Comparison of Three Protocols for Tight Glycemic Control in Cardiac Surgery Patients

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OBJECTIVE — We performed a randomized trial to compare three insulin-titration protocols for tight glycemic control (TGC) in a surgical intensive care unit: an absolute glucose (Matias) protocol, a relative glucose change (Bath) protocol, and an enhanced model predictive control (eMPC) algorithm.

RESEARCH DESIGN AND METHODS — A total of 120 consecutive patients after cardiac surgery were randomly assigned to the three protocols with a target glycemia range from 4.4 to 6.1 mmol/l. Intravenous insulin was administered continuously or in combination with insulin boluses (Matias protocol). Blood glucose was measured in 1- to 4-h intervals as requested by the protocols.

RESULTS — The eMPC algorithm gave the best performance as assessed by time to target (8.8 ± 2.2 vs. 10.9 ± 1.0 vs. 12.3 ± 1.9 h; eMPC vs. Matias vs. Bath, respectively; $P < 0.05$), average blood glucose after reaching the target (5.2 ± 0.1 vs. 6.2 ± 0.1 vs. 5.8 ± 0.1 mmol/l; $P < 0.01$), time in target (62.8 ± 4.4 vs. 48.4 ± 3.28 vs. 55.5 ± 3.2%; $P < 0.05$), time in hyperglycemia >8.3 mmol/l (1.3 ± 1.2 vs. 12.8 ± 2.2 vs. 6.5 ± 2.0%; $P < 0.05$), and sampling interval (2.3 ± 0.1 vs. 2.1 ± 0.1 vs. 1.8 ± 0.1 h; $P < 0.05$). However, time in hypoglycemia risk range (2.9–4.3 mmol/l) in the eMPC group was the longest (22.2 ± 1.9 vs. 10.9 ± 1.5 vs. 13.1 ± 1.6; $P < 0.05$). No severe hypoglycemic episode (<2.3 mmol/l) occurred in the eMPC group compared with one in the Matias group and two in the Bath group.

CONCLUSIONS — The eMPC algorithm provided the best TGC without increasing the risk of severe hypoglycemia while requiring the fewest glucose measurements. Overall, all protocols were safe and effective in the maintenance of TGC in cardiac surgery patients.

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The landmark Leuven Study (1) demonstrated that intensive insulin therapy targeted to maintain normoglycemia between 4.4 and 6.1 mmol/l reduced mortality in the surgical intensive care unit (ICU) and markedly decreased the frequency of organ complications associated with critical illness. Other studies confirmed these findings, particularly in cardiac surgery patients (2–5), whereas others still questioned the safety and universality of the beneficial effect of tight glycemic control (TGC) in different subgroups of critically ill patients (6–9).

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In principle, the need to maintain euglycemia in the ICU has been widely accepted. Numerous insulin protocols of variable effectiveness have been developed (5,10–12). Most of these protocols require considerable ICU staff training and experience, and some call for intuitive decisions. In consequence, some protocols may lead to inconsistent application, mistakes, or misinterpretation. Furthermore, frequent glucose measurements, essential for TGC, may markedly increase the workload of ICU nursing staff (13,14).

Most newly developed glucose management protocols are compared against the so-called standard protocols with which adequate glucose control is not usually achieved. Head-to-head comparison of specifically designed TGC protocols (15–18) is not available, although such information is of the highest importance from the practical point of view.

We carried out such a direct comparison of three different, effective, and published TGC management protocols with a major focus on TGC effectiveness and safety. We performed a monocenter randomized trial and compared a protocol based on the absolute glucose value, the Matias protocol (15,17); a protocol based on the relative glucose change, the Bath protocol (19); and a computer-based model predictive control algorithm with variable sampling rate (eMPC) (16) developed within the 6th Framework Programme e-Health Project "Closed Loop Insulin Infusion for Critically Ill Patients."

RESEARCH DESIGN AND METHODS

— Patients, aged 18–90 years, admitted to the postoperative ICU after elective cardiac surgery, were included. Written informed consent was obtained from all participants before being enrolled in the study. The study was approved by the Human Ethical Review Committee, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic, and was performed in accordance with the guidelines proposed in the Declaration of Helsinki. Exclusion criteria were insulin allergy, mental incapacity, and language barrier.

We enrolled 120 consecutive patients; 40 patients were randomly assigned into the Matias, Bath, and eMPC protocol treatment groups regardless of their preoperative or admission glycemia levels. The TGC protocols were started after patients' admission to the ICU after arrival from the operating theater and lasted until the end of the ICU stay. Because the duration of the ICU stay and the total monitoring time differed among patients, only data for up to 48 h were used for the comparison of the protocols. Forty-eight hours of ICU stay were accomplished in 109 of 120 patients included in the study. The mean follow-up time was 46.7 ± 0.5 h for the Matias, 45.7 ± 0.7 h for the Bath, and 47.2 ± 0.3 h for the eMPC protocols, respectively.

Target glucose range

The target glucose range was 4.4–6.1 mmol/l, which has been demonstrated to reduce mortality and morbidity (1). No routine protocol was used for perioperative glycemia control.

Blood glucose monitoring, insulin treatment regimens, and nutrition

Blood glucose was monitored, and insulin was administered according to the rules/suggestions of each protocol. Undiluted arterial blood for measurement of blood glucose was drawn from an arterial line, inserted for routine monitoring procedures. Whole blood glucose was analyzed by a standard point-of-care testing device (ABL 700; Radiometer Medical, Copenhagen, Denmark).

Insulin (Actrapid HM; Novo Nordisk, Baegsvard, Denmark) was given in a central venous line as a continuous infusion (Bath and eMPC protocols) or as a combination of a continuous infusion and boluses (Matias protocol). A standard concentration of 50 IU of insulin in 50 ml 0.9% NaCl was used. In all patients, infusion of a 10% glucose solution was initiated upon admission to ICU with a glucose dose of 2.5 g/kg ideal body weight (height in centimeters minus 100) per hour and lasted for 18 h, when normal oral food intake was started. In patients receiving mechanical ventilation, the glucose infusion lasted for 48 h, and then standard enteral nutrition was initiated.

Clinical parameters and patients' clinical history data including age, sex, race, height, weight, BMI, EuroSCORE (the European System for Cardiac Operative Risk Evaluation that identifies a number of risk factors, which help to predict mortality from cardiac surgery), history of diabetes, and type of surgery were collected prospectively. Adverse events, medication, and nutrition were continuously monitored and documented.

Outcome measures

Parameters for the assessment of the effectiveness of different TGC management protocols were as follows: entire study average glycemia level; time to the target range of 4.4–6.1 mmol/l (80–110 mg/dl); average glucose level after the target range was reached; number of hypoglycemic episodes (blood glucose <2.9 mmol/l); time within the target range; time between 2.9 and 4.3 mmol/l (54–70 mg/dl) with no clinical manifestations of hypoglycemia but indicating risk for hypoglycemia; time between 6.2 and 8.3 mmol/l (110–150 mg/dl) indicating risk of hyperglycemia; time in >8.3 mmol/l (150 mg/dl) indicating hyperglycemia; and sampling interval indicating workload. The percentage of time in the target range was calculated as number of values in the target range in each patient/number of measurements × 100.

The three TGC management protocols were implemented by the ICU nursing staff with supervision by ICU doctors as required. Protocol training was performed by the ICU physician and a departmental nurse, usually individually, at bedside. A 3-month period was devoted to the implementation of the Bath insulin protocol, whereas the Matias and eMPC protocols have been used in the ICU previously.

Statistical analysis

Statistical analysis was performed using STATISTICA software (StatSoft, Tulsa, OK). The protocols were compared using ANOVA followed by a Holm-Sidak test, Student's *t* test, or Mann-Whitney *U* test as appropriate. The significance level was set at $P = 0.05$.

Table 1—*Baseline characteristics of patients after cardiac surgery at the time of admission to the ICU*

	Matias	Bath	eMPC
Age (years)	69.0 ± 1.7	67.8 ± 1.4	68.2 ± 1.1
Female sex	14	15	12
Caucasian ethnicity (%)	100	100	100
BMI (kg/m^2)	28.4 ± 0.35	27.3 ± 1.0	27.8 ± 0.8
EuroSCORE (logistic)	4.2 ± 0.8	3.9 ± 0.7	4.4 ± 0.9
Type of surgery			
CABG	28	24	12
Valve replacement	4	16	24
CABG + valve replacement	8	–	4
History of diabetes	14	12	16

Data are means ± SEM or *n*. $n = 40$ patients/protocol. CABG, coronary artery bypass graft.

Description of TGC glucose management protocols

The TGC glucose management protocols are described in online appendices 1–3, available at http://care.diabetesjournals.org/cgi/content/full/dc08-1851/DC1.

RESULTS — The baseline characteristics of the study patients at the time of admission to the ICU are listed in Table 1. The study groups did not differ with respect to age, BMI, EuroSCORE, type of surgery, baseline blood glucose level, or occurrence of diabetes. Blood glucose control characteristics are shown in Table 2 and Figs. 1 and 2, respectively.

Table 2 demonstrates significantly better blood glucose control was achieved in the eMPC group compared with the Matias and the Bath groups: entire study average glucose (5.9 ± 0.2 vs. 6.7 ± 0.1 vs. 6.5 ± 0.2 mmol/l; $P < 0.05$) and percentage of time within the target range (46.6 ± 3.0 vs. 38.2 ± 2.9 vs. 39.7 ± 3.1%, $P < 0.05$). To better describe and compare TGC associated with each protocol, we divided glucose profiles into the period before reaching the target range (Table 2 and Fig. 1) and the period after reaching the target range (Table 2). With respect to the time to target range, the eMPC protocol performed significantly better than the Matias and Bath protocols (Table 2; Fig. 2). In the period after reaching the target range, the eMPC algorithm showed superior performance relative to the Matias and Bath protocols with respect to average glycemia (5.2 ± 0.1 vs. 6.2 ± 0.1 vs. 5.8 ± 0.1 mmol/l; $P < 0.05$), time in target range (62.8 ± 4.4 vs. 48.4 ± 3.2 vs. 55.5 ± 3.2% of time; respectively, $P < 0.05$), time in risk of hyperglycemia (13.7 ± 2.6 vs. 27.5 ± 2.2 vs. 24.5 ± 2.4% of time; $P < 0.05$), and

Table 2—*Study blood glucose control data*

	Matias	Bath	eMPC
Baseline blood glucose	7.9 ± 0.4	8.0 ± 0.2	8.1 ± 0.6
Entire study blood glucose control data (or 48 h)			
Average blood glucose (mmol/l)	6.7 ± 0.1	6.5 ± 0.2	5.9 ± 0.2*†
Sampling interval (h)	2.0 ± 0.1	1.7 ± 0.1	2.1 ± 0.1
Time to target range (h)	10.9 ± 1.0	12.3 ± 1.9*	8.8 ± 2.2†
Time in target range (%)	38.2 ± 2.9	39.7 ± 3.1	46.0 ± 3.0*†
Blood glucose control data after reaching the target range (4.4–6.1 mmol/l)			
Average blood glucose (mmol/l)	6.2 ± 0.1	5.8 ± 0.1*	5.2 ± 0.1*†
Sampling interval (h)	2.1 ± 0.1	1.8 ± 0.1*	2.3 ± 0.1†
Time to target range (h)	48.4 ± 3.2	55.5 ± 3.2	62.8 ± 4.4*†
Time in risk of hypoglycemia (2.9–4.3 mmol/l) (%)	10.9 ± 1.5	13.1 ± 1.6	22.2 ± 1.9*†
Time in hypoglycemia (<2.9 mmol/l) (%)	0.4 ± 0.2	0.4 ± 0.3	0.0 ± 0.0
Severe hypoglycemia episodes (<2.3 mmol/l)	1	2	0
Time in risk of hyperglycemia (6.2–8.3 mmol/l) (%)	27.5 ± 2.2	24.5 ± 2.4	13.7 ± 2.6*†
Time in hyperglycemia (>8.3 mmol/l) (%)	12.8 ± 2.2	6.5 ± 2.0*	1.3 ± 1.2*†

Data are expressed as means ± SEM. Arterial blood glucose was measured as prescribed by each protocol in 1- to 4-h intervals. The patients were followed for up to 48 h (mean follow-up time 46.7 ± 0.5 h for the Matias, 45.7 ± 0.7 h for the Bath, and 47.2 ± 0.3 h for the eMPC protocols). The percentages of time in the target range were calculated as number of in-range values of each patient/number of measurements × 100. *Statistically significant difference from the Matias protocol. †Statistically significant difference from the Bath protocol ($P < 0.05$).

time in hyperglycemia (1.3 ± 1.2 vs. 12.8 ± 2.2 vs. 6.5 ± 2.0% of time; $P < 0.05$) (Table 2).

The average insulin infusion rate and the total insulin dose throughout the entire study were significantly higher in the eMPC compared with the Matias and Bath protocols (mean insulin rate 5.1 ± 1.0 vs. 3.7 ± 0.4 vs. 4.1 ± 0.5 IU/h; $P < 0.05$). The average sampling interval, as an indicator of workload, was significantly shorter in the Bath versus both the Matias and eMPC groups (Table 2). Two episodes of severe hypoglycemia defined as glycemia <2.3 mmol/l were observed during the study in the Bath group and one episode in the Matias group, whereas no such episode occurred in the eMPC group. All three hypoglycemic episodes were classified as "asymptomatic" and were not related to established major risk factors of ICU hypoglycemia such as nutritional interruption, delayed glucose measurement, or drug administration.

CONCLUSIONS — In the present study we compared the performance and safety of three insulin-titration protocols for TGC in the postoperative period in cardiac surgery patients. We showed that the most satisfactory glucose control was achieved with a computer-based eMPC algorithm, whereas the use of the relative glucose value–based Bath protocol resulted in less satisfactory glucose control. The absolute glucose value–based algorithm, the Matias protocol, showed the least satisfactory performance. Importantly, all three protocols were reasonably safe. Only three severe hypoglycemic episodes (blood glucose <2.3 mmol/l) occurred throughout the entire study. Strikingly, no such episode was noted in the eMPC group that achieved the best glucose control among the three protocols.

The results of our study further underscore the fact that the ability to correctly implement a glucose management protocol is the key prerequisite to successful and safe glucose control in critically ill patients. Our ICU has >6 years experience with the use of the Matias protocol and 4 years' experience with testing the eMPC algorithm, whereas the Bath protocol has not been used in our center before. However, after a 3-month implementation period, our ICU staff was able to successfully use all three protocols without any major problems or safety concerns. This experience differs markedly from the two large multicenter studies with TGC, the Glucontrol Study and the Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) Study, that were discontinued because of excessive risk of hypoglycemia. It is possible that insufficient time for insulin protocol implementation and the lack of previous experiences with TGC markedly influenced the outcomes of both studies (7,9,20,21).

To our knowledge, our study is the first to compare head-to-head three well-

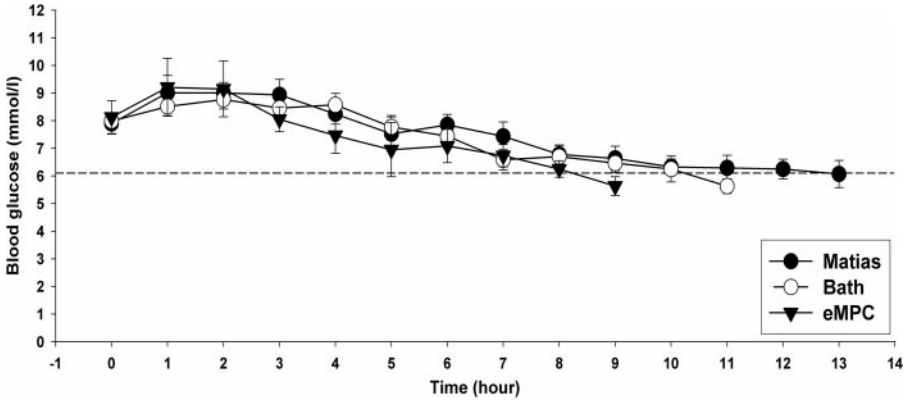

Figure 1— *Blood glucose concentrations and time to target range, expressed as means ± SEM, in patients after cardiac surgery controlled by the Matias, Bath, and eMPC protocols.*

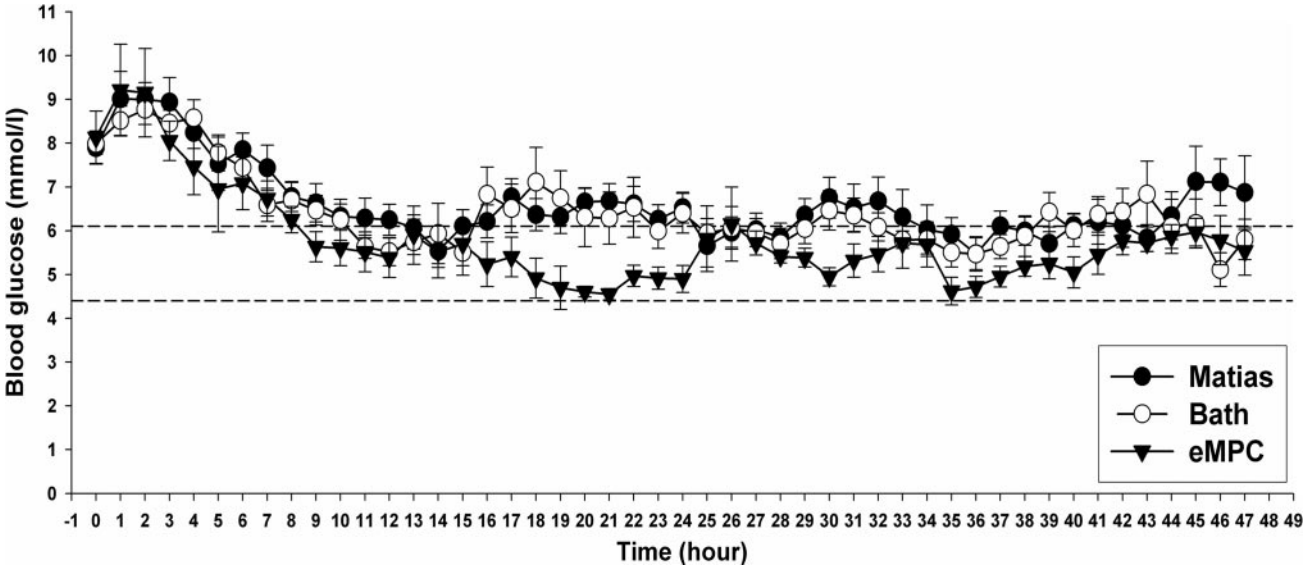

Figure 2— *Blood glucose concentrations, expressed as means ± SEM, in patients after cardiac surgery, controlled by the Matias, Bath, and eMPC protocols during the entire 48-h postoperative period. Average time within the target range was 38.2 ± 2.9% for the Matias protocol, 39.7 ± 3.1% for the Bath protocol, and 45.98 ± 3.0% for the eMPC protocol.*

documented and widely used TGC protocols. We used the simplest and possibly the most straightforward way to analyze the data and calculated the average blood glucose and the percentage of time within the target range. For the sake of clarity and transparency, we did not use any data interpolation and/or other more sophisticated data analysis tools.

Each protocol tested in our study represented a principally different approach to glucose control. The Matias algorithm differs from the other two protocols by combining continuous intravenous insulin infusion with intravenous insulin boluses. This approach might have a possible advantage in the ability to quickly achieve the target range. Interestingly, although the Matias protocol achieved the target range ~1.5 h earlier than the Bath protocol, it was still significantly worse than the computer-based eMPC algorithm that achieved the target range 2 h earlier than the Matias protocol without using intravenous insulin boluses. The superior performance of the eMPC algorithm was not accompanied by a higher risk of hypoglycemia. In fact, the opposite was true because no severe hypoglycemia was detected in the eMPC algorithm group (Table 2).

The principal difference between the Bath protocol and the Matias protocol is that the insulin dose is based on the relative change of the blood glucose between the two measurements rather than on the absolute glucose concentration itself. A major advantage of the Bath protocol may be that relative blood glucose change may give a better indication of the high variability of patients' insulin resistance and the nature and severity of their illness especially in comparison with the Matias protocol. A direct comparison of the Bath algorithm with absolute glucose value–based Matias protocol showed slightly better performance of the former with significantly lower mean blood glucose and time in hyperglycemia after reaching the target range. Conversely, the time to reach the target range was longer and the sampling interval was shorter with the Bath protocol than with the Matias protocol.

The eMPC protocol also uses the rate of change in blood glucose, although this is not carried out in an explicit manner as with the Bath protocol. Instead, the eMPC algorithm derives insulin sensitivity and other physiologically relevant parameters from up to a 10-h blood glucose profile. The eMPC algorithm achieved significantly better results compared with the other two protocols in the majority of the most important parameters (Table 2): in effectiveness (time to target range), in efficiency of glycemia management after reaching the target range (mean glycemia, time in target range, time in risk of hyperglycemia, and time in hyperglycemia), and in sampling interval. Improved glucose control with the use of the eMPC algorithm was accompanied by a longer time within the range at higher risk of hypoglycemia, but the occurrence of moderate or severe hypoglycemia was zero in the eMPC group, suggesting the high level of safety of this protocol.

Overall, compared with some of the previously published studies, all three protocols were able to achieve reasonably tight glucose control without an excessive risk of hypoglycemia and/or other complications (21). The low rate of hypoglycemic events and the overall results in our study could have been partially due to a relatively high constant rate of glucose infusion administered throughout the study. A constant high-rate glucose infusion is expected to accelerate glucose turnover and the overall system response. In consequence, this feature of the protocol should improve the stability of glucose control, especially under the routine protocol, whereas the eMPC protocol should be less affected. It is thus possible that the overall outcome of the three protocols tested would differ under the conditions of a lower parenteral glucose administration, and the results thus cannot be directly applicable to other patient populations.

From the user point of view, the major difference between the eMPC and other protocols is the nonfixed sampling interval of the eMPC algorithm. In typical ICU settings, there is usually a time window within which any therapeutic and/or other procedure including TGC should occur. In reality, such a standard "fixed" interval then may vary considerably. The eMPC algorithm, with its bedside screen interface continuously showing time to

next measurement, emphasizes the importance of on-time sampling. The nurses then tend to adapt their activities so that they can fulfill eMPC instructions within the required time frame. For the sake of our comparative study, we asked our nurses to be as accurate as possible in fulfilling all requirements of the algorithms, especially with respect to timing of blood glucose measurements. Thus, the study conditions for both the Matias and Bath algorithms could have been somehow better compared with a "real-life" situation.

Because two of the three protocols tested were partially implemented in our ICU previously, our study does not answer the question of how difficult it is to implement the protocols from the very beginning. The 3-month implementation period was long enough to safely use the Bath protocol under our ICU settings. We suggest that an appropriate implementation period and previous experience of our ICU staff with TGC may be the reasons that the quality and safety of glucose control in our study were significantly better than the results of most of the previously published studies (22–25).

In summary, we demonstrate that the computer-based eMPC algorithm with a variable sampling interval is more effective in achieving and maintaining TGC in patients after cardiac surgery than both the relative glucose levels change–based Bath protocol and the absolute glucose value–based Matias protocol. Overall, all three protocols were able to achieve reasonable blood glucose control without any major side effects.

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