WAIT: Workshop on the Advances in Information Technology, Budapest, 2021

Insulin sensitivity and blood glucose levels analysis of Hungarian Patients in their early phase of ICU treatment under model-based glycemic control

Yahia Anane[1], J. Geoffrey Chase[2] and Balázs Benyó[1]

[1] Dept. of Control Engineering and Information Technology, Budapest University of Tech. and Eco, Budapest, Hungary
[2] Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand

Abstract

Critically ill intensive care unit (ICU) patients frequently experience acute insulin resistance (low insulin sensitivity) manifesting as stress-induced hyperglycemia and hyperinsulinemia, especially in the early stages of the treatment. High inter/intra-patient variability makes glycemic control difficult. Stochastic TARgeted (STAR) a model-based glycemic control, directly manages this variability using model-based insulin sensitivity (SI) and a second model of its variability. This study analyses insulin sensitivity and blood glucose levels of ICU patients in the Hungarian cohorts and compares the first 24h of the treatment and the rest of the treatment in order to assess the differences. Using clinical data from 93 patients treated with STAR, insulin sensitivity and blood glucose are compared at first between the first 24h and the rest of the treatment, then the first 24h and the successive treatment days. Results show that insulin sensitivity is lower in the first 24h compared to the rest of the treatment and in the first 24h compared to the five successive days. Blood glucose levels were higher in the first 24h compared to the rest of the treatment time and in the first 24h compared to the five successive days. Patients in the early stages of ICU have low insulin sensitivity and high blood glucose levels, as expected, given the stress response physiology. Given the results, this study initiates the idea of implementing a customized model-based control designed only for the early phase of Hungarian ICU patient's model-based treatment that can effectively handle hyperglycemia and insulin resistance and create a space for further development.

Keywords: Blood glucose; Glycemic control; STAR; Insulin resistance; Insulin sensitivity; ICU.

1. Introduction

Effective glycemic control showed a promising improvement in the outcomes in critically ill patients. However, it was always hard to achieve consistent results [1] due to patients' intra-and-inter variability.

Patients in their early stage of treatment after ICU admission due to stress often experience insulin resistance (low insulin sensitivity), resulting in high blood glucose levels (hyperglycemia), making glycemic control very sensitive in the intensive care unit [2].

In this paper, we used patient data of 93 patients from Kalman Pandy Hospital, Gyula, Hungary, Hospitals' ICU treated by STAR protocol. Stochastic TARgeted (STAR) is a Glycemic control protocol that models human metabolic system and handle the patient-specific intra-and-inter variability by an additional stochastic model [3]. STAR is driven by the model-based, insulin sensitivity (SI) parameter used as a key variable to assess the patient variability. It is built on the clinically validated Intensive Control Insulin- Nutrition-Glucose (ICING) model used to characterize the fundamental Glucose-Insulin system dynamics.

We analyzed patients insulin sensitivity and blood glucose levels, and the aim of this work is to examine the inter/intra patients differences in insulin sensitivity and hyperglycemia in the early stages of the treatment (first 24h hours of patient ICU admission) compared to the rest of the treatment time and its potential impact on model-based glycemic control.

This study initiates the idea of implementing a customized model-based control explicitly designed for the early phase of Hungarian patients treatment that can effectively handle hyperglycemia and insulin resistance.

2. Methods

2.1. ICING model

STAR protocol relies on the Intensive Care Insulin-Nutrition-Glucose (ICING) model to simulate the fundamental metabolic dynamics of the human body [4]. Three main out of 7 equations are represented:

$$\frac{dG(t)}{dt} = -p_G G(t) - S_I(t) G(t) \frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+EGP-CNS}{V_G}, \tag{1}$$

$$\frac{dQ(t)}{dt} = n_I(I(t)-Q(t)) - n_C \frac{Q(t)}{1+\alpha_G Q(t)}, \tag{2}$$

$$\frac{dI(t)}{dt} = -n_K I(t) - n_L \frac{I(t)}{1+\alpha_I I(t)} - n_I(I(t)-Q(t)) + \frac{u_{ex}(t)}{V_I} + (1-x_L)\frac{u_{en}(t)}{V_I} \tag{3}$$

The model parameters, the inputs variables, and their detailed description can be found in [4].

2.2. Clinical Data

Clinical data that contains patient's personal information, blood glucose measurements, and insulin/nutrition treatment was collected from 93 patients from Kalman Pandy Hospital, Gyula, Hungary [5].

2.3. Insulin Sensitivity

Insulin sensitivity (SI), the primary key parameters uniquely identified from clinical data on an hourly basis and patient variability is assessed by the hour-to-hour change in SI levels. Low values of SI indicate insulin resistance and the need to either add insulin or reduce nutrition to achieve lower glycemic levels.

Clinical data including two last BG measurements, insulin/nutrition inputs, and ICING model Equations (1)-(7) is utilized to identify SI on hourly bases using the integral-based method [6].

2.4. Analyses

We analyzed the patient's inter-intra insulin sensitivity identified by STAR and the measured blood glucose levels during the treatment. First, we compared values between the first 24h and the rest of the treatment time. Second, we compared values between the first 24h and the next four successive treatment days. For the second part, we exclude patients with a treatment time record of less than 120 hours.

3. Results

3.1. SI in the first 24h vs. the rest of the treatment

Figure 1 shows the cumulative distribution function of insulin sensitivity (SI) of all patients under the Hungarian cohort in the first 24h compared to the SI in the rest of the treatment time. SI values are lower in the first 24h compared to the rest of the treatment. The difference was noticeable with mean values of 3.51 10^{-4} (L/mU/min) in the first 24h compared to 4.64 10^{-4} after as it is shown in Table 1.

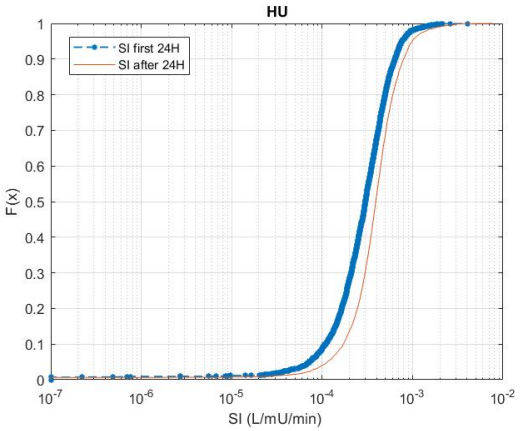

Figure 1: *CDF of SI values in the first 24h compared to SI in the rest of the treatment*

Stats	First 24h	After 24h
MIN	10^{-7}	10^{-7}
MAX	0.41 10^{-2}	0.76 10^{-2}
MEAN	3.51 10^{-4}	4.64 10^{-4}
MEDIAN	3.01 10^{-4}	3.91 10^{-4}

Table 1: *SI values (L/mU/min) comparison in the first 24h vs. rest of the treatment*

The Min value of SI is 10^{-7} in all cohorts, which is the minimum physiological allowed value in the STAR protocol during the SI identification phase.

3.2. SI in the first 24h vs. next four days

Figure 2 shows the cumulative distribution function of insulin sensitivity (SI) of Hungarian cohort in the first 24h compared to SI in the four successive treatment days. Based on SI distribution, the lowest values was at the first 24h compared to the next four days of the treatment, as low as 3.29 10^{-7} . Si values go up starting from the 2nd day. Episodes of Insulin resistance (%IR) are higher in the first 24h compared to the four successive days as it is shown in Table 2.

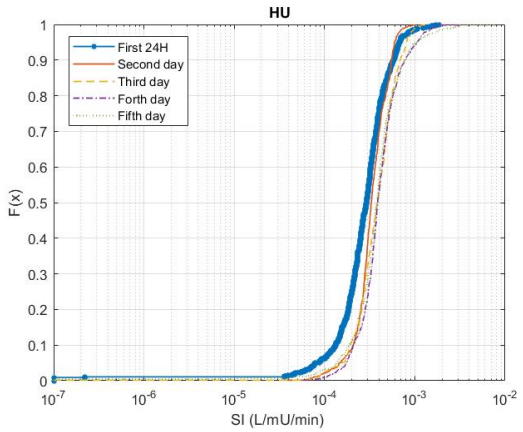

Figure 2: *CDF SI values in the first 24h compared to the next four days of the treatment*

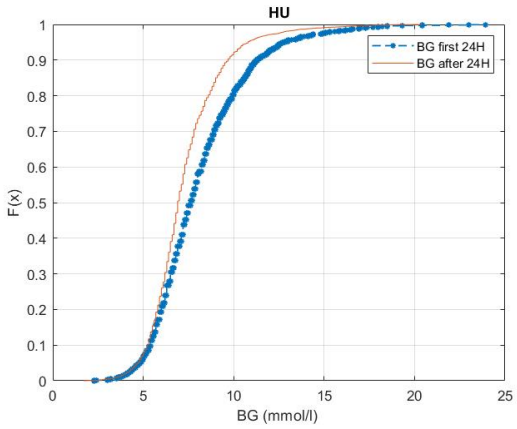

Figure 3: *CDF of BG values in the first 24h compared to the rest of the treatment*

Time period	Mean	% IR
First 24h	$3.29\ 10^{-4}$	1.07
24-48h	$3.56\ 10^{-4}$	0
48-72h	$4.16\ 10^{-4}$	0.15
72-96h	$3.62\ 10^{-4}$	0
96-120h	$4.71\ 10^{-4}$	0.61

Table 2: *SI values (L/mU/min) comparison between the first five days of treatment*

3.3. BG in the first 24h vs. rest of the treatment

Figure 3 shows the cumulative distribution function of blood glucose measurements (BG) of of all the Hungarian cohort patients in the first 24h compared to the BG in the rest of the treatment time. Inter-cohort BG values are higher in the first 24h compared to the rest of the treatment. The differences were not significant in terms of mean values, which is 0.81 mmol/l difference between the first 24h and after. However, there is a noticeable difference in the maximum BG values recorded, in which the difference is up to 3.5 mmol/l, as seen in Table 3.

Stats	First 24h	After 24h
MIN	2.3	1.7
MAX	23.9	20.4
MEAN	8.09	7.28
MEDIAN	7.60	6.90

Table 3: *BG values (mmol/l) comparison in the first 24h vs. rest of the treatment*

3.4. BG in the first 24h vs. next four days

Figure 4 shows the cumulative distribution function of Blood glucose (BG) of all patients in the first 24h compared to SI in the four successive treatment days. Based on BG mean values reported in Table 4, the highest BG mean value was at the first 24h of treatment compared to the next four days of the treatment, and it was as high as 7.8 mmol/l. BG values start droping on the 2nd day.

Episodes of hyperglycemia (HG) are higher in the first 24h of treatment compared to the four successive days.

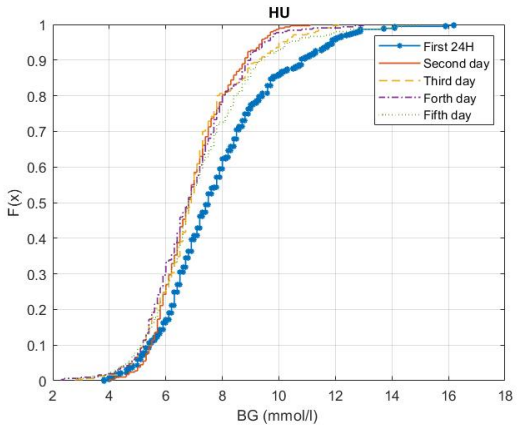

Figure 4: *CDF of BG in the first 24h compared to next 4 days of treatment*

Time period	Mean	%HG
First 24h	7.80	13.85
24-48h	6.70	1.03
48-72h	7.00	5.16
72-96h	6.90	2.28
96-120h	7.16	7.02

Table 4: *BG values (mmol/l) comparison between the first five days of treatment (%HG is the proportion of time when BG was above 8mmol/L)*

4. Discussion

From the distribution of identified SI values and BG measurements of Hungarian cohort, there were noticeable differences between the first 24h and the successive days until the end of the treatment where the lowest SI values and the highest BG values were always in the first 24h also the proportion of hours of insulin resistance and hyperglycemia. considering the analysis of the treatment difference, the carbohydrate (CHO) intake of the Hungarian cohort was significantly higher. These differences may also reflect patient's differences in the incidence of greater complexity and level of critical illness, such as incidence of severe sepsis, in some patients, which can occur from the areas and types of patients treated, as well as from treatment selection or treatment failure bias.

Early occurrence of hyperglycemia episodes is likely due to the surge in EGP seen particularly in severe sepsis and septic shock patients in the first 12-24 hours of the stay [7, 8]

This behavior matches clinical expectations and is due to stress [9], often seen in the first 24 hours of stay, particularly in severe sepsis and septic shock patients, all of which match the metabolic variability seen in the first 24h of stay. Thus, this phenomenon's occurrence qualitatively matches broad clinical expectations.

5. Conclusions

Hungarian ICU Patients in the early stages of ICU treatment have low insulin sensitivity and high blood glucose levels, as expected, given the stress response physiology. Results align with the clinical expectations were the lowest insulin sensitivity values and the highest blood glucose levels tend to be in the first 24h in all cohorts. Given the results, we may have to ask, how can we hundle the first 24h of treatment diffrently?. This question may arise for STAR protocol or any other model-based glycemic protocol.

Acknowledgements

Grants supporting the research presented: National Research Development and Innovation Fund, OTKA K116574; TKP2020 BME-Biotechnology FIKP grant of EMMI (BME FIKP-BIO); EU H2020 MSCA-RISE: DCPM (872488) grant.

References

1. Bagshaw, S. M.,et al, "The impact of early hypoglycemia and blood glucose variability on outcome in critical illness.", *Crit Care ,* **1**3(3): R91. (2009).
2. Krinsley, J. S, "Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients.", *Mayo Clin Proc ,* **7**8(12): 1471-1478. (2003).
3. Evans, A. et al, "Stochastic Targeted (STAR) Glycemic Control: Design, Safety, and Performance.", *Journal of Diabetes Science and Technology,* **6**(1): 102-115. (2012).
4. Lin, J. et al., "A physiological Intensive Control Insulin-Nutrition-Glucose (ICING) model validated in critically ill patients.", *Comput Methods Programs Biomed,* **1**02(2): 192-205. (2011).
5. Stewart, K.W., et al., "., Safety, efficacy and clinical generalization of the STAR protocol: a retrospective analysis. ", *Ann Intensive Care* **6**(1): p. 24. (2016).
6. Chase, J.G., et al., "Next-generation, personalised, model-based critical care medicine: a state-of-the art review of in silico virtual patient models, methods, and cohorts, and how to validation them.", *Biomed Eng Online* **1**7(1): p. 24. (2018)
7. Anane, Y., B. Benyo, A. Szlavecz, C. Pretty and J. G. Chase, "Endogenous glucose production parameter estimation for intensive care patients.", *Scientific Meeting on Electrical-Electronics, Biomedical Engineering and Computer Science* **I**EEE, pp. 1-4. (2019)
8. Thorell, A. et al., "Intensive insulin treatment in critically ill trauma patients normalizes glucose by reducing endogenous glucose production.", *J Clin Endocrinol Metab* **8**9(11): 5382-5386. (2014)
9. McCowen, K. C., A. Malhotra and B. R. Bistrian, "Stress-induced hyperglycemia.", *Crit Care Clin* **1**7(1): 107-124. (2001)