Variability of insulin sensitivity for diabetics and non-diabetics during the first 3 days of ICU stay


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Why concern ourselves with insulin sensitivity in the ICU?

- Safe, effective tight glycaemic control (TGC) can improve outcomes in the ICU
- But, TGC is a balancing act...
  - ... where the balance point keeps changing...
  - Insulin sensitivity ($SI$) defines the overall metabolic balance and response to exogenous insulin
  - Variability of $SI$ is associated with the evolution of the stress response

Understanding the variability and evolution of insulin sensitivity is key to safe, effective TGC.
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

- ICING model [Lin 2010]

Key model equations

\[
\begin{align*}
\dot{G}(t) &= -p_G G(t) - S_I(t) G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P(t) + EGP - CNS}{V_G} \\
\dot{Q}(t) &= -n_I(I(t) - Q(t)) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)} \\
\dot{I}(t) &= -n_K I(t) - \frac{n_L I(t)}{1 + \alpha_L I(t)} - n_I(I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (1 - x_L) \frac{u_{en}}{V_I}
\end{align*}
\]
### Patients

- Patients on the SPRINT glycaemic control protocol for at least 12 hours
- Patients commenced SPRINT within 12 hours of ICU admission

### Diabetic patients

- Includes both type I and type II diabetics
- Peripheral and hepatic insulin resistance is common to both forms of diabetes [DeFronzo 1982, Pang 2008]
- Reduced insulin sensitivity (increased insulin resistance) may make TGC more difficult

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<table>
<thead>
<tr>
<th></th>
<th>Non-diabetics</th>
<th>Diabetics</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>164</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>IDDM/NIDDM</td>
<td>0/0</td>
<td>14/41</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 [56-74]</td>
<td>68 [59-74]</td>
<td>0.42</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>108/56</td>
<td>27/28</td>
<td>0.04</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>19 [15-25]</td>
<td>18 [13-22]</td>
<td>0.21</td>
</tr>
<tr>
<td>APACHE II ROD (%)</td>
<td>29 [14-53]</td>
<td>23 [12-39]</td>
<td>0.09</td>
</tr>
<tr>
<td>Op/Non-Op</td>
<td>81/83</td>
<td>26/29</td>
<td>0.88</td>
</tr>
<tr>
<td>ICU mortality (%)</td>
<td>18%</td>
<td>7%</td>
<td>0.08</td>
</tr>
<tr>
<td>ICU length of stay (hrs)</td>
<td>80 [42-179]</td>
<td>48 [24-86]</td>
<td>0.002</td>
</tr>
</tbody>
</table>
**SPRINT**

- TGC protocol used in Christchurch Hospital ICU since August 2005 [Chase 2008]
- 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
**Overall cohort analysis:**

- *S/I* increases significantly over the first 24 hours within each group (*p*<0.0001).
- For days 2-3, further increases are more moderate.
- Median *S/I* is 25-32% lower for diabetics compared to non-diabetics for all days (*p*<0.05)

<table>
<thead>
<tr>
<th>Cohort analysis</th>
<th>Non-diabetics</th>
<th>Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Increase at median</td>
<td>p-value</td>
<td>% Increase at median</td>
</tr>
<tr>
<td>Days 1-2</td>
<td>45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days 2-3</td>
<td>19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days 3-4+</td>
<td>11</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Empirical cumulative distribution curves**
### Results

**Patient median SI analysis:**

- SI increases significantly over the first 24 hours ($p<0.02$).
- For days 2-3, further increases are limited and not statistically significant.
- Median insulin sensitivity is 29-43% lower for diabetics compared to non-diabetics for days 1-3 ($p<0.05$).
Results

- Cohort variability analysis:
  - Hour-to-hour variability of $SI$ decreases significantly between days 1 and 2 for both groups ($p<0.0001$)
  - There is a further significant reduction in variability between days 2 and 3 for non-diabetic patients ($p<0.005$)
  - Diabetic group significantly more variable than non-diabetic for days 1-3 ($p<0.05$)

\[
\%\Delta SI_{k+1} = \frac{100 \times (SI_{k+1} - SI_k)}{0.5 \times (SI_{k+1} + SI_k)}
\]
Conclusions

- ICU patients have lower insulin sensitivity and are more variable on day 1 compared to later in their stay.

- Diabetic patients have even lower and more variable SI compared to non-diabetic patients during days 1-3 of ICU stay.

- Low SI levels + high SI variability = increased potential glycaemic variability and hypoglycaemia with TGC protocols.

- Greater care may be required with TGC during the first few days of ICU stay to safely minimise glycaemic variability.
  - Reduced reliance on insulin and
  - Explicit specification of carbohydrate nutrition
  - Increase measurement frequency
  - Higher glycaemic targets for early ICU stay

Particularly for patients with a diabetic history.