	1 (-1.9)	0 (1.2)
Postop Glucose Change ≥50 mg/dL	302 (24)	0 (-0.7)	1 (0.9)	1 (1.2)	0 (0.5)	0 (0.9)	-4 (-1.9)	1 (2.5)
Postop Glucose Change ≥50 mg/dL w/o DM or Major Infection	154 (25)	-0.4	.5 (0.6)	1 (1.7)	1 (1.2)	3 (2.2)	-6 (-2.8)	2 (3.3)

CHAPTER FIVE

DISCUSSION

5.1 Introduction

This chapter presents the discussion of the study findings, beginning with the descriptive data findings as well as the primary and secondary research questions results. The limitations of the study are then presented, followed by conclusions and areas for future research.

5.2 Descriptive Data Findings

5.2.1 Undiagnosed Diabetes Mellitus

One of the more significant findings in this study is the fact that more than half of the cohort undergoing CABG surgery at the Veterans Affairs Medical Center may have had pre-existing diabetes mellitus, with 48% (340 out of 706) of that group not diagnosed at time of surgery. Preoperatively 28% of subjects had prior history of diabetes, with an additional 16% presumably having pre-existing, undiagnosed diabetes based on random glucose ≥200 mg/dL or HbA1c ≥7%. Postoperatively another 11% of subjects had serum glucose levels ≥200 mg/dL, for a total of 55% of veteran CABG surgery patients with possible diabetes mellitus. A Department of Veterans Affairs study published in January 2004 using cardiac surgery data from 14 DVAMCs, including the center in our study, reported a DM rate of 26.4% (95% Confidence Interval 17.0-38.0), which is in keeping with the 28% rate of pre-diagnosed DM noted in this study, but significantly below the 44% preoperative rate or the 55% postoperative rate

subsequently identified [101]. This marked disparity in DM rates between diagnosed and actual suggests a system-wide failure to re-screen for diabetes prior to cardiac surgery, despite DM being one of the most widely recognized risk factors for coronary artery disease. Under-recognition of diabetes is not a problem limited to the Veterans Affairs medical system, but has also been reported by other researchers [102,103]. As Harris noted in a 1993 paper on the clinical and public health issues of undiagnosed NIDDM, upwards of 20% of people >50 years of age may meet the criteria for DM at least 12 years prior to diagnosis and half of those with DM may not be receiving treatment [104].

5.2.2 Stress hyperglycemia

Hand-in-hand with the issue of undiagnosed/unrecognized diabetes is the high incidence of untreated stress hyperglycemia within the postoperative cohort. Virtually 100% of study subjects had one or more serum blood glucose readings above 110 mg/dL, 24% had postoperative increases ≥50 mg/dL over preoperative values, 45% had recorded serum glucose ≥200 mg/dL and 27% had values ≥250 mg/dL. There remains controversy regarding how aggressively serum glucose must be controlled postoperatively, but it is becoming standard of care to maintain serum glucose below 200 mg/dL [15,105-107]. It is evident that serum glucose was not being strictly controlled perioperatively at the study center, as noted in TABLE 4.7, with 19% of non-diabetics, 63% of undiagnosed diabetics, 85% of NIDDM and 89% of IDDM having at least one serum glucose measurement ≥200 mg/dL.

5.3 Primary Research Questions #1 and #2

The primary research questions #1 and #2, asking whether elevated perioperative serum glucose was a significant, independent predictor of the collective major post-CABG infections or separately, looking at pneumonia, surgical site infection, sternal SSI and leg SSI in both non-diabetic and diabetic patients required a more complicated answer. Although the stress hyperglycemia threshold value of postoperative glucose ≥250 mg/dL was noted as being significant during univariate analysis, it did not continue to show evidence of independent statistical strength during logistic multivariate analysis. The stress hyperglycemia change variable of glucose change ≥50 mg/dL did exhibit independent significance, but as a protective factor. This may be due to the fact that many of the patients who had a serum glucose increase of ≥50 mg/dL were not diabetic and so by itself , that change was not potentially harmful. However, both of the two stress hyperglycemia variables of postoperative glucose ≥250 mg/dL and postoperative glucose change ≥50 mg/dL were significant interaction variables with other commonly occurring intrinsic patient and extrinsic process variables. Postoperative glucose ≥250 mg/dL interacted with prior heart surgery to increase the risk of major infection and surgical site infection at least four-fold and with low cardiac output to increase the risk of pneumonia almost seven-fold. Postoperative glucose change ≥50 mg/dL interacted with operation time ≥240 minutes to increase the risk of major infection and surgical site infection almost three-fold and pneumonia over

six-fold. Postoperative glucose change ≥50 mg/dL interacted with operation time ≥270 minutes to increase the risk of leg SSI also almost three-fold. Considering that 38% of the CABG cohort experienced stress hyperglycemia as either postoperative glucose ≥250 mg/dL or postoperative glucose change ≥50 mg/dL, 7% were having "redo" surgery, 10% suffered low cardiac output, 42% encountered operation times ≥240 minutes and 27% had operation times ≥270 minutes, a large percentage of cardiac surgery patients may have a three to seven times higher risk of infection as a result of uncontrolled perioperative stress hyperglycemia. One interesting commonality for these interaction variables is that they are essentially all indicators of either surgical complications (low cardiac output) or proxies for complicated surgeries (prior heart surgery, prolonged operation time). It may, therefore, behoove surgeons to more diligently control perioperative serum glucose levels in that subset of complex cardiac surgery patients who experience stress hyperglycemia, if it can be safely undertaken.

5.3.1 Additional Significant Variables

5.3.1.1 Cardiothoracic resident/fellows

Another interesting interaction which was identified during the logistic modeling was the more than three-fold increased risk of sternal surgical site infection in patients ≥73 years old whose primary surgeon was the cardiothoracic resident/fellow as opposed to the attending being the surgeon of record. Resident surgeon was not an independent risk factor for infection and this

increased risk was only noted in conjunction with a subset of patients in the highest quartile for age for one type of surgical site infection. A reasonable explanation for this result may be, as has been noted in some other studies, that although it is safe to train residents to perform cardiac surgery, experience does matter for a better outcome [108]. This may be especially true for both the youngest and oldest of cardiac surgery patients [109,110].

5.3.1.2 Registered nurse first assistants

Registered nurse first assistants (RNFAs) are registered nurses who have received additional, specialized training in order to perform as surgical assistants in the CABG cases, primarily to assist in harvesting the saphenous vein and close the leg incision. The study VAMC had four nurses trained in this capacity who would be scheduled as additional surgical assistants in CABG cases, depending on staffing levels. This means that if there were insufficient nurses available to scrub and circulate on other cases, the CABG surgeries would have to depend on the CT fellow or other available resident to perform graft harvesting and leg suturing. When there is only the CT fellow to harvest the saphenous vein, it is standard practice to leave the leg incision closure until the end of the case. If a general surgery resident assists in this process, it may indicate inexperience with the procedure. Either way this situation increases tissue trauma and likelihood of infection. The logistic modeling identified that when an RNFA was noted as a surgical assistant, the risk of leg surgical site infection was reduced by 40% ($p < 0.01$). The RNFA's primary job is to manage the leg vein

harvesting, insuring that it is performed consistently and the wound closed promptly. Again, this may be evidence that experience improves outcome.

5.4 Secondary Research Question

Secondary Research Question: Is perioperative stress hyperglycemia an independent predictor of increased resource utilization as measured by excess postoperative length of stay including intensive care unit stay, readmission to hospital within 60 days of discharge or extended care length of stay? The secondary hypothesis is that perioperative stress hyperglycemia increases resource utilization in CABG patients.

As noted in TABLES 4.30 and 4.31, compared with patients who have not experienced stress hyperglycemia, defined as postoperative glucose <250 mg/dL or postoperative glucose change <50 mg/dL, those who did had significantly longer median intensive care unit (ICU), postoperative lengths of stay (LOS) and total hospital LOS. Review of TABLE 4.31 notes that patients experiencing stress hyperglycemia as postoperative glucose ≥250 mg/dL had the longest mean ICU postoperative and hospital LOS, while those patients experiencing stress hyperglycemia as postoperative glucose change ≥50 mg/dL, controlling for VA diagnosed or undiagnosed diabetes, had the longest total mean and median lengths of stay, including acute, extended care and readmission LOS.

5.5 Costs Associated with Episodes of Care

Within the past few years the Department of Veterans Affairs has endeavored to associate financial resource utilization with episodes of care. In

this study, the data for specific patient hospitalizations was obtained, and from that data Surgery, ICU, Medical-Surgical and Extended Care LOS costs were calculated. The findings show that for the majority of uncomplicated CABG surgeries, ICU care accounts for 73% of the initial bed days of care costs, with each ICU day of care costing approximately $2500.00, including ancillary services fees. Medical-surgical bed days cost an additional $1100.00 each, including ancillary services, while surgery and anesthesia costs add an additional $6100.00 to the total bill. Extended Care Days of Care add $485.00 per day, but those days of care do not appear to be significantly protracted as a result of stress hyperglycemia. From this data it appears that each episode of stress hyperglycemia, defined as postoperative glucose ≥250 mg/dL or postoperative glucose change ≥50 mg/dL, can increase the ICU LOS cost by at least $2500.00, and the medical-surgical LOS by $1100.00, for an median of $3600.00 and mean of $4700.00 excess resource dollars for at least 25% of the CABG surgery patients. Considering that each of the 42 Department of Veterans Affairs Medical Centers that perform cardiac surgery must complete at least 150 CABG surgeries annually to remain credentialed, this amounts to a minimum of $135,000 in excess costs annually attributed to perioperative stress hyperglycemia at each center. Should a VA system-wide systematic program to control perioperative stress hyperglycemia be developed, there would be a minimum potential savings of $5,670,000.00 annually, just in VA cardiac surgery programs alone.

5.6 Study Limitations

Study limitations include the fact that the study was conducted within the Veterans Health Administration (VHA), utilizing data from only one Southwestern center out of the 42 centers within VHA where cardiac surgery is performed. Ethnicity data was incomplete and the study included only males, limiting the generalizability of the study. The risk factor data was not collected for the study but was either part of patient administrative, demographic, clinical or laboratory data files or collected for the VA National Surgery Quality Improvement Program (NSQIP). Other potentially pertinent variables, which are not yet computerized, such as blood loss, blood replacement, lowest body core temperature etc., were not available for inclusion in this study, so were not considered in the analyses.

5.7 Significance of the Work

The significance of the work may be substantial if the results from this study are considered to be worthy of additional studies to validate and expand the findings. This would be especially true if interventions are developed and implemented which reduce morbidity and excess resource utilization associated with stress hyperglycemia in CABG patients.

5.8 Areas for future research

One primary area for future research is validation of diabetes prevalence within the Veterans Health Administration of the Department of Veterans Affairs. It would be of interest to delineate whether the elevated serum glucose levels noted in the perioperative period are due to glucose intolerance, insulin

resistance or true diabetes mellitus. Additionally of course, it would be a worthwhile challenge to investigate whether the interaction findings of this study are reproducible across the VHA Cardiac Surgery Program and whether a larger sample size would possibly implicate stress hyperglycemia as an independent risk factor or replicate the interaction findings of this study. There also is no reason to believe that stress hyperglycemia may not play a role in adverse outcomes for other major surgeries or critical conditions. It has been shown to be a factor with post-myocardial infarction as well as stroke patients, regardless of pre-existing diabetes [55,111].

5.9 Conclusions

This study answered the primary question regarding stress hyperglycemia as a risk factor for major infections, but not as originally intended. The finding that stress hyperglycemia became clinically and statistically significant in interaction with other important and common risk factors was an important revelation. This result highlighted the fact that major postoperative infection is the outcome of complex interactions and events. It also left us with more questions than answers. Given certain settings, is stress hyperglycemia an independent, significant risk factor for major infections or other adverse outcomes following CABG surgery? What variable most accurately represents stress hyperglycemia? How is stress hyperglycemia best controlled? Is the risk of intensive control of stress hyperglycemia worth the potential benefit of

improved outcome? These are questions worth answering, so the quest will need to continue.

APPENDIX: HUMAN SUBJECTS APPROVAL LETTERS

Human Subjects Protection Program
http://www.irb.arizona.edu

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15 August 2003

Suzanne Pear, RN, MS
Advisor: Michael Lebowitz, Ph.D.
Medicine/Primary Care
Building 2, Room 400
VA Medical Center

RE: RELATIONSHIP OF PERIOPERATIVE HYPERGLYCEMIA AND SURGICAL SITE INFECTIONS IN CARDIAC SURGERY PATIENTS

Dear Ms. Pear:

We received documents concerning your above cited project. This project involves the retrospective review of existing de-identified data. Therefore, regulations published by the U.S. Department of Health and Human Services [45 CFR Part 46.101(b) (4)] exempt this type of research from review by our Institutional Review Board.

Exempt status is granted with the understanding that no further changes or additions will be made to the procedures followed (which we have on file) without the review and approval of the Human Subjects Committee and your College or Departmental Review Committee.

Thank you for informing us of your work. If you have any questions concerning the above, please contact this office.

Sincerely,

Rebecca Dahl

Rebecca Dahl, R.N., Ph.D.
Director
Human Subjects Protection Program

RD/js
cc: Departmental/College Review Committee

Department of Veterans Affairs **Memorandum**

Date: October 02, 2003

From: Chair, Research and Development Committee (151)

Subj: Review of Research Proposal

To: Suzanne M. Pear, R.N. (5-120B)

1. Your research proposal entitled "Relationship of Perioperative Hyperglycemia and Surgical Site Infections in Cardiac Surgery Patients" was reviewed by the Research and Development Committee on the date indicated. The action taken by the Committee is shown.

Research and Development Committee, 10/01/03. Approved

John Galgiani, M.D.

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