Insulin Sensitivity, Its Variability and Glycemic Outcome: A model-based analysis of the difficulty in achieving tight glycemic control in critical care

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Abstract: Effective tight glycemic control (TGC) can improve outcomes in intensive care unit (ICU) patients, but is difficult to achieve consistently. Glycemic level and variability, particularly early in a patient's stay, are a function of variability in insulin sensitivity/resistance resulting from the level and evolution of stress response, and are independently associated with mortality. This study examines the daily evolution of variability of insulin sensitivity in ICU patients using patient data (N = 394 patients, 54019 hours) from the SPRINT TGC study. Model-based insulin sensitivity (SI) was identified each hour and hour-to-hour percent changes in SI were assessed for Days 1-3 individually and Day 4 Onward, as well as over all days. Cumulative distribution functions (CDFs), median values, and inter-quartile points (25th and 75th percentiles) are used to assess differences between groups and their evolution over time. Compared to the overall (all days) distributions, ICU patients are more variable on Days 1 and 2 (p < 0.0001), and less variable on Days 4 Onward (p < 0.0001). Day 3 is similar to the overall cohort (p = 0.74). Absolute values of SI start lower and rise for Days 1 and 2, compared to the overall cohort (all days), (p < 0.0001), are similar on Day 3 (p = .72) and are higher on Days 4 Onward (p < 0.0001). ICU patients have lower insulin sensitivity (greater insulin resistance) and it is more variable on Days 1 and 2, compared to an overall cohort on all days. This is the first such model-based analysis of its kind. Greater variability with lower SI early in a patient's stay greatly increases the difficulty in achieving and safely maintaining glycemic control, reducing potential positive outcomes. Clinically, the results imply that TGC patients will require greater measurement frequency, reduced reliance on insulin, and more explicit specification of carbohydrate nutrition in Days 1-3 to safely minimise glycemic variability for best outcome.

1. INTRODUCTION

There are strong physiological links between maintaining normal glycemic levels and variability, and improved immune response to infection (Weekers et al., 2003) as well as reductions in organ failure (Van den Berghe et al., 2001). Thus, tight glycemic control (TGC) by intensive insulin therapy (IIT) has successfully reduced organ failure and/or mortality in some prior studies (Van den Berghe et al., 2001, Krinsley, 2004, Chase et al., 2008). However, safely achieving improved outcomes with TGC has been difficult (Finfer et al., 2009, Preiser et al., 2009) due largely to significant increases in hypoglycemia and glycemic variability in TGC cohorts.

Glycemic level, range and variability are associated with increased organ failure and risk of death (Egi et al., 2006). Early hypoglycemia and increased glycemic range on Day 1 of a patient's stay, have also shown an increased risk of death (Bagshaw et al., 2009). Finally, hypoglycemia itself has been linked to poor outcome (Egi et al., 2006). All these outcomes result from the variability in these patients response to insulin or their variability in insulin sensitivity. They are exacerbated by TGC protocols that use larger insulin doses and/or infrequent sampling (Wilson et al., 2007), both of which allow outcome glycemia to vary more greatly. As a result there have been calls to increase target glycemic levels to avoid hypoglycemia (Cerra et al., 1997).

This study examines the evolution and variability of insulin sensitivity (1/insulin resistance) over the first days of an ICU patient's stay. It implicitly hypothesizes that it is increased variability in insulin sensitivity early in a patient's stay that makes achieving safe, effective TGC more difficult, increasing the risk of hypoglycemia and glycemic variability, and thus of poor outcomes.

2. METHODS

2.1 Patients and Data:

This study uses data from 394 patients treated on SPRINT (August 2005 – May 2007) for whom all APACHE and other data was available (Chase et al., 2008). Their overall glycemic data are shown combined and independently in Table 1, including summary glycemic control metrics. The Upper South Regional Ethics Committee (NZ) granted ethics approval for the audit, analysis and publication of this data.

Table 1: Patient data summary

	SPRINT
Total patients	394
Age (years)	65 [50 – 74]
% Male	62.9%
Diabetic history	67 (17.0%)
APACHE II score	18 [14 – 24]
APACHE II risk of death	25.6%
	[13.1% - 49.4%]
ICU LoS [median, IQR] (days)	4.0 [1.7 – 10.4]
Median BG (SD) (mmol/L)	6.0 (1.5)
% BG in 4.4-6.1 mmol/L	53.9%
% BG in 4.0-7.0 mmol/L	79.0%
% BG < 2.2 mmol/L	0.1%
Patients on Day 1	394
Patients on Day 2	264
Patients on Day 3	201
Patients on Day 4	181

2.2 Metabolic System Model:

A clinically validated computer model of the metabolic system (Chase et al., 2007) is used to identify patient-specific, time-varying (hourly) insulin sensitivity (SI) every hour:

$$\dot{G} = -p_G.G - \text{SI(t)}*G.\frac{Q}{1+\alpha_G Q}$$
$$+ \frac{P(t) + (P_{END}*m_{body}) - (CNS*m_{brain})}{(V_{G,frac}(t)*m_{body})} \quad (1)$$

$$\dot{Q} = -kQ + kI \quad (2)$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}(t)}{(V_{I,frac}*m_{body})} + e^{-(k_I\frac{u_{ex}(t)}{V_i})} I_B \quad (3)$$

Where $G(t)$ [mmol/L] is plasma glucose $I(t)$ [mmol/L] is plasma insulin, $u_{ex}(t)$ [mU/min] is exogenous insulin input, basal endogenous insulin secretion is I_B [mU/L/min], with k_I representing suppression of basal secretion by exogenous insulin. Interstitial insulin is $Q(t)$ [mU/L], with k [1/min] accounting for losses and transport. Body and brain weight are denoted by m_{body} [kg] and m_{brain} [kg]. Endogenous glucose clearance is p_G [1/min] and time-varying insulin sensitivity is SI or (formally) SI(t) in Equation (1) [L/(mU.min)]. Finally, $V_{I,frac}$ [L/kg] is the insulin distribution volume per kg body weight and n [1/min] is the transport rate of insulin from plasma. Total plasma glucose input is $P(t)$ [mmol/min], endogenous glucose production is P_{END} [mmol/kg/min] and $V_{G,frac}$ [L/kg] represents the glucose distribution volume per kg body weight. CNS [mmol/kg/min] captures non-insulin mediated glucose uptake by the central nervous system. Michaelis-Menten functions model saturation, with α_I [L/mU] for the saturation of plasma insulin disappearance,

and α_G [L/mU] for insulin-dependent glucose clearance saturation.

These parameters and their clinically validated values are well documented in the literature (Lin et al., 2008), and have been used in several clinical TGC studies and to create SPRINT. The model has also shown good correlation to gold standard research assessments (Lotz et al., 2006) in clinical metabolic research studies. Hence, the insulin sensitivity metric (SI) is a well validated metric that captures the whole body metabolic tradeoff of insulin and glucose, thus reflecting the hyperglycemic counter regulatory stress response and its variability that is seen in the critically ill.

2.3 Insulin Sensitivity (SI) and Variability:

The value of SI can be identified every hour using clinical data for blood glucose concentration, insulin administered and the carbohydrate nutrition administered from all sources (Hann et al., 2005). Its hourly variation can be obtained as the difference from one hour to the next, so that at hour (n+1): $\Delta SI_{,n+1} = SI_{n+1} - SI_n$; or as a percentage change from the prior value: $\%\Delta SI_{,n+1} = (SI_{n+1} - SI_n)/SI_{n+1}*100$, normalising values to a patient-specific level. Mathematically, this definition of $\%\Delta SI_{,n+1}$ limits positive changes (increase in SI from hour n to hour n+1) to 100% while drops in SI are not capped. These values for $\Delta SI_{,n+1}$ and $\%\Delta SI_{,n+1}$ are aggregated for each day of ICU stay.

2.4 Analysis and Statistics:

SI and its percent variation are plotted as cumulative distribution functions (CDFs) for Days 1, 2 and 3 of ICU stay. Day 4 Onward values are grouped. Variability at different levels of SI is normalised by presenting it as a percentage change instead of an absolute value.

Absolute values of SI are compared using the non-parametric Mann-Whitney test as distributions are skewed. Variability across days is assessed by comparing the number of $\%\Delta SI_{,n+1}$ values within ±15% to those outside this range, thus comparing the central portions of the CDF to those outlying portions of either positive or negative change. These values are compared using a Chi Squared test on a 2x2 contingency table. The ±15% range was chosen as a level below which clinical assay errors and other clinically insignificant variations dominate the model-based metric's variability. It thus separates clinically insignificant (within) and clinically significant (outside) variations. A value of $p < 0.005$ is considered significant given the large number of data points.

3. RESULTS

Figure 1 shows the CDFs for SI on Days 1-3, 4 Onwards and for the total overall cohort (all days). Table 2 shows the median and inter-quartile ranges (IQR) for SI on each day. Each of Days 1-3 and Day 4 Onwards are different ($p < 0.0001$), and Days 1-2 and Days 4 Onward are different from the overall total cohort (all days, $p < 0.0001$). Day 3 and the overall cohort, as seen in the graph, are similar ($p = 0.72$). It is clear that median and overall SI increase daily, with Days 4 Onward surpassing the total overall cohort (all days) results.
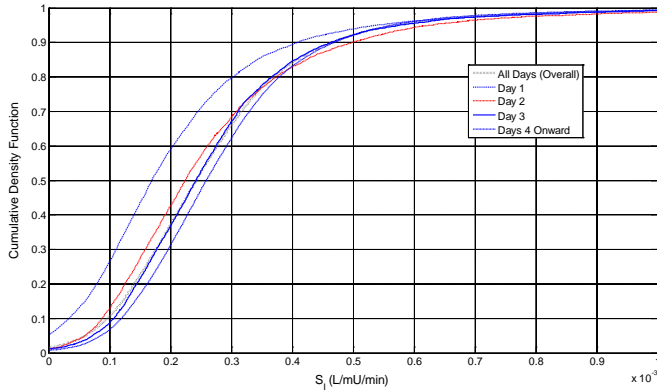
Figure 1: CDFs of SI for Days 1-3, Day 4 Onwards and the total overall cohort (all days).

Table 2: SI values (median [IQR]) for each day(s) analysed, where SI has units of (L/mU/min * 10^{-3}).

Day	SI: median [IQR]
1	0.169 [0.095, 0.270]
2	0.224 [0.143, 0.339]
3	0.242 [0.162, 0.336]
4 Onward	0.261 [0.182, 0.354]
Total (all days)	0.242 [0.159, 0.341]

For clarity, Figure 2 shows the CDFs of percent change SI variability for the total overall cohort (all days) and for Days 1 and 2. The figure is repeated, but for Days 3 and 4 Onward in Figure 3. It is clear that variability decreases on all days from Days 1-3 and then Days 4 Onward. All curves for each day noted are different (p < 0.0001) from each other. Days 1-2 and Days 4 Onward are different from the total overall (all days) with (p < 0.0001).

In particular, Days 4 Onward have less variability, and Days 1 and 2 greater variability, as is evident in the figures. Day 3 and the total overall cohort (all days) have similar variability (p = 0.74). The median and IQR values for each curve are shown in Table 3.
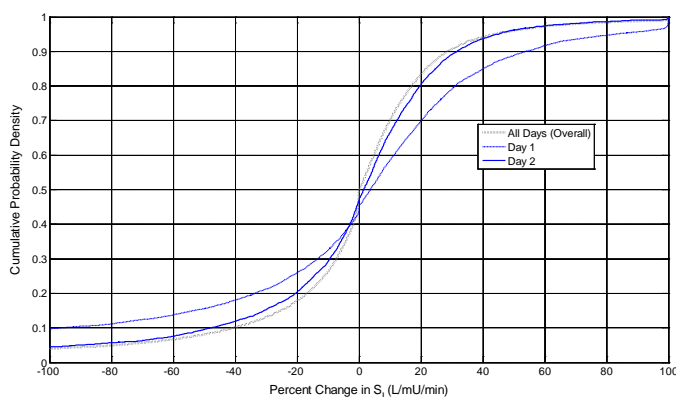

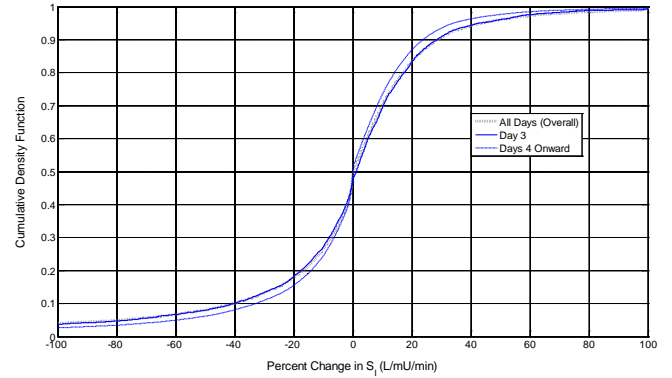**Figure 2**: CDFs of SI variability for Days 1 and 2 versus the overall cohort (all days).

Figure 3: CDFs of SI variability for Days 3 and 4 Onwards versus the overall cohort (all days).

Table 3: %ΔSI values (median [IQR]) for each day(s) analysed in (%).

Day	ΔSI: median [IQR]
1	3.6 [-22.0, 25.3]
2	1.5 [-14.5, 15.9]
3	1.2 [-12.2, 13.5]
4 Onward	-0.15 [-9.3, 10.5]
Total (all days)	<0.01 [-11.2, 13.1]

Similar to the trends for SI, amount of changes greater than ±15% decrease for each day that passes. Days 1-2 are more variable than the total overall cohort (p < 0.0001), Day 3 is less different (p = 0.74), and Days 4 Onward are less variable (p < 0.0001). These results are also evident in the curves of Figures 2-3, and data of Table 3.

4. DISCUSSION

Several studies have examined inflammation and stress response, and their metabolic outcome as stress hyperglycemia in critically ill cohorts (e.g. (Marik and Raghavan, 2004)). With respect to TGC, the anti-inflammatory role of insulin has also been examined. However, to the authors' knowledge, none have made specific comparisons of the strength, time course or behaviour of the stress response across a broad cohort. This study effectively compares the evolution and strength of this stress response using its metabolic impact (assessed by SI here) as a surrogate marker.

Figures 1-3 and Tables 2-3 clearly show four main outcomes: **1**) ICU patients have a lower insulin sensitivity (greater resistance) in the first 1-2 days compared to analyses that have in past looked only at the whole cohort and all days (Langouche et al., 2007, Lin et al., 2008); **2**) ICU patients are more dynamically variable in their SI (more variable insulin resistance) than the overall cohort (over all days) in the first 1-2 days and similar on Day 3; **3**) SI and its variability are reduced, compared to the overall cohort (all days) behaviours for Days 4 Onward; and **4**) SI rises and variability decreases over each day of stay, and the differences between days are significant both statistically and clinically.

In the original SPRINT study (Chase et al., 2008), glycemic control metrics, as seen in Table 1, were not a significant factor in differentiating survivors and non-survivors within the SPRINT cohort. Thus, given the large number of hours shown and significant variability, the quality of glycemic control was not a factor in these results.

It should also be noted that the trends for increasing SI over time matches results reported in other studies (Langouche et al., 2007). Similarly, TGC-based mortality improvements were evident in SPRINT after 3 days of ICU stay, at which point the overall cohort average is equal to the daily behaviour of SI and its variability. Hence, Day 3 represents a crossover point in patient behaviour versus its overall long term total behaviour.

More specifically, the insulin sensitivity variability observed may be the primary reason for the outcome variability and hypoglycemia seen in many other TGC studies. In particular, many TGC protocols administer insulin to relatively high levels in the face of the initial high insulin resistance (low SI) seen here, including doses of up to 15 U/hour for a blood glucose concentration of 8.0-9.0 mmol/L, as reported in (Wilson et al., 2007). This insulin sensitivity variability, combined with relatively high(er) insulin doses, will result in greater glycemic variability and thus increased risk of hypoglycemia for many protocols, especially in the first days. More insulin sensitive cohorts (higher SI, as in (Suhaimi et al., 2010)) will further multiply this variability if insulin dosing isn't implicitly or explicitly titrated to SI. The direct outcome is poor control, increased hypoglycemia and poor outcome, matching recent reports (Griesdale et al., 2009).

The strong inflammatory stress and immune responses that occur after insult or the onset of all forms of critical illness are well studied (Marik and Raghavan, 2004). Their general persistence and/or decrease over time and treatment has also been studied in some cases (Quaniers et al., 2006), including the impact of insulin (Krogh-Madsen et al., 2004). Changes in whole body glucose uptake and insulin sensitivity due to the impact of counter regulatory hormones and pro-inflammatory cytokines, captured here by SI, are complex and.may be a (currently unknown) function of the severity of illness, stage or time of the disease or insult, evolution of disease state, as well as a function of the treatment with insulin, whether normo-glycemia is maintained, or other anti-inflammatory effects, and/or increased non-insulin mediated glucose uptake. The results presented capture this behaviour with the overall model-based SI metric, which indicates the impact of this whole body stress response on outcome glycemia, providing a source of overall validation for the results found.

While the patho-physiology of these stress responses is well understood, their specific day-to-day dynamic evolution, and thus the variability observed here, is not as well understood. In many forms of critical illness, inflammatory cytokines and counter regulatory hormones have been observed to rise (Quaniers et al., 2006). However, whether these rises persist or decrease depends on the study and the treatment, particularly with respect to elements that reduce inflammation – notably the use of insulin and the ability to maintain normoglycemia (Weekers et al., 2003). Further, the potentially large and rapid changes seen may also be due to the high secretion rates due to stress, combined with relatively short half lives in plasma, of inflammatory cytokines and counter-regulatory hormones in these cohorts.

One overall potential limitation in the generality of this study is the level of tight control provided by SPRINT. Lower glycemic levels reduce physiological stress and inflammatory markers (e.g. (Weekers et al., 2003)). Thus, the control provided by SPRINT, which was consistent across all patients, may have resulted in the decrease in variability and general increase in SI over Days 1-4. It should be noted that this general increase in insulin sensitivity over time and as patients improve matches results seen in other studies (Langouche et al., 2007). However, and in contrast, a less well controlled cohort might see increased variability and/or reduced SI for longer periods of time. This issue would require data from another study for confirmation, linking variability to glycemic level (and thus inflammatory status), and thus remains an open issue.

It should also be noted that the number of patients decreases over time, as expected. However, the number of hours on any day is never less than 1700. Thus, there are enough data points and data density to ensure a consistent result that is unaffected by outliers. All patients were grouped in this analysis, regardless of diagnostic code. There may exist variability across diagnoses, which may be further elucidated by analysing sub-sets of larger cohorts of patient data.

With respect to the metric chosen, the SI parameter is a model-based measure of overall metabolic balance and whole body insulin sensitivity. It is highly correlated to the gold standard euglycemic clamp (R = 0.98) (Lotz et al., 2006), and has been extensively used and validated in a wide range of insulin sensitivity tests . It has also been shown to capture overall patient status in its use as part of a sepsis biomarker (Blakemore et al., 2008), and in predictive, real-time ICU glycemic control studies. Hence, it is a well validated measure that captures the fundamental metabolic behaviours important in this study.

Prior work by the authors group had shown that variability in metabolic response, using the same SI parameter, could be quite large (Lin et al., 2008). However, these studies had not considered differences over time. Advanced glycemic control protocols can take advantage of this knowledge to improve safety by accounting for the variability in SI and thus the variability outcome glycemia in response to an insulin intervention (Le Compte et al., 2009, Lin et al., 2008).

Clinically, these results have significant implications for the implementation of TGC. Enhanced variability in SI leads potentially to enhanced variability in the blood glucose level resulting from a given insulin intervention (Lin et al., 2008). In addition, the variability shown in Figures 2-3 is hourly,

where the greater variability shown implies a greater variability in blood glucose for longer intervals between measurements (Lonergan et al., 2006). These effects are multiplied by the overall insulin sensitivity of the cohort, where, for example, the Glucontrol cohort at the Liege centre were approximately 1.5-2.0x more sensitive than the SPRINT cohort (Suhaimi et al., 2010). The overall outcome is greater glycemic variability and a greater risk of both hyperglycemia and hypoglycemia. Thus, since glycemic variability and hypoglycemia are independent risk factors for the critically ill, it is important to manage these dynamics when implementing TGC.

More specifically, in implementing TGC, these results indicate that protocols should seek to minimise or reduce excessive insulin usage in the first 1-3 days while maintaining control to a given target. Given a high level of insulin resistance and the saturation of insulin action (Natali et al., 2000), the implication is that the level of carbohydrate administration and thus nutrition inputs, formulas and practice should be explicitly considered. In particular, SPRINT explicitly controlled nutritional inputs and used a low-carbohydrate nutritional formula to ensure better and more robust control. Thus, excessive nutritional regimes (high or low) might be avoided in consideration of an explicit choice that also helps manage the metabolic dynamics observed in this study, as supported by other studies (Krishnan et al., 2003).

Finally, these findings have clinical implications for advocates of early and/or high nutritional therapies (Martin et al., 2004). The potential benefit of early enteral or parenteral feeding may be lost if the variability it induces through requiring higher insulin doses to maintain normal or near-normal glycemia result in excessive glycemic variability and range, and/or hypoglycemia. Similarly, the benefits of early nutritional support may be difficult to delineate if glycemic control is not similar, resulting in ambiguous clinical and research outcomes (Doig et al., 2008).

5. CONCLUSIONS

This study presents results from a unique analysis that evaluates the metabolic dynamics of patients over time. Three main conclusions are drawn from this analysis. It is the first such study of its kind and shows the ability of clinically validated physiological models to quantitatively capture clinically important trends that might otherwise be missed, but have significant impact on the delivery of care and thus patient outcome.

First, SI rises over time, matching reports from other studies that looked only at selected days. This analysis clearly shows that SI is much lower (resistance is much higher) on Days 1-2 compared to the overall cohort, and keeps improving up through Day 3-4. Second, the same trends hold for insulin sensitivity variability, with variability decreasing over time. Hence, insulin sensitivity variability may be the primary reason for the outcome variability and hypoglycemia seen in many other TGC studies. In particular, those protocols that

utilise higher insulin doses and/or measure infrequently will be more likely to see greater glycemic variability and hypoglycemia in the first days, which is linked to poor outcome. Cohorts and patients with higher insulin sensitivity will multiply these effects. Third, managing this variability will require minimising relative insulin use in the first 2-3 days of care, as well as more explicit consideration of carbohydrate and overall nutritional inputs if tight glycemic control is to be safely achieved and maintained.

Overall, these results imply that TGC protocols should be able to accurately estimate insulin sensitivity as part of their operation, providing a strong impetus to support model-based control methods as a best-practice approach.

These main conclusions remain to be prospectively tested. However, this unique data driven analysis highlights several important outcomes with respect to the analysis and implementation of TGC protocols, and should inform future protocol designs and studies.

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