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Characterization of Persistent Hyperglycemia: What Does It Mean Postinjury?

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Abstract

Background—Strict glycemic control has been shown to reduce both morbidity and mortality in critically ill surgical patients; however, overly aggressive management of hyperglycemia may also be associated with deleterious effects. We sought to characterize clinical outcomes associated with different levels of persistent hyperglycemia (PH) in a cohort of severely injured patients with trauma, when a strict glycemic control protocol (target glucose 80–110 mg/dL) was implemented.

Methods—Data were obtained from a multicenter prospective cohort study evaluating clinical outcomes in blunt injured adults with hemorrhagic shock. Glycemic control was analyzed using the average maximum daily glucose values from postinjury day 2 (>48 hours after injury) to postinjury day 5. PH was defined as a mean glucose value >130 mg/dL, and was categorized into three different severity levels (I–III) based on the distribution of mean 4-day glucose values for the cohort. Separate Cox proportional hazard regression models were then used to determine whether PH was independently associated with mortality and nosocomial infection (NI), and the level of glycemic control that was associated with these poor outcomes.

Results—Overall mortality and NI rates for the study population (n = 862) were 10.8% and 49.6%, respectively. Cox proportional hazard regression revealed that PH was independently associated with almost an 80% higher mortality in patients with mean 4-day glucose values >145 mg/dL (group II) and almost a twofold higher mortality in patients with >165 mg/dL (group III). However, PH was not independently associated with a higher risk of NI at any level. Patients with

PH did have a higher incidence of early multiple organ failure (within first 48 hours: 30.2% vs. 41.6% $p = 0.001$), which preceded the documentation of PH in the majority of patients.

Conclusion—Maintenance of daily maximum glucose values <145 mg/dL was independently associated with a survival benefit after injury. Patients with PH, despite aggressive insulin therapy, had a higher incidence of multiple organ failure and an associated higher risk of mortality. However, the strict glycemic control protocol in the current trauma cohort seems to have prevented the association of PH and infectious complications, which has been documented in prior studies. This analysis further validates the importance of strict glycemic control after injury, and highlights the need for further studies on the mechanism responsible for these findings.

Keywords

Persistent hyperglycemia; Multiple organ failure; Nosocomial infection; Cox proportional hazard regression

Prospective randomized evidence has demonstrated that aggressive management of hyperglycemia in the intensive care unit (ICU) reduces infectious outcomes, organ failure, and mortality, particularly, in elective surgical critical care patients.¹ As a result, it has been proposed that strict glycemic control be incorporated into routine care practices, be measured as an index of the quality of ICU care, and is a primary component of the Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock.^{2,3} More recent evidence suggests, however, that overly aggressive management of hyperglycemia may also be associated with deleterious effects in specific critically ill patient populations.^{4,5} Injured patients represent a specific subset of the critically ill, where appropriate target range glucose values have not been adequately characterized.

A recent analysis by the current authors suggests that early hyperglycemia soon after injury (less than 24 hours) is a marker for the severe physiologic derangement, which occurs in some patients after injury, and is independently associated with a higher risk of multiple organ failure (MOF) and mortality.⁶ The acute stress response that is initiated by significant injury results in an early hormonal cascade that promotes insulin resistance and glucose mobilization.^{7–9} The significance of ongoing persistent hyperglycemia (PH), which occurs beyond the time of injury and this early stress response, has not been adequately characterized.

The purpose of the current analysis was to characterize clinical outcomes associated with different severity levels of PH (greater than 48 hours out from injury) in a cohort of severely injured patients with trauma, where a strict glycemic control protocol was used. We hypothesized that patients with PH would be at a greater risk for the poor clinical outcomes known to be associated with inadequate glycemic control.^{10–13}

METHODS

This study was a secondary analysis of data derived from an ongoing multicenter prospective cohort study. The *Inflammation and the Host Response to Injury Large Scale Collaborative Program* is supported by the National Institute of General Medical Sciences

and is designed to characterize the genomic and proteomic response in injured patients at risk for MOF after traumatic injury and hemorrhagic shock.¹⁴ Standard operating procedures (SOPs) were developed and implemented across all institutional centers to minimize variation in postinjury care, including a strict glycemic control protocol (target glucose 80–110 mg/dL).^{14–18} Endpoints evaluated included in-hospital mortality and nosocomial infection (NI) rates.

Patients admitted to one of the seven institutions, during a 3.5-year period (November 2003 to March 2007), were included in the analysis. Inclusion criteria included blunt mechanism of injury, presence of prehospital or emergency department systolic hypotension (<90 mm Hg) or an elevated base deficit (≥ 6 meq/L), blood transfusion requirement within the first 12 hours, and any body region, exclusive of the brain, with an Abbreviated Injury Score ≥ 2 , allowing exclusion of patients with isolated traumatic brain injury. Patients younger than 16 or older than 90 years, those with cervical spinal cord injury were excluded from enrolment. Patients who died within the first 96 hours were also excluded from all calculations because they did not have complete glucose data available as defined for PH in this analysis.

Clinical data were entered and stored in TrialDb, a web-based data collection platform, by trained research nurses.¹⁹ Integrity of the data was maintained through ongoing curation and external data review by an independent chart abstractor. Although patients were admitted to the ICU, multiple organ dysfunction (MOD) scores for renal, hepatic, cardiovascular, metabolic, hematologic, respiratory, and neurologic systems were determined daily.^{20–22} Maximum daily serum glucose levels (single value per day) and insulin requirements (summed hourly insulin requirements averaged more than 24 hours, units/hr) were recorded, although all nosocomial infectious complications were similarly documented (infection type, culture specimen source, and bacteriology). The diagnosis of NI required specific clinical criteria along with positive-culture evidence. All time variables to the respective outcome event were determined from the day of initial injury, whereas the time to the first NI was used in those patients with multiple infections. Diagnosis of pneumonia required a quantitative culture threshold of $\geq 10^4$ CFU/mL for bronchoalveolar lavage specimens.¹⁵ Diagnosis of a blood stream infection (BSI) required ≥ 2 positive peripheral cultures from different sites, whereas urinary tract infections (UTI) required $>10^5$ organisms/mL of urine.

The strict glycemic control protocol employed allowed for the use of aggressive sliding scale insulin or intravenous insulin infusion. Subcutaneous regular insulin could be used during the initial 4 hours, but patients with levels remaining outside the target range (80–110 mg/dL) at that time would then be started on an insulin infusion. Infusion administration would be titrated to blood glucose levels using a scheduled combination of intravenous bolus insulin and adjustments of the continuous infusion rate. Adjustments would be performed every 2 hours, and a rate of 30 units/hr was the maximum infusion rate used. For glucose levels <60 mg/dL, the infusion would be stopped and dextrose would be administered with levels rechecked 1 hour subsequently. Hourly glucose measurements for patients whose glucose would be difficult to control would be at the discretion of the bedside nurse or physician.

Data are summarized as mean $\pm$ SD, median (interquartile range), or percentage (%). Student's *t* or Mann-Whitney statistical tests were used to compare continuous variables, whereas χ^2 or Fisher's exact test were used for categorical variables. Glycemic control was analyzed using the average maximum daily glucose values from postinjury day 2 (>48 hours post injury) to postinjury day 5. PH was defined as a mean glucose value >130 mg/dL (>50th percentile for study group), and was further categorized based on hyperglycemic severity into three separate groups (increasing severity, I–III). First, crude rate comparison for mortality and NI between those with and without PH was performed. Second, separate Cox proportional hazard regression models were used to determine whether PH was independently associated with the outcomes of interest for each severity range. Patients who died or who were discharged from the hospital without a respective outcome event were censored, thus, adjusting for the effect of early death on subsequent NI rates. NI outcome was then further stratified into pneumonia, BSI, and UTI, and a similar regression analysis was performed for each. Finally, logistic regression modeling was used to determine a propensity score representing the probability of development of NI for each individual patient. Receiver operating characteristic curves were used to assess the accuracy of this propensity score relative to the actual outcome event. The propensity to develop a NI was then correlated with the 4-day mean glucose values for each individual patient, to see if the probability of a NI increased in a linear fashion as average glucose values increased.

Covariates included in the final hazard models were determined using a 5% change in estimates approach.^{23,24} Covariates were placed individually into a regression model with the PH variable. Those covariates that changed the odds ratio for PH by greater than 5% were considered important confounders and were kept in the final model. Potential covariates tested for inclusion into the final models included patient age, gender, Injury Severity Score (ISS), presenting Glasgow Coma Scale, hypotension on arrival (systolic blood pressure <90 mm Hg), presence of comorbidities (history of myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, cirrhosis, diabetes, smoking, and alcoholism), resuscitation (blood, crystalloid, and vasopressor) requirements and base deficit in the first 12 hours, steroid requirement, mean maximum daily insulin requirements (during the 96-hour period, units/hr), 4-day mean calories received via enteral or parenteral nutrition, and requirement of an early (<48 hours) exploratory laparotomy or thoracotomy/sternotomy. Clinically relevant interaction terms were tested and kept in the model if statistically significant ($p < 0.05$). The institutional review board of each participating center approved the cohort study, whereas the institutional review board at the University of Texas Southwestern Medical Center approved this current secondary analysis.

RESULTS

Of the 1,036 patients in the entire trauma cohort, 909 survived beyond 96 hours postinjury with 862 patients having complete glucose data and constituting the study population. Overall mortality and NI rates for the study population were 10.8% and 49.6%, respectively. This group of patients were significantly injured with a mean ISS score of 31 ± 13 , with more than 45% of patients requiring early exploratory laparotomy and more than 42% requiring >6 units of blood transfusion. The mean 4-day maximum daily glucose values for the study group was 132 mg/dL $\pm$ 25 mg/dL (median, 129.6 mg/dL; range, 76–287 mg/dL).

PH was defined as an average 4-day maximum glucose >130 mg/dL and was further categorized into three different severity levels (I–III) based on the distribution of mean glucose values for the cohort (Fig. 1). Three different ranges of hyperglycemia were used to further stratify those patients with PH; 130 mg/dL to 145 mg/dL (group I), 146 mg/dL to 165 mg/dL (group II), and >165 mg/dL (group III). Patients with and without PH were clinically similar in gender, rate of presenting systolic hypotension, ISS, emergency department Glasgow Coma Scale, initial base deficit, and early operative intervention (Table 1). However, those patients with PH received greater amounts of insulin and caloric supplementation, were older, more commonly required early vasopressors, had longer ICU and ventilator requirements, and more commonly had diabetes.

Crude rate comparison revealed that patients with PH had a higher crude mortality rate (no PH 9.8% vs. PH 16.8%, $p = 0.002$) overall; however, there was no statistical difference in overall crude NI rates (no PH 48.7% vs. PH 54.9%, $p = 0.069$). Crude mortality and NI rates at each severity level of PH (I, II, and III) revealed a worsening mortality as average glucose values increased, whereas no trend is seen with NI (Table 2). The difference in crude mortality again highlights the importance of Cox proportional hazard regression, which allowed censoring of patients who died before a respective outcome event, in this analysis.

After controlling for all important confounders, Cox proportional hazard regression revealed that PH was independently associated with almost an 88% higher risk of mortality in patients with mean 4-day glucose values in group II (>145 mg/dL) and almost a twofold higher risk of mortality for patients glucose values in group III (>165 mg/dL), when compared with those without PH. However, at no glucose severity level, was PH independently associated with a higher risk of NI (Table 3). These findings were persistent even when NI was stratified by infection subtype in all glucose level groups (group I hazard ratio for pneumonia 1.15 $p = 0.317$, BSI 0.91 $p = 0.649$, UTI 0.91 $p = 0.622$). To further characterize this lack of association between PH and NI, a propensity score for NI was derived using logistic regression modeling based on all relevant physiologic variables and injury characteristics recorded in the dataset. This allowed for the determination of a probability for NI for each individual patient. This score was highly accurate in predicting NI based on area under the curve determination from receiver operating characteristic curve analysis (area under the curve = 0.90). Plotting this propensity score against each individual patients' average glucose values resulted in a scatterplot as demonstrated in Figure 2. Interpretation of this scatterplot reveals that patients with a high probability of NI could have very adequate glycemic control or very poor control. Similar interpretations can be drawn for those with a low probability of infection. This scatterplot verifies that minimal, if any, trend in NI probability occurs with increasing mean serum glucose values. When the probability of NI was statistically correlated with the patients' mean glucose values, although statistically significant because of our large sample size, negligible correlation existed between mean glucose and the probability of NI (Pearson correlation coefficient, $r = 0.099$, $p = 0.004$).

To further characterize the mortality association with PH, the timing and occurrence of MOF was further analyzed. Because the majority of MOF occurred soon after injury (median time to MOF, 2 days; interquartile range, 2.0–3.0 days), we were unable to look at

MOF as an outcome event because the glucose values for PH, as defined in this analysis, were obtained after the occurrence of MOF in most patients. Crude rate analysis revealed that patients with PH did have a higher incidence of early MOF (within first 48 hours, 30.2% vs. 41.6%; $p = 0.001$). Individual system maximum organ dysfunction scores were then compared across those with and without PH (groups I–III), revealing significantly higher cardiac, respiratory, renal, and hematopoietic organ dysfunction scores as the mean 4-day glucose values increased (Table 4). No difference was found for individual neurologic or hepatic organ failure scores. To see if MOF moderated the mortality risk associated with PH, early MOF within the first 48 hours postinjury (defined by a Marshall MOD score >5) was placed into the mortality regression model. When this was performed, PH at all cut points was no longer significant (group I, $p = 0.639$; group II, $p = 0.102$; group III, $p = 0.085$), suggesting that the mortality associated with PH is, in part, moderated and preceded by a higher incidence of MOF in this severely injured cohort.

DISCUSSION

Strict glycemic control (target glucose 80–110 mg/dL) has been shown to reduce morbidity and mortality in critically ill patients; however, more recent literature suggests that there may be detrimental effects with overly aggressive glycemic control.^{1,4,5} The significance and management of hyperglycemia in patients after injury and the most appropriate target glucose range for injured patients has not been adequately characterized. We have demonstrated that maintenance of average glucose values <145 mg/dL was independently associated with a survival benefit, after controlling for all important confounders. Importantly, the mortality risk associated with PH was not due to a higher rate of NI, at any average glucose value range, in this cohort of severely injured patients. Similarly, the probability of NI shows minimal, if any, correlation with a patients' level of glycemic control. Interestingly, patients with PH did have a higher incidence of MOF, which preceded the documentation of hyperglycemia in the majority of patients, although individual organ failure scores correlated with the severity of hyperglycemia a patient developed. The mortality associated with PH may be due to, in part, this organ failure association. When compared with previous literature, this cohort of patients with trauma was uniformly severely injured and had evidence of hemorrhagic shock, due to such specific inclusion criteria. Our findings are consistent with other recent literature published on both medical and less severely injured patients, where poor glycemic control was associated with a higher mortality.^{25,26} It is not known if even more aggressive attainment of target glucose values would reduce this association with mortality; however, this analysis validates the utility of strict glycemic control after injury and additionally offers insight into how hyperglycemia is associated with poor outcome.

Despite a well-standardized strict glycemic control protocol, a proportion of patients in the current analysis continued to have maximum daily glucose values beyond 96 hours from the time of injury, which were out of the target range. It is unknown whether this is a result of inadequate insulin administration and poor protocol adherence or because of the severe physiologic derangement that occurs after injury. Patients with PH received greater amounts of insulin than those without PH; however, even more aggressive insulin administration may have resulted in a further lowering of the 4-day mean glucose values. The stress response

after acute injury promotes insulin resistance and an overall catabolic state, secondary to the acute effects of corticosteroid, growth hormone, glucagon, and catecholamines (innate or exogenously administered).^{7-9,27-29} It may be that, despite more aggressive insulin management, target range glucose values are not attainable in all patients after injury, particularly, those with significant organ failure. It is plausible that hyperglycemia after injury is simply a pathophysiologic symptom or marker of “metabolic organ failure,” which is proportional to the severity of injury and the ongoing MOD, that an individual patient sustains.⁶ Similarly, hyperglycemia may also be a secondary response associated with our ICU interventions, such as early vasopressor use, to manage these critically ill injured patients. This analysis suggests that patients with and without PH were similarly injured, had similar initial parameters for shock, and had similar resuscitation requirements; however, those with PH had a more severe inflammatory response with resultant end-organ effects, which may have resulted in hyperglycemia rather than occurring as a result of hyperglycemia.

The most probable explanation for a lack of association between PH and NI is the strict glycemic control protocol that was implemented across all centers. Previous literature where strict glycemic control was not used has demonstrated a greater rate of infectious complications in those patients with PH.¹⁰ Patients considered to have PH in the previous literature had serum glucose levels far exceeding 200 mg/dL. Except for a small proportion of patients (10%) in the current analysis, the average 4-day maximum daily glucose values were <165 mg/dL. It is important to realize that the glucose values were recorded as a single daily maximal value. This value by definition represents the worse glucose value and underestimates the level of glycemic control attained for that day. It is conceivable that a less stringent target range may not result in an increase risk for infectious complications, despite the patient’s overall glycemic control shifting to higher levels. Even at mean 4-day glucose values above the 90th percentile (165 mg/dL), PH was not associated with NI. However, this lack of association occurred while a strict glycemic control protocol with a target goal of 80 mg/dL to 110 mg/dL was in place. An explanation for these findings may be that in patients with PH who survive and resolve their early organ dysfunction, acceptable levels of glycemic control are subsequently obtained, which reduce the risk of infectious complications that have been documented previously in patients with PH.¹⁰

This analysis has several potential limitations. First, this study is a secondary analysis of a prospective cohort study looking at the genomic and proteomic response after severe injury and hemorrhagic shock. As with any secondary analysis, data were not recorded to answer the specific hypothesis stated for this study. Glucose values were recorded as a daily single value, which represented the maximum glucose value for that day, whereas hypoglycemic complications were not specifically recorded in the dataset. There was no significant association between patients with mean 4-day glucose values <90 mg/dL and mortality (data not shown); however, because only the maximum daily values were recorded, these findings may not truly reflect patients who had hypoglycemic complications. These represent significant limitations of this analysis. Enrolled patients represent a select subset of patients with trauma, those severely injured with hemorrhagic shock. Although the most severely injured patients who survive are expected to be at greatest risk for developing NI, our results may still not be reproducible and applicable in a less severely injured cohort. Potential

confounding variables, which were not recorded in the prospective data collection and were thus unable to be controlled for in the multivariate regression models, may be responsible for the associations described and the conclusions formulated in this analysis. Finally, we are attributing our findings to implementation of a strict glycemic control regimen. As described previously, the *Inflammation and the Host Response to Injury Large Scale Collaborative Program* used multiple SOPs to minimize variation in postinjury care across institutions. These also included early goal-directed resuscitation,¹⁶ venous thromboembolism prophylaxis, low tidal volume strategy,¹⁷ ventilator-associated pneumonia management,¹⁵ and restrictive transfusion protocols,¹⁸ which were utilized for all enrolled patients. It is possible that one of these alternative SOPs may be partially responsible for our findings, or a combination of protocols are involved. However, our findings do suggest an overall reduction in infectious risk and the strict glycemic control protocol used is most likely responsible for our findings.

In conclusion, average daily maximum glucose values <145 mg/dL after injury are associated with an independent survival benefit. Those with PH have a higher risk of mortality that was not associated with a greater NI risk, but was preceded by a higher incidence of early MOF and worsening individual organ failure scores as the severity of hyperglycemia increased. This analysis validates the utility of strict glycemic control (target glucose 80–110 mg/dL) after severe traumatic injury, but additionally provides insight into how hyperglycemia is associated with detrimental outcome. Further research is needed to decipher if PH is causally related to this mortality risk and if even more aggressive insulin therapy would improve these associated poor outcomes after injury.

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Fig. 1.
Distribution of average 4 day maximum daily glucose values for the entire cohort.

Fig. 2.

Scatterplot of each individuals probability of nosocomial infection versus their average 4 day maximum daily glucose value.

Table 1

Group Comparison for Those With and Without Persistent Hyperglycemia (PH)

	No PH, (n = 461)	PH, (n = 401)	<i>p</i>
Age (yrs)	38.8 ± 17	44.9 ± 19	0.001*
Gender (% male)	65.5	64.4	0.736
Injury severity score	31.2 ± 13	32.0 ± 12	0.390
ED GCS	4.8 ± 4	5.0 ± 4	0.472
Initial base deficit (meq/L)	8.9 ± 5	8.7 ± 5	0.533
ED hypotension (SBP <90 mm Hg)	65.4%	65.8%	0.905
Blood transfusion (>6 units)	46.3%	48.5%	0.522
12 hr crystalloid (L)	12.3 ± 7	11.5 ± 7	0.060
24 hr vasopressors	14.8%	25.6%	0.001*
Mean 4 d max daily insulin (u/hr)	1.3 ± 2	2.2 ± 3	0.001*
Mean 4 d calories received (kcal/d)	661 ± 732	959 ± 867	0.001*
Early exploratory laparotomy	44.0%	41.9%	0.520
Early thoracotomy/sternotomy	5.9%	7.3%	0.403
Steroid requirement	15.2%	26.7%	0.001*
Length of stay (d)	23.9 ± 19	24.5 ± 19	0.601
ICU days	13.6 ± 13	15.7 ± 13	0.014*
Vent days	10.2 ± 12	12.3 ± 11	0.010*
History of MI	2.6%	4.5%	0.128
History COPD	3.5%	4.0%	0.677
History of CHF	0.4%	1.5%	0.103
History of DM	3.0%	12.8%	0.001*
History of liver disease	4.6%	4.8%	0.866
History of renal disease	0.4%	1.8%	0.058

* Statistically significant.

ED indicates emergency department; SBP, systolic blood pressure; GCS, Glasgow Coma Scale; ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; DM, diabetes mellitus.

Table 2

Crude Mortality and Nosocomial Infection Rates for Each Glycemic Control Level

Average 4 d Glucose Range	n	Crude Mortality Rate	Crude NI Rate (%)
No PH (<130 mg/dl)	461	9.7%	47.9
Group I (130–145 mg/dl)	198	9.8%	56.1
Group II (146–165 mg/dl)	104	16.9%	55.6
Group III (>165 mg/dl)	99	30.8%	51.0

PH indicates persistent hyperglycemia; NI, nosocomial infection.

Table 3

Cox Proportional Hazard Regression Model for Mortality and NI

Mortality	Hazard Ratio	<i>p</i>	95% CI
<i>PH</i>			
Group I (130–145 mg/dL)*	0.95	0.850	0.54–1.67
Group II (146–165 mg/dL)*	1.88	0.045	1.02–3.46
Group III (>165 mg/dL)*	1.99	0.018	1.12–3.51
Age	1.02	0.001	1.01–1.03
<i>ISS</i>			
25–41 [†]	1.82	0.050	1.00–3.34
>42 [†]	3.27	0.001	1.74–6.14
Blood transfusion (>6 units)	2.87	0.001	1.80–4.57
Early 48 hr steroid requirement (Y/N)	1.58	0.070	0.96–2.59
Mean 4 d insulin requirement (u/hr)	1.11	0.001	1.05–1.19
Mean 4 d caloric supplementation (kcal/d)	0.99	0.001	0.99–1.00
24 hr vasopressor requirement (Y/N)	3.03	0.001	1.97–4.65
History of diabetes (Y/N)	0.47	0.055	0.21–1.02
<i>NI</i>			
PH	1.06	0.641	0.84–1.32
Group I (130–145 mg/dL)*			
Group II (146–165 mg/dL)*	1.11	0.475	0.82–1.51
Group III (>165 mg/dL)*	1.08	0.618	0.78–1.52
Gender (male vs. female)	1.28	0.019	1.04–1.57
<i>ISS</i>			
25–41 [†]	1.42	0.003	1.12–1.79
>42 [†]	1.61	0.001	1.22–2.11
Early 48 hr steroids (Y/N)	1.58	0.001	1.22–2.05
Mean 4 d insulin requirement (u/hr)	1.03	0.068	0.99–1.07
History of diabetes (Y/N)	0.86	0.429	0.59–1.24
History of liver disease (Y/N)	1.15	0.504	0.76–1.75

* Mean 4 d maximum glucose <50th percentile (serum glucose below 130mg/dl).[†] ISS (1–24).

PH indicates persistent hyperglycemia; NI, nosocomial infection, ISS, injury severity score.

Table 4

Individual System Maximum Organ Dysfunction Scores for Each Glycemic Control Level

	Reference No PH (Mean Glucose < 130 mg/dL), n = 461	Group I (130–145 mg/dL), n = 198	Group II (146–165 mg/dL), n = 104	Group III (>165 mg/dL), n = 99
Cardiac	2.62 ± 1.0	2.94 ± 0.9*	3.07 ± 0.9*	3.10 ± 0.6*
Respiratory	1.64 ± 1.1	1.83 ± 1.1	2.08 ± 1.1*	2.12 ± 1.0*
Renal	0.99 ± 1.1	1.05 ± 0.7	1.13 ± 0.8*	1.31 ± 0.8*
Hematopoietic	0.80 ± 1.1	0.85 ± 0.8	1.00 ± 0.8*	1.21 ± 1.1*

* $p < 0.05$ relative to reference group (no PH).

PH indicates persistent hyperglycemia.