Multicentric, Randomized, Controlled Trial to Evaluate Blood Glucose Control by the Model Predictive Control Algorithm Versus Routine Glucose Management Protocols in Intensive Care Unit Patients

JOHANNES PLANK, MD[1]
JAN BLAHA, MD[2]
JEREMY CORDINGLEY, MBBS[3]
MALGORZATA E. WILINSKA, PHD[4]
LUDOVIC J. CHASSIN, PHD[4]
CLIFF MORGAN, PHD[3]
STEPHEN SQUIRE, BSC[3]
MARTIN HALUZIK, PHD[2]
JAROMIR KREMEN, MD[2]
STEPAN SVACINA, PHD[2]
WOLFGANG TOLLER, MD[5]
ANDREAS PLASNIK, MD[1]
MARTIN ELLMERER, PHD[1]
ROMAN HOVORKA, PHD[4]
THOMAS R. PIEBER, MD[1]

OBJECTIVE — To evaluate a fully automated algorithm for the establishment of tight glycemic control in critically ill patients and to compare the results with different routine glucose management protocols of three intensive care units (ICUs) across Europe (Graz, Prague, and London).

RESEARCH DESIGN AND METHODS — Sixty patients undergoing cardiac surgery (age 67 ± 9 years, BMI 27.7 ± 4.9 kg/m^2, 17 women) with postsurgery blood glucose levels >120 mg/dl (6.7 mmol/l) were investigated in three different ICUs (20 per center). Patients were randomized to either blood glucose management (target range 80–110 mg/dl [4.4–6.1 mmol/l]) by the fully automated model predictive control (MPC) algorithm (n = 30, 10 per center) or implemented routine glucose management protocols (n = 30, 10 per center). In all patients, arterial glucose was measured hourly to describe the glucose profile until the end of the ICU stay but for a maximum period of 48 h.

RESULTS — Compared with routine protocols, MPC treatment resulted in a significantly higher percentage of time within the target glycemic range (% median [min–max]: 52 [17–92] vs. 19 [0–71]) over 0–24 h ($P < 0.01$). Improved glycemic control with MPC treatment was confirmed in patients remaining in the ICU for 48 h (0–24 h: 50 [17–71] vs. 21 [4–67], $P < 0.05$, and 24–48 h: 65 [38–96] vs. 25 [8–79], $P < 0.05$, for MPC [n = 16] vs. routine protocol [n = 13], respectively). Two hypoglycemic events (<54 mg/dl [3.0 mmol/l]) were observed with routine protocol treatment. No hypoglycemic event occurred with MPC.

CONCLUSIONS — The data suggest that the MPC algorithm is safe and effective in controlling glycemia in critically ill postsurgery patients.

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Epidemiological studies have revealed a significant relationship between impaired glycemic control and poor outcome in patients with acute cardiovascular events (1–3), postoperative wound infections (4,5), and trauma (6). Patients with diabetes are affected, but patients with stress hyperglycemia with no previous diagnosis of diabetes also have a poor prognosis (1,2,7,8). Critical illness and trauma induce counterregulatory hormone release and alterations in carbohydrate metabolism such as enhanced hepatic gluconeogenesis, insulin resistance, and relative insulin deficiency (9,10).

A growing body of evidence indicates that treatment of hyperglycemia improves clinical outcome (11). In a prospective randomized trial in Leuven, postoperative patients were treated with an intensive insulin protocol (12). Strict glycemic control (80–110 mg/dl) resulted in a reduction of in-hospital mortality and a decrease in organ system dysfunction compared with moderate hyperglycemia (180–200 mg/dl). In another study performed on a mixed medical-surgical population, the implementation of an intensive glucose management protocol led to decreased mortality, morbidity, and length of intensive care unit (ICU) stay of critically ill adult patients (13).

Based on this clinical evidence, efforts have to be made to maintain strict glycemic control in critically ill patients. To achieve this goal, the implementation of complex intensive insulin infusion protocols based on frequent bedside glucose monitoring is required. Numerous guidelines have been developed and tested to implement tight glycemic control in ICUs (13–18). However, most of these guidelines still require user interventions or intuitive decisions of ICU staff.

The development of a closed-loop control system that automatically regulates the dose of insulin based on glucose measurements could permit tight glycemic control without increasing the work-

From the [1]Department of Internal Medicine, Medical University Hospital, Graz, Austria; the [2]Faculty of Medicine, Charles University, Prague, Czech Republic; the [3]Adult Intensive Care Unit, Royal Brompton Hospital, London, U.K.; the [4]Department of Paediatrics, Cambridge University, Cambridge, U.K.; and the [5]Department of Anaesthesiology and Intensive Care Medicine, Medical University Hospital, Graz, Austria.

Address correspondence and reprint requests to Johannes Plank, Department of Internal Medicine, Medical University Graz, Auenbruggerplatz 15, 8036 Graz, Austria. E-mail: johannes.plank@klinikum-graz.at.

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Abbreviations: ICU, intensive care unit; MPC, model predictive control.

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

Table 1—*Baseline characteristics of study participants*

	Graz	Prague	London
Patients	20	20	20
Age (years)	69 ± 7	67 ± 11	68 ± 8
Female	5	6	6
Caucasian	20	20	20
BMI (kg/m^2)	28.2 ± 4.9	27.0 ± 4.0	28.1 ± 5.8
Blood glucose at entry (mg/dl)	157 ± 79	162 ± 44	146 ± 24
Type of surgery			
CABG	13	15	8
Valve replacement	5	1	10
CABG and valve replacement	—	4	2
Aortic replacement	2	—	—
History of diabetes	6	6	2
APACHE score	10.1 ± 3.2	11.4 ± 4.5	12.7 ± 3.5

Data are means ± SD and *n*. CABG, coronary artery bypass grafting. APACHE, Acute Physiology and Chronic Health Evaluation.

load of the ICU nursing staff. An algorithm for calculation of the appropriate insulin infusion rate is one prerequisite for the establishment of such an automated glycemic control system. For patients with type 1 diabetes, a fully automated algorithm using an adaptive model predictive control (MPC) approach has been developed and successfully tested for a modular extracorporeal artificial pancreas (19–21).

The objective of the present study was to test a modified version of the MPC algorithm for the establishment of tight glycemic control in critically ill postoperative patients and to compare the results with routine treatment of hyperglycemia as currently established in different clinical centers across Europe.

RESEARCH DESIGN AND METHODS

— The study was approved by the institutional ethical review board local ethics committee of the Medical University (Graz), Charles University (Prague), and Royal Brompton Hospital (London). Written informed consent was obtained preoperatively from all subjects.

The study population consisted of adult men and women undergoing elective cardiac surgery followed by a stay in the ICU. Patients aged 18–90 years, both with or without an established diagnosis of diabetes, were eligible for inclusion. Exclusion criteria included allergy against insulin and mental incapacity or language barriers precluding adequate understanding. The study population baseline characteristics are shown in Table 1.

The study was conducted as a multicenter (Graz, Prague, and London), randomized, parallel trial. The subjects fulfilling the study day inclusion criteria (glucose >120 mg/dl [6.7 mmol/l], time 0) after admission to the ICU were randomly assigned to either the intervention (blood glucose control by the MPC) or the control group (routine blood glucose management protocol implemented in the respective ICU). Overall, 60 patients were randomized by individual centers in blocks of 10. In all patients, undiluted arterial blood for measurement of blood glucose was drawn manually every 60 min from an arterial line available for routine monitoring procedures. Whole blood glucose was analyzed by a standard point-of-care testing device (Graz: Omni S, Roche Diagnostics, Basel, Switzerland; Prague and London: ABL 700, Radiometer Medical, Copenhagen, Denmark). Insulin (Actrapid HM; Novo Nordisk, Baegsvard, Denmark) was given intravenously through a central venous catheter using a 50-ml syringe and standard infusion pumps. All trial-related activities were carried out until the end of the ICU stay or for a maximum period of 48 h.

MPC and routine glucose management protocols

The MPC algorithm used in this study has been described in detail previously (19,20). Briefly, the main component of the MPC is a model representing the glucoregulatory system. It enables the prediction of the glucose excursion by a dose optimizer. The dose optimizer proposes future insulin infusion rates and tunes the rates until the predicted glucose excursion fits into a desired glucose excursion. The desired excursion is a slow normalization in case of hyperglycemia, a fast recovery in case of hypoglycemia, or maintenance of normoglycemia. This optimization process is the key benefit of using the MPC algorithm in place of classical control algorithms (22). Classical algorithms use feedback control to maintain normoglycemia; therefore, instead of preventing hypo- and hyperglycemia, they respond to it. The glucoregulatory model of the MPC has individual parameters that are adapted online. Glucose concentration, insulin dosage, and carbohydrate intake are the input variables for the MPC. Input of glucose concentration is required every 60 min and triggers the online adaptation of the parameters and the calculation of the insulin infusion rate for the following 60 min. The rate is provided as the output parameter. MPC was implemented on a laptop computer (Graz and Prague) or a bedside patient management system (London). In the case of MPC treatment, glucose values were provided every 60 min to the MPC and the insulin infusion rate adjusted hourly, as suggested by the algorithm.

In the case of routine care management, blood glucose values were provided to the ICU staff as required by the routine glucose management protocol implemented in the respective ICU. Whereas in Prague and London the protocols are using continuous intravenous insulin infusion for all patients, in Graz only patients with a history of insulin-dependent diabetes are treated with continuous insulin infusion. All other patients in Graz are routinely managed with intravenous insulin bolus regimen.

The target range for blood glucose levels, as defined by the study protocol, was 80–110 mg/dl (4.4–6.1 mmol/l), which has been demonstrated to reduce mortality and morbidity in postcardiac surgery patients (12). The MPC algorithm and the routine care management protocol in Graz are aiming for exactly the same target range, while in Prague a slightly higher level for the upper limit (81–117 mg/dl [4.5–6.5 mmol/l]) and in London a slightly lower level for the lower limit (72–108 mg/dl [4–6 mmol/l]) is implemented in the routine glucose protocol.

Likewise, small differences in the definition of hypoglycemia can be found among the routine management protocols (London: 54 mg/dl [3.0 mmol/l], Graz: 60 mg/dl [3.3 mmol/l], and Prague: 63 mg/dl [3.5 mmol/l]). For the study protocol, blood glucose levels <54 mg/dl

(3.0 mmol/l) were defined as hypoglycemic events. Detailed information regarding the different routine care management protocols can be found at www.clinicip.org/clinical.htm.

Statistical analysis

Except where noted, statistical analysis was performed on the intention-to-treat population. The primary end point for the assessment of the glucose profiles was time within the target range of 80–110 mg/dl (4.4–6.1 mmol/l). Futher parameters used were time above the target range of 110 mg/dl (6.1 mmol/l); time between 54 and 79 mg/dl (2.9 to <4.4 mmol/l), indicating risk for hypoglycemia; average glucose levels; and number of hypoglycemic episodes (blood glucose level <54 mg/dl [<3.0 mmol/l]). All comparisons were performed using the Mann-Whitney *U* test. All tests of significance were two tailed. The conventional significance level of $\alpha = 0.05$ was used. The SPSS 11.5.1 software package was applied for statistical analysis.

RESULTS — A total of 94 patients undergoing cardiac-thoracic surgery were screened to participate in the trial, 4 patients refused to be screened, and 34 patients eligible after screening were not randomized. Reasons for noninclusion were blood glucose levels <120 mg/dl (6.7 mmol/l) at ICU admission (30 patients) and surgery postponed (4 patients).

Patients were followed until transfer to the telemetry unit but for a maximum period of 48 h. Mean duration of follow-up for the intervention MPC vs. control groups, respectively, was (means ± SD) 43.5 ± 9.0 vs. 28.3 ± 16.3 h in Graz, 47.8 ± 0.6 vs. 48.0 ± 0 h in Prague, and 28.2 ± 8.4 vs. 23.5 ± 8.1 h in London.

Glucose control

Profiles of mean glucose values for MPC treatment and routine glucose management are displayed in Fig. 1. The mean glucose profiles for MPC treatment in all three centers were almost superimposable. After ~9 h, the target range was achieved and glycemic levels remained for the most part within the target range (Fig. 1*A*). In contrast, glucose profiles obtained with routine glucose treatment protocols showed distinct heterogeneity (Fig. 1*B*). Whereas in Prague and London the profiles were touching and further oscillating around the upper limit after 9 h, in Graz the requested glycemic target range was not reached by routine care.

Glucose control by MPC resulted in a significantly higher percentage of time in which glucose levels were within the target range (80–110 mg/dl [4.4–6.1 mmol/l]) than by routine control (% median [min–max]) (0–24 h: 52 [17–92] vs. 19 [0–71], $P < 0.01$, for MPC vs. routine protocol, respectively). Improved glycemic control with MPC treatment was confirmed in patients remaining in the ICU for 48 h (0–24 h: 50 [17–71] vs. 21 [4–67], $P < 0.05$, and 24–48 h: 65 [38–96] vs. 25 [8–79], $P < 0.05$, for MPC [$n = 16$] vs. routine protocol [$n = 13$], respectively).

As can be suspected from the mean glucose profiles (Fig. 1*B*), center-specific analysis of the time within glucose target range indicated differences in glycemic control between routine protocols of individual ICUs in comparison with MPC treatment (% median [min–max]) (0–24 h: 56 [42–67] vs. 9 [0–21] in Graz, 42 [17–71] vs. 29 [4–67] in Prague, and 60 [38–92] vs. 36 [0–71] in London for MPC vs. routine protocol, respectively). Differences were significant for Graz ($P < 0.01$) and London ($P < 0.05$). A summary of the results describing glycemic control are presented in Table 2.

In a post hoc analysis, the target range for the routine glucose management protocol was adopted to the actual routine ranges in Prague (81–117 mg/dl) and London (72–108 mg/dl). Correction for the target range did not reveal different results (data not shown).

Hypoglycemia as defined by the protocol (<54 mg/dl [3.0 mmol/l]) was a rare event over the 48-h observational period. No hypoglycemic events occurred with MPC treatment. Two episodes (45 and 52 mg/dl) in two patients were observed during routine care in Prague but were brief and not accompanied by complications.

Glucose sampling frequency, insulin, nutrition, and concomitant treatment

The average blood glucose sampling interval for routine glucose management protocols was (means ± SD) 3.1 ± 1.4, 2.3 ± 0.7, and 3.2 ± 1.5 h in Graz, Prague, and London, respectively.

Details on insulin need and supply of carbohydrates are shown in Fig. 2. In Prague and London, comparable carbohydrate intake was provided to patients during both MPC and routine management. In Graz, glucose infusions immediately after surgery are avoided. Insulin dosages used for the first 24 h were as

Table 2—*Glycemic control expressed as percentage of time within a predefined range and average glucose (0–24 h)*

	Overall		Graz		Prague		London	
Glucose range	MPC	RTP	MPC	RTP	MPC	RTP	MPC	RTP
54–80 mg/dl (3.0–4.4 mmol/l)	0 (0–17)	0 (0–23)	0 (0–14)	0 (0–4)	0 (0–17)	0 (0–13)	0 (0–13)	0 (0–23)
80–110 mg/dl (4.4–6.1 mmol/l)	**52 (17–92)***	**19 (0–71)**	**56 (42–67)***	**9 (0–21)**	**42 (17–71)**	**29 (4–67)**	**60 (38–92)†**	**36 (0–71)**
>110 mg/dl (6.1 mmol/l)	46 (8–79)*	77 (21–100)	41 (33–58)*	91 (79–100)	54 (29–79)	69 (29–92)	40 (8–50)	57 (21–100)
Average glucose (mg/dl)	117 (102–144)	131 (97–237)	111 (108–131)	152 (115–237)	122 (114–144)	126 (105–154)	111 (102–134)	117 (97–147)

Data are median (min–max). *$P < 0.01$, †$P < 0.05$ for MPC vs. RTP. RTP, routine treatment protocol. Data in bold indicate values within the target range for blood glucose levels (80–110 mg/dl).

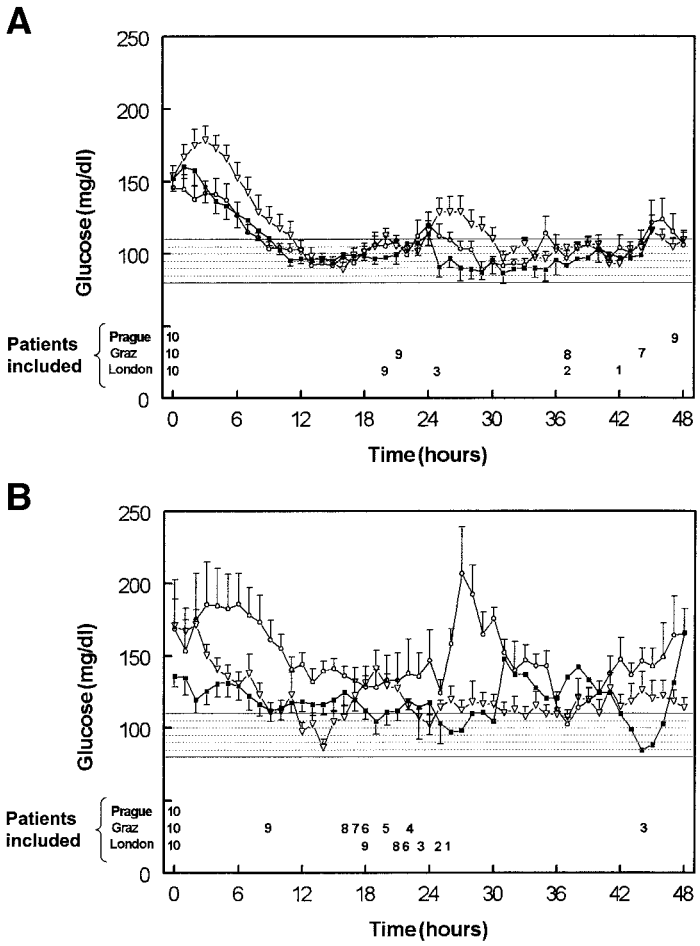

Figure 1—*Average glucose profiles for MPC treatment* (A) *and routine management protocols* (B) *in Prague* (△)*, Graz* (○)*, and London* (■)*. Data are means ± SE.*

follows: [median (min–max)] Graz: 45.3 (21.4–124.7) vs. 16.0 (0–319.5) insulin units/24 h, Prague: 95.7 (52.4–332.4) vs. 95.9 (52.0–276.9) insulin units/24 h, and London: 58.8 (18.2–231.0) vs. 58.1 (31.0–94.6) insulin units/24 h for MPC vs. routine treatment, respectively.

There was no apparent difference in terms of concomitant treatment among the different centers. No systemic glucocorticoids were used in any patients, and no patient died during the study.

CONCLUSIONS — The present trial has demonstrated that the automated MPC algorithm allows safe and tight glycemic control in postcardiac surgery critically ill patients. This was a consistent finding in the environment of three different clinical centers across Europe. In comparison with routine care, the MPC was at least as effective in controlling glycemia in the intensive care setting.

The European community–funded project CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients) aims to develop a low-risk monitoring and control system that allows health care providers to maintain metabolic glucose control in ICUs. Based on continuous measurement using biosensors, an adaptive control algorithm generates advice and thus represents a decision support system.

While our results are suggestive of a positive effect of the MPC algorithm on the establishment of tight glycemic control, some matters must be viewed with caution. It is a fact that the results of our investigation are advantageously influenced by a higher sampling frequency in the MPC group. Hourly monitoring of glucose values allows a more precise adoption of the intravenous insulin infusion rate to reach target glycemic levels. A routine sampling interval of 60 min would markedly increase work demands for the ICU nursing staff and is not feasible during routine care (15). However, the primary aim of the MPC algorithm is to serve as an integrated part of a closed-loop insulin infusion system using continuous glucose monitoring. For the use of the MPC alone as a tool to establish glycemic control, the sampling frequency clearly needs to be extended to an interval that is conceivable in clinical care. One could argue that nonblinding of the ICU staff led to only moderate glycemic control in the routine treatment groups and biased the results. However, the average sampling interval of every 2–3 h as used during routine treatment indicates that extensive nursing efforts were made in the ICUs during this study.

The target range of 80–110 mg/dl (4.4–6.1 mmol/l) for glucose control was chosen in accordance with the best available evidence in the postcardiac care setting (12). In the conception stage of this trial, differences in the established glucose management protocols at the individual ICUs were realized but were regarded to be of minor relevance. Moreover, changing an established protocol could have brought more bias in evaluation of the routine care proceedings in the respective centers. The post hoc analysis, taking into account the actual target levels in Prague and London, did not substantially change the results and consolidated the results obtained for the common target range.

The trial was designed to manage and document glucose values until the end of the ICU stay but for a maximum period of 48 h. Significant differences in duration of the postoperative ICU stay among the different centers were observed (London ~24 h, Graz ~36 h, and Prague ~48 h); limits in ICU capacity are the major underlying reasons. To account for this imbalance, analysis for glycemic control was targeted to the first 24 h in order to allow a comparison across all three centers. Nevertheless, results in the population remaining in the ICU for 48 h confirmed that the MPC algorithm was also capable of maintaining improved glucose control over the whole observational period. This suggests that the MPC algorithm will be effective in critically ill patients who require therapy for several days and will particularly benefit from intensive insulin therapy (12,14). However, this needs to be confirmed formally in further investigations.

Our trial also gained insight into glycemic control achieved by different glucose management protocols. Significantly higher glucose levels were observed in Graz, where the regimen is mainly driven

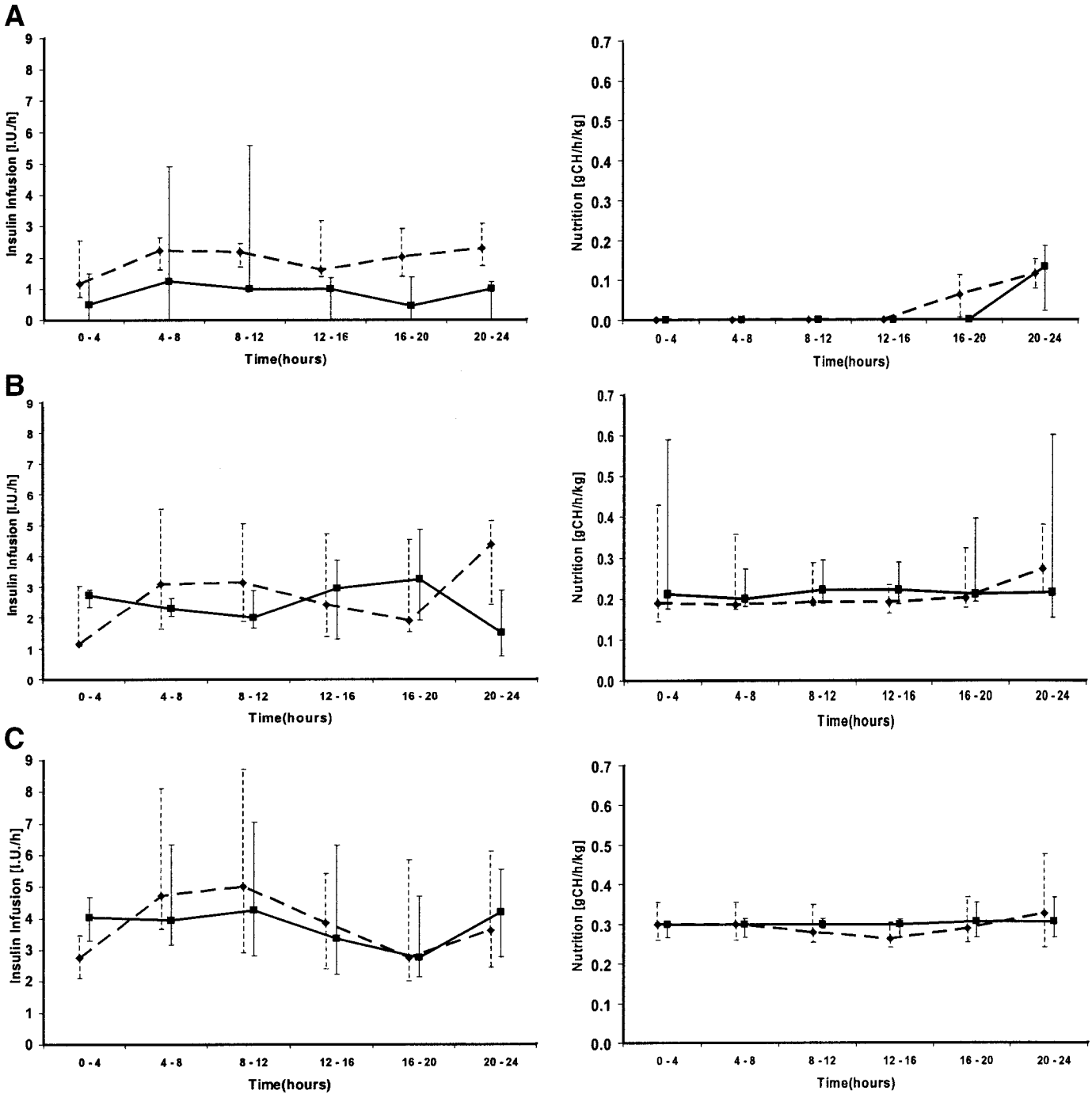

Figure 2—*Insulin dose and carbohydrate intake at 0–24 h in Graz* (A)*, London* (B)*, and Prague* (C) *for MPC treatment* (♦) *and routine management protocols* (■)*. Data are median (0.25/0.75 quantile).*

by intravenous insulin bolus. In contrast, the MPC algorithm and routine protocols in London and Prague are using continuous intravenous insulin infusion in all patients. It has been demonstrated that the change of a subcutaneous insulin bolus regimen to a continuous intravenous insulin infusion algorithm improved glycemic levels and reduced morbidity and mortality in patients with diabetes undergoing coronary bypass grafting (23). One may speculate whether an intravenous bolus regimen similarly results in impaired glycemic control in comparison with continuous intravenous insulin infusion. However, a higher dose of insulin was used in the MPC group in Graz and therefore explains the differences in glycemic control in this center. Another potential shortcoming of the management protocol in Graz is that it does not automatically foresee to increase the insulin dose to a level higher than 8 insulin units in the hyperglycemic range (blood glucose level >220 mg/dl).

Our investigation demonstrates that the MPC algorithm was safe and effective in controlling glycemia in critically ill postsurgery patients. Accordingly, the MPC algorithm will provide a reliable tool and a basis for the establishment of a system for automated glycemic control for critically ill patients.

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