Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Automated Glucose Control in the ICU: Effect of Nutritional Protocol and Measurement Error

Malgorzata E. Wilinska, Ludovic J. Chassin, and Roman Hovorka, *Member, IEEE*

Abstract—Tight glycaemic control has been shown to reduce mortality and morbidity in critically ill subjects. Using *in silico* computational approach, the objective of this study was to evaluate the effect of nutrition and the measurement error on glucose control. *In silico* simulation environment describing 21 synthetic subjects was used to simulate a 48h clinical trial with an adaptive model predictive controller in the intensive care unit. Two types of nutritional protocols, simple and complex, and various levels of the measurement error (ME) were evaluated. The simple nutritional protocol resulted in more efficacious glucose control compared to that obtained with the complex nutritional protocol. A considerable deterioration was noted with the increasing level of the ME. Severe hypoglycaemia episodes (<2.8 mM) were observed with the ME > 10%. We conclude that nutritional protocol should be kept simple to facilitate efficacious glucose control with an adaptive model predictive controller. The measurement error of the glucose measuring device should be less or equal to 10%.

I. Introduction

In 2001, a large randomized controlled trial demonstrated that tight glycaemic control (TGC) within a narrow range 4.4 to 6.1mmol/l by intensive insulin therapy improves clinical outcomes in patients admitted to a surgical intensive care unit (ICU) [1]. The study reduced ICU mortality by 42% and also reduced the incidence of bloodstream infections, the incidence of acute renal failure, the need for prolonged ventilatory support, and the duration of ICU stay. In 2006, a similar study in medical ICU showed that TGC in patients staying over three days in a medical ICU results in less marked but clinically highly relevant improvements of mortality and morbidity [2]. TGC is also beneficial in other intensive care settings such as in diabetic subjects following acute myocardial infarction [3].

In 2004, the EC funded project "Closed Loop Insulin Infusion for Critically Ill Patients" (Clinicip) commenced with the aim to develop prototype systems for closed loop control for the use at ICUs (www.clinicip.org). As part of the Clinicip project, glucose controllers are being developed and evaluated such as that based on the model predictive control (MPC).

A recent Clinicip's study demonstrated good glucose control with our MPC and hourly sampling [4]. As the study was performed at three different surgical ICUs in three different countries, we were able to observe that the variations in nutritional protocols and the extent of the measurement error among the ICUs may affect glucose control. The present study aims to quantify these effects using an *in silico* approach.

We used *in silico* simulation environment developed using of our earlier work in type 1 diabetes [5] extended by modeling endogenous insulin secretion and reflecting the range of insulin resistance observed in critically ill subjects. We adopted simple and complex nutritional protocols reflecting the different nutritional approaches used at surgical ICUs and covering at least in part the wide spectrum of realistic nutritional protocols. We also varied the measurement error associated with glucose sampling over a wide range between 2.5 and 15%. The lower limit represent the measurement error associated with a standard point of care testing device such as ABL 700, Radiometer Medical A/S. The middle-to-high of the range represents measurement with a bed-side blood glucose meter such as Accu Check Inform, Roche. Extensive computations with our virtual population of critically ill subjects then gave performance of the MPC controller with each setting providing rational means to indicate the expected performance in clinical conditions.

II. Methods

A. In silico simulation environment

The simulation environment reflects clinical trials where the main components are the subjects, the glucose sensor, the insulin pump, the controller, and the study protocol. Subjects in the simulator are represented by individual parameter sets, which in turn characterise the physiological model. The experiment description is at the top level of the simulation environment pointing to seven main components: the protocol, the parameters of the critically ill subject, the model of carbohydrate metabolism, the insulin pump, the glucose sensor, the glucose controller, and finally the metrics summarizing results.

The simulated critically ill subject is represented by a set of interacting sub-models. The external inputs to those sub-models include enteral and parenteral feeding, and an insulin infusion by the insulin pump. The rate of the insulin infusion is calculated by the control algorithm and is updated hourly to four-hourly. The controller requires regular information about glucose concentration, which is provided by the

Manuscript received April 3, 2006. This work was supported by the EC Clincip Project (IST-2002-506965).

M. E. Wilinska, L. J. Chassin, and R. Hovorka are with the Department of Paediatrics, University of Cambridge, Hills Road, Cambridge CB2 2QQ, UK (phone: +44 1223 762 862; fax: +44 1223 266 966; e-mail: {mew37, ljc45, rh347}@ medschl.cam.ac.uk).

glucose sensor. Blood glucose is measured by the glucose sensor hourly to four-hourly. Simulations were executed over 48h.

B. *Virtual population of critically ill subjects*

In total, 21 synthetic subjects have been used. The subjects were generated employing clinical data and informed probability distributions. The number of subjects was dictated by the availability of clinical data to determine the core of the model, i.e. the submodel of glucose kinetics and insulin action.

C. *Study design*

In silico simulation environment was used to simulate a 48h clinical trial with an MPC in the intensive care unit.

D. *Model predictive control*

The MPC algorithm has been described previously [6]. The main component of the MPC is a model representing the glucoregulatory system. It enables the prediction of the glucose excursion by a dose optimiser. The dose optimiser 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 normalisation in case of hyperglycemia, a fast recovery in case of hypoglycemia, or maintenance of normoglycemia. This optimisation process is the key benefit of using the MPC algorithm in place of classical control algorithms. The glucoregulatory model of the MPC has individual parameters, which adapted online. Glucose concentration, insulin dosage, and carbohydrate intake are the input variables for the MPC. Input of glucose concentration is required every 60 to 240 minutes and triggers the online-adaptation of the parameters, and the calculation of the insulin infusion rate for the following 60-240 minutes. The MPC also advises on the next glucose sampling time, which can range from hourly to four hourly.

E. *Nutritional protocols*

Two types of nutritional protocols, simple and complex, were simulated. The simple protocol consisted of a constant parenteral glucose infusion of 4 g/h and a 40g CHO meal at 44h. The complex protocol consisted of varied parenteral and enteral glucose infusions, a parenteral glucose bolus of 12g at 15h and a meal of 40g CHO at 44h. The parenteral glucose infusion commenced at a rate of 4 g/h at the beginning of the study. The rate was increased to 8 g/h at 12h and dropped back to 4 g/h at 24h. At 30h the infusion rate was increased to12g/h and continued until the end of the study. The enteral glucose infusion commenced at 33h and 20 min at a rate of 8 g/h and continued until the end of the study.

F. *Measurement error*

The coefficient of variation of the measurement error associated with the blood glucose measurement ranged from 2.5 to 15%.

G. *Outcome measures*

The mean blood glucose concentration, the hyperglycaemic index (HGI) [7], and the percentages of time spent in target glucose region 4.4 – 6.1mM were used to measure the efficacy of glucose control. The HGI represents the average glucose concentration above 6.0 mM over 48h. The number of hypoglycaemia episodes (< 3.3mM) and the number of severe hypoglycaemia episodes (< 2.8mM) were used to assess safety of glucose control by the MPC controller.

TABLE I
GLUCOSE CONTROL INDICATORS DURING *SIMPLE* NUTRITION PROTOCOL FOR SELECTED LEVELS OF THE MEASUREMENT ERROR (N = 21)

	Measurement error (CV)			
	2.5%	5%	10%	15%
Mean glucose [mM]	6.00	5.92	5.97	6.08
Time in band [%]*	80	69	51	36
Hyperglycaemic index [mM]	0.23	0.24	0.33	0.49
Hypo episodes (<3.3mM) [unitless]	0	1	2	11
Severe hypo episodes (<2.8mM)[unitless]	0	0	0	2

*Target glucose band 4.4 to 6.1mM

TABLE II
GLUCOSE CONTROL INDICATORS DURING *COMPLEX* NUTRITION PROTOCOL FOR SELECTED LEVELS OF THE MEASUREMENT ERROR (N = 21)

	Measurement error (CV)			
	2.5%	5%	10%	15%
Mean glucose [mM]	6.16	6.12	6.25	6.53
Time in band [%]*	53	51	38	29
Hyperglycaemic index [mM]	0.50	0.48	0.60	0.89
Hypo episodes (<3.3mM) [unitless]	1	0	0	3
Severe hypo episodes (<2.8mM)[unitless]	0	0	0	0

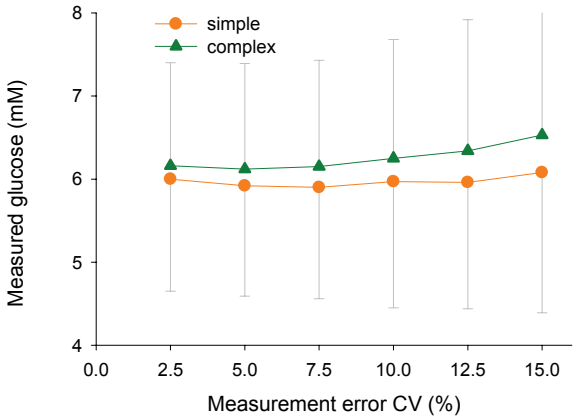

Fig. 1. Mean±SD blood glucose level for the simple and complex nutritional protocol and various levels of the measurement error (N = 21).

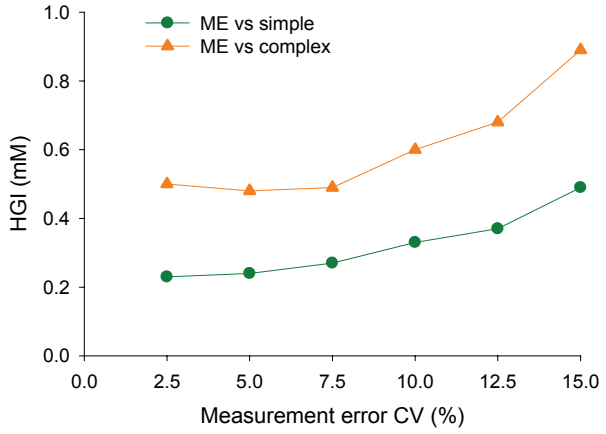

Fig. 2. The hyperglycaemic index for the simple and complex nutritional protocol and various levels of the measurement error (N = 21).

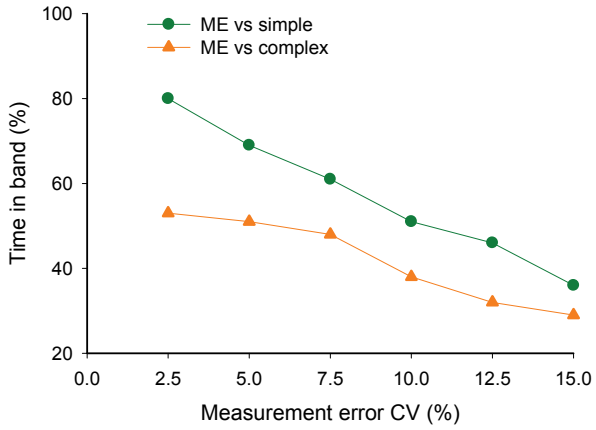

Fig. 3. The percentage of time spent in the target band (4.4 – 6.1 mM) for the simple and complex nutritional protocol and various levels of the measurement error (N = 21).

III. Results

The results are shown in Table I and Table II for the simple and the complex nutritional protocol, respectively. The tables also list the results for selected levels of the measurement error.

The visual representation of the results is shown in Figure 1 – 3.

IV. Discussion

The present study suggests that both the nutritional protocol and the level of the measurement error influence the glucose control in critically ill subjects.

The effect of the nutritional protocol was particularly remarkable. The simple nutritional protocol facilitated more efficacious glucose control compared to that obtained with the complex nutritional protocol. Among the various levels of the measurement error, the time spent in the target region 4.4 – 6.1mM was higher by 22-27% with the simple protocol. The HGI reduced about two-fold, see Table I and Table II. Unexpectedly, the number of hypoglycaemia events had a tendency to be higher with the simple nutritional protocol. At 15% CV of the measurement error, severe hypoglycemia events occurred with the simple but not the complex nutritional protocol. The higher number of hypoglycaemia events can be explained by a lower frequency of glucose measurements associated with the simple protocol (data not shown).

The MPC controller utilizes information about the enteral and parenteral infusions. However, the deterioration of glucose control was not avoided when parenteral and enteral infusions were changed. This can be explained by the inter-subject variability of (i) the bioavailability of the enteral infusion, (ii) the endogenous glucose production, and (iii) the glucose distribution volume among the synthetic population of critically ill subjects. The parameters are estimated inaccurately from data collected during routine glucose control at the ICU by the adaptive MPC controller. Inaccurate parameter estimates and model misspecification cause reduced accuracy of model predictions, which in turn lead to a loss of glucose control following the change of nutritional infusion rate. A constant parenteral and enteral infusion allows the adaptive MPC controller to improve its prediction accuracy and to improve the overall glucose control.

An increase from 2.5 to 15% CV of the measurement error has the same influence on the time spent in the target band and the HGI as switching from the simple to complex nutritional protocol, see Table I and Table II. This underlines the impact of the nutritional protocol on glucose control and contrasts it against the properties of glucose measurement devices available at the ICUs. Where possible, the nutritional protocol should be simplified to facilitate good glucose control with automated glucose control systems.

At the lower levels of the measurement error, hypoglycaemia and severe hypoglycaemia were not affected by the nutritional protocol. At 15% CV of the measurement error, two severe hypoglycaemia events occurred with the simple protocol suggesting that glucose measurement devices with > 10% CV of the measurement error should not be used.

The simple and the complex nutritional protocols are plausible examples of nutritional provision and reflect the wide range of nutritional provisions at surgical ICUs. A small meal is often digested at the end of the routine stay at the surgical ICUs following an elective cardiac surgery. Thus the meal was included with the simple nutritional protocol. Some ICUs adopt the policy of an early enteral infusion and this is sometimes combined with alterations of the infusion rates for both the parenteral and enteral infusion rates. This corresponds to the complex nutritional protocol.

It is generally recognized that constant parenteral and

enteral infusions simplify the glucose control in critically ill subjects treated by paper-based insulin titration protocols. Our results support these observations and quantify the extent of the effect.

The results of our study are limited by the use of the synthetic rather than the “real” population of critically ill subjects. The results should therefore be validated by a real clinical study for a subset of the combinations of the nutritional protocols and the measurement errors. The strength of the present study is that it allowed the effect of all combinations of the measurement error and the nutritional protocols to be explored.

We conclude that when using automated glucose control with an adaptive model predictive controller, the nutritional protocol should be kept simple to facilitate an efficacious glucose control. The measurement error of the glucose measuring device should not be higher than 10%.

REFERENCES

[1] G. Van den Berghe, P. Wouters, F. Weekers, C. Verwaest, F. Bruyninckx, M. Schetz, D. Vlasselaers, P. Ferdinande, P. Lauwers, and R. Bouillon, "Intensive insulin therapy in the surgical intensive care unit," *N. Engl. J. Med.*, vol. 345, no. 19, pp. 1359-1367, Nov.2001.

[2] B. G. Van den, A. Wilmer, G. Hermans, W. Meersseman, P. J. Wouters, I. Milants, W. E. Van, H. Bobbaers, and R. Bouillon, "Intensive insulin therapy in the medical ICU," *N. Engl. J. Med.*, vol. 354, no. 5, pp. 449-461, Feb.2006.

[3] K. Malmberg, "Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group," *Br. Med. J.*, vol. 314, no. 7093, pp. 1512-1515, May1997.

[4] J. Plank, J. Blaha, J. Cordingley, M. E. Wilinska, L. J. Chassin, C. Morgan, S. Squire, M. Haluzik, J. Kremen, S. Svacina, W. Toller, A. Plasnik, M. Ellmerer, R. Hovorka, and T. R. Pieber, "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," *Diabetes Care*, vol. 29, no. 2, pp. 271-276, Feb.2006.

[5] L. J. Chassin, M. E. Wilinska, and R. Hovorka, "Evaluation of glucose controllers in virtual environment: Methodology and sample application," *Artif. Intell. Med.*, vol. 32, no. 3, pp. 171-181, 2004.

[6] R. Hovorka, V. Canonico, L. J. Chassin, U. Haueter, M. Massi-Benedetti, M. Orsini-Federici, T. R. Pieber, H. Schaller, L. Schaupp, T. Vering, and M. Wilinska, "Non-linear model predictive control of glucose concentration in subjects with type 1 diabetes," *Physiol. Meas.*, vol. 25, no. 4, pp. 905-920, 2004.

[7] M. Vogelzang, d. H. van, I, and M. W. Nijsten, "Hyperglycaemic index as a tool to assess glucose control: a retrospective study," *Crit Care*, vol. 8, no. 3, p. R122-R127, June 2004.