Predisposing factors for hypoglycemia in the intensive care unit*

Titia M. Vriesendorp, MD; Susanne van Santen, MSc; J. Hans DeVries, MD, PhD; Evert de Jonge, MD, PhD; Frits R. Rosendaal, MD, PhD; Marcus J. Schultz, MD, PhD; Joost B. L. Hoekstra, MD, PhD

Objective: **The introduction of strict glycemic control in the intensive care unit has increased the risk for hypoglycemia. In this study we examined the association between predefined circumstances and the occurrence of hypoglycemia in the intensive care unit.**

Design: **Retrospective cohort study.**

Setting: **Academic medical center.**

Patients: **All episodes of hypoglycemia (glucose value <45 mg/dL) in our intensive care unit between September 2002 and September 2004 were identified. Presence of predefined circumstances previously associated with hypoglycemia was scored around the moment of hypoglycemia using a patient data management system and in-hospital charts. Patients with a first hypoglycemic event were contrasted to controls from the same cohort, who were matched for time since admission, to correct for the effect of length of stay. Data were analyzed using conditional logistic regression analysis.**

Interventions: **None.**

Measurements and Main Results: **Of 2,272 patients, 156 (6.9%) experienced at least one episode of hypoglycemia. Continuous venovenous hemofiltration with bicarbonate-based substitution fluid (odds ratio [OR], 14; 95% confidence interval [CI], 1.8–106), a decrease of nutrition without adjustment for insulin infusion (OR, 6.6; 95% CI, 1.9–23), diabetes mellitus (OR, 2.6; 95% CI, 1.5–4.7), insulin use (OR, 5.3; 95% CI, 2.8–11), sepsis (OR, 2.2; 95% CI, 1.2–4.1), and inotropic support (OR, 1.8; 95% CI, 1.1–2.9) were associated with hypoglycemia. Simultaneous octreotide and insulin use (OR, 6.0; 95% CI, 0.72–50) may also be associated with hypoglycemia. Gastric residual during enteral nutrition without adjusting insulin infusion, liver failure, continuous venovenous hemofiltration with lactate-based substitution fluid, diminished glomerular filtration rate, dose diminishment of glucocorticoids or catecholamines, and use of β-blocking agents were not associated with hypoglycemia. Adjusting for age, gender, and Acute Physiology and Chronic Health Evaluation II score at admission did not materially change ORs.**

Conclusion: **Use of bicarbonate-based substitution fluid during continuous venovenous hemofiltration, a decrease of nutrition without adjustment for insulin infusion, a prior diagnosis of diabetes mellitus, sepsis, and need for inotropic support were found to be associated with hypoglycemia. Simultaneous use of insulin and octreotide may be associated with hypoglycemia. (Crit Care Med 2006; 34:96–101)**

KEY WORDS: hypoglycemia; intensive care unit

In 2001, Van den Berghe et al. (1) reported that intensive insulin therapy in a surgical intensive care unit (ICU) population reduces mortality and morbidity rates. The occurrence of hypoglycemia was increased in the intensive treatment group: 5.1% of patients experienced a glucose value <40 mg/dL at least once vs. 0.8% in the control group (1). In our ICU, we found hypoglycemia rates comparable to the conventional group before publication of the Van den Berghe study, and after publication we found hypoglycemia rates comparable to the intensive treatment group (2). Little is known about the pathophysiology and consequences of hypoglycemia in the ICU, in contrast with an extensive body of literature on pathophysiology and consequences of hypoglycemia in diabetes mellitus (3). However, the (perceived) risk of hypoglycemia may impair implementation of intensive insulin therapy in intensive care units.

To develop preventive measures for hypoglycemia, we examined the association of candidate circumstances with hypoglycemia in the ICU.

METHODS

Patient Cohort

All 2,272 patients who were admitted to our ICU between September 1, 2002, and September 1, 2004, were identified.

Defining the Hypoglycemia Cases

All occurrences of hypoglycemia (defined as a glucose value <45 mg/dL) between September 1, 2002, and September 1, 2004, were collected from the patient data management system (Metavision, iMDsoft, Sassenheim, the Netherlands). Hypoglycemic values within 1 hr of the index episode in the same patient were considered to be repeated measurements and were disregarded. All patients were included in the analysis with the first hypoglycemic event only; subsequent events were not analyzed.

Defining the Controls

The aim of this study was to examine whether certain circumstances predispose patients to develop hypoglycemia during ICU admission. Therefore, circumstances of a case were compared with circumstances of a control at the same point in time (nested case-control method), which leads to complete adjustment for the effect of duration and its determinants. The control patients were ran-

*See also p. 246.

From the Department of Internal Medicine (TMV, SvS, JHD, JBLH) and Department of Intensive Care Medicine (EdJ, MJS), Academic Medical Center, Amsterdam, The Netherlands; the Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, and the Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands (FRR).

The authors have no financial interest to disclose.

DOI: 10.1097/01.CCM.0000194536.89694.06

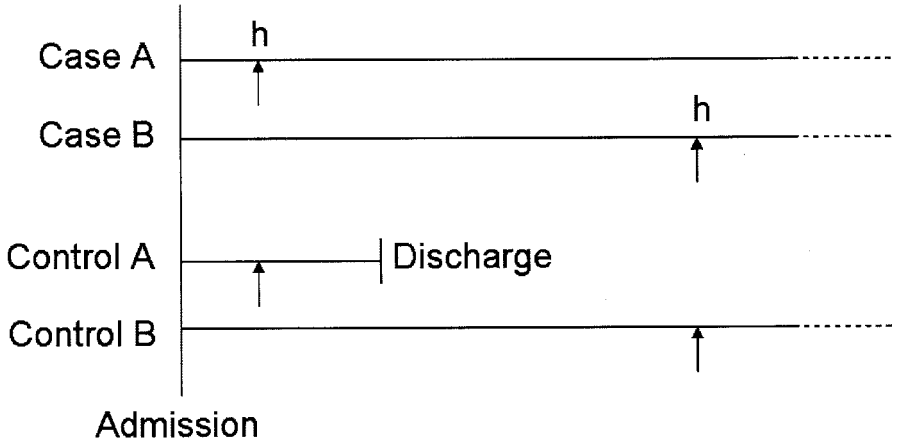

Figure 1. Matching of cases. Arrows indicate index moment; *h* indicates a hypoglycemic episode. Controls were drawn from the at-risk population. This means that controls had to be admitted at least as long as the case was admitted until the first episode of hypoglycemia (*h*) and that controls did not have a hypoglycemic episode before the hypoglycemic episode in the case. Thus, control A could not have served as a control for case B. Circumstances were scored around the moment of hypoglycemia in the case and around the time-matched moment in the control (referred to as "index moment").

domly selected from the "at-risk" population between September 1, 2002, and September 1, 2004. The at-risk population (risk set) comprised all patients at the time of the event in a case who had a stay in the ICU of at least the same duration as the cases and had not had a hypoglycemic event (glucose value <45 mg/dL) until the first hypoglycemic episode in the case. This sampling method may also be seen as matching on time, which needs to be taken into account given the variable durations of stay in the ICU. A patient could serve as a control only once. However, the nested-case-control method implies that a patient may be included both in the case and in the control group. The circumstances before and during hypoglycemia were scored in the case group and before and during the matched moment in the control group (index moment, Fig. 1).

Setting

Our ICU is a 28-bed "closed-format" department of a university teaching hospital, in which medical and surgical patients (including cardiothoracic and neurosurgical patients) are under the direct care of the ICU team. The ICU team comprises eight full-time intensivists, eight subspecialty fellows, and 12 residents. All beds are equipped with a patient data management system. Strict glycemic control, with target glucose levels between 81 and 144 mg/dL, was aimed for after the publication of the Van den Berghe study. A higher target range than 80–110 mg/dL, which was used in the Van den Berghe study (1), was chosen because of concern of the ICU staff for hypoglycemia in a "real-life," nonstudy setting. A glucose level at which insulin treatment should be started was left to the discretion of the attending physician. Insulin infusion was increased by 1 IU/hr in case of blood glucose >144 mg/dL, and an additional bolus of 8 IU of insulin was administered in case of blood glucose >288 mg/dL. In case of blood glucose <80 mg/dL, insulin infusion was stopped. Insulin was administered through continuous intravenous infusion (Actrapid®, Novo Nordisk Farma, Alphen aan de Rijn, the Netherlands) and was nurse-driven. Implementation of this protocol led to a decrease in mean blood glucose from 162 mg/dL (SD ±58, before implementation, in 2000) to 133 mg/dL (SD ± 45, after implementation, in 2003) (2). There was no standard protocol for treatment of hypoglycemia or for the frequency of glucose measurements after hypoglycemia. Whole blood glucose was measured with an on-site arterial blood gas analyzer (Ciba Corning 865, Chiron Diagnostics, Medford, MA). Creatinine was routinely measured every morning; other laboratory variables, such as bilirubin, were measured only when clinically indicated.

Candidate Risk Factors for Hypoglycemia

We predefined a number of factors we considered to be associated with hypoglycemia, based on literature review and clinical reasoning. These included a) discontinuation or lowering of nutrition or glucose containing fluids without adjusting insulin administration (1); b) gastric residual during enteral nutrition without adjusting insulin administration; c) presence of conditions previously described to predispose for hypoglycemia (4, 5), including diagnosis of diabetes mellitus before ICU admission, sepsis, hemodynamic shock, liver failure, renal failure, or renal replacement therapy; and d) medication use previously described to be associated with hypoglycemia (6, 7) and discontinuation or dose diminishment of drugs associated with hyperglycemia.

Nutrition and Glucose-Containing Fluid Administration

As a rule, patients admitted to our ICU receive intravenous glucose 5% at a rate of 30 mL/hr, and enteral or parenteral feeding is initiated within 24 hrs of ICU admittance. Gastric residual during enteral nutrition was defined as residual >50% of the hourly enteral feeding dose within 6 hrs before the index moment. Changes in nutrition or administration of glucose-containing solutions within 6 hrs before the index moment were scored. Changes in insulin administration were scored within 3 hrs before the index moment, and insulin dosage was scored immediately before the index moment.

Predisposing Conditions

Prior diagnosis of diabetes mellitus and insulin use before ICU admittance was retrospectively scored by reviewing in-hospital charts. Sepsis was defined as systemic inflammatory response syndrome at the index moment and a culture-proven infection within 48 hrs before or after the index moment (8). For patients with hypoglycemia, heart rate during the last glucose value >80 mg/dL before the moment of hypoglycemia was retrieved, to avoid using tachycardia as a result of hypoglycemia for classification of systemic inflammatory response syndrome. Hemodynamic status was scored at the index moment according to Sepsis-related Organ Failure Assessment (SOFA) classification for hemodynamic status (9). Liver failure was scored according to SOFA classification (9) for liver failure using the plasma bilirubin concentration in the last 24 hrs before the index moment. Creatinine level <24 hrs before the index moment and estimated body weight at ICU admittance were used to calculate creatinine clearance with the Cockcroft-Gault formula (10). Patients with acute renal failure were treated with continuous venovenous hemofiltration (CVVH; Diapact, B-Braun, Melsungen, Germany). Either bicarbonate-based or lactate-based substitution fluid (SH-53/SH-19, B-Braun, Melsungen, Germany) was used as predilution fluid. Substitution fluid was generally infused at a rate of 2000 mL/hr with a blood flow of 150 mL/min. In our institution, lactate-based substitution fluid is the first choice; septic patients and patients with cardiac failure are treated with bicarbonate-based substitution fluid.

Medication Use

Drug use previously associated with hypoglycemia (insulin, oral antidiabetic drugs,

Table 1. Characteristics of study patients

	Total Cohort n = 2272	Hypoglycemia Cases n = 156	Controls n = 155
Male gender, n (%)	1412 (62)	81 (52)	103 (66)
Age, yrs, mean (SD)	60.3 (±16.4)	60.8 (±16.2)	60.9 (±16.5)
SAPS score at admission, median (IQR)	36 (27–47)	47 (37–59)	42 (31–55)
APACHE II score at admission, median (IQR)	16 (12–21)	20 (16–26)	18 (14–24)
ICU mortality, n (%)	279 (12)	42 (27)	32 (20)
ICU length of stay, days, median (range)	1.8 (0.004–103)	6.8 (0.01–103)	5.1 (0.5–68)
Referring specialty, n (%)			
Internal medicine	268 (12)	41 (26)	25 (16)
Cardiology/pulmonology	194 (8.5)	21 (14)	18 (12)
Neurology/neurosurgery	282 (13)	12 (7.7)	19 (12)
General surgery	451 (20)	37 (24)	41 (26)
Thoracic surgery	1058 (47)	51 (25)	39 (33)
Obstetrics/gynecology	18 (0.8)	1 (0.6)	1 (0.6)
Glucose value at index moment, mg/dL, median (IQR)	—	37 (31–41)	124 (108–146)
Mechanical ventilation at index moment	—	114 (74)	108 (71)

SAPS, Simplified Acute Physiology Score; IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.

β-blocking agents, quinine or quinine derivatives, simultaneous octreotide and insulin treatment, pentamidine, disopyramide, aspirin, trimethoprim sulfamethoxazole) (6, 7) and drugs associated with hyperglycemia (glucocorticoids, catecholamines) were scored either when they were discontinued or the dose was diminished. We scored insulin and catecholamine use within 3 hrs before the index moment, long-acting sulfonylurea drugs within 96 hrs before the index moment, and all other medication within 24 hrs before the index moment.

Statistical Analysis

Conditional logistic regression analysis was used to calculate odds ratio (OR) and 95% confidence interval (CI), using SPSS version 11.5.1 (SPSS, Chicago, IL). This analysis takes the stratified sampling of the matching into account and resembles an analysis stratified for each paired case and control. This implies that all analyses, including the univariate analysis, are adjusted for duration of admission. All factors were entered as dichotomous variables except for creatinine clearance, which was entered as a continuous variable. All predefined putative risk factors were analyzed with univariate regression analysis and with multivariate regression analysis correcting for age, gender, and Acute Physiology and Chronic Health Evaluation (APACHE) II score at admission and for number of glucose measurements before the index moment in an additional analysis. All odds ratios are presented with 95% confidence intervals, which were derived from the likelihood functions of the models.

The Ethical Review Board of the Academic Medical Center waived the need for informed consent because of the retrospective nature of the study.

RESULTS

Between September 1, 2002, and September 1, 2004, 2,503 ICU admissions of 2,272 different patients were identified, comprising 32.1 patient-years. Almost half of all admitted patients were cardiosurgical patients. The median duration of stay was 1.8 days. Mortality rate in our ICU during this period was 12.3% (Table 1).

We found 245 hypoglycemic events in 156 patients, indicating that 6.9% of patients experienced at least one hypoglycemic episode during one or more ICU admittance. The incidence of hypoglycemia was 245 of 32.1 (7.6) per patient-year. Fifty-two patients (33%) experienced more than one hypoglycemic event (31 patients two events, 12 patients three events, five patients four events, three patients five events, and one patient eight events). The first hypoglycemic event occurred after 1.7 days of ICU admittance (range 0–60 days). Our matching strategy, drawing patients from the "risk set," implied that the pool of control patients became smaller with increasing time to the first hypoglycemic event. Moreover, for one patient, no adequate control could be identified because hypoglycemia occurred too long after admission to be matched with a control.

Baseline characteristics of patients with and without hypoglycemia are listed in Table 1 (data were >99% complete). More patients with hypoglycemia were female compared with controls (OR, 1.7; 95% CI, 1.1–2.7).

The number of glucose measurements until the index moment was similar in the case and the control group (median 13 [interquartile range 5–42] in patients with hypoglycemia vs. median 17 [interquartile range 6–50] in controls). The first blood glucose after hypoglycemia was determined after a median of 74 mins (range 8–450 mins). Within 1 hr after hypoglycemia, 60 of 156 (38%) patients had a glucose value measured, 42 of whom (70%) had a glucose value >80 mg/dL. Within 3 hrs after hypoglycemia, 143 of 156 (92%) patients had a glucose value measured, 135 of whom (94%) had a glucose >80 mg/dL.

Nutrition and Glucose-Containing Fluid Administration

Forty-four percent of the cases vs. 42% of the controls did not receive any nutrition at the index moment. Patients generally received continuous enteral nutrition only (43% of the cases vs. 44% of the controls). The remainder received parenteral nutrition (4.5% of cases vs. 7.7% of controls), oral nutrition (3.2% of cases vs. 4.5% of controls), or a combination of enteral with oral or parenteral nutrition (4.5% of cases vs. 0.6% of controls). Lowering or discontinuing nutrition (enteral, parenteral, or oral) without adjusting insulin infusion was associated with hypoglycemia (OR, 6.6; 95% CI, 1.9–23). Lowering glucose 5% solution without adjusting insulin infusion seemed associated with hypoglycemia (OR, 6.0; 95% CI, 0.72–49), although it was not statistically significant. The frequency of gastric residual in patients with enteral feeding without adaptation of insulin infusion did not differ in both cohorts (OR, 1.0; 95% CI, 0.43–2.3).

Predisposing Conditions

Diabetes Mellitus. Patients with hypoglycemia had more often been diagnosed with diabetes mellitus (OR, 2.6; 95% CI, 1.5–4.7) and used insulin before ICU admittance more frequently (OR, 17; 95% CI, 2.3–127) than control patients. Patients with a prior diagnosis of diabetes mellitus were also more likely to experience more than one hypoglycemic event (OR, 2.3; 95% CI, 1.1–4.7). At the time of hypoglycemia, patients with diabetes received a similar dose of insulin compared

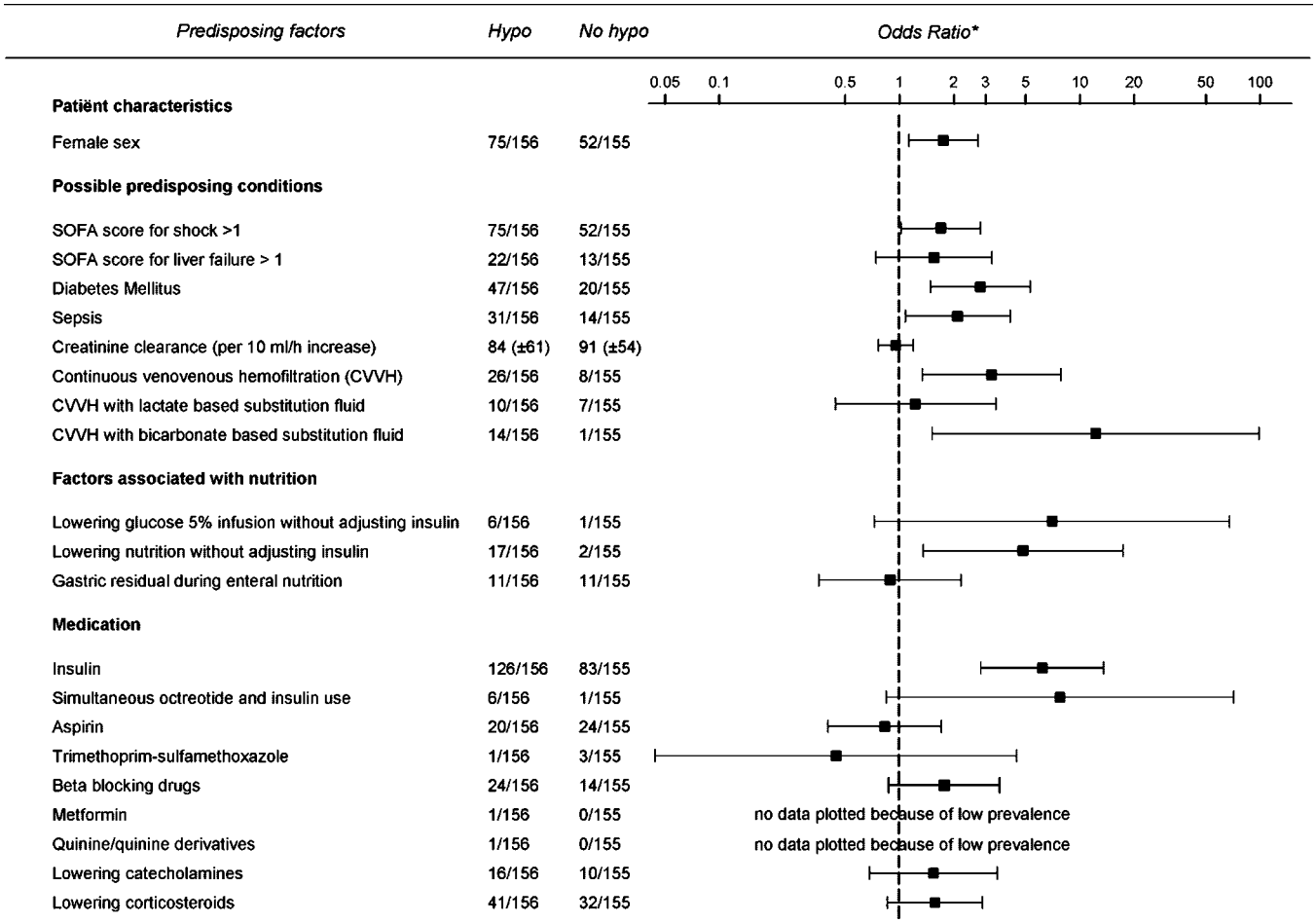

Figure 2. Results of conditional regression analysis. *All odds ratios except the odds ratio for female gender were adjusted for age, gender, and Acute Physiology and Chronic Health II score at admission. Error bars indicate 95% confidence intervals. *SOFA*, Sepsis-related Organ Failure Assessment; *CVVH*, continuous venovenous hemofiltration.

with patients without a prior diagnosis of diabetes (3.9 IU/hr, range 0.5–20.5 for cases vs. 3.6 IU/hr, range 1.0–12 for controls).

Sepsis. Hypoglycemia occurred more often in patients with sepsis than in patients without sepsis (OR, 2.2; 95% CI, 1.2–4.1).

Liver Failure. A SOFA score for liver failure of ≥1 was not associated with hypoglycemia (OR, 0.33; 95% CI, 0.04–3.2 and OR, 1.7; 95% CI, 0.85–3.3 when considering all patients with missing bilirubin data [>60%] as having no liver failure).

Hemodynamic Status. Having a SOFA score of ≥1 for shock was associated with an increased risk for hypoglycemia (OR, 1.8; 95% CI, 1.1–2.9).

Renal Function and Renal Replacement Therapy. Patients with hypoglycemia had a similar creatinine clearance rates compared with controls (Fig. 2). Patients with hypoglycemia were more often treated with CVVH compared with controls (26 of 153 vs. eight of 155; OR, 3.7; 95% CI, 1.6–8.6). In subanalysis, the increased risk was only found in patients receiving bicarbonate substitution fluid (OR, 14.0; 95% CI, 1.8–106). Patients receiving lactate-based substitution fluid were not at higher risk for hypoglycemia (OR, 1.4; 95% CI, 0.5–3.8).

Medication

The association between occurrence of hypoglycemia and use of drugs previously associated with hypoglycemia or hyperglycemia is summarized in Figure 2. As expected, insulin use was associated with hypoglycemia (OR, 5.4; 95% CI, 2.8–10). Octreotide use was found in six cases (3.8%) compared with one control (0.6%; OR, 6.0; 95% CI, 0.72–49). In all cases of octreotide use, insulin was administered concomitantly via continuous intravenous infusion. None of the patients received pentamidine or disopyramide.

Figure 2 provides ORs and 95% CI of predefined risk factors adjusted for age, gender, and APACHE II score at admission. Additional analysis showed that also adjusting for number of glucose values measured before the index moment did not materially change ORs (data not shown).

DISCUSSION

In this study we examined predefined candidate circumstances associated with occurrence of hypoglycemia in ICU patients. We found that glucose values <45 mg/dL are common in our ICU and occurred at least once in almost 7% of all patients. This is similar to the results of Van den Berghe et al. (1), who found that 5.1% of patients who received strict glucose control experienced at least one glucose value <40 mg/dL. Furthermore, we

found that treatment with CVVH, particularly when bicarbonate-based substitution fluid was used, discontinuing nutrition without adjusting insulin therapy, a prior diagnosis of diabetes mellitus, insulin treatment, sepsis, and need for inotropic or vasopressor drugs were associated with hypoglycemia in the ICU, independent of age, gender, and APACHE II score at admission.

It is difficult to define causal factors for hypoglycemia in the ICU. Many known and unknown, interrelated factors may play a role in the development of hypoglycemia in the ICU that cannot be corrected for in multivariate analysis. However, by matching the hypoglycemia cases to control patients with the same ICU exposure (nested case-control method), the reported ORs are independent of time spent in the ICU and of factors that are closely related to length of ICU stay, including, for instance, the number of glucose measurements before hypoglycemia. Furthermore, in multivariate analysis we also corrected ORs and 95% CIs for the most important possible confounders (age, gender, and APACHE II score at admission). A second limitation is that more patients than expected had hypoglycemia without reported insulin therapy (n = 30, 19%). Data on drug use before ICU admittance, such as insulin use, were limited. We searched for insulin use before ICU admittance for all patients who experienced hypoglycemia within 6 hrs after admittance without reported insulin use (n = 16; 10%), but we could only confirm insulin use in two of these patients. A third limitation of our study is that the investigators were aware of the patient being a case or a control at the time of data collection, which may have led to a bias in the data collection.

More than 40% of patients did not receive any means of nutrition, even though the policy in our ICU is to start nutrition in all patients within 24 hrs after admission. The fact that all patients who were admitted to the ICU were eligible for the study, including patients who were admitted for ≤24 hrs, may explain the relatively high percentage of patients who received no means of nutrition at the index moment. Lowering or discontinuing nutrition without adjusting insulin therapy was associated with hypoglycemia but did not occur as frequently as we expected (only in 11% of all hypoglycemia cases), whereas Van den Berghe (11) reported this as the most frequent cause of hypoglycemia in her study. Awareness and education may prevent these unintended errors. In ICUs equipped with a patient data management system, a pop-up message to warn the attending nurse to adjust insulin administration as soon as nutrition is lowered or discontinued may be a simple method to lower the incidence of hypoglycemia.

Patients with a diagnosis of diabetes mellitus before ICU admission were more likely to experience (recurrent) hypoglycemia. Patients with a prior diagnosis of diabetes did not receive more insulin at the time of hypoglycemia compared with patients without known diabetes. Patients with type 1 diabetes and patients with longstanding type 2 diabetes may have an impaired counterregulatory response (3). This may help to explain why patients with insulin use before ICU admittance were at a higher risk to develop hypoglycemia.

Patients treated with CVVH were almost four times more likely to experience hypoglycemia. It may be hypothesized that in patients treated with CVVH, insulin action is prolonged because insulin clearance is impaired. However, in CVVH with hemodialysis, no difference was found between insulin concentrations before and after the hemofiltration dialysis filter (12), and in our study, creatinine clearance was hardly different in patients with and without hypoglycemia. Theoretically, CVVH may ameliorate insulin sensitivity through increased clearance of inflammatory molecules, such as tumor necrosis factor-α and interleukins, analogous to the controversial hypothesis that CVVH is beneficial for patients with sepsis (13).

Interestingly, patients who received bicarbonate-based substitution fluid were at higher risk for hypoglycemia, in contrast to patients who received lactate-based substitution fluid. The bicarbonate-based substitution fluid used in our institution contains less glucose (100 mg/dL) than the lactate-based substitution fluid (260 mg/dL). However, because of predilution with substitution fluid and the equimolar filtration of glucose, no major glucose loss in the ultrafitrate can be expected. Indeed, in our study blood glucose levels were similar before hypoglycemia in patients with and without CVVH and in patients with bicarbonate-based and lactate-based substitution therapy (data not shown). A recent study suggests that during hemodialysis, erythrocyte glucose consumption is increased, caused by high concentrations of bicarbonate in the dialysate fluid. High bicarbonate concentrations would initiate changes in cytoplasmic pH, which in turn would increase anaerobic glycolysis in erythrocytes (14). Moreover, lactate can serve as a substrate for gluconeogenesis whereas bicarbonate cannot. The most likely explanation, however, is that the sickest patients receive bicarbonate-based substitution fluid rather than lactate-based substitution fluid in our hospital and that the sickest patients are at increased risk for hypoglycemia.

Simultaneous insulin and octreotide use tended to be associated with hypoglycemia, although this was not statistically significant, probably because of low prevalence. There is, however, pathophysiologic evidence that simultaneous octreotide and continuous intravenous insulin administration may predispose patients to hypoglycemia. Octreotide is a long-acting somatostatine analogue that is usually prescribed in ICU in patients after abdominal surgery because of its vasoconstrictive effect on the splanchnic circulation (15). However, octreotide also has profound endocrine effects, as it inhibits the secretion of growth hormone, insulin, and glucagon. Exogenous insulin infusion suppresses endogenous insulin production, thereby abolishing the decrease of endogenous insulin production as a first defense against hypoglycemia. Counterregulation is further impaired by inhibitory effects of octreotide on glucagon secretion and, to a lesser extent, its inhibitory effects on growth hormone secretion. Simultaneous use of insulin and octreotide may therefore predispose patients to hypoglycemia.

An additional finding of our study was that more patients with hypoglycemia were female compared with patients without hypoglycemia. Women may have a lower counterregulatory threshold for hypoglycemia then men (16). Female gender was also found to be associated with an increased occurrence of hypoglycemia in elderly hospitalized patients (4).

Because some clinics have separate medical and surgical ICUs, and because hypoglycemia rates and possible predisposing factors for hypoglycemia may be different in surgical vs. medical ICUs, it would be interesting to examine whether the same associations can be found in surgical and nonsurgical patients. Although this study was not designed for such a subanalysis, we did perform a separate analysis for surgical and nonsurgical patients. As can be expected with a

In this study, we found that continuous venovenous hemofiltration treatment with bicarbonate substitution fluid, discontinuation of nutrition without adjustment of insulin therapy, a prior diagnosis of diabetes mellitus, insulin treatment, sepsis, and need for inotropic or vasopressor drugs were associated with occurrence of hypoglycemia in our intensive care unit.

50% loss of power, 95% CIs increased and some of the observed relationships lost their significance. Nevertheless, general tendencies were similar overall.

It can be concluded from the large mortality reduction with strict glycemic control observed in the Van den Berghe study that the beneficial effects of lowering hyperglycemia outweigh possible detrimental effects of hypoglycemia. However, the (perceived) risk of hypoglycemia is likely to impair full implementation of intensive insulin therapy. Hypoglycemia should therefore be avoided, but not at the cost of worsening glycemic control. Awareness of possible risk factors and more frequent glycemic control may lower the occurrence of hypoglycemia in patients who are at increased risk for hypoglycemia.

CONCLUSIONS

In this study, we found that CVVH treatment with bicarbonate substitution fluid, discontinuation of nutrition without adjustment of insulin therapy, a prior diagnosis of diabetes mellitus, insulin treatment, sepsis, and need for inotropic or vasopressor drugs were associated with occurrence of hypoglycemia in our ICU.

REFERENCES

1. Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345:1359–1367
2. Moeniralam H, Spronk P, Graat M, et al: Tight glycemic control increases the incidence of hypoglycemia in intensive care unit patients. Abstr. *Crit Care* 2005; 9(Suppl 1): S162
3. Cryer PE, Davis SN, Shamoon H: Hypoglycemia in diabetes. *Diabetes Care* 2003; 26: 1902–1912
4. Kagansky N, Levy S, Rimon E, et al: Hypoglycemia as a predictor of mortality in hospitalized elderly patients. *Arch Intern Med* 2003; 163:1825–1829
5. Fischer KF, Lees JA, Newman JH: Hypoglycemia in hospitalized patients. Causes and outcomes. *N Engl J Med* 1986; 315: 1245–1250
6. Seltzer HS: Drug-induced hypoglycemia. A review of 1418 cases. *Endocrinol Metab Clin North Am* 1989; 18:163–183
7. Ben Ami H, Nagachandran P, Mendelson A, et al: Drug-induced hypoglycemic coma in 102 diabetic patients. *Arch Intern Med* 1999; 159:281–284
8. Bone RC, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101:1644–1655
9. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22:707–710
10. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31–41
11. Van den Berghe G, Wouters PJ, Bouillon R, et al: Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. *Crit Care Med* 2003; 31:359–366
12. Bellomo R, Colman PG, Caudwell J, et al: Acute continuous hemofiltration with dialysis: Effect on insulin concentrations and glycemic control in critically ill patients. *Crit Care Med* 1992; 20:1672–1676
13. Sieberth HG, Kierdorf HP: Is cytokine removal by continuous hemofiltration feasible? *Kidney Int Suppl* 1999; 72:S79–S83
14. Takahashi A, Kubota T, Shibahara N, et al: The mechanism of hypoglycemia caused by hemodialysis. *Clin Nephrol* 2004; 62: 362–368
15. de Franchis R: Somatostatin, somatostatin analogues and other vasoactive drugs in the treatment of bleeding oesophageal varices. *Dig Liver Dis* 2004; 36(Suppl 1):S93–S100
16. Merimee TJ, Tyson JE: Stabilization of plasma glucose during fasting; Normal variations in two separate studies. *N Engl J Med* 1974; 291:1275–1278