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Insulin Sensitivity Variability during Hypothermia

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Abstract: Hypothermia is often used to treat Out of Hospital Cardiac Arrest (OHCA) patients, who often simultaneously receive insulin for stress induced hyperglycemia. This study analyzes insulin sensitivity (S_I) variability profiles of OHCA patients undergoing hypothermic treatment to assess its impact on metabolism particularly during cool period. A retrospective analysis of clinically validated model-based insulin sensitivity is identified using data from 240 patients (9988 hours) treated with hypothermia, shortly after admission at the Intensive Care Unit (ICU). The impact on S_I is analyzed per-cohort and per-patient for each period of cool and warm by: 1) median S_I [IQR], and 2) Hour-to-hour percentage change in S_I, (%Δ S_I) median [IQR]. These non-parametric metrics assess level and hour-to-hour variability of S_I, which will be compared over time on 6-hour timescales.

Overall results show cohort and per-patient median S_I levels increased by 35.1% and 26.4% ($p < 0.001$) between the 0-6 hour block and 6-12 hour block during cool period, and consistent increments are recorded for the consequent blocks. Conversely, cohort and per-patient S_I variability decreased by 11.1% and 33.6% ($p < 0.001$) between the 0-6 hour block and 6-12 hour block. Lower variability decreases are recorded between the 6-12 hour, 12-18 hour and 18-24 hour blocks. However, S_I variability rise is recorded between the 18-24 hour and 24-30 hour blocks over the cool to warm transition. It is followed by a significant decreases between the remaining 6-hour blocks. These results represent overall statistically significant trends for this patient cohorts. In summary, OHCA patients treated with hypothermia have significantly lower and more variable insulin sensitivity during the cool period, particularly during the first 12 hours of ICU stay, and improve over time. As the treatment continues, insulin sensitivity variability decreases consistently while rising S_I except for a large, significant increase during the cool-warm transition. These results demonstrates a unique evolution for insulin resistance and metabolic variability in this cohort that could be exploited to improve control.

Keywords: Biomedical Control, Physiological Models, Variability, Non-linear Models.

1. INTRODUCTION

Hyperglycemia is prevalent in critical care (Capes, Hunt et al. 2000, McCowen, Malhotra et al. 2001, Mizock 2001, van den Berghe, Wouters et al. 2001) and increases the risks of further complications and mortality (Capes, Hunt et al. 2000, van den Berghe, Wouters et al. 2001, Krinsley 2003). Glycaemic control has shown benefits in reducing mortality (van den Berghe, Wouters et al. 2001, Krinsley 2004, Chase, Shaw et al. 2008). However, due in part to excessive metabolic variability (Chase, Le Compte et al. 2011) , many studies have found it difficult to reproduce these results (Brunkhorst, Engel et al. 2008, Investigators, Finfer et al. 2009, Preiser, Devos et al. 2009). Out-of-Hospital Cardiac Arrest (OHCA) patients have low survival rates and often experience hyperglycemia (Taylor, Griffiths et al. 1994, Neumar, Nolan et al. 2008). However, these patients belongs to one group who has shown benefit from accurate glycaemic control (AGC), but can be highly insulin resistant and variable, particularly on the first two days of stay (Pretty, Le Compte et al. 2012).

Hypothermia is often used to treat OHCA patients. In general, it leads to a lowering of metabolic rate that induces changes in energy metabolism. However, its impact on metabolism and insulin resistance in critical illness is

unknown, although one of the adverse events associated with hypothermic therapy is a decrease in insulin sensitivity and insulin secretion (Hayashi 2009). However, this decrease may not be notable in the cohort that is already highly resistant and variable (Pretty, Le Compte et al. 2012). Hence, understanding metabolic evolution and variability would enable safer and more accurate glycaemic control using insulin in this cohort.

This study analyses the evolution of a clinically validated model-based insulin sensitivity (S_I) metric (Chase, Suhaimi et al. 2010, McAuley, Berkeley et al. 2011) in OHCA patients to assess the impact of hypothermia at both a cohort and patient-specific, to enable better understand patient condition and physiology, as well as providing insight to enable safer metabolic management.

2. METHODS

2.1 Patients and Data

A retrospective analysis of glycaemic control data from 240 OHCA patients (9988 hours) treated with hypothermia, shortly after admission in Intensive Care Units (ICUs) of Christchurch Hospital, New Zealand, Erasme Hospital, Belgium and Lausanne Hospital, Switzerland. Patients from Christchurch Hospital (20) were on the SPRINT glycaemic control protocol (Chase, Shaw et al. 2008), whereas the remaining 220 patients from Erasme (122) and Lausanne (98) Hospitals used local AGC protocols. Blood glucose (BG) and temperature readings were taken 1-2 hourly. Data were divided into three periods: 1) cool (T<=35^{o}C); 2) idle period of 2 hours as hypothermia was removed; and 3) warm (T>35^{o}C). A maximum of 24 and a minimum of 15 contiguous hours for each period were considered, ensuring a balance of contiguous data between periods. Demographics are shown in Table 1.

Table 1: Demographic data for both cool and warm periods. Values are median [IQR] where appropriate

Variables	Values	
	Cool	Warm
Patients (n)	240	240
Total hours (h)	4987	5001
BG (mmol/L)	7.40 [6.20-9.70]	6.56 [5.61-7.78]
Insulin Rate (U/hr)	3.37 [1.33-8.00]	3.51 [1.60-7.00]
Glucose Rate (g/hr)	2.69 [1.04-5.26]	5.41 [2.71-8.11]

2.2 Model-based Insulin Sensitivity (S_I)

Model-based insulin sensitivity (S_I) in this study is a patient-specific parameter describing the whole body effect of insulin. The analysis of patient-specific insulin sensitivity employs a glucose-insulin system model developed and clinically validated in critical care glycaemic control and insulin sensitivity studies (Chase, Suhaimi et al. 2010, Evans, Shaw et al. 2011, Lin, Razak et al. 2011, McAuley, Berkeley et al. 2011, Fisk, Le Compte et al. 2012). It is shown schematically in Figure 1 and is defined:

$$\dot{G} = -p_G.G(t) - S_I.G(t).\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+EGP-CNS}{V_G} \quad (1)$$

$$\dot{I} = -n_K I(t) - \frac{n_L I(t)}{1+\alpha_I I(t)} - n_I(I(t)-Q(t)) + \frac{u_{ex}(t)}{V_I} + (1-X_L)\frac{u_{en}(t)}{V_I} \quad (2)$$

$$\dot{Q} = n_I(I(t)-Q(t)) - n_C\frac{Q(t)}{1+\alpha_G Q(t)} \quad (3)$$

$$\dot{P}_1 = -d_1 P_1 + D(t) \quad (4)$$

$$\dot{P}_2 = -\min\left(d_2 P_2, P_{\max}\right) + d_1 P_1 \quad (5)$$

$$P(t) = \min\left(d_2 P_2, P_{\max}\right) + PN(t) \quad (6)$$

Where $G(t)$ [mmol/L] denotes the absolute total blood glucose concentration and $I(t)$ [mU/L] is the plasma insulin. $Q(t)$ [mU/L] is the effect of previously infused insulin concentration being utilized over time, with n_I [1/min] accounting for the rate of transport between plasma and interstitial insulin compartments and n_C [1/min] denotes the interstitial insulin degradation rate. Endogenous insulin is denoted by $u_{en}(t)$ [mU/min] and $u_{ex}(t)$ [mU/min] represents exogenous insulin input while first-pass hepatic insulin extraction is represented by x_L. Non-insulin mediated glucose disposal rate and insulin sensitivity are denoted p_G [1/min] and S_I [L/mU/min], respectively. The parameter V_I [L] is the insulin distribution volume and n_K [1/min] and n_L [1/min] the clearance rate of insulin from plasma via renal and hepatic routes respectively. Endogenous glucose production is assumed constant and, denoted by EGP [mmol/min], and V_G [L] represents the glucose distribution volume. Finally, CNS [mmol/min] represents a constant, non-insulin mediated glucose uptake by the central nervous system. Michaelis-Menten functions are used to model effect saturation, with α_I [L/mU] used for the saturation of plasma insulin disappearance, and α_G [L/mU] for the saturation of insulin-dependent glucose clearance.

P_1 [mmol] represents the glucose in the stomach and P_2 [mmol] represents glucose in the gut. The rate of transfer between the stomach and gut is represented by d_1 [1/min], and the rate of transfer from the gut to the bloodstream is d_2 [1/min]. Amount of dextrose from enteral feeding is $D(t)$ [mmol/min]. P_{max} represents the maximum disposal rate from the gut. Exogenous inputs are glucose appearance $P(t)$ [mmol/min] from enteral food intake, flux out of the gut P_2. Any additional parenteral dextrose is represented by $PN(t)$.

Insulin sensitivity S_I is identified hourly from patient data, producing a step-wise hourly varying profile (Hann, Chase et al. 2005). This profile effectively describes the patients' metabolic behaviour under various time-varying physiologic conditions. The validity and independence of this patient-specific parameter have been validated using data from

independent, clinically matched cohorts (Chase, Suhaimi et al. 2010).

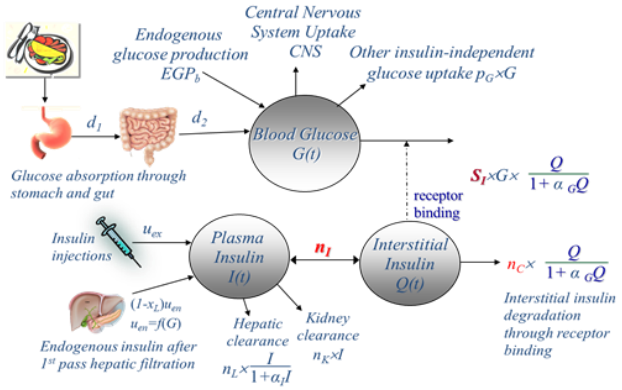

Fig. 1: Intensive Control Insulin-Nutrition-Glucose (ICING) model overview

2.3 Analyses and Metrics

S_I level and variability during the cool (T<35°C) and warm (T>35°C) periods are analysed on per-cohort and per-patient bases using 6-hour blocks defined in Table 2.

Table 2: Descriptions of 6-hour blocks for data analysis

Day	Period	Analysis	Block	Hour Range
1	Cool	6-hour block	1	0 – 6 hours
			2	6 – 12 hours
			3	12 – 18 hours
			4	18 – 24 hours
Idle 2 hour period in between cool and warm				
2	Warm	6-hour block	5	24 – 30 hours
			6	30 – 36 hours
			7	36 – 42 hours
			8	42 – 48 hours

S_I level is compared directly as a cohort median and by per-patient S_I median value for each period. Similarly, S_I variability ($\%\Delta S_I$) analyzed per-cohort for each period is calculated as the hour-to-hour percentage change in *SI* defined:

$$\%\Delta S_I = \frac{(SI_{n+1} - SI_n)}{SI_n} \times 100$$

Thus, $\%\Delta S_I > 0$ implies rising S_I level. However, to quantify per-patient variability, the interquartile range (IQR: 25th – 75th percentile) of $\%\Delta S_I$ is calculated and this metric captures the width of the hour-to-hour variability distributions for each patient.

S_I level and variability are non-Gaussian and thus compared using non-parametric cumulative distribution functions (CDFs) which can be calculated by assigning a probability of 1/n to each datum, orders the data from smallest to largest in value, and calculates the sum of the assigned probabilities to and including each datum. Data is compared using a Wilcoxon rank-sum test for whole-cohort comparisons, and a Wilcoxon signed rank test for patient-specific cool-warm pairs. In all cases, $p < 0.05$ is considered statistically significant.

3. RESULTS

3.1 S_I Level Analysis

Figures 2 and 3 present the cumulative distribution functions (CDFs) of hourly *SI* level by cohort and median *SI* per-patient, respectively, using 6-hour blocks. Table 3 presents the increase in median insulin sensitivity and corresponding p-values between successive time blocks.

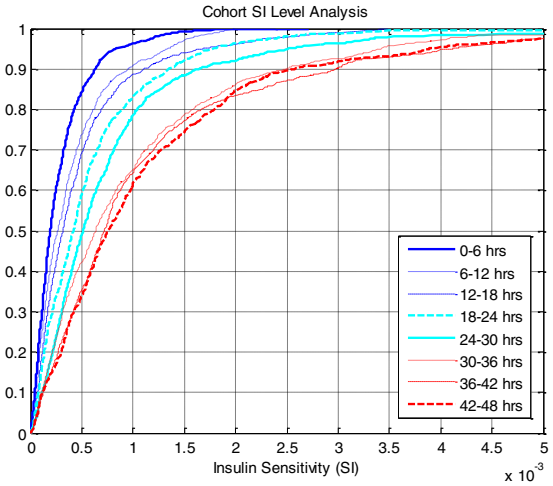

Fig. 2: Insulin sensitivity (S_I) level distribution per-cohort for OHCA patients, treated with hypothermia using 6-hour blocks for both cool and warm periods.

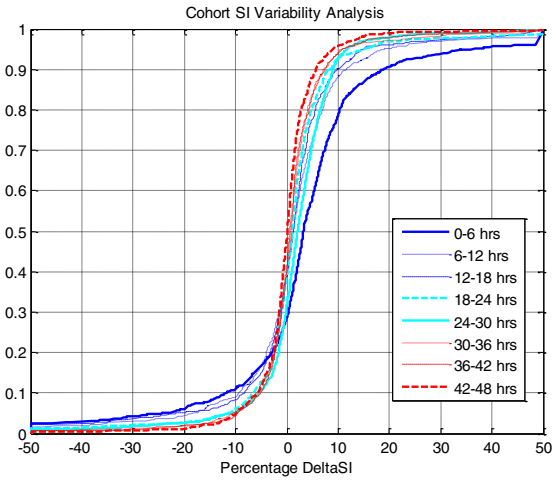

Fig. 3: Insulin sensitivity (S_I) level distribution per-patient for OHCA patients, treated with hypothermia using 6-hour blocks for both cool and warm periods.

Table 3: Increasing cohort and per patient median S_I during cool (Blocks 1-4) and warm (Blocks 5-8) periods

S_I level analysis	**Cohort analysis**		**Per-patient analysis**	
	% S_I	*p-value*	% S_I	*p-value*

	Median Increase		Median Increase	
Block 1-2	35.1	< 0.001	26.4	0.002
Block 2-3	19.2	< 0.001	31.1	0.037
Block 3-4	31.8	< 0.001	42.4	0.005
Block 4-5	23.4	< 0.001	18.3	0.019
Block 5-6	23.9	< 0.001	23.2	0.048
Block 6-7	13.1	0.05	15.8	0.177
Block 7-8	4.4	0.35	3.2	0.50

The results suggest that insulin sensitivity levels are initially low during the cool period and significantly increase ($p < 0.001$) over time for the first 36-42 hours (~2 days) of ICU stay. It is evident that the increments between each time block are significantly larger for the first 36 hours of treatment. However, subsequent increases are smaller and not significant.

3.2 S_I Variability Analysis

Figures 4 and 5 present the CDFs for changes in *SI* ($\%\Delta S_I$) for each time block per-cohort and per-patient, respectively. Table 5 presents the reductions in *SI* variability between consecutive blocks.

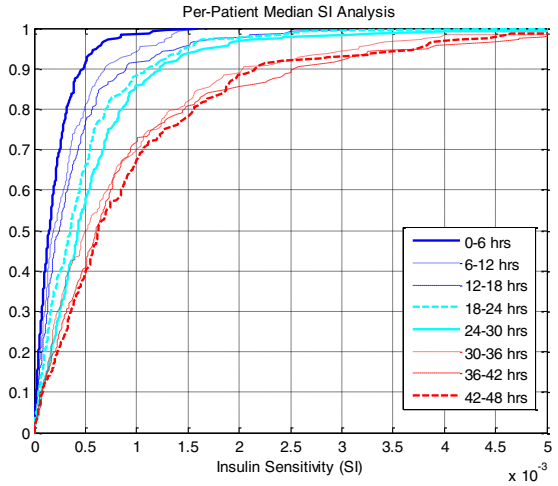

Fig. 4: Insulin sensitivity variability distribution ($\%\Delta S_I$) per-cohort for OHCA patients, treated with hypothermia using 6-hour blocks for both cool and warm periods.

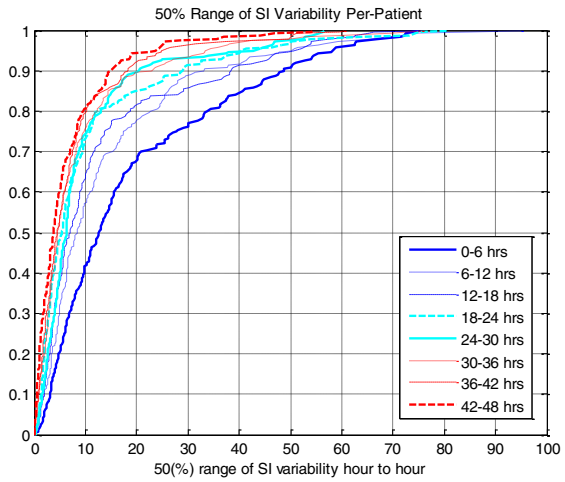

Fig. 5: Per-patient 50% range of *SI* variability distribution of OHCA patients, treated with hypothermia using 6-hour blocks for both cool and warm periods.

Table 5: Reductions in the interquartile range (IQR) and percentage of median S_I variability decrease per patient during cool (Block 1-4) and warm (Block 5-8)

S_I variability analysis	Cohort analysis		Per-patient analysis	
	% Reduction of IQR	*p-value*	% Median Decrease	*p-value*
Block 1-2	11.1	< 0.001	33.6	< 0.001
Block 2-3	20.7	0.860	15.8	0.104
Block 3-4	14.4	0.442	22.6	0.052
Block 4-5	-19.7	<0.001	-14.9	< 0.001
Block 5-6	23.1	< 0.001	26.4	0.017
Block 6-7	4.6	0.773	0.8	0.451
Block 7-8	13.0	< 0.001	17.1	0.060

These results show that *SI* variability decreases during the first 24 hours (i.e. during cool period). During this period, the difference between the 0-6 hour and 6-12 hour blocks is statistically significant ($p < 0.001$), but comparison between blocks 2-3 and 3-4 are similar. However, the variability rise recorded between the 18-24 hour and 24-30 hour blocks where the transition between cool and warm occurs, shows a sharp significant rise in variability for both cohort and per-patient analyses. The remaining blocks show decreasing variability.

In summary, the increase of S_I level is consistent from cool to warm throughout the entire treatment. In contrast, decreased S_I variability is inconsistent, particularly during the cool-warm transition period, despite significant variability decreases for the first 24 hours and subsequent 18 hours of treatment.

4. DISCUSSION

4.1 Insulin sensitivity level

The insulin sensitivity level results for both per-cohort and per-patient analyses suggest that OHCA patients undergoing hypothermic treatment have significantly lower insulin sensitivity during the earlier cool period on day 1 than the later warm period on day 2. Both results follow the general trend for insulin sensitivity level for critically ill patients over time and are consistent with other ICU studies (Langouche, Vander Perre et al. 2007, Pretty, Le Compte et al. 2012).

4.2 Insulin sensitivity variability

Both per-cohort and per-patient analyses suggest that OHCA patients undergoing hypothermic treatment are more variable initially and that S_I variability decreases over time. However, this trend is interrupted at cool-warm transition period due to change in body temperature. These results broadly match those of (Pretty et al, 2012) and (Langouche et al, 2007)

except for the sudden change at cool-warm transition, and are unique findings for this cohort which will impact glycaemic control.

4.3 The Impact of S_I variability on glycaemic control

Clinically, these results have shown significant implications for managing glycaemia in view of S_I variability. Enhanced S_I variability can lead to enhanced variability in BG resulting from a given insulin intervention (Chase, Le Compte et al. 2011). With low and highly variable insulin sensitivity, glycaemic levels might appear to remain unchanged and difficult to control effectively with exogenous insulin. This situation leads to increased insulin doses during initial treatment. However, coupled with high insulin sensitivity variability (Table 3) and increasing sensitivity (Table 2), it can result in the increased glycaemic variability and increased risk of hypoglycaemia during the first 36 hours of treatment. This issue is especially true during the cool-warm transition where SI rises and variability also rises. Thus, since glycaemic variability and hypoglycaemia are independent risk factors for the critically ill, it is important to understand and manage these patient-specific dynamics, especially those unique to a cohort, when implementing any tight glycaemic control.

Finally, it is important to note that consistently rising S_I level is also evident in the biased variability seen in Figure 4. For the first 36 hours, the $\%\Delta S_I$ plot has zero change below 0.5 on the CDF. Thus, S_I is biased towards rising as seen in Figures 2 and 3. More specifically, these results suggest that AGC protocols should seek to try to regulate insulin usage particularly during the cool period in the first 12-24 hours of ICU stay, while still maintaining glycaemic control to a given target. Due to high levels of insulin resistance and the saturation of insulin action, modulating carbohydrate and nutrition inputs might also be explicitly considered. In particular, early or, excessive nutritional regimes might be avoided or moderated to better manage the metabolic dynamics observed in this study.

5. CONCLUSION

This study analyses the metabolic evolution of OHCA patients treated with hypothermia. These analyses characterize the metabolic impact of hypothermic treatment on the level and variability of insulin sensitivity to inform control.

Two main conclusions are drawn as a result for these cohorts. i) S_I level is much lower during hypothermia and consistently increases over time, both cool and warm periods. ii) Insulin sensitivity is more variable during the cool period and shows contrasting behavior during cool-warm transition period between 18 – 30 hours, which indicates that there are major changes in physiology and metabolic conditions between cool and warm as influenced by human body temperature. Otherwise, it decreases over time.

Finally, this study shows the need for patient-specific glycemic management to ensure good control and safety during treatment. These results have significant potential clinical impact on the metabolic treatment of these patients, and changes in clinical therapy are required to safely treat patients as they transition from cool to warm.

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