Continuous Insulin Infusions Reduce Mortality in Diabetic CABG patients

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Ultra-mini Abstract (Word count =50)

Intravenous insulin infusions are shown to markedly reduce absolute and risk-adjusted mortality in hyperglycemic diabetic CABG patients. This technique eliminates the incremental increase in CABG hospital mortality due to diabetes. Insulin infusions exert protective effects on mortality independent of the constellation of risk factors in the STS risk model.
Abstract (Word count = 250)

Objective: Diabetes is a risk factor for mortality following CABG. Its relative risk may be related to the level of perioperative hyperglycemia. We hypothesized that strict glucose control with a continuous insulin infusion (CII) in the perioperative period would reduce hospital mortality.

Methods: All diabetic CABG patients (n=3554) were treated aggressively with either subcutaneous insulin (SQI) (1987-1991) or with CII (1992-2001) for hyperglycemia. Predicted and observed hospital mortality were compared using both internal and external (STS 1996) multivariable risk models.

Results: Observed mortality with CII (2.5%, 65/2612) was significantly lower than with SQI (5.3%, 50/942, P < 0.0001). Likewise, glucose control was significantly better with CII (177 ± 30 vs 213 ± 41 mg/dl, P<0.0001).

Internal comparison: Multivariable analysis showed that CII was independently protective against mortality (OR=0.43, p=0.001). Conversely, cardiogenic shock, renal failure, reoperation, non-elective operative status, older age, concomitant peripheral or cerebro-vascular disease, decreasing ejection fraction, unstable angina, and history of atrial fibrillation increased the risk of death.

External comparison: Observed mortality with CII was significantly less than predicted by the model (Observed:Expected = 0.63; P<0.001). Multivariable analysis revealed that CII added an independently protective effect on mortality (OR=0.50, p=0.005) to the constellation of risk factors in the STS risk model.

Conclusion: CII eliminates the incremental increase in CABG hospital mortality due to diabetes. The protective effect of CII may stem from the effective
metabolic utilization of excess glucose to favorably alter pathways of myocardial ATP production. CII should become the standard of care for glycometabolic control in diabetic CABG patients.
Introduction

Diabetes Mellitus (DM) is a well established risk factor for postoperative mortality following coronary artery bypass grafting (CABG).\textsuperscript{1-3} Diabetes has been an independent risk factor for CABG mortality since the inception of the Society of Thoracic Surgeons (STS) national risk model in 1991\textsuperscript{1}. Diabetes is present in 2.5\% of the population in the United States\textsuperscript{4} but its national prevalence in patients undergoing CABG is as high as 28\%,\textsuperscript{1} making it an important component of the cardiac surgical milieu.

Diabetes is associated with higher incidences of preoperative co-morbidities including obesity, small vessel coronary artery disease, more severe and extensive atherosclerosis, peripheral vascular disease, renal insufficiency, hypertension and increased rates of life-threatening postoperative infection. Conventional wisdom has held that the increase in diabetic CABG mortality is related to the increased incidence of these comorbid factors associated with diabetes.\textsuperscript{3, 5, 6} However, this may not be the case.

In the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, Malmberg and associates showed that survival rates in diabetic patients with acute myocardial infarction were improved when they were treated with insulin infusions designed to achieve normoglycemia.\textsuperscript{7} In this study absolute survival rates were improved by 11\% at one year and by 15\% at 3.5 years. It was felt by the authors that glycometabolic control at the time of acute infarct
played a leading role in the observed improvement in outcomes. These findings were corroborated in a prospective randomized trial by the ECLA collaborative group which showed a 66% relative reduction in post-infarction mortality with insulin and glucose metabolic modulation in addition to vessel reperfusion.

Studies with glucose-insulin-potassium (GIK) metabolic modulation in CABG patients have, to date, failed to reveal a survival advantage, even in diabetic patients. However, it has been shown that oxidative glycometabolic ATP generation is impaired in the ischemic diabetic myocardium. Diabetics are known to have increased risk of low cardiac output syndrome and intra-aortic balloon pump usage following CABG. We have previously shown that the relative risk for a given diabetic patient is independently related to the level of perioperative hyperglycemia. Thus, poor glycometabolic control may be detrimental to myocardial function and clinical outcome.

Since January 1987 all diabetic heart surgery patients at Providence St. Vincent Medical Center have been enrolled into our ongoing prospective interventional study of the effects of hyperglycemia and its pharmacologic reduction on morbidity and mortality. This phase of the project was designed to test the hypothesis that a continuous intravenous insulin infusion (CII) in the perioperative period would reduce mortality in diabetic CABG patients.

Methods
Patients

Between January 1987 and December 2001 a total of 14,051 patients underwent isolated coronary artery bypass grafting at St. Vincent Medical Center. All diabetic patients who had CABG alone, without a concomitant procedure (n=3554; 25% of all CABG patients), were included in this study. Patients who had CABG combined with other operations (valve replacement or repair, aortic operations, closure of septal defects, or transmyocardial laser revascularization) were excluded from this study. All isolated on-pump CABG procedures at this institution are performed using short periods of intermittent fibrillation without the use of cardioplegia as a method of myocardial protection. The conditions and conduct of cardiopulmonary bypass remained constant throughout the study period.

All patients in the St. Vincent Diabetic Project undergo prospective measurement of blood glucose levels (by fingerstick or arterial line drop sample) every 30 minutes to 2 hours in the perioperative period. Average daily glucose levels, along with known preoperative risk factors for morbidity or mortality were routinely entered into a database for later analysis. These variables included:

Demographic: age, sex, height, weight, type of preoperative diabetic control (insulin, oral, diet, or none);

Historical: hypertension, congestive heart failure, renal failure, renal insufficiency, chronic obstructive pulmonary disease, pulmonary hypertension, smoking history, current smoking status, recent CVA (within 2 wks), remote CVA (> 2 wks
prior to surgery), peripheral vascular disease, NYHA class;

*Cardiovascular:* Left main trunk disease, number of diseased vessels, unstable angina, ejection fraction, acute MI, prior MI, timing of prior MI, history of atrial fibrillation, cardiogenic shock, PTCA, IABP insertion;

*Preoperative laboratory:* serum glucose, albumin, hemoglobin A-IC, creatinine;

*Preoperative medications:* diuretics, digoxin, intravenous nitrates, steroids;

*Intraoperative:* Society of Thoracic Surgeons operative status (elective, urgent, emergent, salvage), redo cardiac procedures, cardiopulmonary bypass time;

*Postoperative:* total units of blood transfused, prolonged (>48 hours) intubation, inotropic use >48 hours, epinephrine usage, new onset atrial fibrillation, mediastinitis, and seminal cause of death\(^\text{14}\) (hemorrhage, arrhythmia, pump failure, respiratory failure, neurologic, infection, and renal failure.)

**Definitions**

Definitions from the STS database committee were used for all variables common with that database. Definitions of other variables unique to this study included:

*Diabetes* – includes all patients admitted to the hospital with a co-morbid diagnosis of diabetes mellitus. Patients not previously diagnosed as being diabetic but who had persistently elevated postoperative glucose levels (>200mg/dl) and a discharge requirement for pharmacologic glycemic control were also included. These patients were identified as newly diagnosed diabetics during their admission for CABG.
Average Postoperative Glucose – the composite average of the daily mean glucose levels from the day of surgery, and the first and second postoperative days. This variable was used as the primary indicator of the pharmacologic effectiveness of hyperglycemic treatment in this study.

Mortality / Death – any in-hospital death occurring at any time during admission for CABG surgery following the start of that surgery.

Cardiac Related Mortality -- All deaths in which arrhythmia or pump failure were identified as the seminal cause of death.

Study Groups

All diabetic patients were divided into two sequential groups based on the type of perioperative glycemic control they received.

Subcutaneous Insulin Group (SQI): Patients operated on between January 1987 and September 1991 received subcutaneous insulin injections every 4 hours in a directed attempt to maintain their blood glucose levels below 200mg/dl (n= 942). Sliding scale dosage of insulin was titrated to each patient's glycemic response over the previous 4 hours. These every 4-hour sliding scale SQI injections were continued throughout the patients’ hospital course, even after they were restarted on their preoperative glucose control regimen.

Continuous Intravenous Insulin Group (CII): All diabetic CABG patients operated on between October 1991 and December 2001 (n=2612) received a continuous intravenous insulin infusion titrated by protocol in the perioperative period (“The Portland Protocol”). The current Portland Protocol (Appendix) was
implemented in gradual steps designed to maintain patient safety, prevent hypoglycemia, and ensure nursing comfort and compliance. This protocol prescribes insulin initiation, infusion and titration rates and glucose testing frequency requirements to safely maintain a patient’s blood glucose between desired “target” levels. Between 1991 and 1998 the target glucose was 150-200 mg/dl; in 1999 it was dropped to 125-175 mg/dl; and in 2001 the target glucose was again lowered to 100-150 mg/dl. From 1991 to 1995 the Portland protocol was used postoperatively only in the intensive care unit (ICU) and was stopped when the patient was transferred to the telemetry unit. In January 1996 the protocol was expanded with initiation in the operating room (prior to sternotomy, after induction of anesthesia, with continuation during cardiopulmonary bypass) and uniform continuation until 7 AM of the 3rd postoperative day, even for patients who had transferred out of the ICU.

Serum potassium levels were maintained between 4.0 and 5.5 mmol/l through the administration of exogenous potassium. In the intensive care unit this was accomplished through the administration of intravenous potassium by standardized protocol. Oral potassium supplementation was given to maintain these levels once patients’ were tolerating enteral nutrition and their CII and glucose levels had stabilized.
Data Analysis

In hospital mortality was the primary end point of this study. Patient groups were analyzed on an intent-to-treat basis. Using this method, intraoperative and first postoperative day deaths were included in the endpoint analysis, even though those patients did not complete the 3-day treatment SQI or CII protocols. This was felt to be the most rigorous method to test our hypothesis.

An “internal” logistic regression model was developed to determine the effect of perioperative hyperglycemic treatment method (SQI vs CII) on operative mortality after adjusting for other known preoperative risk factors. The "external" risk model was taken from the 1996 STS risk algorithm. The 1996 model was chosen as that year contained the median patient of the current data set. Using this nationally recognized risk assessment all patients were assigned an expected probability of mortality. Predicted and observed hospital mortality were then compared along with the Observed:Expected risk ratios. The composite STS risk score was calculated as the logit of the probability of death.

Univariate analyses between groups were done using t-tests and chi-square analyses. Bonferroni’s correction was applied to adjust for multiple comparisons between groups. Stepwise logistic regression was used to produce risk models for hospital death. C-statistics (area under the ROC curve) were used to measure model discrimination and Hosmer-Lemeshow statistic to measure calibration. The purpose was to make internal comparisons rather than to
produce a prediction equation for use outside of this dataset. Thus, all patients were used, rather than separating the data into training and testing subsets, or applying shrinkage methods to the coefficients. All statistical analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, Ill.)

Results

Between January 1987 and December 2001 14,051 patients underwent isolated CABG at St Vincent Hospital with an overall mortality of 2.8% (388/14051). Of these patients 3554 (26%) were diabetic and were enrolled in this study. The two study groups into which these diabetic CABG patients were divided were slightly heterogeneous. (Table 1)

CII was extremely effective in controlling postoperative hyperglycemia. Mean postoperative glucose levels were significantly lower in the CII group as compared to the SQI group on the day of surgery through the 2nd postoperative day. (Table 1) As the Portland CII protocol was implemented in the series of increasingly aggressive steps (described above) postoperative glycemic control gradually improved. (Figure 1)

The postoperative mortality rate for all diabetic CABG patients in this study was 3.2% (115/3554). Hospital mortality occurred at a median of 11.2 ± 13 postoperative days (range 0 – 68 days). The overall mortality in the CII group of 2.5% was significantly lower than that of the SQI group (5.3%) (65/2612 vs
This analysis was performed on an intent-to-treat basis. One could make the argument that those patients who expired in the operating room or within 24 hours of surgery (n=24) were “operative catastrophes” who did not survive long enough to derive a benefit from initiation of CII therapy. If our analysis was evaluated on an actual treatment (as opposed to intent-to-treat) basis, SQI mortality would have been 4.5% (42/934) and CII mortality would have been 1.9% (49/2596, p<0.0001).

**Cause of Death**

The seminal causes of death for each of the 115 patients who expired were pump failure 54% (62), arrhythmia 17% (20), neurologic 19% (22), respiratory failure 5% (6), renal failure 3% (3), hemorrhage 1% (1) and infection 1% (1). Cardiac-related mortality accounted for the majority (71%, 85/120) of the deaths in this series. Cardiac-related mortality was significantly more prevalent in the SQI group (4.2%) as compared to the CII group (1.6%) (40/942 vs 42/2612; p<0.001) implicating a myocardial mechanism of action for CII. There was no difference in the incidence of non-cardiac deaths between the two groups (1.1% (10/942) vs 0.9% (23/2612); P=0.5). Conversely stated, the reduction in operative mortality seen with CII was accounted for solely by a reduction in cardiac related deaths.

An analysis of mortality by glucose quantile is presented in Figure 2. This shows a highly significant relationship (p<0.001) between mortality and postoperative
glucose levels rising above 175 mg/dl. Figure 2 also reveals that the increase in overall mortality is principally accounted for by an increase in cardiac related mortality. Non-cardiac related mortality did not increase as postoperative glucose levels rose (p=0.9).

**Internal Multivariable Analysis of Mortality**

An “internal” logistic regression model, based solely on these data, was developed to determine the effect of CII on operative mortality after adjusting for other known preoperative risk factors (Table 2). Treatment of hyperglycemia with CII independently reduced the odds of mortality by a factor of 57% (Odds Ratio = 0.43, p=0.001). Cardiogenic shock, renal failure, reoperation, increasing urgency of operation, increasing age, a history of peripheral or cerebro-vascular disease, decreasing ejection fraction, unstable angina, and a history of atrial fibrillation were all found to increase the risk of death. The c-statistic for this model was 0.874, indicating high predictability for post-CABG mortality in diabetic patients.

Several other preoperative variables, known from other logistic regression models to predispose to death following CABG, did not enter this model. These included gender (p=0.8), congestive heart failure (p=0.2), left main trunk disease (p=0.2), prior myocardial infarction (p=0.8), acute myocardial infarction (p=0.5), preoperative intra-aortic balloon pump (p=0.5), prior PTCA (p=0.3), COPD (p=0.2), intravenous nitrates (p=0.4), diuretic (p=0.4), Digoxin (p=0.2), pulmonary
hypertension (p=0.3), and steroid use (p=0.9). Importantly, neither date of operation (p=0.6) nor year of operation (p=0.8) were found to independently influence mortality.

Postoperative epinephrine use and deep sternal infections have both been shown to increase glucose levels and mortality. They are, however, not "preordained" variables and should not be used to infer risk in predictive models. Nonetheless, when added into the internal model they are both highly significant (p<0.001). When these additions are made to this model they actually increase the protective significance of CII (p<0.001, OR 0.36), while history of atrial fibrillation becomes non-significant and ejection fraction, cardiogenic shock and redo operation all slightly decrease in significance. The c-statistic of this "postoperatively enhanced" model improves to 0.9.

When the continuous variable “average postoperative blood glucose” was entered into the logistic regression, as a potentially more accurate reflection of glycometabolic control, it displaced the categorical variable “CII” from the equation, leaving all other variables in place (P< 0.001, Odds ratio = 1.018 per mg/dl, c-statistic = 0.886). This again implies that CII is exerting a protective effect on mortality through a direct reduction of hyperglycemia, which may reflect an underlying detrimental metabolic defect within the post-ischemic diabetic myocardium.
The individual daily average glucose levels from the day of surgery (P< 0.003, Odds ratio = 1.006 per mg/dl) and from the first (P< 0.001, Odds ratio = 1.013 per mg/dl) and second postoperative days (P< 0.015, Odds ratio = 1.018 per mg/dl) were each significant independent predictors of death when entered into the model in lieu of the composite 3 day average glucose. Glucose levels on the third postoperative day did not have a significant independent effect on mortality (P=0.1). This further implies that the protective effects of CII are in play at least until the third postoperative day.

The excluded subset of 340 patients who underwent CABG combined with valve repair or replacement had blood cardioplegia delivery as a method of myocardial protection. Mortality with CII was 7.4%, compared to 12.7% with SQI. Logistic regression analysis in this population revealed a similar protective effect of CII against mortality (Odds Ratio 0.48), though it was not significant (P=0.11) because of the small sample size. This suggests that the effects of CII are not idiosyncratically related to our method of myocardial protection for isolated CABG patients.

**External Multivariable Analysis of Mortality**

To determine the effect of CII on risk-adjusted mortality, the predicted operative risk derived from the 1996 STS risk algorithm, was calculated for every patient with all such variables present (n=2834) and compared to observed mortality (Table 3). STS predicted mortality for the CII group was lower than that of the
SQI group. Observed mortality with SQI did not significantly differ from that predicted by the STS model. However, observed mortality with CII was significantly less than predicted. These data show a 36% reduction in the expected mortality resulting from CII.

To further confirm the significance of the reductive effect of CII on risk-adjusted mortality, the STS composite risk score, was entered into a new multivariable analysis of death along with CII. Both variables were significant (STS Risk Score: Odds ratio 3.3, 95% C.I. (2.7, 4.0), P<0.001; CII: Odds ratio 0.50, 95% C.I. (0.30, 0.76), P=0.005; c-statistic= 0.839). Thus, CII added a protective effect against mortality to the constellation of risk factors already in the STS risk model. This external model suggests that CII confers a 50% reduction to the risk-adjusted mortality of diabetic CABG patients. This translates into 21 lives saved for every 1000 patients in whom CII is effectively implemented.

The surrogate variable “average postoperative glucose” was again found to displace the categorical variable “CII” from the external model (P <0.001, Odds ratio = 1.02 per mg/dl, c-statistic= 0.853), again implicating a glycometabolic mechanistic effect for CII. To account for the confounding influences of time and sequential controls, the continuous variable “surgery date” was once again forced into the equation and found not to be significant (p=0.9).
The temporal effect of the Portland CII protocol on diabetic CABG mortality is seen in Figure 3, which depicts the annualized operative mortality for all CABG patients at our institution. Diabetic CABG mortality has fallen significantly since CII implementation in 1992. Perioperative mortality in non-diabetic CABG patients has not changed during the same time period (slope=0.9, p=0.4). There are now no significant differences between the operative mortality of diabetic and non-diabetic CABG patients at this institution.

Discussion

The principal finding of this study was that CII in perioperative diabetic CABG patients independently reduced absolute mortality by 57% and reduced risk-adjusted mortality by 50%. Improved survival with CII came about exclusively through a reduction in cardiac-related deaths. CII had the resultant effect of eliminating the incremental risk of diabetes on mortality in our CABG patient population. (Figure 3)

The limitations of this study should be noted. First, this is a non-randomized study that compares sequential groups of patients. Second, the use of asynchronous controls resulted in heterogeneous study groups, between which the primary endpoint of death is difficult to directly compare because the accompanying concomitant risks are not equally dispersed. Finally, the prolonged timeframe of this study induces further questions concerning temporal technical biases that are difficult to measure.
Due to the automated and aggressive nature of the Portland CII protocol, it was not feasible for us to conduct this study in synchronously randomized fashion. Nursing comfort and confidence with the perceived safety of CII titration in patients with, what was considered to be, euglycemia or mild hyperglycemia was programatically difficult. Nursing and administrative concerns of iatrogenically induced hypoglycemia in this “high-visibility” patient population had to first be assuaged. This was gradually accomplished first in the intensive care unit and then on the telemetry floor through rigorous and repeated in-service training conferences. When the protocol was finally functioning smoothly in the desired units, target glucose levels were then gradually lowered. As can be seen in figure 1, tight perioperative glycemic control took years to fully implement and achieve. Once the other beneficial effects (decreased wound infections, decreased length of stay) of tight glucose control on patient outcomes became known,\textsuperscript{13, 15, 17} both we, and the institutional review board, considered a synchronously randomized study with SQI controls unethical. Thus, the non-randomized nature of this study, at this institution, is -- and will remain -- a statistical “design flaw” to which some reviewers may object.

Although these technical limitations cannot be fully abrogated, we sought to minimize temporal bias and heterogeneity through appropriately sound statistical methods. Multivariable analyses serve well to smooth out baseline constitutional differences between groups.\textsuperscript{18, 19} A well-accepted, nationally-derived, external
risk model was used to normalize both constitutional makeup and temporal biases. All multivariable analyses, both internal and external, continued to reveal the protective significance of CII.

The long timeframe of this study was necessary to accumulate enough diabetic CABG patient outcome data to effectively power the study. We accumulated an average of 237 diabetic CABG patients per year towards the goal of 4000 patients – the number that would have been required to detect a 30% decrease in an overall mortality of 5%.

Temporal bias is further excluded by the facts that: 1.) date of surgery had no significant effect on either multivariable model and 2.) the mortality rate in the non-diabetic CABG population did not change over time. Nonetheless, we cannot rule out a conglomeration of minute improvements in operative technique over the 15-year study period that may have contributed to a decline in diabetic mortality.

Analysis of average postoperative glucose level does not carry with it the biases of non-randomization and asynchronous controls. Rather it is a direct measure of the underlying glycometabolic state of the myocardium, which by itself, is devoid of group selection and temporal bias. Thus, it is important to note that in both multivariable models mortality is independently also linked to average
postoperative glucose level. This relationship holds regardless of the study group into which the patient was entered.

This study was not intended to definitively establish a biochemical mechanism of action for the mortality-reducing effects of CII. However, based on previously published literature, we have theorized that alterations in myocardial metabolism in ischemic diabetic CABG patients are detrimental, while insulin-enhanced alterations in myocardial energy formation are one of the potential mechanisms for the favorable effects of CII on mortality. The following sub-sections of the discussion are offered as an expository discussion of previously-published works in this field which support this theory.

**Normal myocardial energetics**

The myocardium has been described as an “omnivore”, being able to use any one of several substrates for the production of ATP to power the continuous cycle of ventricular contraction and relaxation. The known substrates include free fatty acids (FFA), glucose, pyruvate, lactate, ketones and even amino acids.\(^{20}\) In normal non-diabetic, non-ischemic myocardium 60% of ATP production is derived from lipolysis and beta-oxidation of palmitate or free fatty acids (FFA), while 35% is derived from glycolytic sources.\(^{21}\) Both glycolysis and FFA beta-oxidation eventually produce Acetyl CoA. This is the primary substrate that produces hydrogen ions for oxidative phosphorilation via the Krebbs Cycle in the
mitochondria. Feedback mechanisms related to the concentration of Acetyl CoA in the mitochondria ensure a balance between these two pathways.\textsuperscript{22, 23}

Aerobic glycolysis occurs in the cytosol and produces pyruvate while it regenerates cytosolic ATP, which is critical for the maintenance of cell membrane integrity.\textsuperscript{24} It is also used to phosphorylate extracellular glucose for active transport into the cytosol and subsequently on to glycolysis.\textsuperscript{25} Pyruvate passively diffuses into the mitochondria where it is decarboxylated to Acetyl CoA by pyruvate dehydrogenase complex (PDH).\textsuperscript{23} “Oxidative glycolysis” can then be competed via the Krebbs Cycle. In the absence of insulin PDH activity decreases in the mitochondria, pyruvate builds up in the cytosol and excess amounts are converted to lactate. The reduction and decarboxylation of pyruvate by PDH thus becomes the rate-limiting step for further oxidative glycolysis. Lypolysis derived FFA are actively transported into the mitochondria where they undergo beta-oxidation to produce of Acetyl CoA. Increased levels of FFA-derived Acetyl CoA inhibit PDH and thus inhibit oxidative glycolysis.\textsuperscript{23}

**Alterations in myocardial energetics in diabetic CABG patients**

In diabetic CABG patients myocardial metabolism is negatively altered by both the ischemic and diabetic pathologic states. In non-diabetic patients during periods of ischemia, the supply of molecular oxygen is limited. FFA oxidation is inhibited and oxygen-efficient glycolytic ATP production predominates. However,
in poorly controlled diabetic CABG patients this is not possible as glycolysis is hormonally inhibited and lipolysis is paradoxically enhanced. Deficiencies of insulin bioavailability increase serum concentrations of, and myocardial utilization of, FFA which further inhibit glucose utilization. Serum glucose levels consequently rise in proportion to the underlying glycometabolic defect in the cells. A paucity of bioavailable insulin in the cell also slows phosphorylation of glucose and fails to activate PDH. In diabetic myocardium glycolysis is thus inhibited and FFA oxidation is paradoxically and detrimentally activated. Ischemic myocardiocytes must now derive as much as 90% of their energy from FFA metabolism. Because of limited oxidative capacity, the FFA taken up by the myocardium are not completely metabolized. FFA and their partially beta-oxidized intermediates accumulate in the myocardium. These compounds are known to decrease contractility and increase the incidence of ventricular arrhythmias. Although FFA produce more ATP then glucose does during complete aerobic oxidation, they do so at the expense of a higher rate of oxygen consumption. This further increases myocardial oxygen consumption and exacerbates cellular ischemia at a time when oxygen supply is limited.

Glycolysis-derived cytosolic ATP preferentially supports cell membrane ion transport and hence helps to preserve cellular integrity. Even after successful revascularization and reperfusion of the underlying ischemia, postoperative deficiencies in glucose metabolism persist in poorly controlled diabetic patients.
The persistent lack of glycolysis-derived ATP prolongs membrane destabilization and leads to increased cellular edema and arrhythmogenic potential.\textsuperscript{27}

In summary, serum glucose level may act as a “fuel gage” that varies inversely with the ability of the myocardiocyte to effectively absorb and utilize that fuel. In poorly controlled diabetic CABG patients glycolysis is inhibited, serum glucose is elevated, FFA metabolism is paradoxically activated and FFA intermediates accumulate in myocardial cells. The serum glucose level thus portrays the underlying glycometabolic state of the myocardium to the astute clinician.

\textbf{Mechanism of action of CII}

The administration of insulin to the hyperglycemic diabetic CABG patient reverses the aforementioned metabolic deficiencies. Exogenous intravenous insulin causes both intracellular and extracellular insulin levels to rise. As intracellular insulin rises pyruvate dehydrogenase is activated.\textsuperscript{29} As mitochondrial pyruvate levels fall cytosolic pyruvate is depleted by diffusion, opening up the pathway for increased cytosolic glycolysis. Glycolysis, again stimulated by insulin, replenishes cytosolic ATP which is in turn used to stabilize cellular membranes, phosphorylate extracellular glucose for transport into the cell, and facilitate membrane ion transport. These processes are crucial to endothelial, vascular smooth muscle and myocardial cellular integrity.\textsuperscript{30} Blood glucose levels are in turn lowered as myocardial glucose uptake is enhanced.\textsuperscript{26} Preservation of myocyte, endothelial and smooth muscle cell membranes results in decreased
cellular edema, reduced microvascular compression and prevention of the “no reflow” phenomena that may occur during reperfusion. The preservation of endothelial integrity and vascular smooth muscle function may additionally improve myocardial function by increasing native myocardial perfusion and by lowering systemic and pulmonary afterload resistance.

Intracellular glycerol esterifies intracellular FFA, preventing them from being transported into the mitochondria. In addition, the increase in mitochondrial Acetyl CoA derived from active glycolysis inhibits the carnitine-assisted transport of FFA into the mitochondria. This explains how increases in glucose oxidation are able to down-regulate myocardial FFA oxidation. Myocardial oxygen consumption is thus decreased by shutting down the beta oxidation of FFA. Accumulation of the negatively inotropic intermediaries of fatty acid oxidation ceases, free radical formation stops and myocardial efficiency and function improves. Insulin may further protect subcellular function by serving as a scavenger of free radicals generated during the ischemic/reperfusion process. Insulin thus directly enhances glycolysis, mediates active transport of phosphorilated glucose across the cell membrane and inhibits further lipolysis preventing buildup of toxic intermediates.

The clinical effects of the CII protocol may also be related to other sequelae of insulin administration on the myocardium such as increased uptake of potassium or magnesium into the myocyte. It may also be possible that some of the
beneficial outcomes seen with CII relate to its effects in tissues other than the heart -- improved energetics of skeletal muscle, lower circulating lactate levels during the interval on cardiopulmonary bypass, and improved endothelial function as mentioned above. It is important to note that our study provides no data on levels of serum insulin, free fatty acids, intracellular metabolites, myocardial ATP levels, enzyme activity levels or glycolic rates. Therefore a definitive, direct relationship between serum glucose levels and myocardial glucose utilization production is not proven by our study.

**Clinical Evidence**

There is, however, abundant clinical evidence that glycometabolic processes are indeed playing a role in critically ill patients. Not only is diabetes a risk factor for CABG mortality\(^1-3\), it also independently predicts higher incidences of postoperative arrhythmias, low cardiac output syndrome and intra-aortic balloon pump use.\(^{35-37}\).

Glucose does appear to be a superior substrate during periods of myocardial ischemia.\(^{31}\) However that substrate must be made biologically available by an adequate supply of insulin. In the DIGAMI study Malmberg and associates demonstrated that intensive glycometabolic control with CII in diabetic myocardial infarction patients led to improved long-term survival.\(^7\) The ECLA study group demonstrated a 66% reduction in acute post-infarction mortality with GIK modulation in addition to reperfusion.\(^{38}\)
GIK solutions in acutely ischemic myocardium have been shown to enhance contractility, decrease arrhythmias, and decrease myocardial oxygen consumption. Rao has shown that insulin-enhanced cardioplegia improves post-arrest stroke work and cardiac indices. In addition, it hastens the return of myocardial oxygen extraction to baseline following cardioplegic arrest.

Lazar’s extensive clinical and experimental work with GIK has shown us that this therapy limits post-ischemic tissue necrosis, infarct size and acidosis, and prevents myocardial stunning. Clinically this has resulted in increased cardiac indices, decreased weight gain, shortened ventilator times and reduced atrial arrhythmias in CABG patients undergoing urgent revascularization for ongoing ischemia. In diabetic CABG patients GIK had the additional effect of shortening hospital stay. Recently, GIK solutions have also been shown to improve left ventricular contractility and ventriculo-arterial coupling in diabetic sheep.

Although they were not the primary endpoints of the current study, there were univariate reductions in the incidences of new onset atrial fibrillation and low cardiac output syndrome with the use of CII (Table 1). These findings further support our theoretical assertion that alterations in glycometabolic function are playing an etiologic role in the outcome alterations we have seen.
Portland CII protocol

We propose that the glycometabolic state of the myocardiocyte is the final and true variable that directly affects outcomes in diabetic CABG patients. The serum glucose level merely portrays the level of the underlying glycometabolic deficiency to the clinician. The Portland CII protocol is a directed therapy designed to normalize the glycometabolic state of the myocardium in diabetics.

The Portland CII protocol is similar to GIK therapy in that insulin and potassium are iatrogenically administered to safely enhance glucose utilization. However, the Portland CII protocol is an insulin therapy that is precisely tailored to correct the specific glycometabolic defect that exists in each patient. Every diabetic patient has a unique degree of glucose-insulin mismatch and an accompanying unique glycometabolic deficiency. Exogenous glucose is not “force fed” to the cells in an attempt to turbocharge ATP production and reduce FFA utilization as it is with GIK regimens in non-diabetic patients. Rather, excess endogenous glucose is utilized as myocardial substrate. Therefore, by monitoring serum glucose levels, the clinician can directly monitor the cellular metabolic effectiveness of CII therapy. The induced physiologic hyperinsulinemia alleviates the glycolytic deficiency in direct proportion to its severity.

Previous studies have failed to demonstrate a clinical survival benefit from the administration of GIK to CABG patients. There are several methodological
reasons why this might be so. Most clinical GIK studies have been done in ischemic non-diabetic patients. Unlike diabetic CABG patients, these patients do not have a persistent and prolonged glycometabolic defect after reperfusion. Even the beneficial effects of insulin-enhanced cardioplegia are dissipated by eight hours in non-diabetic CABG patients.⁰⁰ Furthermore, with the addition of exogenous glucose there is no clinical mechanism of monitoring the effectiveness of cellular glucose loading to increase oxidative glycolysis. In addition to applying a non-tailored glycometabolic therapy to non-diabetic patients most studies were underpowered to detect small differences in mortality.

In Lazar’s study on diabetic patients GIK was used in the operating room and only for 12 hours postoperatively in the ICU.¹¹ Because glycolytic-derived ATP is critical to myocardial, endothelial, and smooth muscle membrane stability while accumulation of FFA intermediates are detrimental these cells' function,³¹ we feel that glucose metabolism should be maintained at optimum levels for at least the first 2 postoperative days. This has now been elucidated by our findings that daily average glucose levels are significant independent predictors of death until the third postoperative day – when their significance ceases. Maintenance of tight glycometabolic control throughout this period of maximum postoperative cellular edema should serve to stabilize cell membranes enhance endothelial function and reduce further fluid accumulation.

There is one previously published study that shows a survival advantage with CII in postoperative surgical patients.⁴² In that study, CII was used in a
heterogeneous group of hyperglycemic patients in an ICU setting. Insulin was
titrated to a euglycemic target of 80 – 110 mg/dl, and exogenous glucose was not
used. Most interestingly, the survival advantage with CII was only seen in those
patients who remained in the ICU and on the CII for 5 days or more. This
corroborates our assertion that strict glycometabolic correction and continuation
of CII therapy for the day of surgery and at least the first two postoperative days
are both key elements in the clinical success of our protocol.

Our study is the first to show a decrease in CABG mortality using insulin
infusions. We believe that the previously published basic scientific literature
supports our postulate that this mortality reduction has been brought about by
enhanced glycometabolic control with a resultant reduction in FFA intermediates.
This non-surgical intervention reduced both absolute and risk-adjusted mortality
in diabetic CBAG patients. The striking relationship of glucose levels to cardiac-
related death also implicates a potential myocardial glycometabolic etiology for
improved survival. These findings corroborate our methodological theory that
myocardial energetics are being enhanced by strict glycometabolic control.

Summary
This study has shown that perioperative glycometabolic control with a CII on the
day of surgery and through the first two postoperative days reduced absolute
mortality in our diabetic CABG population by 57%. The reduction in mortality
was completely accounted for by a reduction in cardiac-related deaths.
Conversely overall mortality and, specifically, cardiac-related mortality, increased significantly in association with rising postoperative glucose levels. These findings implicate enhanced myocardial glycometabolic function as the underlying source of improved outcomes with CII. Strict glycometabolic control with CII normalized diabetic CABG mortality in our institution to that of the non-diabetic population. CII decreased risk-adjusted mortality by 50% and thus exerted a protective effect on mortality independent of the constellation of risk factors in the STS CABG risk model.

Conclusion
We conclude that diabetes mellitus is not the true risk factor for mortality following CABG. Rather, we would propose that it is the underlying glycometabolic state of the myocardium that independently affects postoperative mortality. Excellent glycometabolic control can be safely achieved through the use of a CII in the perioperative period. Insulin infusions may induce biochemical changes in the production of myocardial ATP that are beneficial to cellular integrity, endothelial and ventricular function. This is amplified clinically into reduced postoperative mortality. Insulin infusions in diabetic CABG patients reduce mortality and eliminate the incremental increase in risk-adjusted mortality previously ascribed to “diabetes.” Insulin infusions should become the standard of care for glycometabolic control in diabetic CABG patients.
### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>SQI</th>
<th>CII</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>3554</td>
<td>942</td>
<td>2612</td>
<td></td>
</tr>
<tr>
<td><strong>Preoperative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>64 ± 10</td>
<td>65 ± 9</td>
<td>64 ± 10</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>2316 (65)</td>
<td>603 (64.0)</td>
<td>1713 (65)</td>
<td></td>
</tr>
<tr>
<td>Diabetic Control (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin dependent</td>
<td>1171 (33)</td>
<td>314 (33)</td>
<td>857 (33)</td>
<td></td>
</tr>
<tr>
<td>Oral agent</td>
<td>1784 (50)</td>
<td>455 (48)</td>
<td>1329 (51)</td>
<td></td>
</tr>
<tr>
<td>Diet only</td>
<td>405 (11)</td>
<td>108 (12)</td>
<td>297 (11)</td>
<td></td>
</tr>
<tr>
<td>No Rx</td>
<td>194 (6)</td>
<td>65 (7)</td>
<td>129 (5)</td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>880 (25)</td>
<td>150 (16)</td>
<td>730 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>2426 (68)</td>
<td>545 (58)</td>
<td>1881 (72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure (%)</td>
<td>738 (21)</td>
<td>222 (24)</td>
<td>516 (20)</td>
<td></td>
</tr>
<tr>
<td>Renal failure (%)</td>
<td>141 (4.0)</td>
<td>47 (5.1)</td>
<td>94 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency (%)</td>
<td>234 (6.6)</td>
<td>29 (3.1)</td>
<td>205 (7.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>649 (18)</td>
<td>160 (17)</td>
<td>489 (19)</td>
<td></td>
</tr>
<tr>
<td>Cerebral Vascular Disease (%)</td>
<td>315 (9)</td>
<td>97 (11)</td>
<td>218 (9)</td>
<td></td>
</tr>
<tr>
<td>COPD (%)</td>
<td>365 (11)</td>
<td>74 (8)</td>
<td>291 (11)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Hypertension (%)</td>
<td>71 (2.0)</td>
<td>14 (1.5)</td>
<td>58 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>29.7 ± 5.6</td>
<td>28.4 ± 5.1</td>
<td>30.2 ± 5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>54.9 ± 16</td>
<td>53.2 ± 17</td>
<td>55.4 ± 15</td>
<td></td>
</tr>
<tr>
<td>Parameter</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>p-value</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
<td>----------</td>
</tr>
<tr>
<td>Pre-op IABP (%)</td>
<td>63 (1.8)</td>
<td>23 (2.6)</td>
<td>40 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Number of diseased vessels</td>
<td>2.6 ± 0.6</td>
<td>2.6 ± 0.6</td>
<td>2.6 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Left Main Trunk &gt; 50% (%)</td>
<td>545 (16)</td>
<td>117 (13)</td>
<td>428 (17)</td>
<td></td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>1926 (55)</td>
<td>541 (58)</td>
<td>1385 (53)</td>
<td></td>
</tr>
<tr>
<td>Acute MI (%)</td>
<td>747 (22)</td>
<td>201 (22)</td>
<td>546 (21)</td>
<td></td>
</tr>
<tr>
<td>PTCA (%)</td>
<td>71 (2.1)</td>
<td>27 (3.0)</td>
<td>44 (1.7)</td>
<td></td>
</tr>
<tr>
<td>IV nitrates (%)</td>
<td>745 (22)</td>
<td>165 (19)</td>
<td>580 (23)</td>
<td></td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>504 (15)</td>
<td>185 (21)</td>
<td>319 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>1163 (34)</td>
<td>363 (41)</td>
<td>800 (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Steroids (%)</td>
<td>154 (4.3)</td>
<td>33 (3.5)</td>
<td>121 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.7 ± 0.5</td>
<td>3.9 ± 0.6</td>
<td>3.6 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission glucose (mg/dl)</td>
<td>171 ± 60</td>
<td>176 ± 63</td>
<td>170 ± 59</td>
<td></td>
</tr>
</tbody>
</table>

**Perioperative**

Postoperative blood glucose (mg/dl)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>187 ± 37</td>
<td>214 ± 41</td>
<td>177 ± 30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day of Surgery</td>
<td>201 ± 53</td>
<td>242 ± 61</td>
<td>187 ± 41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>POD #1</td>
<td>181 ± 34</td>
<td>205 ± 36</td>
<td>173 ± 28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>POD #2</td>
<td>181 ± 40</td>
<td>195 ± 39</td>
<td>176 ± 39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mediastinitis (%)</td>
<td>33 (0.9)</td>
<td>17 (1.8)</td>
<td>16 (0.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Redo sternotomy (%)</td>
<td>416 (12)</td>
<td>138 (15)</td>
<td>278 (11)</td>
<td>0.04</td>
</tr>
<tr>
<td>Urgent/emergent status (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Elective</td>
<td>1866 (53)</td>
<td>469 (50)</td>
<td>1397 (53)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urgent</td>
<td>Emergent</td>
<td>Salvage</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>146 (41)</td>
<td>400 (42)</td>
<td>1067 (41)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>187 (5)</td>
<td>52 (5.5)</td>
<td>135 (5.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38 (1)</td>
<td>23 (2.4)</td>
<td>15 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Internal thoracic artery use (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>929 (26)</td>
<td>352 (37)</td>
<td>577 (22)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2571 (72)</td>
<td>589 (63)</td>
<td>1982 (76)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>52 (1.5)</td>
<td>1 (0.1)</td>
<td>51 (2.0)</td>
<td></td>
</tr>
<tr>
<td>OPCAB</td>
<td>37 (1.0)</td>
<td>0 (0)</td>
<td>37 (1.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>80.5 ± 34</td>
<td>85.2 ± 39</td>
<td>78.7 ± 32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transfused PRBC (units)</td>
<td>1.8 ± 5.9</td>
<td>2.2 ± 2.9</td>
<td>1.6 ± 6.7</td>
<td></td>
</tr>
<tr>
<td>Epinephrine usage</td>
<td>137 (3.9)</td>
<td>33 (3.5)</td>
<td>104 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Inotropes &gt; 48 hrs (%)</td>
<td>294 (8.3)</td>
<td>99 (10.5)</td>
<td>195 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Low Cardiac Output Syndrome</td>
<td>370 (11)</td>
<td>115 (13)</td>
<td>225 (10)</td>
<td>0.09</td>
</tr>
<tr>
<td>Ventilation &gt; 48 hrs (%)</td>
<td>192 (5.4)</td>
<td>61 (6.5)</td>
<td>131 (5.0)</td>
<td></td>
</tr>
<tr>
<td>New onset Atrial Fibrillation</td>
<td>729 (21)</td>
<td>253 (27)</td>
<td>476 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>8.6 ± 5.7</td>
<td>10.4 ± 6.6</td>
<td>8.0 ± 5.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Observed Mortality (%)</td>
<td>115 (3.2)</td>
<td>53 (5.3)</td>
<td>67 (2.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>STS predicted Mortality (%)</td>
<td>4.0</td>
<td>4.7</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>p-value</td>
<td>Odds Ratio</td>
<td>95% CI for OR</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------</td>
<td>------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>Insulin infusion</td>
<td>0.001</td>
<td>0.43</td>
<td>(0.26, 0.70)</td>
<td></td>
</tr>
<tr>
<td>Cardiogenic Shock</td>
<td>&lt; 0.001</td>
<td>5.5</td>
<td>(2.4, 12.8)</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>&lt; 0.001</td>
<td>3.5</td>
<td>(1.8, 6.9)</td>
<td></td>
</tr>
<tr>
<td>Reoperation</td>
<td>&lt; 0.001</td>
<td>2.8</td>
<td>(1.7, 5.0)</td>
<td></td>
</tr>
<tr>
<td>Operative Status</td>
<td>&lt; 0.001</td>
<td>2.3</td>
<td>(1.7, 3.3)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.001</td>
<td>1.05 / year</td>
<td>(1.02, 1.08)</td>
<td></td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>0.001</td>
<td>0.98 / %</td>
<td>(0.96, 0.99)</td>
<td></td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>0.001</td>
<td>3.2</td>
<td>(1.6, 6.5)</td>
<td></td>
</tr>
<tr>
<td>Hx PVD / CVD</td>
<td>0.002</td>
<td>2.1</td>
<td>(1.3, 3.5)</td>
<td></td>
</tr>
<tr>
<td>History of Atrial Fibrillation</td>
<td>0.05</td>
<td>2.0</td>
<td>(1.01, 3.9)</td>
<td></td>
</tr>
</tbody>
</table>

N = 2933

Area under the ROC curve = 0.874

Hosmer Lemeshow goodness-of-fit p = 0.6
### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Observed mortality</th>
<th>Predicted Mortality</th>
<th>O:E ratio (95% C.I.)</th>
<th>O vs. E P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQI</td>
<td>5.35% (36/673)</td>
<td>4.68±7.8%</td>
<td>1.14 (0.87, 1.51)</td>
<td>0.3</td>
</tr>
<tr>
<td>CII</td>
<td>2.36% (51/2161)</td>
<td>3.77±5.5%</td>
<td>0.64 (0.45, 0.87)</td>
<td>0.005</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>0.2</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>SQI vs. CII</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Appendix

Portland Continuous Intravenous Insulin Protocol (v.2001)

Target Blood Glucose 100 – 150 mg/dl

1. Start “Portland Protocol” during surgery and continue through 7 AM of the 3rd POD. Patients who are not taking enteral nutrition on the 3rd POD should remain on this protocol until taking at least 50% of a full liquid or soft ADA diet.

2. For patients previously undiagnosed DM who present with hyperglycemia: start PDX protocol if blood glucose > 200 mg/dl. Consult endocrinologist on POD #2 for DM workup and follow-up orders.

3. Start infusion via pump piggyback to maintenance I.V. as follows:

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>IV Insulin Bolus</th>
<th>Initial insulin rate: units/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NIDDM preop</td>
</tr>
<tr>
<td>≥ 80 - 119</td>
<td>0</td>
<td>0.5 u/h</td>
</tr>
<tr>
<td>≥ 120 - 179</td>
<td>0</td>
<td>1.0 u/hr</td>
</tr>
<tr>
<td>≥ 180 - 239</td>
<td>0</td>
<td>2.0 u/hr</td>
</tr>
<tr>
<td>≥ 240 - 299</td>
<td>4 u</td>
<td>3.5 u/hr</td>
</tr>
<tr>
<td>≥ 300 - 359</td>
<td>8 u</td>
<td>5.0 u/hr</td>
</tr>
<tr>
<td>≥ 360</td>
<td>12 u</td>
<td>6.5 u/hr</td>
</tr>
</tbody>
</table>

4. Test Blood glucose (BG) by finger stick method or arterial line drop sample.

   Frequency of BG testing as follows:
a. If BG \( \geq \) 200 check BG every 30 minutes

b. If BG <200 check BG every hour.

c. When titrating vasopressors, (e.g. Epinephrine) check q. 30 minutes

d. When BG 100-150 with <15 mg/dl change **and** insulin rate remains unchanged x 4hr., = “stable infusion rate” -- then may test q. 2 hrs

e. May stop q. 2 hr testing on **POD #3** (see items #4 & #7 below).

f. **At night** on telemetry unit: Test q. 2 hr if BG 150 - 200; Test q4 hr if BG <150 and “stable infusion rate” exists.

5. Insulin titration:

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>Stop insulin; give 25 cc D50; recheck BG in 30 minutes. When BG &gt; 75 restart with rate 50% of previous rate.</td>
</tr>
<tr>
<td>50 - 75</td>
<td>Stop insulin; recheck BG in 30 minutes; if previous BG &gt;100 then give 25 cc D50. When BG &gt; 75 restart with rate 50% of previous rate.</td>
</tr>
<tr>
<td>75-100</td>
<td>If less than 10 mg/dl lower than last test, decrease rate by 0.5 u/hr. If more than 10 mg/dl lower than last test, decrease rate by 50%. If ( \geq ) last test maintain same rate.</td>
</tr>
<tr>
<td>101-150</td>
<td>Same rate</td>
</tr>
</tbody>
</table>
151-200  If 20 mg/dl lower than last test – same rate. Otherwise --
increase rate by 0.5 u/hr

>200  If ≥ 30 mg/dl lower than last test – same rate
If < 30 mg/dl lower than last test (OR if higher than last test)
increase rate by 1 u/hr

**AND** -- if >240 mg/dl -- IV bolus with regular insulin as per
"Initial IV Insulin Bolus" dosage scale above (see Item #1)

**Recheck BG in 30 minutes**

If BG > 200 mg/dl and has not decreased after 3 consecutive increases in
insulin, then double insulin rate.

If BG > 300 for 4 consecutive readings: call MD for additional IV bolus orders.

---

6. 1800 ADA Diabetic diet starts with any PO intake

7. **Postmeal S.Q. Humalog Insulin Supplement** in addition to insulin infusion
when oral intake advanced beyond clear liquids:

   If patient:
   a. eats **50% or less** of servings on breakfast, lunch, or dinner tray, then
give 3 units of Humalog insulin S.Q immediately following that meal
   b. eats **more than 50%** of serving on breakfast, lunch, or supper tray,
then give 6 units of Humalog insulin S.Q immediately following that meal
8. On third POD: Restart preadmission glycemic control medication unless patient is not tolerating enteral nutrition and is still on insulin drip.
Figure Legend

**Figure 1:** Scattergram of the average postoperative glucose levels of all 3554 diabetic CABG patients by date of surgery. A smoothed local regression (Loess) curve is superimposed. Initiation of the Portland protocol is marked by the vertical line. Note the gradual reduction of glucose levels over time.

**Figure 2:** Diabetic CABG mortality by glucose quantile. Overall mortality in each quantile is represented by the total height of the bar. Note the increase in overall mortality is overwhelmingly accounted for by an increase in cardiac-related mortality.

**Figure 3:** Annualized mortality in all CABG patients – diabetic versus non-diabetic – during the years of the study. Mortality in the non-diabetic group has not changed over time. However, mortality in the diabetic CABG population has been dramatically lowered. There is currently (1995 – 2001) no statistical difference between these two groups.
References


