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Variability of Blood Glucose Concentration and Short-term Mortality in Critically Ill Patients

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Background: **Intensive insulin therapy may reduce mortality and morbidity in selected surgical patients. Intensive insulin therapy also reduced the SD of blood glucose concentration, an accepted measure of variability. There is no information on the possible significance of variability in glucose concentration.**

Methods: **The methods included extraction of blood glucose values from electronically stored biochemical databases and of data on patient's characteristics, clinical features, and outcome from electronically stored prospectively collected patient databases; calculation of SD of glucose as a marker of variability and of several indices of glucose control in each patient; and statistical assessment of the relation between these variables and intensive care unit mortality.**

Results: **There were 168,337 blood glucose measurements in the study cohort of 7,049 critically ill patients (4.2 hourly measurements on average). The mean ± SD of blood glucose concentration was 1.7 ± 1.3 mM in survivors and 2.3 ± 1.6 mM in nonsurvivors ($P < 0.001$). Using multiple variable logistic regression analysis, both mean and SD of blood glucose were significantly associated with intensive care unit mortality ($P < 0.001$; odds ratios [per 1 mM] 1.23 and 1.27, respectively) and hospital mortality ($P < 0.001$ and $P = 0.013$; odds ratios [per 1 mM] 1.21 and 1.18, respectively).**

Conclusions: **The SD of glucose concentration is a significant independent predictor of intensive care unit and hospital mortality. Decreasing the variability of blood glucose concentration might be an important aspect of glucose management.**

ACUTE hyperglycemia associated with insulin resistance is common in critically ill patients.[1,2] Acute control of blood glucose is considered important.[3–8] Recently, intensive insulin therapy (target glucose concentration of 4.4–6.1 mM) was reported to reduce mortality and morbidity in selected surgical patients.[9] Therefore, decreasing mean blood glucose concentration may improve patient outcome in the critical care setting. Intensive insulin therapy was also associated with a reduction in the SD of blood glucose concentration, an accepted measure of variability (1.05 mM in intensive insulin therapy group *vs.* 1.83 mM in conventional control group; relative reduction of 42%). However, the benefit of intensive insulin therapy was ascribed to a reduction in the mean glucose concentration rather than minimization of its variability. Currently, there is no information on the possible significance of variability in glucose concentration. This is unfortunate, because fluctuations in glucose concentration might be pathophysiologically important, especially from a neurologic perspective,[10] and possibly as important as sustained hyperglycemia. We hypothesized that the SD (a parameter commonly used to describe variability of measurement) of blood glucose concentration would independently predict mortality in a population of critically ill patients.

We tested this hypothesis in patients admitted to the intensive care units (ICUs) of four hospitals and compared the predictive ability of SD with other indices of blood glucose control: mean glucose concentration (Glu_{Ave}), maximum blood glucose concentration during ICU stay (Glu_{Max}),[11,12] and blood glucose concentration on admission (Glu_{Adm}).[13,14] We further compared the mean and SD of blood glucose concentration during the first 24 h ($Glu1_{Ave}$ and $Glu1_{SD}$), because glucose concentration on the day of admission has been shown to be an accurate predictor of ICU patient outcome.[15,16]

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Materials and Methods

The data collection for this study was part of a preexisting quality assurance activity, approved by local institutional ethics committees. The Austin Hospital Ethics Committee (Heidelberg, Victoria, Australia) approved this investigation.

Study Population and Data Sources

The current study was conducted as a multicenter retrospective observational study. Hospitals A and B are tertiary public hospitals in Melbourne, Australia. Hospital C is a large private hospital in Melbourne. Hospital D is a tertiary public hospital in Sydney. All patients admitted to these ICUs from January 2000 to October 2004 were included. Time frames in each hospital were fixed according to time periods within which reliable and

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complete blood glucose data and patient characteristics could be extracted.

The blood glucose data used for this study were stored electronically by the Bayer Rapidlab blood gas machine systems (Bayer Diagnostics Rapilab 865; Bayer Australia, Sydney, Australia) and captured and retrieved using the Bayer Rapidlink® blood gas information management system (Bayer Diagnostics Rapilab 865).

Age, sex, requirement of mechanical ventilation, the reason of ICU admission, and the Acute Physiology and Chronic Health Evaluation II score[17] were obtained from the clinical databases of each ICU, which had been collected prospectively by trained data collectors. After collection and entry, the data were corrected for logical errors and sent to a central repository where they were further checked before acceptance. Coding for admission diagnosis was by means of a modified Acute Physiology and Chronic Health Evaluation III system used by the Australian and New Zealand Intensive Care Society. The information on clinical outcomes was collected independently by the Australian and New Zealand Intensive Care Society system as well as by each hospital. Audit of mortality and unit-based outcomes is ongoing for all four institutions.

Blood Glucose Indices

In each patient, the mean and SD of blood glucose concentration during ICU stay (Glu_{Ave} and Glu_{SD}) were calculated as arithmetical mean and SD of the entire set of measurements during ICU stay. To evaluate relative variability, the coefficient of variability ($Glu_{CV} = Glu_{SD} * 100/Glu_{Ave}$) was also calculated for each patient. The maximum blood glucose in each patient (Glu_{Max}) was determined as the highest values during ICU stay. The glucose measurement on admission (Glu_{Adm}) was defined as the first glucose measurement after ICU admission.

We also calculated the mean, SD, and maximum of blood glucose concentration for each ICU day.

Diabetic Patients

Only two hospitals (A and D) had collected prospective information to identify diabetic patients. We used this subcohort to test the effect of diabetes on outcome and the relation between blood glucose control and outcome in diabetic patients.

Blood Glucose Measurements

Blood glucose measurements were performed by the blood gas analyzer in each hospital. Blood samples were collected in heparinized blood gas syringes. The analyzer measured whole blood samples at 37°C. Trained nursing staff performed all blood analysis. All maintenance was regularly reviewed and certified and complied with Australian national laboratory standards. All maintenance was according to manufacturers' specifications.

Approach to Insulin and Glucose Control

There was no specific protocol for the use of insulin or any specific target for glucose control during the study across the four hospitals. Commencement of insulin was decided by the ICU medical staff, and adjustment of insulin dose was by ICU nurses with a general goal of maintaining glucose levels between 6 and 10 mM.

Statistical Analysis

Data are presented as mean with SD, unless otherwise indicated. The primary outcome measure was ICU mortality. The secondary outcome measure was hospital mortality. Patients were separated into ICU survivors and nonsurvivors. Differences were assessed using the Student *t* test, chi-square test, and one-way analysis of variance. The area under the receiver operator characteristics (ROC) curves was calculated for seven blood glucose control indices (Glu_{Ave}, Glu_{SD}, Glu_{CV}, Glu_{Max}, Glu_{Adm}, $Glu1_{Ave}$, and $Glu1_{SD}$). The estimate of the area under the ROC curve was computed using a binegative exponential model and asymptotic 95% confidential intervals (SPSS 12.0; SPSS Inc., Chicago, IL). Curves were compared using their 95% confidence intervals.

We performed multivariate logistic regression analysis entering site, age, sex, Acute Physiology and Chronic Health Evaluation II score, category of ICU admission (cardiac or vascular diseases, thoracic or respiratory diseases, trauma, neurologic diseases, gastrointestinal tract diseases, and other), and surgical or medical admission, as well as six glucose indices (Glu_{Ave}, Glu_{Max}, Glu_{Adm}, $Glu1_{Ave}$, $Glu1_{SD}$, and either Glu_{SD} or Glu_{CV}), independent variables, and either ICU or hospital death as the dependent variable. All variables showed significance in univariate analysis. A backward stepwise elimination process was then used to remove covariates whose multivariate *P* value was greater than 0.15. The final model contained all predictors of mortality with a multivariate $P < 0.15$. In all multivariate logistic regression analyses, we assessed (1) the discrimination of the model with the percentages of appropriately classed patients in the final model, (2) the calibration of the model with Hosmer-Lemeshow test, and (3) the role of multicollinearity using the Variance Inflation Factor. Every Variance Inflation Factor was less than 5, indicating absence of severe multicollinearity.

A *P* value less than 0.05 was considered to indicate statistical significance. All statistical analysis was performed using a commercially available statistical program (SPSS 12.0).

Results

We studied 7,049 patients, including 318 readmissions. These patients had 168,837 blood glucose measurements, with a mean value of 8.4 ± 2.7 mM (glucose measured every 4.2 h on average).

Table 1. Clinical Characteristics and Glucose Indices of the Study Cohort

	Hospital A	Hospital B	Hospital C	Hospital D	Total
Number of patients	3,653	1,192	904	1,300	7,049
Male sex	2,219 (61%)	660 (55%)	617 (68%)	791 (61%)	4287 (61%)
Age, yr	61 ± 18	55 ± 19	69 ± 12	61 ± 18	61 ± 18
APACHE II score	17 ± 7	18 ± 9	12 ± 5	20 ± 8	17 ± 8
Mechanical ventilation rate	2,114 (58%)	567 (48%)	240 (27%)	1,300 (100%)	4,221 (60%)
Surgical patients	1,459 (40%)	291 (24%)	715 (79%)	581 (45%)	3,046 (43%)
ICU mortality	412 (11%)	168 (14%)	19 (2%)	237 (18%)	836 (12%)
Hospital mortality	835 (23%)	357 (30%)	37 (4%)	329 (25%)	1,558 (22%)
ICU stay, days	3 [2–5]	4 [3–6]	3 [3–4]	5 [3–11]	4 [2–6]
Hospital stay, days	17 [9–37]	12 [6–25]	10 [8–14]	20 [10–37]	15 [8–32]
Study periods	Jan 2000–Dec 2003	Jan 2002–Oct 2004	Feb 2003–Jun 2004	Dec 2000–Jun 2003	Jan 2000–Oct 2004
Number of measurements	84,610	31,201	12,024	40, 502	168,337
Mean glucose, mM	8.2 ± 2.1	8.1 ± 2.3	7.7 ± 1.5	7.8 ± 1.8	8.0 ± 2.0
SD of glucose, mM	1.8 ± 1.4	1.7 ± 1.3	1.6 ± 1.1	1.6 ± 1.1	1.7 ± 1.3
Coefficient of variation of glucose, %	21 ± 5	20 ± 12	20 ± 12	20 ± 11	21 ± 12
Maximum glucose, mM	21.3 ± 12.5	11.7 ± 5.1	10.5 ± 3.8	11.4 ± 4.4	11.7 ± 4.9
Admission glucose, mM	9.0 ± 4.3	9.2 ± 4.7	7.9 ± 2.9	8.4 ± 3.7	8.8 ± 4.1
Mean glucose during first 24 h, mM	8.3 ± 2.6	8.0 ± 2.3	7.9 ± 1.7	8.3 ± 2.7	8.2 ± 2.5
SD of glucose during first 24 h, mM	1.7 ± 1.6	1.6 ± 1.6	1.5 ± 1.1	1.6 ± 1.4	1.6 ± 1.5

Data are expressed as mean ± SD, number (percentage), or median [interquartile range].
APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit.

Table 1 shows patient characteristics and glucose control details for each study ICU and for the total cohort. The mean Glu_{SD} for all patients was 1.7 mM, and the mean Glu_{CV} was 21%.

Clinical characteristics and glucose indices for ICU survivors and nonsurvivors are shown in table 2. Glu_{SD} was significantly different between ICU survivors and nonsurvivors (1.7 ± 1.3 and 2.3 ± 1.6 mM, respectively; $P < 0.001$). Glu_{CV} was also significantly different between ICU survivors and nonsurvivors (20 ± 12 and 26 ± 13%, respectively; $P < 0.001$).

Figure 1 shows the daily change in mean, SD, and maximum blood glucose concentrations during the first 14 days. They all changed significantly over time ($P < 0.001$). The highest values for the three glucose indices ($Glu1_{Ave}$, $Glu1_{SD}$, and maximum blood glucose on admis-

Table 2. Comparison of ICU Survivors and Nonsurvivors

	Survivors (n = 6,213)	Nonsurvivors (n = 836)	*P* Value
Male sex	3,807 (61%)	480 (57%)	0.03
Age	61 ± 18	65 ± 16	< 0.001
APACHE II score	16 ± 7	27 ± 8	< 0.001
Mechanical ventilation rate	3,509 (57%)	712 (85%)	< 0.001
Surgical patients	2,831 (46%)	215 (26%)	< 0.001
Reason for ICU admission			< 0.001
Cardiac and vascular	1,342 (22%)	244 (29%)	
Thoracic and respiratory	1,228 (20%)	152 (18%)	
Trauma	451 (7%)	13 (2%)	
Neurologic	665 (11%)	130 (16%)	
Gastrointestinal tract diseases	1,313 (21%)	84 (10%)	
Other	1,214 (20%)	213 (26%)	
ICU stay, days	4 [2–6]	4 [2–7]	< 0.001
Hospital stay, days	16 [9–34]	6 [3–14]	< 0.001
Duration of mechanical ventilation, h	26 [12–88]	39 [17–113]	< 0.001
Mean glucose, mM	7.9 ± 1.9	8.8 ± 2.9	< 0.001
SD of glucose, mM	1.7 ± 1.3	2.3 ± 1.6	< 0.001
Coefficient of variation of glucose, %	20 ± 12	26 ± 13	< 0.001
Maximum glucose, mM	11.5 ± 4.8	13.6 ± 5.4	< 0.001
Admission glucose, mM	8.7 ± 4.0	9.5 ± 4.9	< 0.001
Mean glucose during first 24 h, mM	8.1 ± 2.3	9.0 ± 3.3	< 0.001
SD of glucose during first 24 h, mM	1.5 ± 1.4	2.2 ± 1.8	< 0.001

Data are expressed as mean ± SD, number (percentage), or median [interquartile range].
APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit.

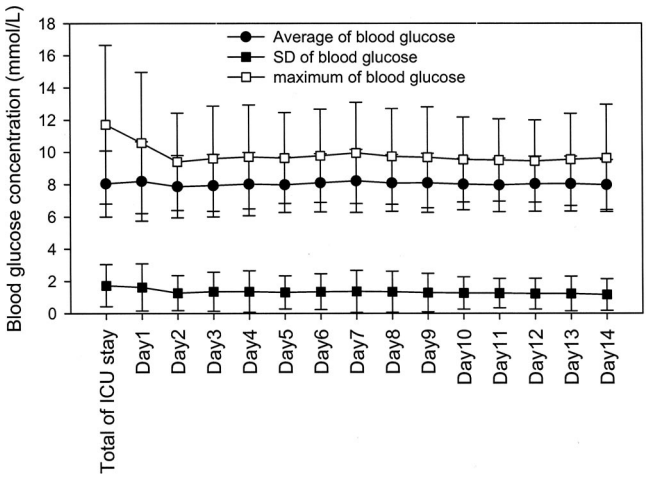

Fig. 1. Average, SD, and maximum of entire blood glucose concentration, for each intensive care unit (ICU) day for all patients for 2 weeks. *Lines* and *error bars* are mean ± SD.

sion day) were obtained on the first ICU day (fig. 1). These indices were controlled within a narrow range after the second ICU day.

Figure 2 shows the relation between increasing Glu_{SD} and Glu_{Ave}, and ICU and hospital mortality, with patients divided into four subgroups according to quartiles of each glucose index. For Glu_{SD}, ICU and hospital mortality were significantly different among each group ($P < 0.01$). For Glu_{Ave}, ICU and hospital mortality were significantly different among each group ($P < 0.01$), except for the two lowest subgroups (< 6.8 *vs.* 6.8–7.9; $P = 0.79$ for ICU mortality and $P = 0.76$ for hospital mortality).

Table 3 shows the area under the ROC curve for the glucose control indices. Glu_{SD}, Glu_{CV}, and Glu_{Max} had a significantly greater area under the ROC curve than Glu_{Ave}, $Glu1_{Ave}$, and Glu_{Adm}.

Using multivariate logistic regression analysis with ICU mortality as the dependent variable, only four glucose control indices (Glu_{Ave}, Glu_{SD}, Glu_{Max}, and Glu_{Adm}) achieved statistical significance (table 4). For this model, the area under the ROC was 0.88, and the Hosmer-Lemeshow goodness-of-fit statistic was 14.4 ($P = 0.072$).

Table 3. Area under the ROC Curves for Each Glycemic Variable

	Area under ROC Curve	95% Confidence Interval	
		Lower Limit	Upper Limit
Average of blood glucose	0.60	0.58	0.62
SD of blood glucose	0.65	0.63	0.67
CV of blood glucose	0.64	0.62	0.66
Maximum blood glucose	0.65	0.62	0.67
Admission blood glucose	0.55	0.53	0.57
Average of blood glucose during first 24 h	0.58	0.56	0.61
SD of blood glucose during first 24 h	0.58	0.56	0.61

CV = coefficient of variability; ROC = receiver operator characteristics.

When we used Glu_{CV} as the index of variability instead of Glu_{SD}, Glu_{CV} also predicted ICU mortality ($P < 0.001$; odds ratio 1.03 per each 1% change).

The same analysis with hospital mortality as the dependent variable showed that only Glu_{Ave}, Glu_{SD}, and Glu_{Adm} remained significant predictors of outcome (table 5). For this model, the area under the ROC was 0.84, and the Hosmer-Lemeshow goodness-of-fit statistic was 12.7 ($P = 0.123$). When we used Glu_{CV} as the index of variability instead of Glu_{SD}, Glu_{CV} also predicted hospital mortality ($P < 0.001$; odds ratio 1.03 per each 1% change).

In two hospitals (hospitals A and D), we identified 728 diabetic patients within a subcohort of 4,946 study patients. Compared with nondiabetic patients within these two hospitals, diabetic patients displayed no significant relation between glucose control (as assessed by Glu_{SD} and Glu_{Ave}) and ICU or hospital survival (figs. 3A and B), except for a comparison of lowest and highest hospital

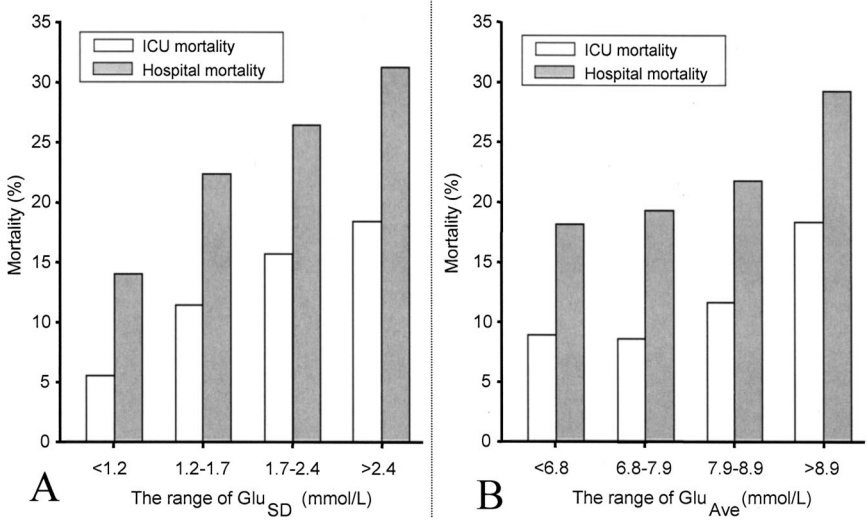

Fig. 2. (*A* and *B*) Relation between blood glucose control and intensive care unit (ICU) and hospital mortality in the total cohort. The SD of blood glucose was used as marker of blood glucose control for *A*, and the mean blood glucose level was used for *B*. Glu_{Ave} = mean blood glucose concentration; Glu_{SD} = SD of blood glucose concentration.

Table 4. Multivariate Logistic Regression Analysis for ICU Death

	Odds Ratio	95% CI of Odds Ratio	*P* Value	Change in −2 Log Likelihood	*P* Value for Likelihood Ratio Tests	VIF
Hospital C	0.67	0.40–1.11	0.122	0	—	1.15
Trauma or burn for ICU admission	0.57	0.30–1.07	0.078	0	—	1.06
GIT disorder for ICU admission	0.68	0.51–0.89	0.006	0	—	1.05
Mechanical ventilation	2.81	2.16–3.70	< 0.001	68.5	< 0.001	1.20
APACHE II score (per 1)	1.18	1.17–1.20	< 0.001	683	< 0.001	1.26
Mean blood glucose during ICU stay*	1.21	1.14–1.29	< 0.001	17.1	< 0.001	2.24
SD of blood glucose during ICU stay*	1.28	1.14–1.44	< 0.001	8.5	0.004	3.58
Maximum blood glucose during ICU stay*	0.95	0.92–0.98	0.003	7.9	0.005	2.04
Admission blood glucose*	0.93	0.91–0.96	< 0.001	16.7	< 0.001	4.74

* Odds ratio for each glucose variable indicates the change in risk of intensive care unit (ICU) mortality per 1-mmol change.

APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; GIT = gastrointestinal tract; VIF = Variance Inflation Factor.

mortality for Glu_{SD} (< 1.7 *vs.* 2.5–3.5; $P = 0.002$). On logistic regression analysis, diabetes was associated with decreased odds ratios for ICU mortality. In these hospitals, the area under the ROC for the predictive model was 0.86 (table 6).

Further multivariate logistic regression analysis was performed with ICU mortality as the dependent variable but also with other patient characteristics and clinical features and each of the seven glucose indices as independent variables. In these models, only Glu_{Ave}, Glu_{SD}, $Glu1_{Ave}$, and Glu_{CV} achieved statistical significance. The odds ratios for ICU mortality were 1.11, 1.12, 1.02, and 1.04 per each millimolar change in Glu_{Ave}, Glu_{SD}, and $Glu1_{Ave}$ and per each percent change in Glu_{CV}. For these models, the Hosmer-Lemeshow goodness-of-fit statistics were 24.1 ($P = 0.002$), 23.8 (0.03), 21.8 (0.05), and 19.1 (0.14), respectively, for Glu_{Ave}, Glu_{SD}, $Glu1_{Ave}$, and Glu_{CV}. Figure 4 shows the time course of such outcome prediction ability for Glu_{Ave} and Glu_{SD}.

Discussion

To understand the possible clinical significance of the variability of glucose concentration in the ICU, we conducted a multicenter retrospective observational study of the correlation between such variability (assessed by its SD and, in addition, by the coefficient of variability) during ICU stay and subsequent ICU and hospital mortality in a large cohort of patients admitted to four different ICUs. We found that variability of glucose concentration was a significant and independent predictor of ICU and hospital mortality and that it was a stronger predictor of ICU mortality than mean glucose concentration. These observations suggest that variability in glucose concentration might be an important dimension of glucose control.

First, the quality, applicability, and generalizability of the data used for this study require assessment. In this regard, our study has several strengths, which include a large number of patients (the largest cohort so far in which glucose control has been assessed), a large number of glucose measurements, prospectively collected databases, a heterogeneous group of critically ill patients with a full spectrum of diagnoses, and a multicenter design.

There are also several potential limitations to this study. First, it is retrospective in nature, with all the inherent limitations of such studies. However, patient characteristics and outcome data were all collected prospectively for entry into the database. These data were

Table 5. Multivariate Logistic Regression Analysis for Hospital Death

	Odds Ratio	95% CI of Odds Ratio	*P* Value	Change in −2 Log Likelihood	*P* Value for Likelihood Ratio Tests	VIF
Hospital A	1.48	1.26–1.75	< 0.001	0	—	1.38
Hospital C	0.60	0.40–0.89	0.011	0	—	1.66
Surgical patients	0.67	0.57–0.79	< 0.001	16.1	< 0.001	1.19
Neurologic diseases	1.42	1.14–1.77	0.002	0	—	1.12
Mechanical ventilation	1.81	1.51–2.17	< 0.001	41.5	< 0.001	1.39
APACHE II score (per 1)	1.16	1.14–1.17	< 0.001	733.4	< 0.001	1.45
Age (per 1 yr)	1.02	1.01–1.02	< 0.001	44.5	< 0.001	1.24
Mean blood glucose during ICU stay*	1.20	1.11–1.30	< 0.001	21.7	< 0.001	2.26
SD of blood glucose during ICU stay*	1.18	1.07–1.31	0.013	5.6	0.017	3.60
Maximum blood glucose during ICU stay*	0.97	0.95–1.00	0.06	4.2	0.042	4.75
Admission blood glucose*	0.95	0.93–0.98	0.001	10.3	0.001	2.05

* Odds ratio for each glucose variables indicates the change in risk of intensive care unit (ICU) mortality per 1-mmol change.

APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; VIF = Variance Inflation Factor.

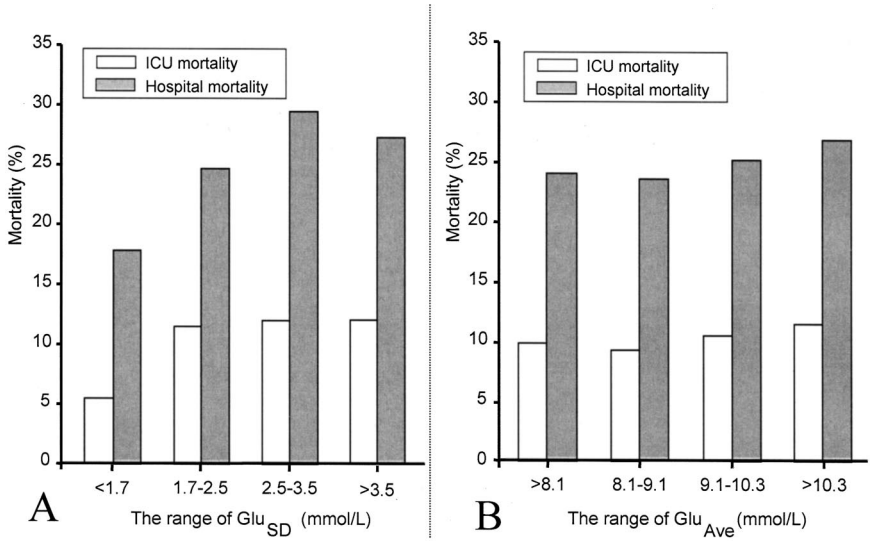

Fig. 3. (*A* and *B*) Relation between blood glucose control and intensive care unit (ICU) and hospital mortality in diabetic patients from hospitals A and D (n = 728). The SD of blood glucose was used as marker of blood glucose control for *A*, and the mean blood glucose level was used for *B*. Glu_{Ave} = mean blood glucose concentration; Glu_{SD} = SD of blood glucose concentration.

collected by trained data collectors, and all glucose data were objective, stored electronically at the time of collection, and verifiable. Furthermore, the outcomes are robust (death) and unlikely to have been incorrectly entered.

Second, we studied only four ICUs. However, we chose hospitals from two cities with a large number of patients. Therefore, our findings are likely to be robust. Nonetheless, we acknowledge that in other units or other countries with different styles of management, the findings might be different.

Third, there is a wide difference in mortality among institutions, which essentially reflects differences in case-mix for each ICU. This may limit the applicability of our findings to other institutions with a different case-mix. However, we performed multivariate logistic regression analysis entering site and reason for ICU admission in our model to adjust for case-mix and local practice style.

Fourth, the SD of blood glucose concentration, as presented, did not consider its time distribution, which might affect our findings.[18] However, assessment of changes in glucose SD over time indicates little time-related effect. More importantly, Glu_{SD} showed a significantly greater area under the ROC curve than Glu_{Ave}. Time-related effects on the distribution of values should have affected both variables equivalently.

Fifth, our values for the area under the ROC curve (from 0.55 to 0.65) seem small. However, the focus of our study related to the comparison between Glu_{Ave} and Glu_{SD} rather than the assessment of glucose control indices as possible early prognostic tools. In this regard, the area under the ROC curve of Glu_{SD} was greater than that of Glu_{Ave}. Finally, it is unlikely that any single biochemical variable would have a sufficiently high value for its area under the ROC curve to be useful for early prognostication in ICU patients.

In our study, lack of information about the use and dose of insulin infusions, the use and dose of catecholamine infusions, the use and dose of corticosteroids therapy or hypoglycemic drugs, and the use and dose of nutritional support is an important limitation. These factors are likely to modulate the predictive ability of glucose control indices and future studies should focus on their impact.[19,20] Nonetheless, it is important to note that we focused on the relative comparison between the

Table 6. Multivariate Logistic Regression Analysis for ICU Death in Subcohort Analysis (Hospitals A and D) Inclusive of Diabetic Patients

	Odds Ratio	95% CI of Odds Ratio	*P* Value	Change in −2 Log Likelihood	*P* Value for Likelihood Ratio Tests	VIF
Hospital A	1.26	1.01–1.58	0.042	0	—	1.25
GIT disorder for ICU admission	0.63	0.47–0.86	0.004	0	—	1.01
Mechanical ventilation	3.30	2.38–4.59	< 0.001	60.8	< 0.001	1.30
APACHE II score (per 1)	1.18	1.16–1.20	< 0.001	542.2	< 0.001	1.14
Mean blood glucose during ICU stay*	1.16	1.09–1.24	< 0.001	8.7	0.003	2.26
SD of blood glucose during ICU stay*	1.42	1.25–1.61	< 0.001	10.5	0.001	3.74
Maximum blood glucose during ICU stay*	0.94	0.90–0.97	< 0.001	11.1	< 0.001	4.67
Admission blood glucose*	0.94	0.91–0.97	< 0.001	13.6	< 0.001	2.03
Diabetes	0.57	0.41–0.80	< 0.001	12.2	< 0.001	1.19

* Odds ratio for each glucose variables indicates the change in risk of intensive care unit (ICU) mortality per 1-mmol change.

APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; GIT = gastrointestinal tract; VIF = Variance Inflation Factor.

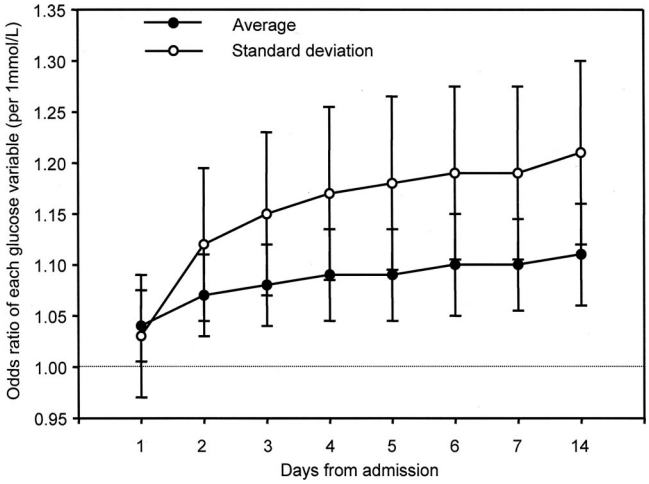

Fig. 4. Time course of the predictive ability of average and SD of blood glucose. Odds ratios (expressed with 95% confidential intervals) for glucose indexes indicate the risk change of intensive care unit mortality per 1-mmol change in each index. For example, average of blood glucose on 7 days from admission means average of entire glucose measurements during 7 days from admission. As time in intensive care unit increased, so did the ability of glucose control indices to predict outcome.

mean glucose concentration and the SD of glucose concentration rather then their absolute value. Our findings from multivariate logistic regression analysis suggest that variability of glucose control might be as important as the mean value of glucose control.

We also note that Glu_{SD} and Glu_{Ave} are not useful prognostic variables, because they can only be measured after ICU discharge. However, our intention was not to develop novel prognostic indices but rather to see whether evidence existed to support the hypothesis that variability of glucose control might be an important dimension of patient care and a predictor of hospital outcome.

It is important to appreciate that mean, SD, and maximum values of daily blood glucose concentration showed a narrow range of control after the second day of ICU stay. Therefore, after the second day, physicians seemed to manage blood glucose similarly, with little change until discharge. On the other hand, blood glucose control indices reached their highest values on the day of admission. This suggests that day 1 values, including Glu_{Adm}, $Glu1_{Ave}$, and $Glu1_{SD}$, might be more likely to reflect the state of the patient's condition (patient's nutritional state, stress response, liver function, endogenous insulin, severity of illness, and other factors) than later measurements. In fact, the maximum level of glucose concentration occurred on day 1 in 65% of patients. Therefore, in this study, Glu_{Max} might have mostly reflected the patients' physiologic condition. In this respect, several studies have reported that hyperglycemia and admission blood glucose and glucose indices during first 24 h in the ICU correlate with a higher mortality.[12,16,21] In these studies, however, glucose control indices were never adjusted for other prognostic variables to assess their independent contribution. In our multivariate logistic regression analysis, against previous reports, Glu_{Max} and Glu_{Adm} showed ICU mortality odds ratios of less than 1.0 (0.95 and 0.94 per 1 mM, respectively). In the absence of information on insulin treatment and nutritional support, we are unable to speculate on the reasons for such observations.

In the same analysis, the mean and SD of blood glucose during the first 24 h did not predict mortality. Both of these glucose control indices, however, developed greater predictive ability as more ICU days were taken into account for their calculation. These results are consistent with the view that 24 h might be too short a time to show the effect of glucose control on outcome. They might also reflect the fact that patients who have a short ICU stay both have better outcomes and contribute no data after the second day of admission creating a possible selection bias. Finally, if variability of glucose levels affects outcome, it may take days for it to do so. Each one of the above factors alone or in combination may explain why glucose indices during first 24 h did not predict mortality. These speculations, however, cannot be verified with our data set.

Our findings must also be seen within the context of previous investigations. Four randomized controlled trials have been performed comparing two levels of glucose control for critical ill patients so far. The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction study was a multicenter trial that included only diabetic patients with acute myocardial infarction. This study compared glucose–insulin–potassium therapy (targeted blood glucose range 7.0–10.9 mM: mean blood glucose 9.6 ± 3.3 mM) with a control group (no specific protocol: mean blood glucose 11.7 ± 4.1 mM) (the relative and absolute reductions of SD were 20% and 0.8 mM).[5,6] This study reported a significant reduction in 1-yr mortality but no change in short-term outcome (coronary care or hospital mortality). Van den Berghe *et al.* [9] showed that postoperative ICU patients allocated to intensive insulin therapy had a 42% risk reduction in ICU and hospital mortality when compared with patients receiving conventional glucose control. Relative and absolute reductions of SD associated with this treatment were 42% and 0.8 mM. Gray and Perdrizet[22] showed that strict glucose control reduced nosocomial infection significantly when compared with standard glucose control. Relative and absolute reductions in SD reported in this study were 41% and 1.4 mM. In the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction II study, the blood glucose information was reported only at randomization and after 24 h.[23] Therefore, no information about variability could be obtained. The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction II study reported no significant difference in outcome among the three different blood glucose groups. Other evidence exists on the possible

benefits of better glucose control for patients.[24–31] More recently, Van den Berghe *et al.*[32] studied the effect of intensive insulin therapy in medical ICU patients. They found that, although mortality was not reduced, morbidity was significantly decreased. However, there is no clear understanding of the mechanisms. In studies with tight glucose control protocols, the mean glucose typically decreases but so does variability. Which of these two is more important in determining the putative benefit of glycemic control remains unclear. Only randomized controlled studies comparing two different targeted glucose ranges in which both group are treated according to similar protocols aimed at decreasing variability would allow us to better understand the clinical significance of variability control. This is more than a simple theoretical concern because, if reducing swings in blood glucose concentration were a major biologic mechanism behind the putative benefits of glucose control, it would not be necessary to pursue lower glucose levels with the attendant risks of hypoglycemia. As recently shown,[33] fluctuations in glucose concentration may indeed trigger adverse biologic events beyond those of chronic sustained hyperglycemia and specifically and independently trigger oxidative stress.

Finally, we found that, in the two hospitals where this could be tested, diabetes affected our findings. First, it decreased the odds ratio for ICU mortality to 0.57. This effect, after glucose control indices have been controlled for, is essentially identical to the findings of van den Berghe *et al.*,[34] who also found that the presence of diabetes was associated with an odds ratio of 0.36 for ICU mortality. Further, we found that, unlike nondiabetic subjects, patients with diabetes did not display an association between increasing levels of blood glucose or glucose variability and ICU or hospital mortality. We have insufficient information to speculate on the mechanisms responsible for these findings. However, they suggest that diabetic patients may behave in a unique way with regard to their response to the biologic effects of hyperglycemia.

In summary, using a large multicenter cohort of patients and set of glucose measurements, we found that the SD and coefficient of variability of glucose were independent predictors of ICU and hospital mortality and that their predictive ability was greater than that of the mean blood glucose concentration. Decreasing variability of blood glucose concentration might be an important dimension of glucose management, a possible mechanism by which intensive insulin therapy exerts its beneficial effects, and an important goal of glucose management in the ICU. In addition, diabetic patients may represent a subpopulation with a unique response to hyperglycemia. Further investigations of the clinical significance of blood glucose variability in other settings and other ICUs seem desirable.

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