Glucose Variability is Associated With High Mortality After Severe Burn

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Background: Hyperglycemia is associated with increased mortality in the severely injured; intensive insulin protocols reduce mortality, improve wound healing, and decrease susceptibility to infection. High glucose variability creates challenges to glycemic control and may be a marker of poor outcome. We wondered whether glycemic variability alone might identify patients at higher risk of death.

Methods: Burn patients admitted in 2005 with >20% total body surface area burned, ≥100 glucose measurements, and one hypo- and hyperglycemic event were included in the analysis; all were treated with intensive insulin (glycemic target: 80–110 mg/dL). Glycemic variability was the sum of percent excursions (defined as values <80 mg/dL or >110 mg/dL); variability above the mean was considered high.

Results: Individual average variability in the 49 subjects was 50% ± 8% (range, 30–65%); the average number of glucose measurements per patient was 840 (range, 103–5314). Percent excursions in those with high (n = 26) compared with low (n = 23) variability scores was 56% ± 6% and 43% ± 5% ($p < 0.001$), respectively. No difference was found between groups in injury severity score, age, total body surface area burned, full thickness burns, gender, or inhalation injury. Both groups were similar for days of ventilator support, intensive care unit stay, and hospital stay. Mortality in the highly variable group was twice that of the less variable group (50% vs. 22%, $p = 0.041$).

Conclusions: High glucose variability (>50% of values outside 80–110 mg/dL) is associated with increased mortality in the severely burned. Individuals with frequent excursions outside the glucose target range of 80 mg/dL to 110 mg/dL are at greater risk of death.

Key Words: Glucose variability, Glycemic control, Intensive insulin, Trauma, Hyperglycemia, Mortality, Critical care.

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The association of hyperglycemia and poor outcomes in severe trauma is becoming increasingly recognized[1–10]; improvements have been demonstrated in multiple studies when glycemic control is achieved with intensive insulin protocols.[11–13] In burned patients, hyperglycemia is linked to bacteremia and fungemia, reduced skin graft take, urinary tract infections, immune dysregulation, increased catabolism, and higher mortality.[8,9,12] Intensive insulin therapy is beneficial in this population, although the specific mechanisms by which these improvements are seen continue to be a matter of debate. Some investigators maintain that control of hyperglycemia is the primary mechanism and propose that glucose toxicity may be due to the effect of excess glucose concentration in cells that use insulin-independent glucose transporters (GLUT), as well as the effects of reactive oxygen species generated by glycolysis and oxidative phosphorylation.[14,15] Others suggest that the benefits seen may also be due to effects of insulin on inhibition of tumor necrosis factor (TNF)-α, macrophage inhibitory factor, myocardial function, and nutrition and protein metabolism.[16,17] In burned patients, insulin has been shown to reduce the systemic inflammatory response, improve net protein balance, and reduce enhanced catabolism associated with hyperglycemia.[18–20] Recently, investigators noted that absolute glucose level may not be the only important parameter in glycemic regulation. Two studies in largely nontrauma populations demonstrated that increased cycling between hyperglycemic and hypoglycemic extremes is associated with greater risk of mortality in critically ill patients.[20,21] We wondered whether a similar association between high blood glucose variability and poor outcomes exists in the severely injured.

PATIENTS AND METHODS

Records from patients admitted to a single burn center in 2005 were reviewed. Patients with 20% total body surface area (TBSA) burns or greater, ≥100 glucose measurements, and at least one hypo- and hyperglycemic event (serum glucose <80 mg/dL) were included in the analysis. Approval for the study was obtained from the Institutional Review Boards at Brooke Army Medical Center and the University of Texas Health Science Center, San Antonio.

Subjects were treated with a nurse-driven intensive insulin protocol (glycemic target: 80–110 mg/dL). Treatment with intravenously administered human regular insulin (1 U/mL; Novo Nordisk, Princeton, NJ) was initiated, when blood glucose surpassed 120 mg/dL, at the dose of 1 U/h for

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glucose 120 mg/dL to 150 mg/dL, 2 U/h if glucose was between 151 mg/dL to 200 mg/dL, and 4 U/h if initial glucose surpassed 200 mg/dL. The intravenous insulin infusion was titrated according to the following parameters: (1) insulin was held and 25 mL of 50% dextrose (Hospira, Lake Forest, IL) was given for glucose level <60 mg/dL; (2) glucose between 60 mg/dL and 79 mg/dL resulted in cessation of the infusion until glucose normalized, after which insulin infusion was resumed at 50% of the previous rate; (3) glucose between 80 mg/dL and 110 mg/dL prompted adjustment of the infusion by 0 units to 0.5 units only in response to increasing and decreasing trends; and (4) glucose levels between 111 mg/dL and 150 mg/dL, 151 mg/dL and 200 mg/dL, and 201 mg/dL and 250 mg/dL triggered rate increases of 0.5 units, 1 units, and 2 units, respectively. Physician assistance was sought for glucose level >250 mg/dL or <60 mg/dL.

Glucose values were measured using point-of-care glucose analyzers (SureStepFlexx, Lifescan, Milpitas, CA) on an hourly basis. This instrument uses photometric quantification of a color change produced as a byproduct of the reaction catalyzed by glucose oxidase as a surrogate for glucose concentration. All bedside measurements obtained during the hospital stay were examined and specific values outside of the range tabulated as a percentage of the total. The number of measurements per subject was indexed per day, and comparisons made between group designations are defined below. Glycemic variability was the percent excursions (or fraction of the whole) above and below target with the total number of measurements as the denominator. While this study was ongoing, systematic error in bedside glucose measurement was discovered, and a formula to correct the error was developed. This correction formula was applied to bedside glucose data before analysis (unpublished data and Ref. 22).

Data were collated and analyzed first by frequency distribution. The data were bisected into groups with low and high variability or the fraction of values outside the desired range. Demographics of the groups including injury severity score (ISS), TBSA burned, and TBSA full-thickness burns, age, inhalation injury, preexisting diabetes mellitus, and significant diagnoses while in the hospital including pneumonia and other identified infections, renal failure, sepsis, and coagulopathy were analyzed followed by an assessment of mortality. Inhalation injury was diagnosed by the attending surgeon based on a history consistent with smoke inhalation with findings of airway erythema and damage on bronchoscopy. Diabetes mellitus was defined by preinjury prescription for insulin or an oral hypoglycemic agent. Further analyses were done for the fraction of values above the target range and again for the fraction of values below the desired range. Groups were compared by Student's t test if variables were quantitative and with χ^2 if qualitative; tests were two sided in all cases. Significance was set at $p < 0.05$.

RESULTS

Forty-nine subjects met inclusion criteria. The mean glucose level measured in these subjects was 97 ± 1. For the entire study population, the values within the desired range were 50% ± 1%, time below was 26% ± 1%, and time above was 24% ± 1%. Therefore, the variability or percentages of measures outside the desired range for the whole group was 50% ± 1%. When the variability or percentages of measures outside the desired range for each subject was considered and categorized, the frequencies were normally distributed (Fig. 1). Then, to compare those with more variability or time out of range with those with less for eventual overall outcomes collected at the end of hospitalization, such as mortality, the entire population was bisected at the mean value; thus two groups were identified. The first consisted of subjects with glucose variability scores below the mean, and the second of those with scores above. No differences were identified between groups in typical prognostic indicators, such as ISS,

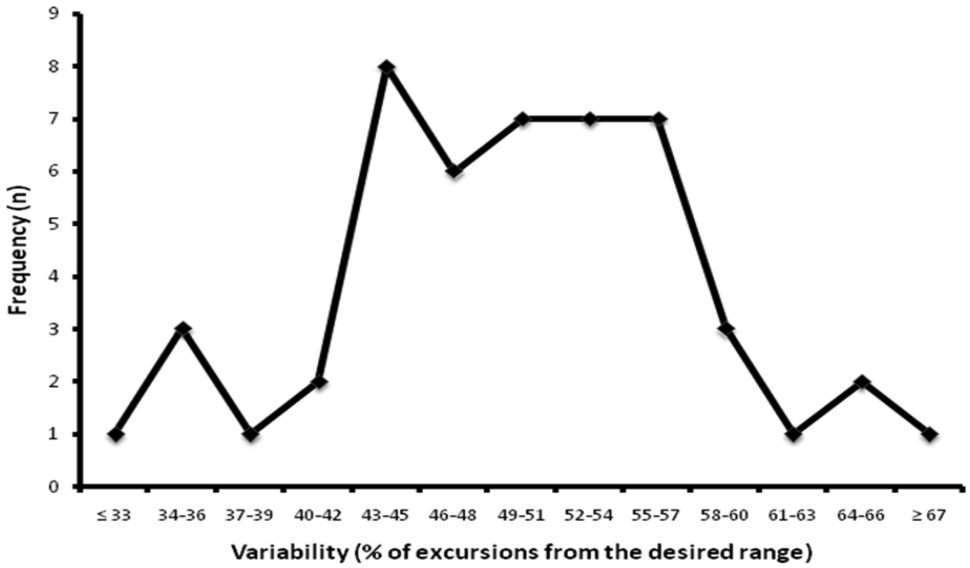

Figure 1. Frequency distribution of subjects with percent of excursions from the desired range during the entire hospitalization as a discrete variable for the 49 subjects.

total or full-thickness body surface area burns, age, or inhalation injury (Table 1). One subject in the low-variability group had preexisting diabetes mellitus. All subjects were treated with an intensive insulin protocol targeted to keep blood glucose level within 80 mg/dL to 110 mg/dL. The number of glucose measurements indexed to days on continuous insulin therapy was not different between groups (20 ± 11 values/d for the low-variability group vs. 20 ± 18 values/d for the high-variability group).

The variability score defined above was different between the groups, with less variability in the low-variability group (n = 23, 43% ± 5%) and more in the high-variability group (n = 26, 56% ± 6%, $p < 0.001$) by design. Mean glucose also differed between groups (94 mg/dL ± 4 mg/dL and 101 mg/dL ± 8 mg/dL, respectively, $p < 0.001$), however, both values were within target range. Standard deviation (SD) calculated per individual, then averaged for the population, has been used as a surrogate for variability.[23] In our population, SD values were significantly higher in the high-variability group (22 mg/dL in the low group and 31 mg/dL in the high group, $p < 0.001$), confirming that our groups were different with respect to variability despite mean values within the glucose target that are clinically indistinguishable from one another.

Direction of glycemic excursions was not distributed equally. Percent measurement of blood glucose below target was similar between groups, however, percent blood glucose values within the range of 80 mg/dL to 100 mg/dL was lower in the high group (57% ± 5% in the low group vs. 44% ± 5% in the high group, $p < 0.001$) and those above 110 mg/dL were significantly greater (30% ± 9% vs. 18% ± 7%, $p < 0.001$) (Fig. 2). Hyperglycemia thus contributed more to the difference in variability between groups than hypoglycemia. However, when we repeated the above analysis for only the variability above the range (or the fraction of values above 100 mg/dL), we found that the frequency distribution no longer followed a Gaussian pattern but instead was skewed to the low percentage range. Frequency analysis of low variability (or the fraction of values below 80 mg/dL), however, continued to reveal a normal distribution (Fig. 3).

Mortality in the highly variable group was twice that of the low (50% vs. 22%, $p = 0.041$) when the fraction above and below 80 mg/dL to 110 mg/dL was considered in aggregate. When the population was bisected into groups based on the mean of the fraction of values above 100 mg/dL or high variability, the groups were different in terms of the percentage above the range as expected (16% ± 5% vs. 33% ± 6%, $p < 0.001$), however, mortality was no different between groups ($p = 0.31$). A similar analysis for the fraction of values below 80 mg/dL or low variability revealed a similar planned difference in groups for the mean fraction (20% ± 4% vs. 31% ± 7%, $p < 0.001$), but mortality was still not different between groups. The p value for mortality in this analysis was 0.07, suggesting that hypoglycemia may have more of an influence on mortality than hyperglycemia. Determining causality for this difference when considering variability in aggregate is beyond the scope of this study, however, these data are intriguing given that mean glucose is within target for both groups. One explanation is that a preponderance of oscillations in either direction taken during the entire hospitalization is associated with conditions that lead to poor outcomes. Mortality was the major outcome variable that differed significantly between groups. All deaths in the low-variability group were due to multiorgan failure (5 deaths in 23 subjects) and 11 deaths due to multiorgan failure with 2 from cardiovascular failure in the high-variability group (13 deaths in 26 subjects). When major diagnoses after hospital discharge were considered, including pneumonia and other identified infections, renal failure, sepsis with hypotension, and coagulopathy, sepsis was statistically different between groups (Table 2) in congruence with the mortality outcome.

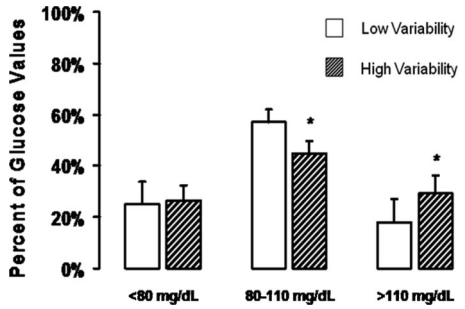

Figure 2. Percent of point-of-care glucometer blood glucose measurement in and out of range for low and high variability groups, *$p < 0.001$.

TABLE 1. Group Demographics

	Low Variability	High Variability
ISS	36 ± 16	34 ± 13
Total body surface area burned (%)	48 ± 23	48 ± 17
Total full-thickness burned (%)	37 ± 27	40 ± 21
Age (yr)	33 ± 16	37 ± 17
Inhalation injury (Y/total) (%)	13/23 (57)	11/26 (42)
Hospital length of stay (d) (survivors only)	79 ± 56	76 ± 44
ICU length of stay (d)	49 ± 53	33 ± 27
Ventilator days	31 ± 43	12 ± 16

DISCUSSION

Surgical intensive care units (ICUs) have adopted intensive insulin protocols in increasing numbers, propelled by the mortality benefits demonstrated in a large study by Van den Berghe et al.[11] Burn ICUs have followed suit, yet little is known about the mechanism of how insulin improves survival. Glycemic regulation in critical care and in burned patients remains largely uncharacterized. Poor outcomes associated with hyperglycemia in severe trauma have been documented by multiple investigators,[1–10,12] and a few noted that outcomes improve with better glycemic control.[12,13] To date, the causal relationship to explain this phenomenon has yet to be identified, however, several theories have emerged. Van den Berghe and coworkers[14,15] advanced the notion that glycemic control is fundamental to explain mortality benefits and that the responsible mechanism most likely relates to

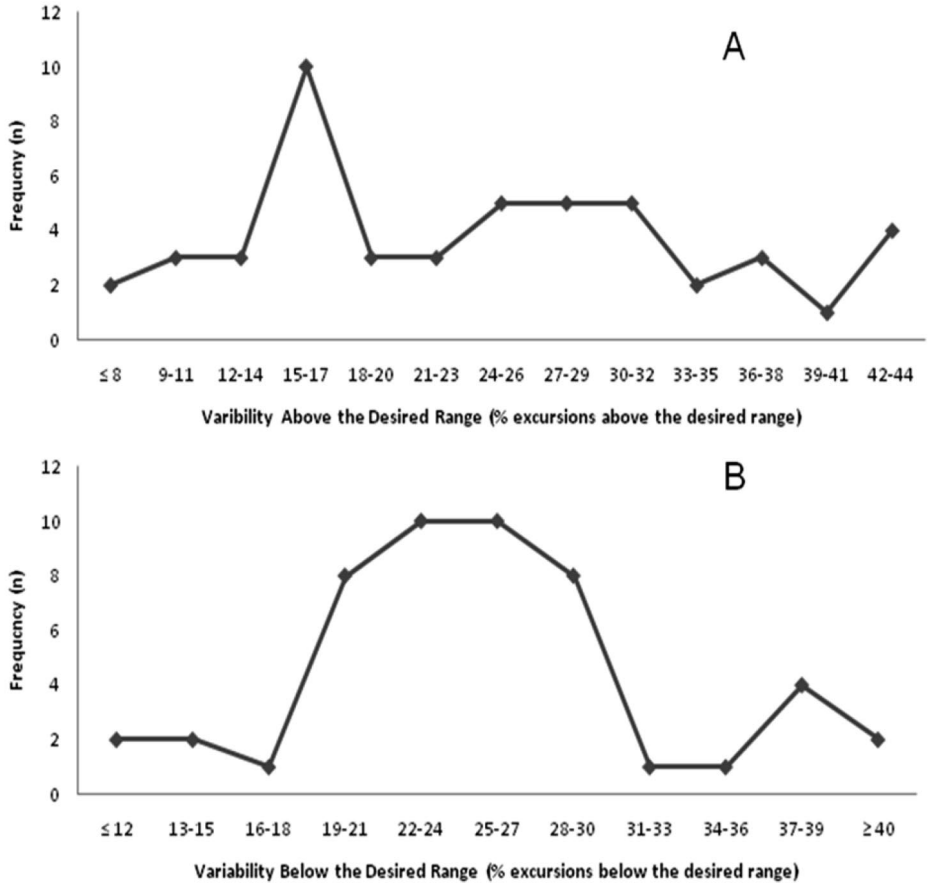

Figure 3. Frequency distribution of subjects with percent excursions above the desired range (*A*) and below the desired range (*B*) as discrete variables.

TABLE 2. Hospital Discharge Diagnoses (%)

	Low Variability	High Variability	*p*
Pneumonia and other defined infections	48	58	0.21
Renal failure	9	15	0.15
Sepsis with hypotension	26	58	<0.001
Coagulopathy	9	8	0.51

improved ability to fight infection and prevent systemic inflammatory response syndrome. This suggests that the inhibitory effect of hyperglycemia on innate and adaptive immunity explains much or all the effect. Other investigators wonder whether the effects of insulin on substrate muscle metabolism and its role in attenuating the catabolic response may play an additional role.[8,18,19] This debate focuses on hyperglycemia versus hypermetabolism as the major target of therapy, but it cannot be resolved until we better understand what constitutes optimal glucose control in the critically injured patient.

The presence of diurnal variations in blood glucose and cortisol levels in normal subjects is well established. Variability in cortisol release is blunted in burned patients,[24] leading to speculation that a similar flattening of the glucose delivery curve may occur. Whether the diurnal glucose variation seen in healthy subjects persists in burned patients is currently not known nor do we know if such a pattern is desirable. Patterns that become abnormally variable, on the other hand, are associated with poor outcomes among diabetics.[25,26] Muggeo et al.[27] reported in a 10-year study that fasting plasma glucose variability is an independent predictor of mortality in diabetic outpatients. Variability in glucose concentration increases apoptosis of many cell types, and this may also contribute to deleterious effects.[28]

Until recently, glucose variability has been largely ignored as a therapeutic target in critical care, and its role in the severely injured has never been reported. In an intriguing article, Finney et al.[29] compared glycemic control with insulin administration and specifically stated that glucose variability was included in the analysis; no conclusions were offered, however, on its role in determining outcome. Instead, the authors joined the debate over whether hyperglycemia versus hypoinsulinemia is most important in improving outcomes in surgical critical care, noting that patients who received more insulin to achieve an equal level of glycemic control had worse outcomes. An alternate interpretation is that increased glucose variability is the cause for the associ-

ation with a greater risk of death, whereas the increase in insulin requirement is a secondary effect.

The role of glucose variability as a harbinger of increased morbidity and mortality is supported by two other recent studies. Wintergerst et al. retrospectively analyzed three parameters in critically ill children: hypoglycemia, hyperglycemia, and glucose variability.[29] All were linked with adverse outcomes, and multivariate analysis showed that variability was most strongly associated with elevated mortality.[21] A second multicenter review used SD of mean glucose as a surrogate for variability in adults and found a significant increase in nonsurvivors.[22] Mean glucose was also significantly higher in nonsurvivors, however, no specific insulin protocol was in place for either study.

This study is the first to examine the role of glucose variability in the severely injured. We examined a population with a large number of measurements to assure adequate representation of the phenomena of interest. Such patients by design will be in the ICU for a significant period of time and are historically at a high risk of mortality, our primary endpoint. We chose to divide the subjects into those with low and high variability (or time outside the desired range), with a division at the mean for all subjects. Analysis of variability per subject by our definition followed a normal distribution, and thus bisecting the group at the mean would not introduce bias.[30] Subjects were uniformly treated with an intensive insulin protocol, and mean glucose in both high and low variability groups were within target. Given that no differences were found between groups in ISS, burn surface area, age, gender, inhalation injury, or preexistent diabetes mellitus, the doubled mortality in the high-variability group is compelling evidence that a causative relationship between the two may exist. The argument is made stronger by the fact that a uniform insulin protocol was in place, and mean variability was significantly different between groups. The average of SD calculated per subject was significantly higher in the high variability group, providing further evidence that individual glucose measurements varied considerably despite normal mean glucose values. Hypoglycemia contributed less to variability differences than glucose elevation.

In addition to the mortality difference, we also found a difference between groups for the diagnosis of sepsis with hypotension, which was more common in the high variability group. The presence of an association between sepsis and glucose variability has been previously described,[31] however, the nature of the relationship is poorly understood. In the study presented here, the variability score was calculated using data averaged during the entire hospital stay, thus we cannot define when sepsis occurred in relation to increased or decreased variability. Further characterization of the relationship of variability to sepsis is therefore outside the scope of this study, and from these data, we cannot do more than conclude that individuals with greater variability scores were also more likely to experience a septic event during their hospital stay. Questions that intuitively arise, however, are whether the variability seen during the hospitalization was due to sepsis or caused by sepsis. In the former case, the increased variability is assumed to result from the septic event and constitutes a marker of sepsis. In the latter, it precedes the septic event, increasing the patient's susceptibility to infectious complications, thus better control of glucose variability through more aggressive insulin therapy or other treatments may prevent septic episodes. We think that prospective studies with greater statistical power should be considered to answer these questions.

In contrast to glucose variability, scientists have more thoroughly examined the relationship of sepsis to glycemic dysregulation as a whole. The association between extremes of glycemia and septicemia is reported, but again, the exact nature of that relationship is not fully described. Recent animal studies have identified a highly conserved family of transcription factors, Forkhead box-o (FOXO), that are active in sepsis and are associated with hyperglycemia, decreased insulin secretion, and degradation of muscle protein, glycogen, and lipids.[32] These findings suggest that hyperglycemia is a response to septic insults resulting in stress-induced substrate mobilization. The relationship to glucose variability is not a direct one as hyperglycemia, if constantly present, would not necessarily increase the variability of glucose measurements per se. The animal data do, however, suggest a potential cause of variability, which would paradoxically be more evident with increased use of insulin therapy for hyperglycemia in critically ill patients. Activation of the insulin receptor, and subsequently of the Akt/protein kinase B pathway, inactivates FOXO transcription factors through nuclear exclusion, initially reducing substrate mobilization and contributing to a reduction in hyperglycemia. The increase in FOXO1 activity associated with sepsis is thus reversed by insulin, however, FOXO transcription factors also act upstream to phosphorylate Akt and attenuate the response to insulin signaling. The result is increased insulin resistance and consequent hyperglycemia.[33] A resulting pattern of fluctuation as the insulin dose is adjusted could explain the increased variability seen in this study. Although the published data are compelling, confirmation of the proposed model would require further research and is beyond the scope of this study.

The data presented here were collected as part of a retrospective study and have all the attendant limitations; causation cannot be demonstrated, and the influence of factors not reviewed cannot be excluded. The timing of glucose measurement was not investigated, and increased measurement during glycemic excursions is a well recognized occurrence. Inflation of the variability effect reduces the likelihood of seeing a mortality effect, however, rather than the reverse. Normal glucose variability in healthy volunteers has been demonstrated, as was mentioned above. No attempt was made to characterize the presence or absence of normal glucose variability or to differentiate its effects from those of variability that is presumed to be abnormal. Our sample size was small and may be the reason that differences in length of stay and ventilator support days were not seen.

This study demonstrates a significant association between glucose variability and mortality after severe trauma. Because a retrospective study cannot demonstrate causation, it would be premature to use these data to recommend

changes in clinical care at the bedside. Clinicians should be aware that glucose variability is associated with higher mortality, and frequent oscillations in glucose may be considered a warning signal that the patient requires close monitoring. Similarly, because glucose variability is associated with sepsis (although the timing is unknown), difficulty in managing glucose may indicate that sepsis could be imminent. The mechanism underlying these associations is not known and warrants further investigation. We speculate that these changes may be associated with deranged insulin signaling associated with clinical decompensation or changes or both in glucose or insulin availability and organ function during similar time periods. Normal patterns in glucose variability in relation to insulin or glucose availability and disposal as they apply to the critically injured patient may need to be described to understand how and why abnormal variability is detrimental. Our analysis demonstrates that mean glucose within the narrow target of 80 mg/dL to 110 mg/dL can still be associated with high mortality in severe trauma, and thus more careful monitoring of glycemic status is required.

In summary, >50% glucose variability is associated with significantly higher mortality in the severely burned and may identify patients at higher risk of death. Mean glucose in the normoglycemic range is not a guarantee of better outcome. Intensive insulin protocols improve glucose control; however, their role in improving glucose variability is unknown.

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