

## Does Tight Glucose Control Prevent Myocardial Injury and Inflammation?

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**Abstract:** Hyperglycemia has been postulated to be cardiotoxic. We addressed the hypothesis that uncontrolled blood glucose induces myocardial damage in diabetic patients undergoing isolated coronary artery bypass graft surgery receiving continuous insulin infusion in the immediate postoperative period. Our primary aim was to assess the degree of tight glycemic control for each patient and to link the degree of glycemic control to intermediate outcome of myocardial damage. We prospectively enrolled 199 consecutive patients with diabetes undergoing isolated coronary artery bypass graft surgery from October 2003 through August 2005. Preoperative hemoglobin A<sub>1c</sub> and glucose measures were collected from the surgical admission. We measured biomarkers of myocardial damage (cardiac troponin I) and metabolic dysfunction (blood glucose and hemoglobin A<sub>1c</sub>) to identify a difference among patients under *tight* (90–100% of

glucose measures  $\leq 150$  mg/dL) or *loose* (<90%) glycemic control. All patients received continuous insulin infusion in the immediate postoperative period. We discovered 45.6% of the patients were in tight control. We found tight glycemic control resulted in no significant difference in troponin I release. Mean cardiac troponin I for tight and loose control was 4.9 and 8.5 (ng/mL), *p* value .3. We discovered patients varied with their degree of control, even with established protocols to maintain glucose levels within the normal range. We were unable to verify tight glycemic control compared to loose control was significantly associated with decreased cardiac troponin I release. Future studies are needed to evaluate the cardiotoxic mechanisms of hyperglycemia postulated in this study. **Keywords:** coronary artery bypass graft surgery, tight glycemic control, continuous insulin infusion, glucose, myocardial injury, inflammation. *JECT. 2011;43:144–152*

Independent of the diagnosis of diabetes, hyperglycemia (abnormally high levels of blood glucose) has been shown to increase the risk of infection (1–4), stroke (5), myocardial infarction (6), and death (1) in coronary artery bypass graft (CABG) patients. Since 1992, Furnary and colleagues (1) have been using a continuous insulin infusion (CII) to tightly control perioperative blood glucose levels in CABG patients and have shown tight glucose control is associated with a decreased risk of infection and mortality. The mechanism by which tight glucose control with insulin improves outcomes is unknown, though Furnary et al. have postulated that hyperglycemia has a direct cardiotoxic effect. Others have hypothesized that

hyperglycemia may induce a systemic inflammatory state, which in turn may result in myocardial damage.

Diabetic patients have a 42% increased incidence of long-term mortality (3.1 vs. 4.4 deaths per 100 person years) following CABG surgery; high glucose levels may attribute to this disadvantage through metabolic dysfunctions (7,8). Several methods for combating high glucose levels have been developed and used during CABG surgery (9,10). However, despite these advances the pernicious effects from high glucose (hyperglycemia) may still be present. There is uncertainty whether these advances, specifically continuous insulin infusion, have adequately controlled each patient's glucose within the specified target range and if variation in control has implications for myocardial injury.

Previous reports on the primary cause of death (11) identified that 64.8% of isolated CABG patients died in the hospital of heart failure. Of those who died from heart failure, 35.6% were diabetic in an ad hoc unpublished analysis. Hyperglycemia is a known risk factor for in-hospital mortality following CABG surgery (10), acute myocardial

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infarction (12,13), heart failure (12–16), sudden death (13), pump failure (13), stroke (5,15,17), acute kidney injury (18), and infection (4,15,19). Most studies confirm hyperglycemic patients, specifically ischemic patients, have worse outcomes over non-hyperglycemic patients (5), suggesting a metabolic mechanism underlying this disadvantage (10).

Tight glucose control was first shown to decrease severe complications in the diabetic outpatient population (20). Tight glucose control in critically ill patients in the intensive care unit with blood glucose levels  $\leq 110$  (mg/dL) reduced the mortality rate from 8.0% to 4.6% and reduced infection by 46% (9). The work done by Furnary and colleagues (10) demonstrated perioperative CII—combined with bolus insulin if necessary—during CABG surgery and in the intensive care unit following the surgery eliminates the higher in-hospital mortality risk for hyperglycemic patients receiving CII. Continuous insulin infusion reversed the pernicious effect of hyperglycemia by 57% (1,10). Hyperglycemia was suggested to be cardiotoxic and the mechanism of CII alters the metabolic pathways in the myocardium resulting in increased myocardial protection. To date, the most effective method in CABG surgery to sustain the metabolism of ischemic myocardial cells is through continuous insulin infusion (10,21).

The primary outcome in this study was to assess hyperglycemia-related cardiotoxicity. We measured cardiac troponin I (cTnI) at 24 hours after CABG as an indicator of cardiotoxicity (myocardial damage). The percent of glucose measures in tight control was the exposure. Cardiac troponin I is an optimal marker for assessing myocardial damage following cardiac surgery (22,23) and is independently associated with mortality (24,25). Baseline hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) was used in the analysis to adjust for each patient's preoperative glucose control. A secondary aim of this study was to assess 48-hour markers of inflammation in a subgroup of patients with stored blood: tumor necrosis factor-alpha (TNF- $\alpha$ ) and high-sensitivity C-reactive protein (hs-CRP).

## MATERIALS AND METHODS

### Data Collection

Data were obtained from a center in the Northern New England Cardiovascular Disease Study Group (NNECDSG). The Institutional Review Board approved the NNECDSG for data collection and analysis of these data.

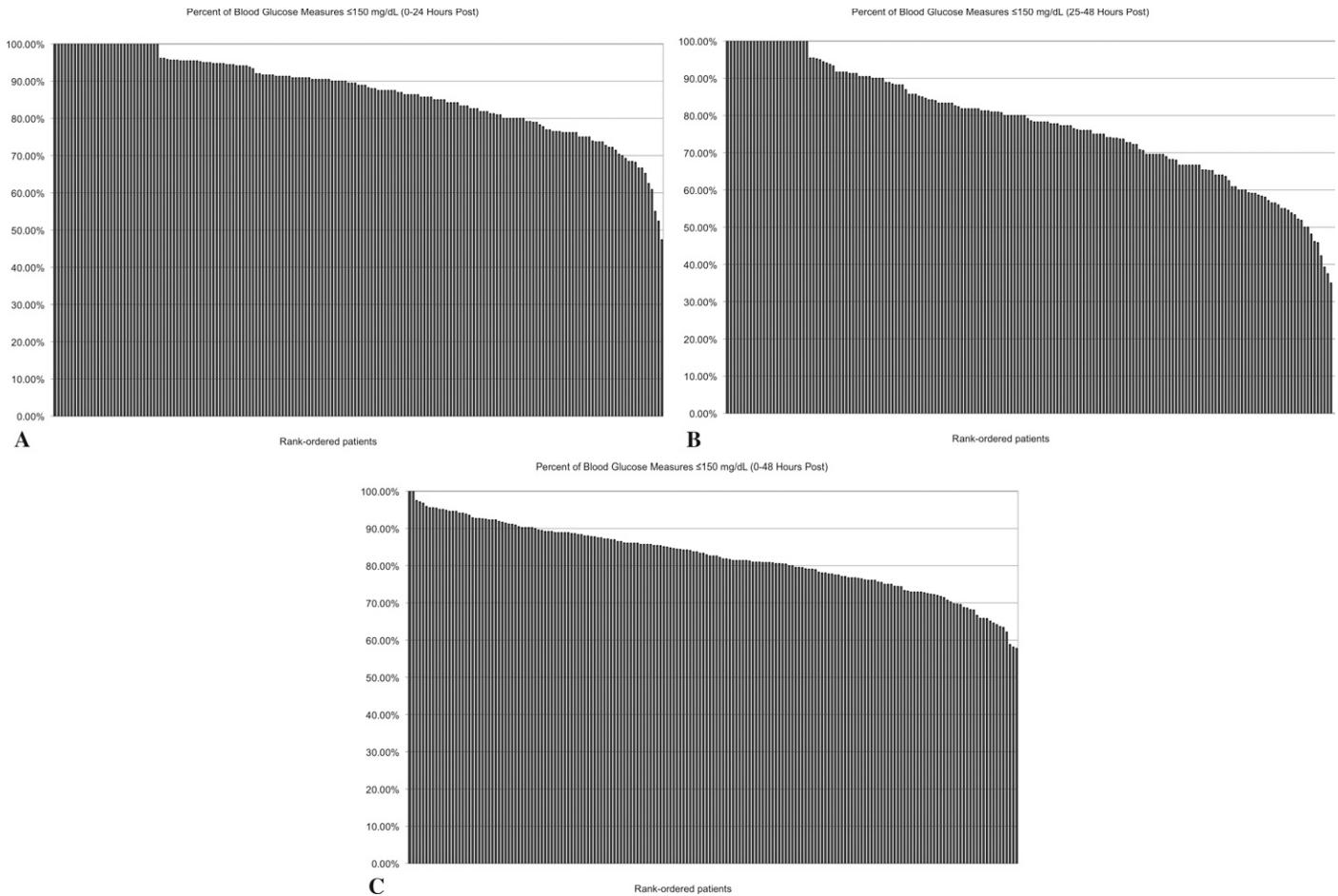
Data were collected on 274 cardiac surgical patients from October 2003 through August 2005. Seventy-five patients undergoing valve or concomitant CABG/valve surgery were excluded from the study; 199 patients who underwent isolated CABG surgery remained. Data on preoperative HbA<sub>1c</sub> and 58,936 glucose measures were collected from the patients' perioperative surgical admission (pre-, intra-,

and postoperative values) and linked to the NNECDSG registry data: age, gender, body mass index, diabetes, preoperative HbA<sub>1c</sub>, chronic obstructive pulmonary disease, vascular disease, hypertension, renal failure, preoperative white blood cell counts, priority at surgery (elective, urgent, and emergent), number of disease vessels, ejection fraction, left ventricular end diastolic pressure, prior myocardial infarction, unstable angina, prior CABG surgery, and mean postoperative length of stay. The preoperative NNECDSG predicted in-hospital mortality score was calculated for each patient.

Cardiac troponin I was measured at 24 hours after CABG surgery. Cardiac troponin I was analyzed on site by the clinical laboratory using an electrochemi-luminescence system. HbA<sub>1c</sub> was measured prior to CABG surgery on the Tosoh G7 Automated HPLC. Blood glucose was measured using an Accu-Chek Advantage glucometer (model 777) manufactured by Roche Diagnostics. Inflammatory biomarkers were measured from a subgroup of 43 patients with frozen serum samples, part of the Northern New England Cardiovascular Disease Study Group Biomarker Study initiative, at the Laboratory for Clinical and Biochemical Research (LCBR) in Colchester, VT. Blood samples were drawn at 48 hours after CABG surgery, separated and frozen by the medical center's clinical laboratory, and shipped to the LCBR on dry ice. Frozen serum was thawed and analyzed. TNF- $\alpha$  was measured on a multiplex bead assay using Linco reagents. Hs-CRP was measured by the BNII nephelometer from Dade Behring utilizing a particle enhanced immunonephelometric assay.

We categorized patients according to their glucose profile during the first 24 and first 48 hours following surgery. We compared each patient's glucose profile with 24 hour postoperative cTnI, 48 hour TNF- $\alpha$ , and 48 hour hs-CRP. All diabetic patients undergoing CABG surgery were started on the CII protocol. Glucose measures were collapsed to count the number of glucose measures in specified ranges of tight control at  $\leq 150$  (mg/dL). These counts of frequency of glucose testing in tight control were divided by the total number of glucose measures within each time period (preoperative, intraoperative, postoperative: 0–24 hours immediately following surgery – POD1, 25–48 hours – POD2, and 0–48 hours – POD1 + 2). Fourteen patients with less than 10 glucose measures in the first 24 hours were excluded from the analysis. The remaining 185 isolated CABG patients were included for this study.

The percent of blood glucose measures  $\leq 150$  (mg/dL) were rank-ordered and plotted in Figure 1A–C by POD1, POD2, and POD1 + 2. We categorized patients according to two subgroups of glucose exposure within the first 24 hours of surgery: *tight control*: diabetic patients on CII protocol with  $\geq 90\%$  glucose measures  $\leq 150$  (mg/dL); and *loose control*: diabetic patients on CII with  $< 90\%$  glucose measures  $\leq 150$  (mg/dL).



**Figure 1.** Distribution of blood glucose measures in glycemic control. Graphs represent the percent of blood glucose measures  $\leq 150$  (mg/dL, Y-axis) rank-ordered by patient (x-axis) across three time-points: (A) post-operative day 1 (0–24 hours); (B) post-operative day 2 (25–48 hours); (C) post-operative day 1 + 2 (0–48 hours). Tight glycemic control was derived by this measure at  $\geq 90\%$  of blood glucose measures  $\leq 150$  (mg/dL).

**Surgical Approach:** Coronary artery bypass graft procedures were carried out with the application of the following principals: complete revascularization with the standard use of left internal mammary artery to the left anterior descending graft in  $>95\%$  of cases, attention to blood usage, single cross clamp technique as well as study of the aorta with epi-aortic probe, myocardial protection with cold blood cardioplegic solution, and weaning from cardiopulmonary bypass with transesophageal echocardiogram (TEE) support to discover segments of poor myocardial function amenable to surgical improvement. TEE was also paramount in the assessment of valve function. The tenet of complete revascularization was applied to all patients affected by coronary artery disease undergoing CABG and this principal was only breached in the unusual circumstance when the risks of a longer bypass time significantly exceeded the benefits of additional grafts to non-life threatening segments of ischemic myocardium. A very conservative approach to blood usage was used when physiologically permissible: if the patient presented with a hema-

tocrit  $>38$ , a unit of blood was removed after induction of anesthesia, to be re-infused post bypass; retrograde aortic priming and retrograde venous priming were implemented in most cases to decrease priming volume and thus reduce hemodilution; ultrafiltration was carried out post bypass to increase the hematocrit; and cell-saver was used in all cases. The aorta was studied with epi-aortic ultrasound probe to demonstrate the area of least atherosclerotic accumulation and therefore guide the choice for aortic cannulation site as well as for the proximal vein grafts. A single cross clamp technique was applied to all patients to reduce the risk of embolic complications. Myocardial protection was achieved with antegrade and retrograde cold blood cardioplegia as well as moderate systemic hypothermia and ice slush for topical cooling. The technique of warm induction cardioplegia was implemented when the heart had suffered a recent ischemic injury. Warm blood was given in a retrograde fashion during re-warming while the proximal anastomoses were being performed to decrease the myocardial ischemic time. Upon weaning from cardiopulmonary

bypass, TEE was used in all CABG cases to discover segments of poor myocardial function and to help in determining if said function was due to technical problems and if it could be corrected with further revascularization.

### Statistical Analysis

Comparison of univariate, independent effects of the regression models were compared to multivariate, adjusted models to check for confounding. Graphical comparisons of perioperative glucose levels were examined over time. Quartiles of glucose control were examined: 95–100%, 89–95%, 81–88%, and  $\leq 80\%$  glucose measures  $\leq 150$  (mg/dL). We used the median percent in tight control (made up of the upper two quartiles) as a cut-off value for generating two-category variables. The mean and median blood glucose for postoperative day 1 (POD1) were correlated with 24 hour cTnI; and the mean and median blood glucose for POD1 and POD2 combined (0–48 hours) were correlated with 48 hour TNF- $\alpha$  and hs-CRP. We also conducted an analysis by categorizing the number of counts above 300 (mg/dL) and associated these counts with elevations in 24-hour cTnI, TNF- $\alpha$ , and hs-CRP.

The analysis incorporated comparisons between the two subgroups of glucose exposure (tight or loose control). Cardiac troponin I was compared between groups (tight vs. loose) using unpaired *t* tests. Multivariate regression was used to adjusted postoperative cTnI for baseline HbA<sub>1c</sub>. The analyses were repeated to assess the effect of glucose control on inflammation by measuring TNF- $\alpha$  and hs-CRP. TNF- $\alpha$  and hs-CRP were measured at 48 hours to examine an on-going inflammatory response.

## RESULTS

We investigated the difference in tight control at the 150 (mg/dL) cutoff and cardiac troponin I release. Eighty-four patients during the first postoperative day were in tight control ( $\leq 150$  mg/dL), while 101 patients were in loose control ( $>150$  mg/dL). Using this metric, baseline patient and disease characteristics (Table 1) were similar with regard to age, gender, body mass index, diabetes, preoperative HbA<sub>1c</sub>, chronic obstructive pulmonary disease, vascular disease, hypertension, renal failure, preoperative white blood cell counts, priority at surgery, number of disease vessels, ejection fraction, left ventricular end diastolic pressure, prior MI, unstable angina, prior CABG surgery, mean postoperative length of stay, and preoperative NNECDSG predicted in-hospital mortality score.

### 24-Hour Cardiac Troponin I

We compared 24-hour postoperative cardiac troponin I (ng/mL) between tight and loose controlled patients within the first 24 hours following CABG surgery. Table 2 compares mean cardiac troponin I. The crude comparison of

**Table 1.** Patient demographics.

Variable	Glycemic Control		<i>p</i> Value
	Tight ( <i>n</i> = 84)	Loose ( <i>n</i> = 101)	
Age (mean)	66.2	66.0	.877
Female (%)	23.8	32.7	.184
BMI (mean)	30.7	30.7	.947
Diabetes (%)	98.8	100.0	.272
HbA <sub>1c</sub> (mean)	7.2	7.4	.392
COPD (%)	11.9	7.9	.363
Any vascular disease (%)	45.2	41.6	.617
Hypertension (%)	94.1	91.1	.449
Renal failure (%)	8.3	5.9	.526
WBC (mean)	8.3	8.3	.994
Priority (%)			
Elective	23.8	25.7	.448
Urgent	73.8	68.3	
Emergent	2.4	5.9	
Number of diseased vessels (mean)	2.4	2.3	.848
Ejection fraction (mean)	49.8	50.6	.711
LVEDP (mean)	21.2	19.3	.234
Prior myocardial infarction (%)	48.8	49.5	.925
Unstable angina (%)	34.5	40.6	.397
Prior CABG surgery (%)	6.0	7.9	.602
Length of stay (mean)	9.5	8.7	.570
NNE mortality score (Mean)	3.8	3.2	.623

Tight: 90% or more of glucose measures at or below 150 (mg/dL) during the first 24 hours following surgery; Loose: Less than 90% of glucose measures at or below 150 (mg/dL) within the first 24 hours following surgery; *p* value: unpaired *t* test, chi-squared test.

BMI, body mass index; Diabetes, diagnosed diabetes prior to CABG surgery admission; COPD, chronic obstructive pulmonary disease; Renal failure, dialysis-dependent renal failure; WBC, white blood cell count (in 1000s); LVEDP, left ventricular end-diastolic pressure; Length of stay, postoperative length of stay; NNE, Northern New England Cardiovascular Disease Study Group.

tight to loose categories showed a higher release of mean cardiac troponin I at 24 hours postoperatively (Figure 2A). Mean cardiac troponin I comparisons were not statistically significant. There were no apparent differences between the tight and loose groups with regard to median troponin I (Figure 2B), nor were differences observed when adjusting for baseline HbA<sub>1c</sub> (a baseline measure of glycemic control). Cardiac troponin I was adjusted for HbA<sub>1c</sub> as we thought preoperative glucose control or management of diabetes could affect the level of 24-hour troponin.

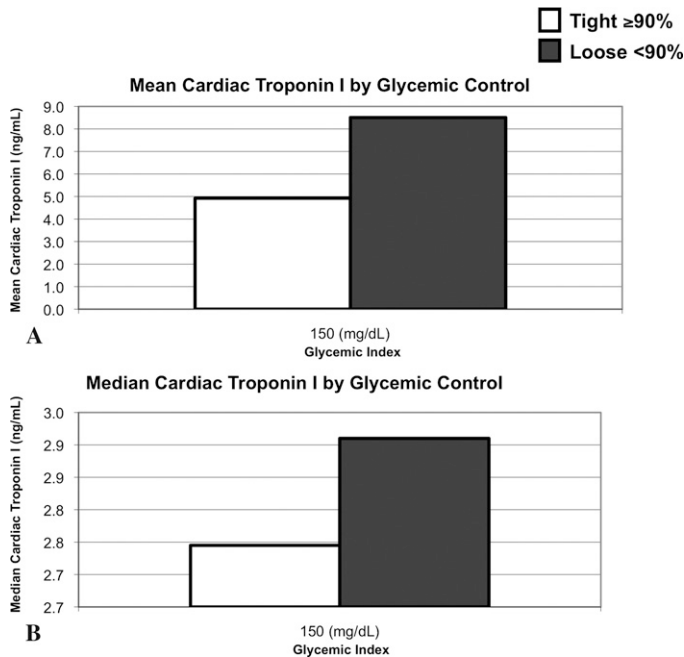
We further stratified the percent of glucose values into quartiles of tight control and assessed at trend in mean and median 24-hour troponin I. In addition, we examined the mean glucose by POD1 with 24-hour troponin I. No significant associations were observed. Median cardiac troponin I was similar across all groups. We did observe an association between the number of perioperative glucose counts above 300 with 24-hour cardiac troponin I (correlation coefficient .1759, *p* value .017). There were too few events for ST-elevation myocardial infarction and low cardiac output failure to effectively evaluate these clinical outcomes.



**Table 2.** Postoperative cardiac troponin I by glycemic control index.

Glycemic Control	Tight			Loose			Mean Difference	<i>p</i> Value
	n	Mean	Median	n	Mean	Median		
150 (mg/dL)	84	4.93	2.75	101	8.51	2.91	3.58	.392
150 (mg/dL)	84	Cardiac Troponin I (ng/mL) Adjusted for Preoperative HbA1c					.08	.958

Tight: 90% or more of glucose measures at or below specified target (150 mg/dL) within the first 24 hours following surgery; Loose: Less than 90% of glucose measures at or below the target; *p* value for *t* test.



**Figure 2.** Cardiac troponin I by glycemic control. Mean (A) and median (B) cardiac troponin I are plotted by the tight (white bars) or loose (black bars) control. Tight control requires  $\geq 90\%$  of glucose measures to be less than or equal to 150 (mg/dL).

### Secondary Analysis: 48-Hour Inflammation

The secondary analysis examined the association of inflammatory markers at 48 hours postoperatively with tight and loose control during the first two postoperative days (first 48 hours, POD1 + 2). We measured tumor necrosis factor-alpha (TNF- $\alpha$ , pg/mL) and high sensitivity-C-reactive protein (hs-CRP, pg/mL). Table 3 summarizes the inflammatory analysis for TNF- $\alpha$  and hs-CRP. There was no significant difference observed in 48-hour postoperative TNF- $\alpha$  values in tight versus loose control. However, a 12% increase in TNF- $\alpha$  (1.72 pg/mL difference) circulation was apparent in patients in loose control for the first two postoperative days compared to tightly controlled patients (Figure 3A). This effect was not statistically significant, but was consistent even after adjustment for preoperative HbA<sub>1c</sub> and/or white blood cell count (Table 3). Median

TNF- $\alpha$  values were higher in the loose group (Figure 3B).

Likewise, using the same measure (tight and loose glycemic control for POD1 + 2), there was no significant difference observed in 48-hour postoperative hs-CRP values in tight versus loose control. There was a 13% mean increase hs-CRP in the loose group relative to the tight group (Figure 3C); however this finding was not statistically significant with *p* = .608 (Table 3). A similar increase was observed with the median values of hs-CRP (Figure 3D), but again was not significant with *p* = .946. Even after adjustment for baseline HbA<sub>1c</sub> and/or white blood cell count, on average patients in the loose controlled group demonstrated a higher hs-CRP level.

### DISCUSSION

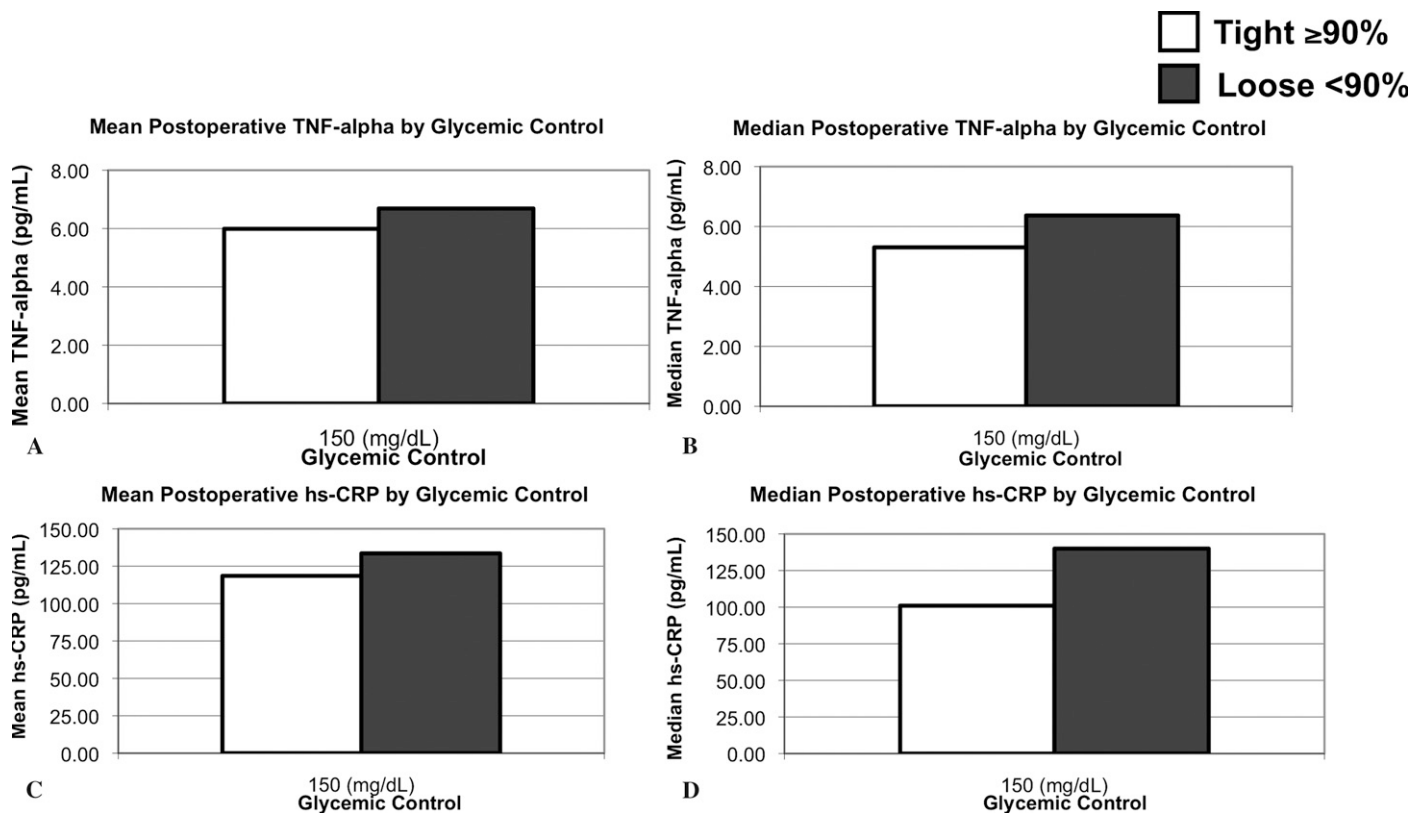
We examined the association between tight glycemic control and 24-hour cardiac troponin I (ng/mL) levels following isolated CABG surgery. We discovered using the percent of glucose measures in tight control was a clinically useful metric to assess glycemic control at the patient level. Tight control was defined as having  $\geq 90\%$  of a patient's glucose measures at or below 150 (mg/dL). Although patients in tight control had a lower mean 24-hour postoperative cardiac troponin I, the difference was not significantly different from patients in loose control. Additionally, our results did not show a significant difference between tight and loose controlled patients with respect to 48-hour TNF- $\alpha$  or hs-CRP.

Carr et al. demonstrated how using the percent in tight control metric provides important information back the clinical care team about each patient's glycemic control and encourages the staff when they are able to manage a patient's glucose within the protocol bounds (26). Similar to our metric, Carr et al. tracked each patient's glycemic control for the target range at 130 (mg/dL); whereby the percentage of glucose measures at or below 130 (mg/dL) were recorded. In addition, each month the percent of patients with at least 50% of their measures within the target range were graphed and reported to clinical care team. Furthermore, they time-weighted their glucose

**Table 3.** Postoperative TNF-alpha and glyceimic control.

Glycemic Control	Tight			Loose			Difference	p Value			
	n	Mean	Median	n	Mean	Median					
150 (mg/dL)	8	5.99	5.31	35	6.69	6.37	.70	.618			
150 (mg/dL)		Mean TNF-alpha (pg/mL) Adjusted for HbA1c			6.48	6.67	.19	.843			
150 (mg/dL)		Mean TNF-alpha (pg/mL) Adjusted for WBC			6.07	6.74	.67	.641			
150 (mg/dL)		Mean TNF-alpha (pg/mL) Adjusted for HbA1c and WBC			6.65	6.77	.11	.890			
150 (mg/dL)	7	Crude hs-CRP (pg/mL)			118.53	101.00	36	133.55	140.00	15.02	.608
150 (mg/dL)		Mean hs-CRP (pg/mL) Adjusted for HbA1c			104.51	131.14				26.63	.446
150 (mg/dL)		Mean hs-CRP (pg/mL) Adjusted for WBC			120.25	134.63				14.39	.632
150 (mg/dL)		Mean hs-CRP (pg/mL) Adjusted for HbA1c and WBC			106.28	132.05				25.77	.471

Tight: 90% or more of the glucose measures within the specified control range (150 mg/dL) within the first 48 hours following surgery; Loose: Less than 90% of glucose measures within the specified range; p value: unpaired t test. WBC, white blood cell count.



**Figure 3.** Postoperative inflammation by glycemic control. Postoperative biomarkers of inflammation, Tumor Necrosis Factor-alpha (TNF-alpha, A, B) and high sensitivity C-Reactive Protein (hs-CRP, C, D), are plotted by mean and median values for tight and loose control. Tight control requires  $\geq 90\%$  of glucose measures to be less than or equal to 150 (mg/dL).

measures to account for variation in time between measures. Our study, rather, focused on the target cutoff of 150 (mg/dL), which was consistent with the upper range for the hospital protocol and we assessed the degree of

tight control on a patient-by-patient level without grouping to monthly reports. In addition, we did not time-weight our glucose measures, but rather restricted patients with at least 10 measures within the first 24 hours. The Carr study

demonstrates that as the degree of tight control increases, infection rates improve. However, our study diverges from the Carr study, where we focused on biomarkers as intermediate endpoints representing myocardial damage and inflammation.

Our study investigated the hypothesis that hyperglycemia was cardiotoxic. This hypothesis was founded in the landmark work done by Furnary and colleagues, who demonstrated that the excess mortality observed in hyperglycemic CABG patients was cardiac related (10). Although we examined the role of mean postoperative day glucose in our exploratory analysis, we did not see an association with the mean postoperative day 1 (POD1) glucose or the degree of tight control with 24-hour postoperative cardiac troponin I (ng/mL). However, we did not use the same blood glucose (BG) metric as was used in Furnary's studies. The 3-blood glucose (3BG) measure used by Furnary and others averages the blood glucose measures for the day of surgery, the first and second postoperative clinical days. The 3BG measure is a good method to determine the average glucose over the course of 3 days. Our metric rather determines how many glucose measures in a given time period are within in the insulin protocol range (or below the upper limit); this new metric has strong potential in assessing how well patients are tightly controlled in a given time period while adhering to an insulin protocol. For this reason, we chose to examine the degree of tight control for each patient and stratified by tight or loose control, which were the exposure groups (exposed to tight or loose control). In addition, the study was not powered to detect mortality and mode of death as we did not seek to re-evaluate Furnary's findings; rather we focused on measuring myocardial damage. Our metric of assessing tight control with cardiac troponin I did not mimic Furnary's findings with regard to myocardial damage, which may suggest that hyperglycemia, or loose control in our case, does not result in more myocardial damage (or cardiotoxicity). One possibility for this finding is that the patients in our study were all diabetic and well controlled (45.4% in tight control at 150 mg/dL during the first 24 hours after surgery), but more importantly nearly all patients were controlled under 200 (mg/dL). This would suggest that as long as patients were under 200 (mg/dL) they were protected from cardiotoxicity resulting from hyperglycemia. Therefore the difference in myocardial damage among patients with tight and loose control is difficult to detect or does not represent a clinically relevant difference in myocardial damage.

In contrast, the glucose control study by Gandhi et al. (27) showed that good intraoperative glycemic control resulted in better 30-day mortality, but not with regard to infection, neurological, or cardiac outcomes. This finding is consistent with our findings with regard to myocardial damage and may suggest that there is no cardiotoxic effect from hyperglycemia. Similarly, Mehta et al. showed no effect

with glucose-insulin-potassium (GIK) on reducing mortality, cardiac arrest, or cardiac shock in acute ST-elevation myocardial infarction patients (28).

The closest comparison we have in the literature to examining the glycemic control and myocardial damage is from the GIK research; however, this differs very much from the standard CII protocols used today for obtaining tight control. There are only three randomized controlled trials for GIK examining the release of cardiac troponin I. Bruemmer-Smith et al. reported cTnI peaked 6 hours after surgery, but cardiac troponin I did not differ at anytime between GIK and no-GIK groups among 42 enrollees (23). Lell et al. reported, on 46 patients, a similar finding that there was no difference in cTnI between GIK groups (29). However, Yazici et al. among 52 patients in a non-CABG trial, demonstrated that GIK significantly reduced the release of cTnI at 12 and 24 hours following percutaneous intervention (30). From these trials we can confer that to-date there is conflicting evidence as to whether or not glycemic control protects against myocardial damage. Additional studies will need to be conducted to confirm or reject the hypothesis that hyperglycemia is cardiotoxic.

Our secondary aim was to examine the effect of tight glycemic control on the 48-hour inflammatory response by measuring TNF- $\alpha$  and hs-CRP. In a nonsurgical study among Type 1 diabetics, Schaumberg et al. examined the effect of intensive glycemic control on markers of inflammation (31). They found no difference in hs-CRP, but a statistically significant difference in TNF- $\alpha$  (receptor 1) between intensive and non-intensive controlled groups. In the only CABG trial, Visser et al. among 21 patients demonstrated GIK significantly reduced 48-hour hs-CRP levels (32). Visser's study also showed that hs-CRP was at its maximum value at 48 hours. Our study is in agreement with Visser's study where hs-CRP was lower in the tightly controlled patients; however our finding was not statistically significant despite a larger sample size. The results from our study suggest tight glycemic control results in less inflammation at 48 hours.

There are several limitations to our study. First, the study population only included diabetic patients at a single medical center undergoing isolated CABG surgery. Although the continuous insulin infusion protocols are in use on hyperglycemic nondiabetics at other medical centers, at this center they are not. We can only generalize our findings to diabetic patients receiving postoperative continuous insulin infusion. Second, our endpoint was 24-hour postoperative cardiac troponin I. We did not measure baseline levels of cTnI, nor did we collect serial measurement during surgery or at intermediate times postoperatively, nor at 48 and 72 hours—where the affects of elevated blood glucose in the second 24-hour periods would be seen. Therefore, we were limited to measured troponin at a single time point (24 hours). However, following myocardial damage

troponin remains elevated for 2–3 weeks and peaks around 6 hours postoperatively. Therefore at 24 hours, we are measuring on-going myocardial damage and not a myocardial-stress induced release of troponin. Third, other biological markers possibly influenced in the proposed cardiotoxic effects from hyperglycemia such as lactate and free fatty acids were not measured. The cardiotoxic mechanism driven by hyperglycemia via an energy switch from aerobic (glucose) to anaerobic respiration free fatty acids (FFAs) has been suggested by Szabo and colleagues who sampled from the coronary sinus, thus measuring the release of these markers of metabolic function directly from the heart (33). Surgeons have agreed to conduct a mechanistic study including sequential sampling from the coronary sinus as well as additional arterial samples. Fourth, there is an issue with the difference in the number of glucose measures among patients; some patients were more closely monitored (glucose measured more often) and others monitored less. We addressed this issue by eliminating patients with less than 10 measures within the first 24 hours. In addition, we used the time-weighted approach to calculate the percent of glucose measures in tight control using the Carr et al. approach (26); we discovered that the time-weight calculation significantly correlated with our measure without the time-weight: correlation coefficient of .97,  $p$  value  $<.001$ . This suggests that either the time-weight approach to the calculation is not necessary or that our glucose measures were evenly spaced within the first 24 hours. Other potential limitations to this study are chance (power), bias (measurement error in measuring troponin or glucose), and confounding. We conducted our study at one medical center and therefore were able to minimize variation in measurement by using a consistent set of monitors, laboratory equipment, and staff.

Although we were unable to demonstrate a cardiotoxic effect of loosely-controlled hyperglycemia, other markers along the metabolic pathway may help look at the issue from additional perspectives. The ad-hoc sample size estimate to demonstrate a significant difference between tight and loose control was 1800 patients. Future investigations on the relationship between glycemic control and cardiotoxicity could be evaluated in a comprehensive cardiac surgery cohort. Lactate and free-fatty acids would be potential biomarkers to look at the effects of glucose on an ischemic heart during the perioperative course of surgery and treatment. In addition, serial measurement of these markers, and troponin, would provide more information during CABG surgery and the postoperative days following surgery. If possible, lactate and free-fatty acids could be measured from the coronary sinus (blood leaving the heart) during the procedure if retrograde cardioplegia is used.

In summary, tight glycemic control compared to loose control was not associated with increased 24-hour cardiac troponin I release. In addition, we saw tight control

was associated with lower levels of hs-CRP at 48 hours; however this comparison was not statistically significant. Further studies are needed to associate the degree of tight control with biomarkers representing intermediate clinical outcomes. Examining the wide range of tight glycemic control may prove to be useful positive-feedback information to the clinical care teams to assess the degree of control patients are under and how to best improve insulin protocols. We believe the later information will assist clinical care team in improving patient care through optimizing glycemic control. We also foresee that this new metric of tight control will demonstrate the importance of maintaining patients in tight control during the immediate postoperative period.

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