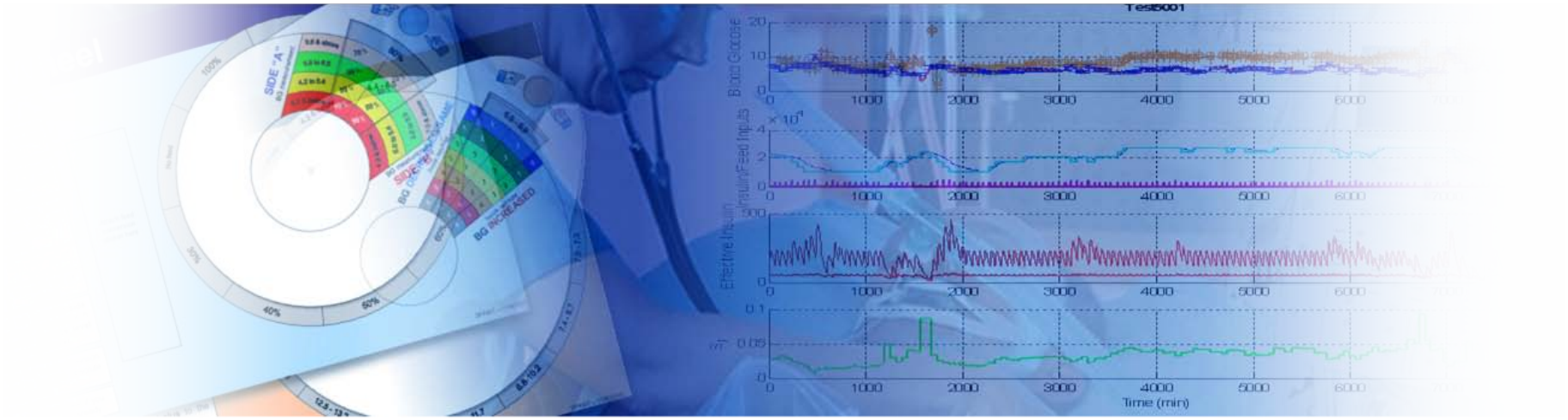
Insulin sensitivity, its variability and glycaemic outcome:

A model-based analysis of the difficulty in achieving tight glycaemic control in critical care



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Introduction

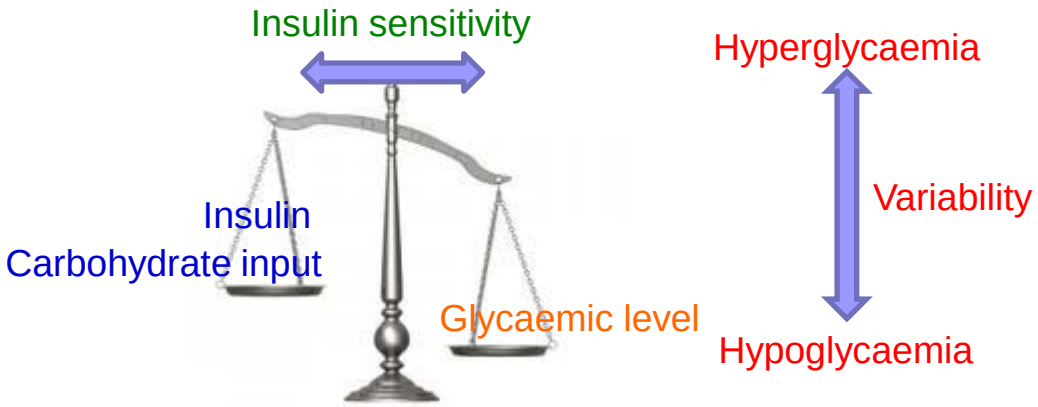
- **Tight glycaemic control is beneficial in the ICU**
  - Critically ill patients are often hyperglycaemic due to the stress-response
  - There are good physiological links between normal glycaemic levels/variability and:
    - Improved immune response to infection [Weekers 2003]
    - Reduced organ failure [Van den Bergre 2001]
  - Several studies have shown improved outcomes with TGC
    - Van den Berghe [2001], Krinsley [2004], Chase [2008], and a few others

- **... But difficult to achieve safely and consistently**
  - Finfer – NICE-SUGAR [2009], Brunkhorst [2008], Preiser - Glucontrol [2009], and others...

- **Due mainly to increased hypoglycaemia and glycaemic variability – both of which increase morbidity and mortality**

Introduction

- **Tight glycaemic control is a balancing act...**
  - Blood glucose level can be modulated with insulin and nutrition



- **... But the balance point keeps changing...**
  - Insulin sensitivity (*SI*) defines the overall metabolic balance and response to exogenous insulin
  - Changes can be very rapid as well, well within typical 2-4 hour measurement intervals

- **Understanding the variability and evolution of *SI* is key to safe, effective TGC**

A further point of interest

- Not all hypoglycemia and variability is the “same”
  - Bagshaw et al (2009) showed that the earlier it occurred in a patients stay the more likely they were to die (up to 2.5x increased odds risk)

- The big extra question then is:
  - Do highly variable ICU patients have greater or lesser variability over time?
  - Is day 1 worse than day 3, or vice versa? Or is there no change?
  - What about by diagnosis or pre-existing diabetes?

- These answers would significantly inform glycaemic control protocols and methods

Background

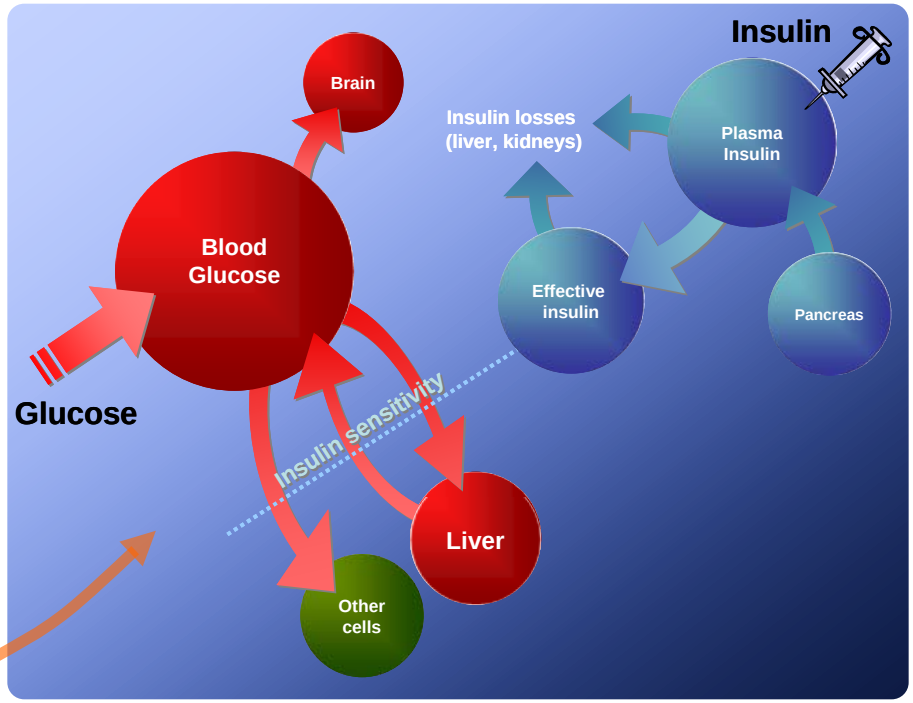
- **What exactly is insulin sensitivity?**
  - A parameter quantifying insulin-mediated glucose uptake
  - Insulin sensitivity (SI) ⊗ Insulin resistance
  - Low insulin sensitivity leads to hyperglycaemia

- **…and how can we measure it?**
  - The gold standard is the euglycaemic clamp
    - A complicated procedure that can take 2+ hours requiring precise IV insulin and glucose and frequent blood sampling
    - Results in an insulin sensitivity index (ISI)

Not easy to do with a critically ill patient!

Model

- **A model-based approach**
  - Use model-based insulin sensitivity (*SI*)
  - Clinically validated
  - Correlates well with euglycaemic-clamp ISI (r > 0.90) [Lotz 2008]
  - Provides a means to quantify *SI* and its evolution over time in critically ill patients
  - **SI identified hourly for every patient**



- **BG system model**
  - ICU model [Lin 2010]

Model equations

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

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

$$\dot{I}(t) = -\frac{n.I(t)}{1+\alpha_I I(t)} + \frac{u_{ex}(t)}{V_I} + e^{-(k_I u_{ex}(t))} I_B$$

Dextrose Absorption

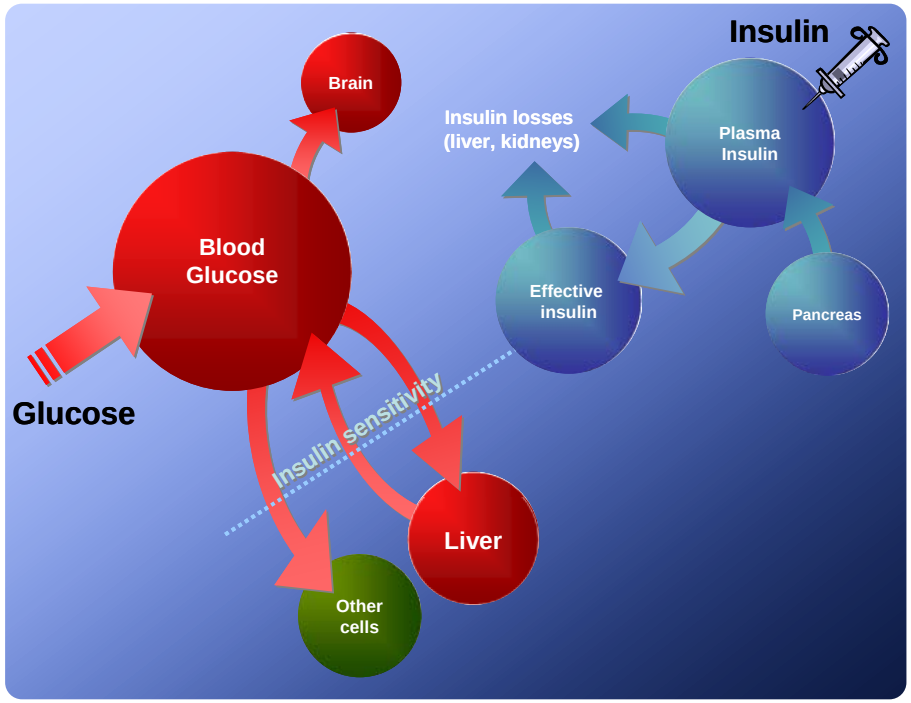
$$P(t) = \min(d_2 P_2, P_{\max})$$

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

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

Model

- **Model-based SI**
  - "Whole-body" insulin sensitivity
  - Captures overall metabolic balance, including the relative net effect of :
    - Altered endogenous glucose production
    - Peripheral and hepatic insulin mediated glucose uptake
    - Endogenous insulin secretion
  - Has been used to guide model-based TGC in several studies
  - Provides a means to analyse the evolution and hour-to-hour variability of *SI* in critically ill patients

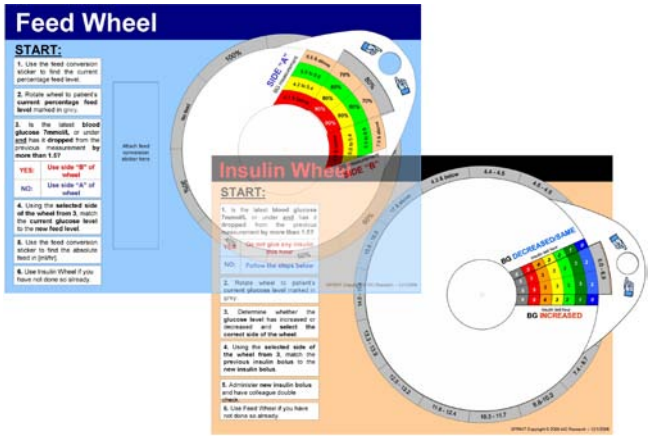


Study cohorts

- **Patients**
  - Retrospective analysis of 393 patients from Christchurch hospital ICU (Aug. 2005-May 2007)
  - All patients on the SPRINT glycaemic control protocol

- **SPRINT**
  - Tight glycaemic control (TGC) protocol used in Christchurch hospital ICU since August 2005
  - Entry criteria for SPRINT:
    - 2 consecutive measurements BG >8mmol/l
    - Clinical decision
  - A simple, lookup-table system derived from a model-based controller
  - Titrates insulin doses and nutrition rates to patient-specific insulin sensitivity
  - 1-2 hourly BG measurements

	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



Analysis methods

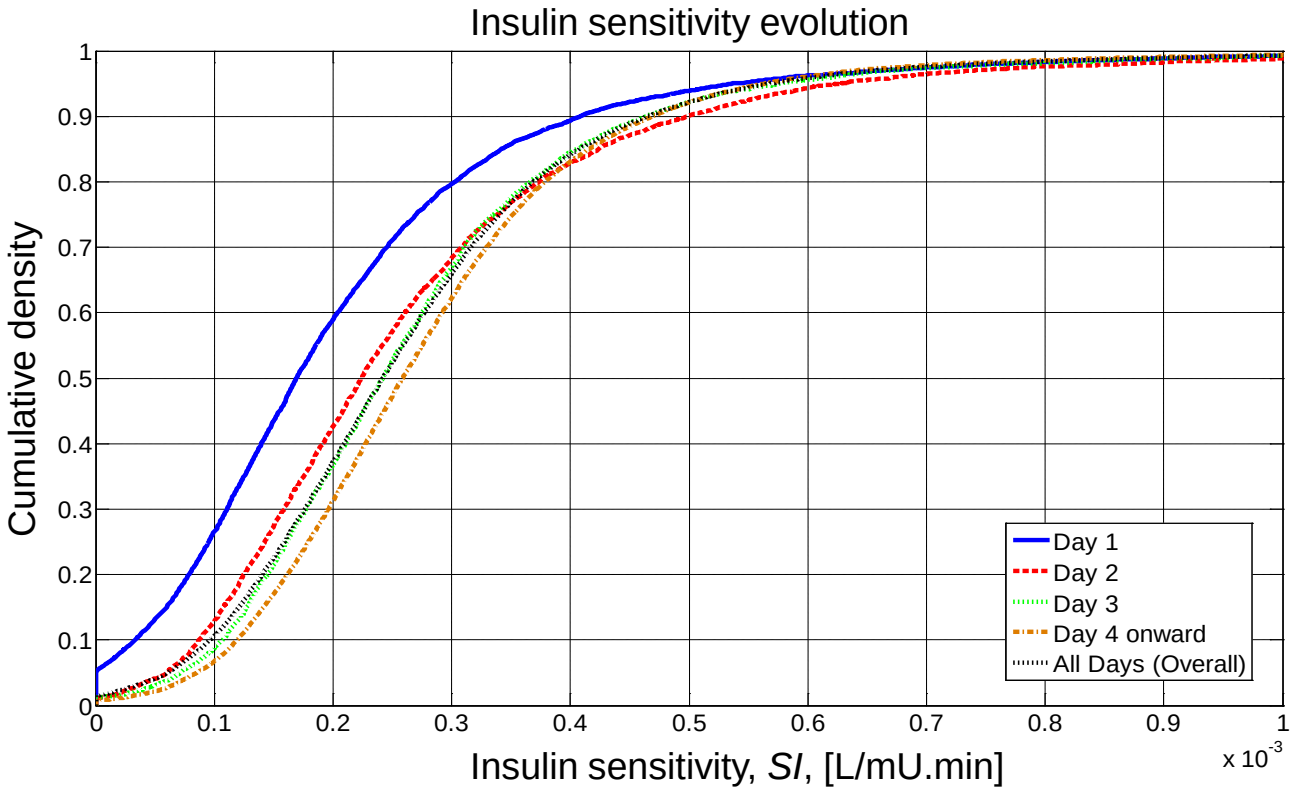
- ***SI* evolution – longer-term trends**
  - *SI* identified hourly from the pharmacokinetic-pharmacodynamic model for each patient
  - Analysed in 24-hour blocks from the commencement of SPRINT

- ***SI* variability– hour-to-hour changes**
  - Defined by hour-to-hour percentage change in *SI*:
    - $\%\Delta SI_{n+1} = \frac{100 \times (SI_{n+1} - SI_n)}{SI_{n+1}}$
      - Percentage change normalises values to a patient-specific level for fair comparison
  - Analysed in 24-hour blocks from the commencement of SPRINT

- **Non-parametric statistics**
  - Typical distributions of *SI* are asymmetric and skewed
  - Non-parametric statistics are used (median, interquartile range)
  - Cumulative distribution functions (CDFs)

Results

- ***SI* evolution over time**
  - Each of Days 1-3 and Day 4 onward are different from each other **(p<0.0001**)
  - Days 1-2 and Day 4 onward are different from the overall total cohort (**all days, p<0.0001**)
  - Day 3 and the overall cohort (as seen in the plot) are similar (**p=0.72**) – Interestingly, 3 days is the average length of stay!
  - **It is clear that median and overall SI increase daily, with Day 4 onward surpassing the total overall cohort (all days) results.**

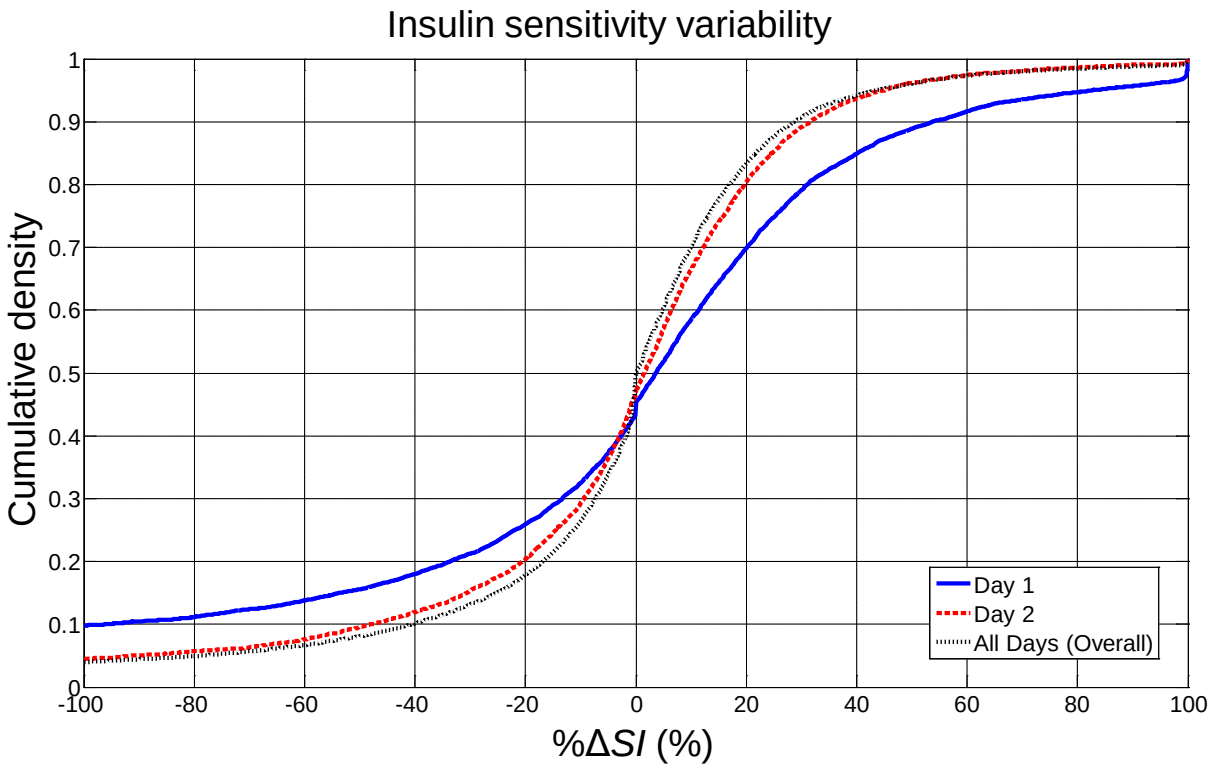


P-values calculated using Mann-Whitney U-test

Day	SI: median [IQR] x 10^{-3}
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]

Results

- ***SI* variability over time**
  - SI variability decreases significantly over the first two days (**p<0.0001**)
  - SI variability decreases on all days from Days 1-3 and then Day 4 onward (**p<0.0001**).
  - Days 1-2 and Day 4 onward are different from the overall total cohort (**all days, p<0.0001**)
  - Days 3 and Day 4 onward are shown on the next slide for clarity

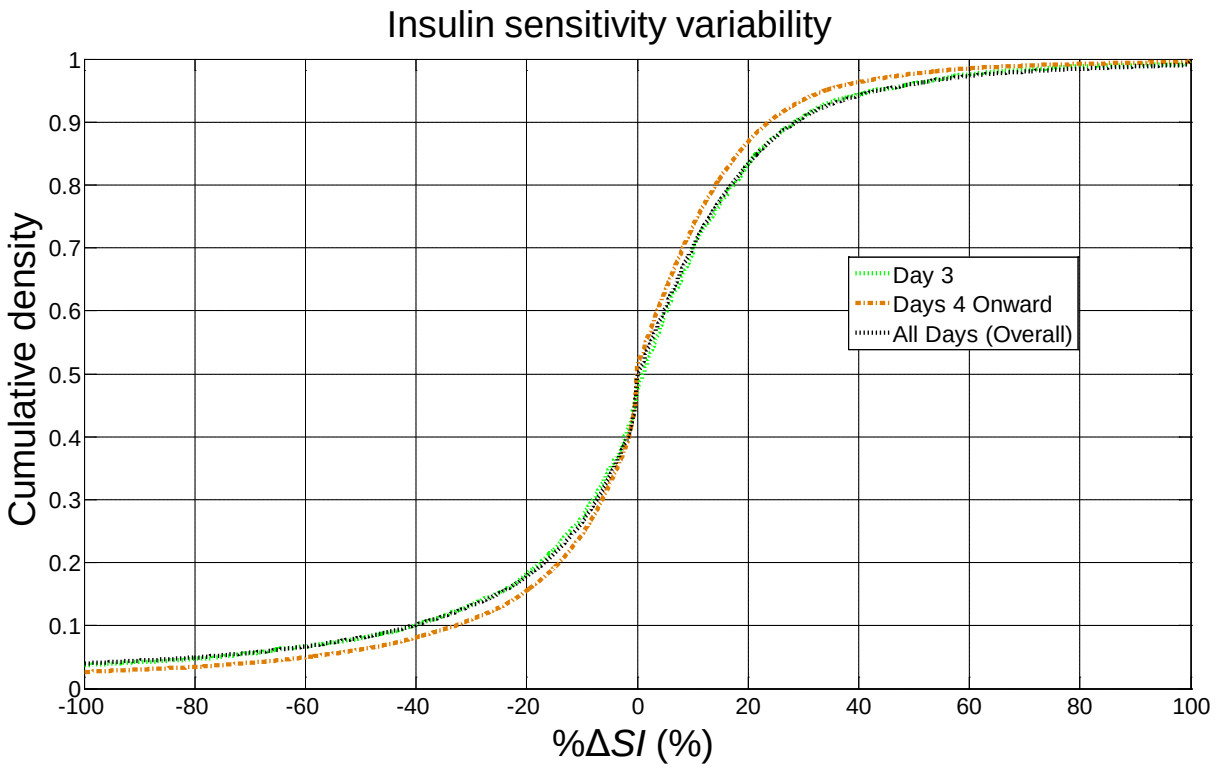


P-values calculated using Mann-Whitney U-test

Day	SI: median [IQR] x 10^{-3}
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]

Results

- ***SI* variability over time**
  - SI variability decreases on all days from Days 1-3 and then Day 4 onward (**p<0.0001**).
  - Days 1-2 and Day 4 onward are different from the overall total cohort (**all days, p<0.0001**)
  - Day 3 and the overall cohort (as seen in the plot) have similar variability (**p=0.74**) – again!
  - **The number of %Δ*SI* values > ±15% decrease for each day that passes → Less variable**



P-values calculated using Fisher exact test

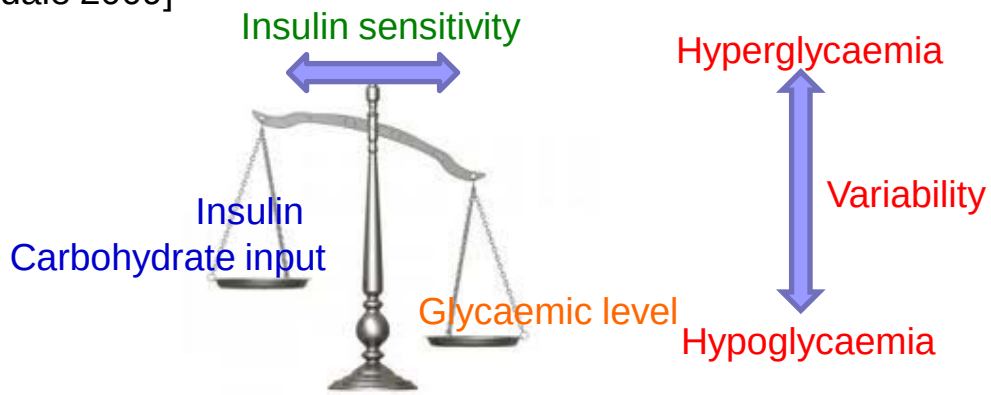
Day	SI: median [IQR] x 10^{-3}
1	3.6 [-22.0, 25.3]
2	1.5 [-14.5, 15.9]
3	1.2 [-12.2, 13.5]
4 Onward	-0.15 [-9.3, 10.5]
Total (all days)	<0.01 [-11.2, 13.1]

Summary of results

- **Changes in *SI* level and variability over time**
  - 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 2007, Lin 2008]
  - 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
  - *SI* and its variability are reduced, compared to the overall cohort (all days) behaviours for Days 4 Onward
  - *SI* rises and variability decreases over each day of stay, and the differences between days are significant both statistically and clinically.
  - These trends for increasing *SI* over time matches results reported in a previous study [Langouche 2007].

Discussion

- **Impact of *SI* variability on glycaemia**
  - The *SI* variability observed may be the primary reason for the outcome variability and hypoglycemia seen in many other TGC studies
  - Many TGC protocols administer insulin to relatively high levels in the face of the initial high insulin resistance (low *SI*) seen here
    - Doses of up to 15 U/hour for a blood glucose concentration of 8.0-9.0 mmol/L, have been reported [Wilson 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 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 2009]



Discussion

- **Clinical implications**
  - Outcome glycaemia is a function of *SI* variability + insulin and CHO inputs
    - Protocols should seek to minimise or reduce insulin usage in the first 1-3 days
    - In the face of increased insulin resistance and possible insulin saturation during the first few days, modulation of CHO nutrition should be considered
    - Increased measurement frequency and higher glycaemic targets should be considered for the first few days of TGC
  - Advanced glycaemic control protocols can take advantage of this knowledge to improve safety and effectiveness of TGC by accounting for the variability in *SI*

Conclusions

- ***SI* level increases over the first 3 days of TGC**
- ***SI* variability decreases over the first 3 days of TGC**
- **Outcome glycaemia is a function of *SI* variability + insulin and CHO inputs**
- **Greater variability coupled with lower *SI* during the early stages of TGC greatly increase the difficulty in achieving safe and effective glycaemic control**

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Questions?