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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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
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 patient’s 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
What exactly is insulin sensitivity?
- A parameter quantifying insulin-mediated glucose uptake
- Insulin sensitivity (SI) is inversely proportional to 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!
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

\[
\dot{G}(t) = -p_G G(t) - S_I(t) G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P(t) + EGP - CNS}{V_G} \\
\dot{Q}(t) = -kQ(t) + kI(t) \\
\dot{I}(t) = -\frac{n_I(t)}{1 + \alpha_I(t)} + \frac{u_{ext}(t)}{V_I} + e^{-(k_{ext}(t))} I_B \\
P(t) = \min(d_2 P_2, P_{max}) \\
\dot{P}_2 = -\min(d_2 P_2, P_{max}) + d_1 P_1 \\
\dot{P}_1 = -d_1 P_1 + D(t)
\]
Model-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
### Patients
- 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

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

### Results

**Insulin sensitivity evolution**

**P-values calculated using Mann-Whitney U-test**

<table>
<thead>
<tr>
<th>Day</th>
<th>SI: median [IQR] x 10^{-3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.169 [0.095, 0.270]</td>
</tr>
<tr>
<td>2</td>
<td>0.224 [0.143, 0.339]</td>
</tr>
<tr>
<td>3</td>
<td>0.242 [0.162, 0.336]</td>
</tr>
<tr>
<td>4 Onward</td>
<td>0.261 [0.182, 0.354]</td>
</tr>
<tr>
<td>Total (all days)</td>
<td>0.242 [0.159, 0.341]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative density</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
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<table>
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<tr>
<th>Insulin sensitivity, SI, [L/mU.min]</th>
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</table>
- **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

### Results

**Insulin sensitivity variability**

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<td>3</td>
<td>1.2 [-12.2, 13.5]</td>
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<td>4 Onward</td>
<td>-0.15 [-9.3, 10.5]</td>
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<td>Total (all days)</td>
<td>&lt;0.01 [-11.2, 13.1]</td>
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P-values calculated using Mann-Whitney U-test
- **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 %ΔSI values > ±15% decrease for each day that passes → Less variable

### Results

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P-values calculated using Fisher exact test
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].
**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]
**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?