

# Intensive Insulin Therapy in the Intensive Care Unit

## Assessment by continuous glucose monitoring

CHRISTOPHE DE BLOCK, MD, PHD<sup>1,2,3</sup>  
BEGOÑA MANUEL-Y-KEENOY, MD, PHD<sup>3</sup>

LUC VAN GAAL, MD, PHD<sup>1,3</sup>  
PETER ROGIER, MD<sup>2</sup>

**OBJECTIVE**— Hyperglycemia occurs in most critically ill patients. Using continuous glucose monitoring (CGM), we investigated whether intensive insulin therapy based on discontinuous glucose monitoring can achieve normoglycemia (80–110 mg/dl) in a medical intensive care unit (MICU).

**RESEARCH DESIGN AND METHODS**— Fifty adults (men/women 31/19, age 62 ± 16 years, nondiabetic/diabetic 30/20, intravenous/subcutaneous insulin 22/28, and Acute Physiology and Chronic Health Evaluation II score 22 ± 7) were prospectively recruited. Forty-eight-hour CGM was performed using a subcutaneous glucose sensor (GlucoDay) and compared with arterial glycemia. Main outcome measures were percent of time in normoglycemia and accuracy/applicability of CGM.

**RESULTS**— During 48-h CGM, glycemia reached target (80–110 mg/dl) in only 22 ± 18%, was >140 mg/dl in 39 ± 27%, and was <60 mg/dl in 5 ± 10% of the time. Patients on subcutaneous versus intravenous insulin had more glycemia readings >110 mg/dl ( $P = 0.016$ ). Glycemia was higher in diabetic patients (170 ± 77 vs. 129 ± 35 mg/dl,  $P = 0.013$ ). BMI was an independent determinant for bad glycemic control ( $\beta = 0.73$ ,  $P < 0.0001$ ). Diabetic state ( $\beta = 0.47$ ,  $P < 0.0001$ ), septic shock ( $\beta = 0.22$ ,  $P = 0.045$ ), sequential organ failure assessment score ( $\beta = 0.40$ ,  $P = 0.001$ ), and use of corticoids ( $\beta = 0.28$ ,  $P = 0.014$ ) and inotropics ( $\beta = -0.24$ ,  $P = 0.035$ ) were independent determinants of insulin dose. GlucoDay values and arterial glycemia correlated well ( $r = 0.85$ ,  $P < 0.0001$ ,  $n = 555$  after six-point calibration), with 97% of data falling in regions A and B of error grid analysis. There were no adverse events using GlucoDay.

**CONCLUSIONS**— GlucoDay, a well-tolerated 48-h CGM system, revealed that normoglycemia was only achieved 22% of the time in MICU patients. Further studies should investigate whether application of CGM to titrate insulin therapy can improve patient outcome.

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Hyperglycemia occurs in the majority of critically ill patients (1–7). Critical illness induces counterregulatory hormones (glucagon, growth hormone, catecholamines, and glucocorticoids) (8,9). In addition, several clinical interventions, such as corticosteroids, va-

sopressors, dextrose solutions, enteral or parenteral nutrition, and dialysis, further promote hyperglycemia (10,11). Moreover, changes in carbohydrate metabolism occur in critical illness, including increased peripheral glucose needs, enhanced hepatic glucose production, insu-

lin resistance, and relative insulin deficiency (7,12).

Hyperglycemia (at admission or throughout hospitalization) is associated with adverse outcome following myocardial infarction (3,13,14), coronary artery bypass graft (15,16), stroke (17,18), and surgery (19). In the intensive care unit (ICU), the mortality rate for newly hyperglycemic patients approaches one in three (20).

Intensive insulin therapy to maintain glycemia at 80–110 mg/dl significantly reduced mortality and morbidity (acute renal failure, need for prolonged mechanical ventilation, and length of ICU stay) in a surgical ICU (1). Similar results were reported in a medical ICU (MICU) (2) and in a heterogeneous group of critically ill patients (5,6).

Achieving normoglycemia (80–110 mg/dl) appears crucial to obtaining the benefit of intensive insulin therapy (21). However, this requires extensive nursing efforts (frequent glucose monitoring and adjusting insulin dose), which may not be accepted by a busy ICU staff (22). The inherent clinical perturbations of critically ill patients (fluctuating severity of illness, changes in nutritional delivery, off-unit visits to diagnostic imaging, and administration of corticosteroids or vasopressors) produce frequent changes in insulin requirements (22). Continuous glucose monitoring (CGM) might aid in the monitoring of glycemic excursions and optimize insulin therapy.

To assess the reliability of CGM in an MICU, its technical performance and accuracy were compared with discontinuous glucose monitoring using error grid analysis (EGA). CGM was then applied in a prospective, observational pilot study at an MICU to determine whether currently used insulin regimens (subcutaneous or intravenous) based on discontinuous glucose monitoring are adequate in achieving normoglycemia.

### RESEARCH DESIGN AND METHODS

This prospective observational study was performed at a single-center 13-bed MICU at Middelheim

From the <sup>1</sup>Department of Diabetology, Metabolism and Clinical Nutrition, Antwerp University Hospital, Antwerp, Belgium; the <sup>2</sup>Medical Intensive Care Unit, Middelheim General Hospital, Antwerp, Belgium; and the <sup>3</sup>Antwerp Metabolic Research Unit, University of Antwerp, Antwerp, Belgium.

Address correspondence and reprint requests to Christophe De Block, MD PhD, Diabetology, Faculty of Medicine, University of Antwerp, Antwerp University Hospital, Wilrijkstraat 10, B-2650 Edegem, Belgium. E-mail: christophe.deblock@ua.ac.be.

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**Abbreviations:** APACHE-II, Acute Physiology and Chronic Health Evaluation II; CG-EGA, continuous glucose error grid analysis; CGM, continuous glucose monitoring; EGA, error grid analysis; ICU, intensive care unit; MICU, medical ICU; SOFA, sequential organ failure assessment.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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General Hospital, a university-affiliated tertiary care center. The nurse-to-patient ratio averages 1:2.5. After obtaining written informed consent from the patient or closest family member, adult patients admitted to the MICU between 1 April 2004 and 31 March 2005, were consecutively recruited based on availability of the CGM device (GlucoDay). Exclusion criteria were pregnancy, a “do not resuscitate” code, and a suspected stay in the MICU of <3 days. The protocol was approved by the ethics committee of the Middelheim Hospital (approval no. 2345).

Other than a different insulin regimen (subcutaneous or intravenous) (Actrapid; Novo Nordisk, Bagsvaerd, Denmark), both groups received identical interventions. A continuous intravenous insulin regimen was used according to the protocol of the Leuven study (1,2). For the subcutaneous insulin regimen, 5 units were injected if glycemia was 150–199 mg/dl, 10 units if glycemia was 200–249 mg/dl, 15 units if glycemia was 250–299 mg/dl, and 20 units if glycemia was  $\geq$ 300 mg/dl; glycemia was tested at least every 3 h. Assignment to intravenous insulin was based on glycemia at admission (if >200 mg/dl) and clinical criteria (severity of illness, brittle diabetic state). Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE-II) and the Sequential Organ Failure Assessment (SOFA) scores (23,24). Zero points were given for the neurologic evaluation, since most patients were sedated. All patients were primarily initiated on intravenous fluids (dextrose 5%/NaCl 0.45%) upon admission to the ICU, and enteral or parenteral nutrition was started within 24 h.

Forty-eight-hour CGM was initiated within 3 days after admission at the MICU, using a glucose sensor that measures glucose concentrations in the dialysate from subcutaneous interstitial fluid (GlucoDay; A. Menarini Diagnostics, Florence, Italy). Before insertion of the GlucoDay, sensitivity of the glucose sensor was checked in vitro using a standard D-glucose solution (90 mg/l), which gives a signal of 6–40 nanoamperes. A microdialysis fiber (Medica, Medulla, Italy) was inserted subcutaneously into the periumbilical region, without local anesthesia, using an 18-gauge Teflon catheter as a guide (25). The fiber was then connected to a portable 245-g apparatus, powered by a 9-volt battery.

Glucose-oxidase (sensor) and two plastic bags (one for the buffer reservoir

and one for waste products) complete the apparatus, which is contained in a small wearable pouch. A perfusion buffer (Dulbecco's solution, containing sodiumbenzoate as preservative) circulates at a rate of 10  $\mu$ l/min by means of a programmable peristaltic pump (26). Glucose concentrations in the dialysate were then measured every 3 min by the glucose sensor over a 48-h period. The lag time between subcutaneous and arterial blood glucose concentrations is <3 min (25). The blind mode of the CGM system was used, and after 48 h of monitoring, data were downloaded into a computer. Nanoampere values reported by the GlucoDay device were converted into glucose values after two-point calibration using arterial glucose values obtained after 12 and 24 h and then represented as a graph (Fig. 1). To account for possible changes in subcutaneous glucose recovery due to hemodynamic alterations (e.g., hypotension, shock, vasoactive drugs) we performed six-point calibration (after 2, 6, 12, 18, 24, and 36 h) and compared it with data after the two-point calibration (Fig. 2A and B). Both datasets were compared with arterial blood glucose measurements by point EGA (27). In order to evaluate the accuracy of CGM systems to prompt appropriate clinical action, continuous glucose-EGA (CG-EGA) was applied using blood glucose values collected every 15 min in three different 4-h blocks (2–6, 20–24, and 26–30 h after insertion of the GlucoDay) in an additional group of five patients. CG-EGA evaluates glucose point accuracy EGA and accurate direction and rate of glycemic fluctuations EGA, taking into account physiological time lags (28,29).

For the primary end point of evaluating the performance of the insulin protocol to maintain normoglycemia, a number of parameters were examined: 1) percent and time of glycemia within target range; 2) percent of time of glycemia <60, >110, >140, and >200 mg/dl; 3) mean glycemia; and 4) insulin dose per 24 h.

### Statistical analysis

Results were analyzed using SPSS (Chicago, IL). Distributions of continuous data were tested for normality by Kolmogorov-Smirnov test. The unpaired *t* test, Mann-Whitney *U* test, or ANOVA was used to determine differences between groups. Bonferroni adjustments for multiple comparisons were made. Pearson or Spearman rank correlation test was used. Differences in distributions of categorical

data were evaluated by  $\chi^2$  or Fisher's exact test. Stepwise forward logistic or linear regression analysis was done to assess the strength and independency of associations. A two-tailed *P* < 0.05 was considered significant.

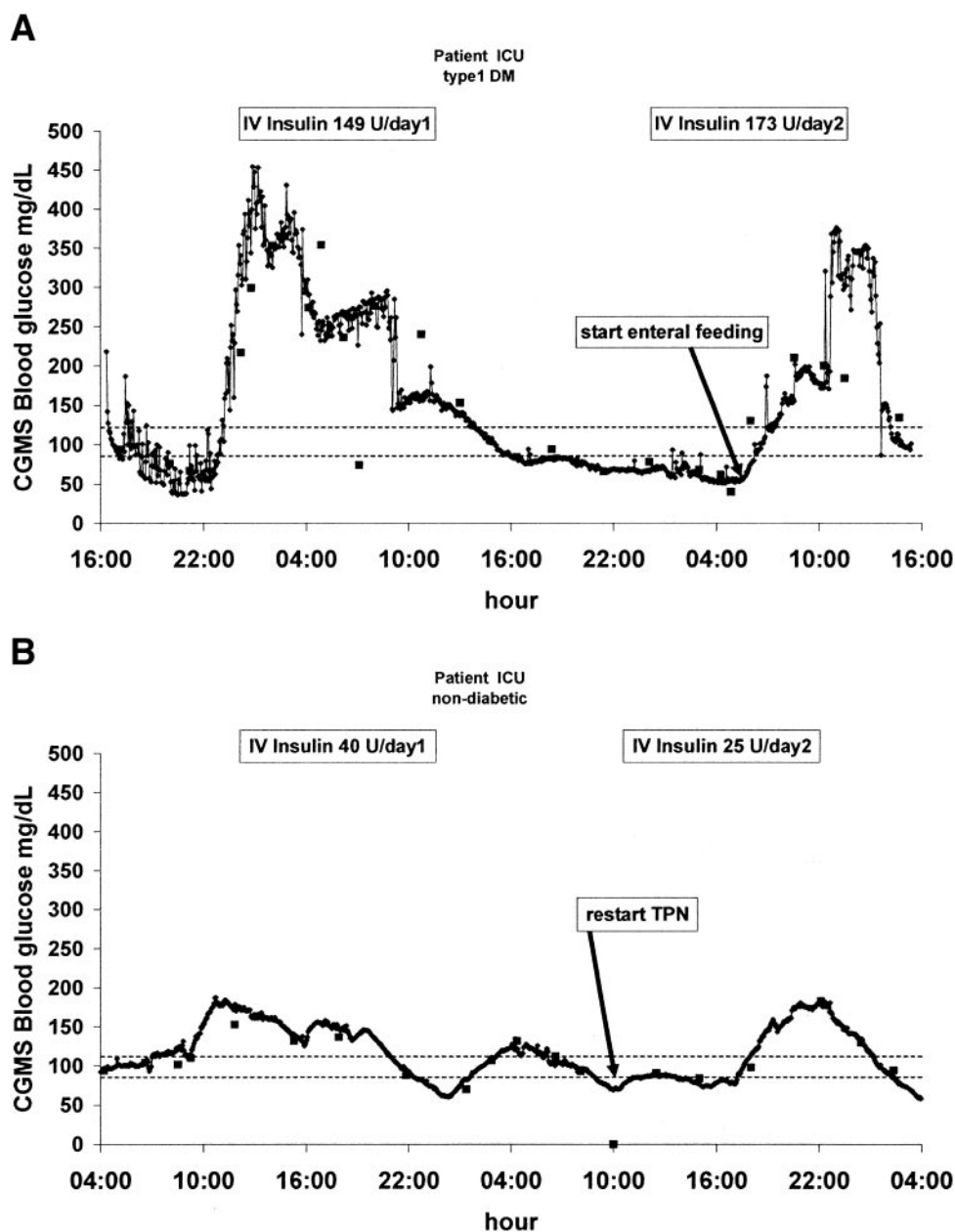
**RESULTS**— Fifty adults (31 men, 19 women) were recruited, including 30 nondiabetic and 20 diabetic patients with a mean age of  $62 \pm 16$  years. Over 50,000 glucose measurements were performed. The median APACHE-II score was 22 (5–42), and the median SOFA score was 8 (1–16). Twenty-two patients received continuous intravenous insulin therapy and 28 subjects a subcutaneous insulin regimen. Only 13 patients had a mean glycemia between 80 and 110 mg/dl. Target glycemia (80–110 mg/dl) was reached in only  $22 \pm 18\%$  of 48 h CGM. Glycemia was >140 mg/dl in  $39 \pm 27\%$  and <60 mg/dl in  $5 \pm 10\%$  of the time. The mean insulin dose per day was 71 units (0–393).

### CGM

CGM data, calculated after two-point calibration, correlated linearly with arterial glycemia ( $r = 0.76$ ,  $P < 0.0001$ ,  $n = 820$ ), with 95% of the data falling in regions A and B of the error grid (Fig. 2A). After six-point calibration, the correlation was stronger ( $r = 0.85$ ,  $P < 0.0001$ ,  $n = 555$ ), with 97% of data falling in regions A and B and with fewer data points in zone C (Fig. 2B). Patients in septic shock, with hypotension, and those in acute renal failure had a marginally better EGA compared with those without these conditions, whereas the opposite situation was observed in patients receiving inotropics.

In the five patients recruited for CG-EGA, no rapid increments/decrements of glycemia were collected ( $<3 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{min}^{-1}$ ) (Fig. 2C). The error matrix combining rate and point EGA zones (Fig. 2D) shows that in the hypoglycemic range, 100% of data were “accurate.” In the hyperglycemic range, 88.1% of data result as accurate, 10.4% as “benign errors,” and 1.5% as “erroneous readings.” In the euglycemic range, 93.8% of data were accurate, 4.8% are considered benign errors, and 1.4% were erroneous readings.

Using CGM, fast increases or decreases in glycemia were noted immediately, whereas this was noted much later ( $\sim 1$ –2 h) when using intermittent blood glucose determinations.



**Figure 1**—Examples of CGM profiles. A: A brittle type 1 diabetic (DM) patient in cardiogenic shock; enteral feeding was started after 36 h. ■, arterial blood glucose readings. B: A stable nondiabetic patient admitted due to respiratory insufficiency; parenteral nutrition was started after 30 h.

Both the insertion of the fiber and the wearing of the device were well tolerated. There were no adverse events with the use of the GlucoDay. Even patients receiving full-dose heparin did not show bleeding complications.

**Intravenous versus subcutaneous insulin regimen**

Age, sex, and BMI were similar in both groups (Table 1). In the intravenous group, diabetes ( $P = 0.021$ ) and septic shock ( $P = 0.002$ ) were more frequent and patients had a higher APACHE-II ( $27 \pm 7$  vs.  $19 \pm 6$ ,  $P < 0.0001$ ) and

SOFA ( $9 \pm 4$  vs.  $7 \pm 4$ ,  $P = 0.014$ ) scores. Intravenous insulin was also more often used in patients receiving intravenous corticoids ( $P = 0.001$ ), parenteral nutrition ( $P = 0.001$ ), and renal replacement therapy (continuous venovenous hemofiltration) ( $P = 0.006$ ).

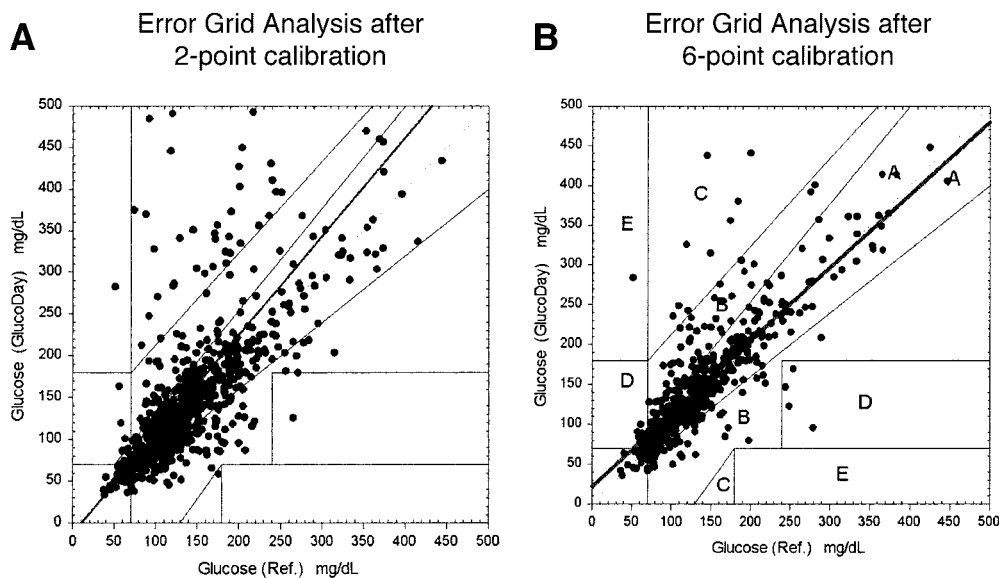
Patients on subcutaneous insulin spent more time at glycemia  $>110$  mg/dl ( $71 \pm 24$  vs.  $55 \pm 22\%$ ,  $P = 0.016$ ) but similar time at glycemia  $<60$  mg/dl. Despite a higher insulin dose in the intravenous group ( $141 \pm 100$  vs.  $15 \pm 26$  units/day,  $P < 0.0001$ ), mean glycemia was similar (Table 1). The mean intravenous

insulin infusion rate was 5.9 units/h, with some patients receiving  $\sim 20$  units/h.

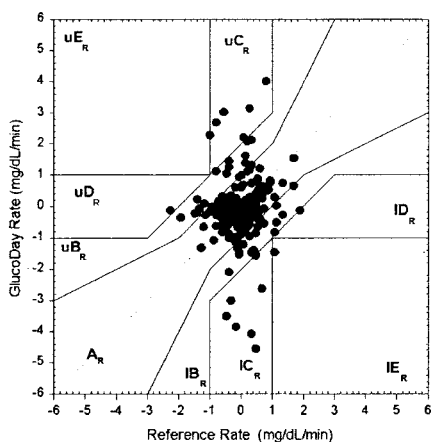
**Glycemic control and insulin requirements**

Diabetic compared with nondiabetic patients were not different in age, sex, or severity of illness (APACHE-II and SOFA scores), but had a higher BMI ( $31.6 \pm 7.6$  vs.  $23.3 \pm 4.6$  kg/m<sup>2</sup>,  $P < 0.0001$ ), required a higher insulin dose ( $126 \pm 104$  vs.  $34 \pm 64$  units/day,  $P < 0.0001$ ), and had a higher mean glycemia ( $170 \pm 77$  vs.  $129 \pm 35$  mg/dl,  $P = 0.013$ ).

Patients with a mean glycemia  $>140$



	N	Zone E	Zone D	Zone C	Zone B	Zone A	R
Total 6 pts	555	0.18	1.44	1.62	16.22	80.54	0.8451
Total 2 pts	820	0.12	0.73	4.51	22.19	72.45	0.7569



		Point Error Grid Zones										
		Hypoglycemia BG < 70 mg/dL			Euglycemia 70 < BG < 180 mg/dL			Hyperglycemia BG > 180 mg/dL				
		A	D	E	A	B	C	A	B	C	D	E
R-EGA Zones	A	100%	0%	0%	74.30%	7.64%	0.70%	46.27%	19.41%	0%	0%	0%
	B	0%	0%	0%	9.72%	2.10%	0.70%	19.41%	2.98%	0%	0%	0%
	uC	0%	0%	0%	1.38%	1.38%	0%	2.98%	0%	0%	0%	0%
	IC	0%	0%	0%	1.38%	0%	0%	4.48%	2.98%	0%	0%	0%
	uD	0%	0%	0%	6.70%	0%	0%	0%	0%	0%	0%	0%
	ID	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	uE	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	IE	0%	0%	0%	0%	0%	0%	0%	1.49%	0%	0%	0%

**Figure 2**—EGAs. The Clarke error grid assesses the clinical significance of differences between the GlucoDay and the arterial blood glucose measurements. The method uses a Cartesian diagram, in which the values generated by the continuous monitoring device (GlucoDay) are displayed on the y-axis, and the reference values (arterial blood glucose) are displayed on the x-axis. The diagonal represents the perfect agreement between the two, whereas the points below and above the line indicate overestimation and underestimation of the actual values. Zone A (acceptable) represents the glucose values that deviate from the reference values by  $\leq 20\%$ . These values are clinically exact and are thus characterized by correct clinical treatment. Zone B (benign errors) is located above and below zone A; this zone represents those values that deviate from the reference values, which are incremented by 20%. The values that fall within zones A and B are clinically acceptable, whereas the values included in areas C–E are potentially dangerous, and there is a possibility of making clinically significant mistakes. A: EGA after two-point calibration. B: EGA after six-point calibration. C: Rate EGA. D: Error matrix combining R-EGA and point EGA (P-EGA) zones.

**Table 1—Clinical and metabolic parameters of 50 MICU patients according to the insulin regimen used**

Insulin regimen	Intravenous	Subcutaneous	Statistics
<b>Baseline characteristics</b>			
Men/women	13/9	18/10	NS
Age (years)	60 ± 13	63 ± 18	NS
BMI (kg/m <sup>2</sup> )	27.5 ± 7.1	25.9 ± 7.3	NS
Diabetes (no/type 2/type 1)	9/9/4	21/7/0	0.021
APACHE II score	27 ± 7	19 ± 6	<0.0001
SOFA score (at start)	9 ± 4	7 ± 4	0.014
<b>Primary condition</b>			
Septic shock	13	4	0.002
Cardiogenic shock	3	3	NS
Respiratory failure	1	9	0.029
Neurologic event	0	4	NS
Cardiopulmonary resuscitation	1	4	NS
<b>Clinical outcome</b>			
Mortality	7	8	NS
Corticosteroid therapy	12	3	0.001
Vasopressor therapy	14	10	NS
Enteral nutrition	3	11	0.061
Parenteral nutrition	10	1	0.001
Renal failure (CVVH or HD)	9	2	0.006
Mechanical ventilation	16	17	NS
<b>Metabolic outcome</b>			
Insulin dose (day 1) (units/day)	141 ± 100	15 ± 26	<0.0001
Insulin dose (day 2) (units/day)	125 ± 99	19 ± 31	<0.0001
Mean glycaemia (mg/dl)	141 ± 56	149 ± 61	NS
% time at glycaemia			
<60 mg/dl	6 ± 9	4 ± 11	NS
80–110 mg/dl	26 ± 21	19 ± 22	NS
>110 mg/dl	55 ± 22	71 ± 24	0.016
>140 mg/dl	35 ± 24	42 ± 29	NS
>200 mg/dl	13 ± 19	16 ± 23	NS

Data are means ± SD or number (n). CVVH, continuous venovenous hemofiltration; HD, hemodialysis.

mg/dl had a higher BMI (31 ± 9 vs. 24 ± 5 kg/m<sup>2</sup>, *P* < 0.0001) and needed more insulin (108 ± 117 vs. 43 ± 56 units/day, *P* = 0.015) than those with glycaemia ≤140 mg/dl, but APACHE-II and SOFA scores were similar. C-reactive protein level decreased (*P* = 0.0028) and total protein concentration increased (*P* < 0.0001) over 48 h in patients with fair glycaemic control (defined as mean glycaemia ≤140 mg/dl), whereas it did not change in those with bad glycaemic control. Glycaemia correlated with leukocyte count (*r* = 0.39, *P* = 0.005), hemoglobin (*r* = 0.39, *P* = 0.005), total protein (*r* = 0.32, *P* = 0.022), and lactate level (*r* = 0.29, *P* = 0.044). Stepwise logistic regression analysis identified BMI, but not diabetes, reason for MICU admission, severity of illness, use of corticoids, or caloric intake as independent determinants for bad glycaemic control (defined as mean glycaemia >140 mg/dl). Stepwise linear

regression analysis gave the same result (BMI: β = 0.73, *P* < 0.0001).

Independent determinants for insulin dose were diabetic state (β = 0.47, *P* < 0.0001), septic shock (β = 0.22, *P* = 0.045), SOFA score (β = 0.40, *P* = 0.001), use of corticoids (β = 0.28, *P* = 0.014), and inotropics (β = -0.24, *P* = 0.035) but not BMI, caloric intake, or use of vasopressor therapy. Not including reason for MICU admission, stepwise linear regression analysis identified diabetic state (β = 0.56, *P* < 0.0001), SOFA score (β = 0.34, *P* = 0.004), and use of parenteral nutrition (β = 0.35, *P* = 0.003) as independent determinants of insulin requirements.

Patients who died at MICU (*n* = 15) were older (*P* = 0.012), had higher APACHE-II (25 ± 6 vs. 21 ± 7, *P* = 0.042) and SOFA (10 ± 4 vs. 7 ± 4, *P* = 0.012) scores, and had a higher lactate level (*P* = 0.012) but similar glycaemic

profiles (% time >200, >140, >110, <80, and <60 mg/dl) and insulin dose. Presence of diabetes, insulin regimen, and dose did not influence mortality.

**CONCLUSIONS**— Despite the pioneering work by Van den Berghe et al. (1) and the almost worldwide application of her suggestions, target glycaemia (80–110 mg/dl) is rarely achieved in the ICU. It requires extensive nursing efforts and implementation of complex insulin protocols (22). In this study, we investigated the use of CGM to assess glycaemic control in the MICU and observe that discontinuous glucose monitoring is insufficient to optimize glycaemia.

**Stress hyperglycemia and insulin therapy**

Hyperglycemia was present in 74% of MICU patients, and target glycaemia (80–110 mg/dl) was reached in only 22 ± 18% of the time, revealing the inadequacy of current insulin protocols. In this setting, the availability of an accurate continuous glucose monitoring system would be of great potential. Patients on subcutaneous insulin had worse glycaemic control than those on intravenous insulin, as illustrated by the longer time spent at glycaemia >110 mg/dl, and we propose to abandon the use of subcutaneous insulin protocols. Intravenous insulin was used more often in patients with diabetes, with a higher APACHE-II or SOFA score, or in septic shock or in those receiving corticoids, parenteral nutrition, and renal replacement therapy. This approach imposes a bias on the results but is performed in daily practice.

BMI was significantly related to the effectiveness of the insulin protocol to achieve normoglycemia. This suggests that insulin resistance may be an important factor in the pathogenesis of stress hyperglycemia. Diabetic state, septic shock as reason for MICU admission, SOFA score, and use of corticoids and inotropics were identified as independent determinants of insulin requirements to reach target glycaemia, in agreement with data of previous studies (1,2,10,11,21,22,30). Parenteral nutrition also aggravated glycaemic control (11). Glycaemia correlated with leukocyte count, total protein, and lactate level. Moreover, in patients with fair glycaemic control, C-reactive protein level decreased significantly, whereas it remained unchanged in those with bad glycaemic control. Hyperglycemia is associated with impaired immune function (9,15,19),

whereas insulin exerts anti-inflammatory effects (10,31). The increase in total protein concentration in patients with fair glycemic control may be related to anabolic actions of insulin.

### Glucose monitoring

The inherent clinical alterations of critically ill patients (fluctuating severity of illness, changes in nutritional delivery, administration of corticosteroids, etc.) produce frequent changes in insulin requirements (22). Using CGM, changes in glycemia are noted immediately, whereas this was observed much later (~1–2 h) when using intermittent glucose monitoring.

Standardization of intravenous insulin therapy improved the efficiency and safety of glycemic control in critically ill adults and improved nursing acceptance but also significantly increased the nursing workload, as 35% more glucose measurements were required with the intensive insulin protocol (32). CGM might help to guide the monitoring of glycemic excursions and the prescribing of insulin infusions.

For a CGM system to be used in the ICU, the technical performance and accuracy of the monitor system must prove reliable. In the ICU, many variables can interfere with CGM system performance (hypotension, vasoactive drugs, etc.). However, these variables would rather affect the process of subcutaneous glucose recovery (microdialysis through the subcutaneous fiber), resulting in a calibration issue, rather than in a sensor performance issue. Frequent calibration improved the accuracy. EGA after a six-point calibration showed a reduction of data points in zone C and an increase in the percentage in zones A+B (from 95 up to 97%). Goldberg et al. (33) investigated the use of another CGM device (CGMS; Medtronic MiniMed, Northridge, CA) in the MICU and found a similar Pearson correlation coefficient ( $r = 0.88$  compared with  $r = 0.84$  in our study after six-point calibration). EGA categorized 98.7% of the glucose pairs within “clinically acceptable” zones A+B, compared with 96.8% in our study after six-point calibration.

Vriesendorp et al. (34) investigated the use of the GlucoDay during and after surgery and encountered a high technical failure rate, which was mainly attributed to breaking of the microdialysis fiber, possibly during transfer from the surgical bench to the ICU bed. In our study, only one fiber broke. Although accuracy of the

GlucoDay device is comparable with that used in ambulatory diabetic patients, it still needs to be improved. It is important to avoid values in zones of the EGA other than zone A because target values are narrow. Accepting values in zone B might lead to hypoglycemia. CG-EGA has been proposed to evaluate the accuracy of CGM systems to prompt appropriate clinical action (28,29). However, Wentholt et al. (35) observed no differences with the classical assessment tools. Although CG-EGA in our small group of patients revealed acceptable point and rate accuracy (<1.49% unacceptable data), more data should be collected during episodes of pronounced glycemic fluctuations.

What level of glycemia should we aim for? The target glycemia in the Leuven study was 80–110 mg/dl (1,2). The College of Critical Care Medicine recommended maintaining a glycemia <150 mg/dl in patients with severe sepsis (36). Finney et al. (4) observed the best survival with a glycemia between 110 and 145 mg/dl, whereas Krinsley observed the lowest mortality in patients with a glycemia between 80 and 99 mg/dl (5). Data are difficult to interpret because of the diverse clinical settings, the varying methods of insulin administration, and different glycemic targets. Based on literature, optimal benefits appear to be achieved with maintenance of glycemia <100–110 mg/dl. However, because any single cutoff value is arbitrary, we suggest aiming for a glycemia that is as near to normal as is safe and practical.

How to evaluate glycemic control in the ICU? An objective measure assessment of glucose control in acutely ill patients should reflect the magnitude and duration of hyperglycemia (37). In ICU patients, there is no measure such as HbA<sub>1c</sub>, which predicts long-term complications. In acutely ill patients, indexes of glucose regulation that have been used are admission glucose, maximum glucose, mean morning glucose, and mean glucose (38). However, they are based on either a single measurement or on a subset of measurements and are therefore not indicative of overall glycemia. Similar to a continuous, online display of blood pressure and cardiac output for optimal titration of inotropes and vasopressors, a continuous display of glycemia seems mandatory for optimal titration of insulin therapy in the ICU (38,39). Our data and those of Goldberg et al. (33) suggest that using CGM in critically ill patients looks promising. If further developed as a “real-

time” glucose sensor, CGM system technology could ultimately prove clinically useful in the ICU by providing alarm signals for impending glycemic excursions, rendering intensive insulin therapy easier and safer. Closed-loop systems, with computer-assisted titration of insulin dose, will go a step further and will reduce nursing workload and lower the risk of hypoglycemia (39).

In conclusion, the GlucoDay system constitutes a good and well-tolerated method to monitor glucose profiles in MICU patients. Continuous monitoring of glucose levels may help to signal glycemic excursions and eventually to optimize titration of insulin therapy in the ICU, as target glycemia between 80 and 110 mg/dl was only reached 22% of the time. Certainly in diabetic or septic shock patients, in subjects with a high APACHE-II score, or those receiving corticoids or parenteral nutrition, intravenous insulin therapy is better than a subcutaneous regimen to obtain target glycemia.

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