

Glucose variability is associated with intensive care unit mortality*

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Objective: Mounting evidence suggests a role for glucose variability in predicting intensive care unit (ICU) mortality. We investigated the association between glucose variability and intensive care unit and in-hospital deaths across several ranges of mean glucose.

Design: Retrospective cohort study.

Setting: An 18-bed medical/surgical ICU in a teaching hospital.

Patients: All patients admitted to the ICU from January 2004 through December 2007.

Interventions: None.

Measurements and Main Results: Two measures of variability, mean absolute glucose change per hour and *SD*, were calculated as measures of glucose variability from 5728 patients and were related to ICU and in-hospital death using logistic regression analysis. Mortality rates and adjusted odds ratios for ICU death per mean absolute glucose change per hour quartile across quartiles of mean glucose were calculated. Patients were treated with a computerized insulin algorithm (target glucose 72–126

mg/dL). Mean age was 65 ± 13 yrs, 34% were female, and 6.3% of patients died in the ICU. The odds ratios for ICU death were higher for quartiles of mean absolute glucose change per hour compared with quartiles of mean glucose or *SD*. The highest odds ratio for ICU death was found in patients with the highest mean absolute glucose change per hour in the upper glucose quartile: odds ratio 12.4 (95% confidence interval, 3.2–47.9; $p < .001$). Mortality rates were lowest in the lowest mean absolute glucose change per hour quartiles.

Conclusions: High glucose variability is firmly associated with ICU and in-hospital death. High glucose variability combined with high mean glucose values is associated with highest ICU mortality. In patients treated with strict glycemic control, low glucose variability seemed protective, even when mean glucose levels remained elevated. (Crit Care Med 2010; 38:838–842)

KEY WORDS: glucose; intensive care unit; mortality; epidemiology; metabolism; physiological stress

The results of the Leuven studies have led to a worldwide increase in the implementation of strict glycemic control in the intensive care unit (ICU) (1, 2). The mortality reduction in these landmark trials was attributed to the strict lowering of mean glucose (target 80–110 mg/dL) during admission in the intervention group (3). Interestingly, the positive results of the Leuven studies have not been reproduced in later studies (4–8). It is therefore of importance to examine whether factors other than mean glucose are of influence. As mean glucose is lowered and glyce-

mic excursions are targeted, glucose variability (GV) is likely to be reduced as well. Several studies have shown that GV is strongly associated with short-term ICU mortality (9, 10). This can be understood from a pathophysiological viewpoint, because hyperglycemia as well as GV can contribute to ICU mortality by increasing oxidative stress, neuronal damage, mitochondrial damage, and coagulation activation (11–15). In a study by Krinsley (16) in an ICU population, the *SD* as a marker of GV was a predictor of mortality within different ranges of mean glucose and a stronger predictor than mean glucose itself. However, the *SD* is not the most appropriate method for defining the GV of repeated glucose measurements (17). Two patients with the same mean glucose and *SD* can express completely different patterns of variability (Fig. 1). Furthermore, the majority of the results gathered so far on the predictive value of GV come from populations that are not treated or are partly treated with strict glycemic control (9, 10, 16).

The aims of this study were to measure GV over time in a large strict glucose control-treated ICU population across several ranges of mean glucose and to investigate

the association of GV and mean glucose values with ICU and in-hospital mortality.

MATERIALS AND METHODS

Setting. We performed a retrospective cohort study in an 18-bed medical/surgical ICU in a teaching hospital (Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, The Netherlands). On average, a nurse takes care of two patients depending on the severity of disease. All beds were equipped with a clinical information system (iMD-Soft; MetaVision, Tel Aviv, Israel), and all clinical and laboratory data were stored here. The glucose regulation protocol was implemented in April 2001, and set at a target glucose range of 72 to 126 mg/dL. Using a sliding scale computerized algorithm, the nursing staff was instructed to adjust the insulin infusion rate depending on the current glucose value and the rate of glucose change (based on the previous five measurements). The software also provided the time the next glucose measurement was due, which could vary from 15 mins up to 4 hrs. Routinely, enteral feeding was started within 24 hrs after admission, aiming at 2000 mL within 48 hrs or 1500 mL within 24 hrs. A duodenal feeding tube was inserted in case of persistent gastric retention. When patients resumed normal eating, the tight glucose algorithm was deactivated. The successful implementation of the algorithm has been reported previously (18). An integrated decision sup-

*See also p. 993.

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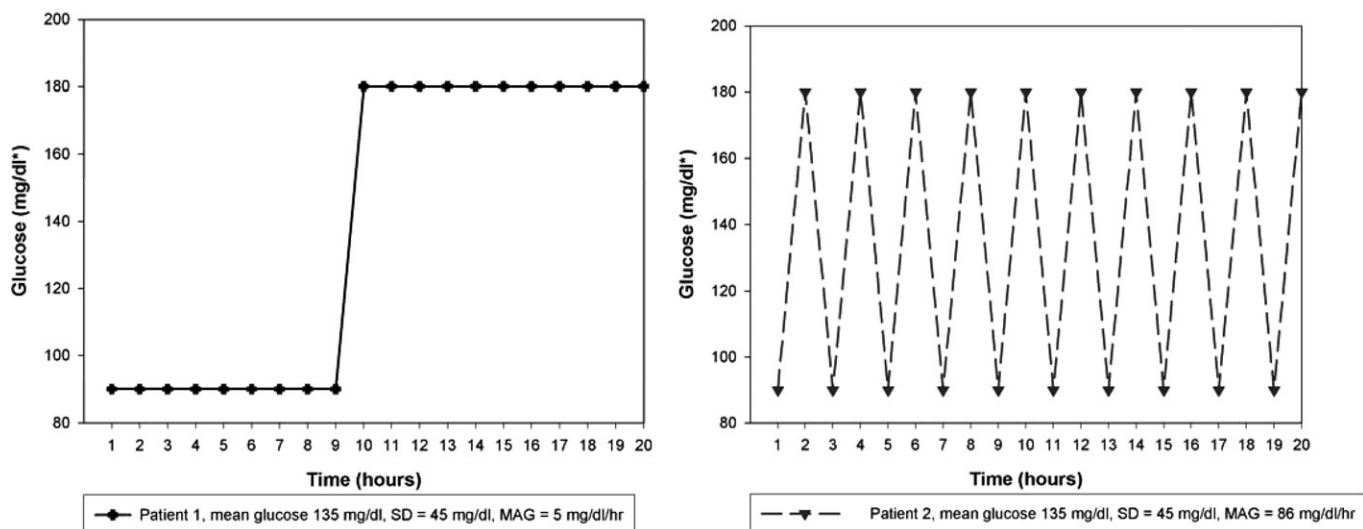


Figure 1. Two fictitious patients with identical mean glucose and SD but different patterns of variability expressed by mean absolute glucose change (MAG).

port module controlled the algorithm and was connected to the clinical information system. Because a retrospective analysis of anonymized data was performed, informed consent was not required according to Dutch Ethical Review Board regulations.

Cohort and Data Collection. We extracted data from the clinical information system concerning patients admitted between January 2004 and December 2007. Readmissions, patients with a withholding care policy, and patients with <3 glucose values measured during admission were excluded. We assessed demographic variables, medical history, and mortality in the ICU and in-hospital mortality. Furthermore, we collected information on severity of disease, the occurrence of severe hypoglycemia (glucose ≤ 45 mg/dL), and diabetes mellitus, because these variables are associated with GV (16, 19). As measures for severity of disease, we evaluated both the maximal Sequential Organ Failure Assessment (SOFA) score during admission and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score on admission (20, 21).

Measures of Glucose. Glucose was measured from blood samples obtained from an arterial catheter using the Accu-check (Roche/Hitachi, Basel, Switzerland), a handheld glucose measurement device. Results were automatically stored in the clinical information system. We collected all glucose values measured for every patient and calculated the mean glucose during admission and the SD. To obtain a measure of GV that was less dependent on the mean glucose and took into account all variability over time, we calculated the mean absolute glucose (MAG) change per patient per hour (formula 1). This is done by taking the sum of all absolute glucose changes during admission and dividing this by the total time spent in the ICU in hours.

$$\text{Mag} = |\Delta\text{BG}|/\Delta\text{Time}$$

Table 1. Characteristics of the studied cohort

	Cardiothoracic Surgery (n = 3560)	Medical and Other (n = 2168)	Total Cohort (n = 5728)
Age, years (mean \pm SD)	67 \pm 11	63 \pm 17	65 \pm 13
Gender, female, n (%)	1106 (31.1)	865 (39.9)	1971 (34)
APACHE II score on admission, median (IQR)	15 (12–17)	20 (15–27)	16 (13–20)
Maximum SOFA score during admission, median (IQR)	5 (4–6)	7 (5–10)	6 (5–7)
ICU stay, median days (IQR)	0.9 (0.8–1.1)	1.9 (0.8–4.4)	1.0 (0.8–2.0)
Diabetes mellitus, n (%)	681 (19.1)	18 (0.8)	699 (12.2)
Died in ICU, n (%)	27 (0.8)	334 (15.4)	361 (6.3)
Died inhospital, n (%)	93 (2.6)	516 (23.8)	609 (10.6)
Severe hypoglycemia (≥ 1 event), n (%)	66 (1.9)	223 (10.3)	299 (5.2)

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; IQR, interquartile range; ICU, intensive care unit.

Statistical Analyses

Results are presented as mean \pm SD or median with interquartile range (IQR), depending on the distribution of the data. Mean glucose, the glucose SD, and MAG change were divided into quartiles. The area under the receiver operating characteristic curve of the MAG change and the SD were calculated and any difference in predictive value was examined using parametrical bootstrapping with 1000 replicates. To select the best measure for disease severity, we compared the relations of the APACHE II and maximal SOFA score with ICU mortality in univariate regression analysis. Using multivariate logistic regression, we calculated odds ratios (ORs) for ICU and in-hospital death for each MAG quartile and corrected for clinical relevant confounders: sex, age, diabetes mellitus, severity of disease, severe hypoglycemia, and mean glucose. In addition, length of stay in the ICU was included as a possible confounder because of its relation to mortality and likely relation to variability, because variability may change over time

and the precision of variability assessment depends on the observation time. Also, cardiothoracic surgery was included, because mortality in this group is generally lower compared with other surgical patients. Furthermore, several demographic and physiological characteristics of this group differed from the general ICU population, which could be reflected in differences in mean glucose levels and glucose variability (22). Furthermore, we explored differences in predictive value of the MAG in surgical and medical patients using an interaction term in the multivariate model. Hereafter, we calculated ORs for ICU death and in-hospital death for different ranges of GV subdivided into quartiles of mean glucose. All statistical analyses were performed in SPSS 16.0 (SPSS Inc, Chicago, IL) and SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Between January 2004 and December 2007, there were 6725 ICU admissions. We excluded 656 readmissions, 86 pa-

tients with a withholding care policy, and 255 patients with <3 glucose values measured during admission, leaving 5728 patients for our analyses. The characteristics of the studied cohort are displayed in Tables 1 and 2. In total 154,189 glucose values were collected, a median of 12 values per patient (IQR 6–23) and 11 values per day (IQR 7–14).

Measures of Glucose and ICU. For the entire cohort, the median glucose SD was 32 mg/dL (IQR, 25–43 mg/dL) and the median MAG was 11 mg/dL/hr (IQR, 7–16 mg/dL). The MAG was significantly stronger associated with ICU death compared with the SD in univariate analysis, a difference in area under the of the receiver operating characteristic curve of 5.4% (95% confidence interval [CI], 3.0–7.7; $p < .001$). The ranges of mean glucose quartiles and MAG quartiles with the number of patients per stratum and ICU mortality are shown in Table 3. The highest ICU and in-hospital mortality was seen in the upper MAG and upper mean glucose quartile with mortality rates of 24.5% and 28.7%, respectively (Fig. 2). ICU mortality rates in the lowest MAG quartile ranged from 0.7% to 5.2%.

Severity of Disease and Glucose Variability. The OR for death in the highest

quartile of the APACHE II score was 33.8 (95% CI, 17.9–63.8) and 64.8 (95% CI, 28.8–145.9) for the maximal SOFA score. Thus, we corrected for quartiles of maximal SOFA score instead of APACHE II score as a measure of disease severity in our multiple regression model (20). The median MAG change increased from 10 mg/dL/hr (IQR, 6–16 mg/dL/hr) in the lowest quartiles SOFA quartile to 13 mg/dL/hr (IQR, 8–18 mg/dL) in the highest SOFA quartile ($p < .001$). The association of the MAG and ICU mortality did not significantly differ between surgical and medical patients ($p = .74$).

Multivariate Analyses. The ORs for ICU death and in-hospital death, adjusted for mean glucose and other confounders, are displayed in Table 4; in the highest MAG quartile, the OR for ICU death was 3.3 (95% CI, 2.1–5.4) and for in-hospital death 2.8 (95% CI, 2.0–3.9). The risk of death increased per MAG quartile (p for trend $< .001$). We performed logistic regression with ICU death as the dependent variable and MAG quartiles as the covariate. Per quartile of mean glucose, we calculated ORs for ICU death. We corrected for age, sex, diabetes mellitus, cardiothoracic surgery, severe hypoglycemia, length of ICU stay, and maximal SOFA score during admission. The highest OR for ICU death was found in patients with the highest MAG in the upper glucose quartile: OR 12.4 (95% CI, 3.2–47.9; $p < .001$). Also in the first quartile of mean glucose, high MAG change in the fourth quartile was associated with ICU death with an OR of 4.1 (95% CI, 1.9–9.1; $p < .001$). Finally, we performed analyses for in-hospital death. In each quartile of mean glucose, the upper MAG quartile seemed predictive of in-hospital death compared with the first quartile with ORs for in-hospital death of 2.7 (95% CI, 1.6–5.2), 1.9 (95% CI, 0.9–4.2), 2.5 (95% CI, 0.9–6.8), and 6.4 (95% CI, 2.7–15.0)

across the first to the fourth mean glucose quartiles, respectively.

DISCUSSION

In this retrospective cohort study, we have shown that GV, expressed as MAG, is highly associated with ICU death in both high and low ranges of mean glucose. In combination with a high mean glucose, GV seems most detrimental. It can be debated whether GV reflected by MAG change is a causative harmful phenomenon or whether it is an epiphenomenon resulting from metabolic deterioration during severe illness and dying (23). We have attempted to elucidate this by excluding patients who were on a withholding care policy and correcting for the maximal SOFA score during admission. From a pathophysiological viewpoint, a causal relationship can be substantiated; *in vitro*, varying glucose levels have been shown to enhance cell apoptosis (24). In rats, glycemic reperfusion after hypoglycemia caused neuronal death (25), and altering glucose levels were impairing endothelial function in healthy volunteers (26). Even more, tubulointerstitial cells exposed to intermittent high glucose concentrations showed enhanced cell growth and collagen syntheses compared with stable high glucose concentrations (27). Possibly, the adaptive cell mechanisms that are initiated in case of constant hyperglycemia are ineffective when the hyperglycemia is not constant but varying, explaining the toxicity of GV (28).

Our findings are in accordance with previous studies that have investigated the relationship between GV and mortality. In the studies of Krinsley (10) and Egi (16), the glucose SD in the ICU was a predictor of mortality independent of mean glucose. In the study from Bagshaw et al (9), GV, defined as the occurrence of both hypoglycemia and hyperglycemia within 24 hrs of ICU admission, was related to ICU mortality. Although these studies reported data from large multicenter cohorts, a strict glycemic control algorithm was not fully implemented, limiting external validity for the ICU populations treated with strict glycemic control. Furthermore, Krinsley and Egi used the SD as a measure of variability. Because the blood glucose scale was not normally distributed and asymmetric, the assumptions of parametric statistics did not apply, and the SD was, therefore, not the optimal measure of GV (17). In addition, the SD did not take the change per time into account. Indeed, in our cohort, the MAG change was a stronger predictor of ICU

Table 2. Number of patients per Acute Physiology and Chronic Health Evaluation II admission category (surgical/medical)

	Surgical (n = 4409)	Medical (n = 1319)
Cardiovascular	3895	235
Sepsis	52	220
After cardiac arrest	10	287
Gastrointestinal	235	57
Hematologic	7	7
Renal	12	26
Metabolic	7	48
Neurologic	40	150
Respiratory	151	289

Table 3. The number of patients per stratum are depicted with the intensive care unit mortality per stratum (n and %)^a

	MAG Quartiles, mg/dL/hr			
	<7.1 (n = 1432)	7.1–10.8 (n = 1432)	10.9–15.8 (n = 1432)	>15.8 (n = 1432)
Mean glucose quartiles, mg/dL (%)	18/346 (5.2)	41/485 (8.5)	41/385 (10.6)	44/216 (20.4)
<124.7 (%)	4/204 (2.0)	14/402 (3.5)	24/465 (5.2)	24/365 (6.6)
124.7–136.9 (%)	2/344 (0.6)	4/236 (1.7)	13/353 (3.7)	32/496 (6.5)
137.0–160.1 (%)	4/538 (0.7)	1/309 (0.3)	8/229 (3.5)	87/355 (24.5)

^aRanges of quartiles of mean absolute glucose change (MAG) and mean glucose are given.

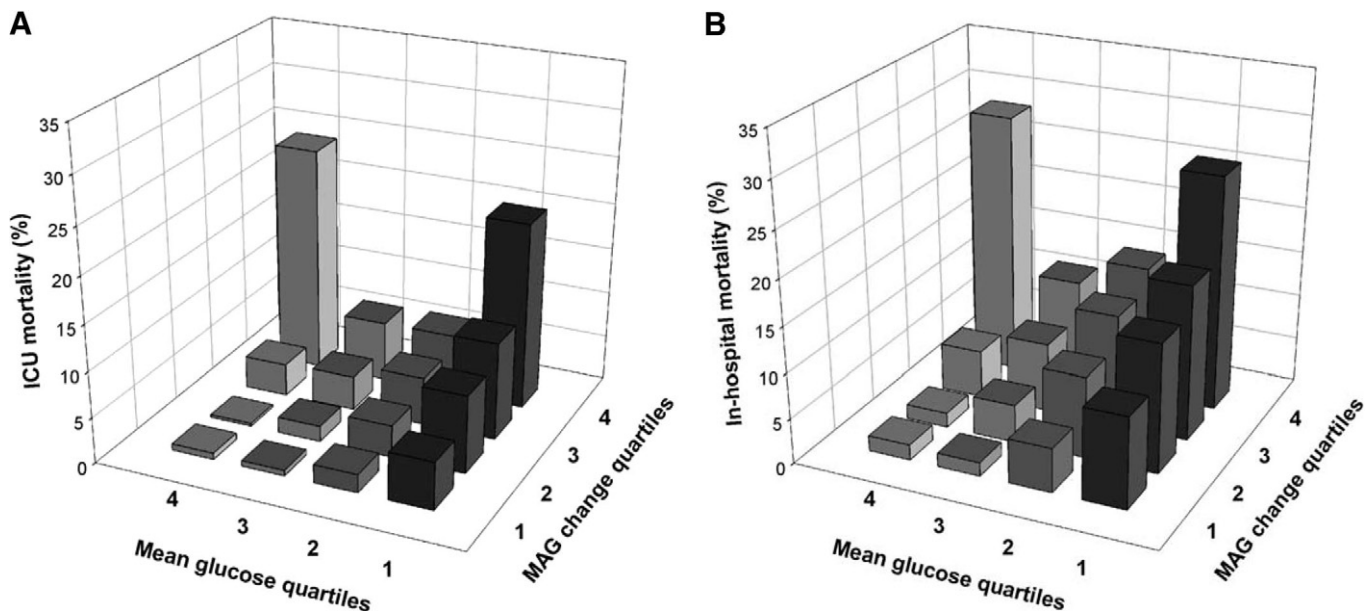


Figure 2. A, Intensive care unit mortality (%). B, In-hospital mortality (%). All mortality rates were calculated per quartiles of mean absolute glucose change (MAG) divided by quartiles of mean glucose.

Table 4. Odds ratio for intensive care unit and inhospital death per mean absolute glucose change quartile adjusted for age, sex, diabetes mellitus, maximal Sequential Organ Failure Assessment score, mean glucose, severe hypoglycemia, and cardiothoracic surgery

Quartiles of MAG Change	OR ICU Death (95% CI)	OR Inhospital Death (95% CI)
First: <7.1 mg/dL/hr	Reference	Reference
Second: 7.1–10.8 mg/dL/hr	1.5 (0.9–2.5)	1.5 (1.0–2.1)
Third: 10.9–15.8 mg/dL/hr	1.8 (1.1–2.9)	1.6 (1.2–2.3)
Fourth: >15.8 mg/dL/hr	3.3 (2.1–5.4)	2.8 (2.0–3.9)
	<i>p</i> for trend <.001	<i>p</i> for trend <.001

ICU, intensive care unit; OR, odds ratio; CI, confidence interval; MAG, mean absolute glucose change.

death than SD. Similar results were reported by Dosset et al (29), who investigated a surgical ICU population and found that the largest absolute change in successive blood glucose measurements during an ICU admission was a strong predictor of ICU death, whereas the SD was not.

The APACHE II model is the most widely used parameter when correcting for disease severity in GV studies in the ICU (9, 10, 16). However, the APACHE II model was originally designed to predict mortality in the first 24 hrs of ICU admission (21). Indeed, we found disease severity to be a confounder with a relation to both glycemic variability and mortality. Correction for disease severity using maximum SOFA score during admission seemed superior to using APACHE scores at admission.

Our findings suggest that high mean glucose is less harmful when GV is low, and patients with identical mean glucose can have different mortality rates depending on

their MAG change. GV was not reported as an outcome measure in the Leuven studies, the GluControl study, the Volume Substitution and Insulin Therapy in Severe Sepsis study, and the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation study (1, 2, 4, 7, 8). Differences in these study outcomes may be attributed to several factors (30). It can be hypothesized that more stable glucose profiles, with less GV, can be reached when insulin therapy is combined with a constant administration of glucose-containing fluids analogous to the insulin clamp technique (31). Because we have found that GV is such a strong predictor of ICU death, there is the possibility that differences in GV can be part of the explanation of differences in mortality reduction in these trials. It would be interesting to examine the results of these previous trials in the context of glycemic variability.

Of note, ICU mortality in the mean glucose quartiles in our study decreased from 10.1% (<124.7 mg/dL) to 3.6% (137.0–160.1 mg/dL) and rose hereafter to 7.0% (>160.1 mg/dL). Such a J-shaped mortality curve has been seen before in patients with myocardial infarction (32–34) and in a large cohort of 66,184 ICU patients in whom glucose values during the first 24 hrs of admission were taken into account (35). We cannot explain the increased mortality in the lower glucose quartile solely by the occurrence of severe hypoglycemia (as defined by glucose <45 mg/dL). Previous results regarding the relation between severe hypoglycemia and ICU mortality are conflicting (4, 36–38). In our study, the association between ICU mortality in the lowest mean glucose quartile and highest MAG quartile holds after correcting for severe hypoglycemia in the multivariate analysis. This is in concordance with the study from Bagshaw et al (9), who found that GV was a stronger predictor of ICU death than hypoglycemia alone.

An important limitation of this study is that it was performed in one center only and is retrospective in nature. Most patients were admitted for cardiothoracic surgery; we have, however, corrected for this potential confounder. A strong point is that we studied a large and representative group of 5728 mixed ICU patients who were treated with strict glycemic control using a computerized algorithm, which brought a high number of patients

in target (18). Furthermore, we used a novel indicator for GV.

CONCLUSIONS

We have confirmed findings of previous studies that GV is related to ICU and in-hospital death. Additionally, we have shown that, for those with persistently high mean glucose values during admission, low GV seems protective. There appears to be a synergistic negative effect of high mean glucose in combination with high GV. To elucidate whether GV is a treatable risk factor in the ICU or a risk marker only, the effect of lowering GV on ICU survival remains to be investigated, for example, by designing an algorithm that aims at lowering variability rather than the mean glucose and comparing this with an algorithm that lowers the mean glucose.

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