

The Impact of Insulin Sensitivity Variability and Dynamics on Tight Glycemic Control in Neonatal and Adult Intensive Care

J.G. Chase, A. Le Compte, C Pretty, A. Lynn, G.M. Shaw, J. Lin, N. Razak, J. Parente

INTRODUCTION

Hyperglycemia and glycemic variability increase mortality and poor outcomes in adult and neonatal intensive care units (ICU, NICU). Safe, effective tight glycemic control has proven difficult due to significant insulin resistance and its dynamic change over time in these patients.

Successful glycemic control protocol design must account for glycemic variability. Model-fitted insulin sensitivity can provide a measure of the dynamic effects of insulin in the context of a real-time, clinically viable

control setting. This data can be used to identify patterns and/or trends within patient groups and between patient groups, guiding the adaptation of therapies from the controlled adult intensive care environment to other critical care settings, less acute wards, and ambulatory cases.

Insulin sensitivity (S_t) and its hour-to-hour (ΔS_t) change are analyzed to define the inter- and intra- patient variability for both adult critical care and neonatal cohorts.

MODELS AND METHODS

A clinically validated insulin-glucose model is used to identify hourly insulin sensitivity (S_t) from retrospective clinical data for ICU and NICU cohorts. The ICU cohorts contained 393 patients with 44,386 hours of data from patients on the SPRINT insulin/nutrition modulation protocol.

The NICU cohort comprised 25 episodes of insulin infusions from 21 patients with 3,567 hours of data.

Insulin sensitivity for both groups of data was fitted using integral-based fitting methods on models adapted to each patient group.

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

$$\dot{Q} = -kQ + kI$$

$$I = \frac{nI}{1 + \alpha_I I} + \frac{u_{in}(t)}{(V_{I,fast}(t) * m_{body})} + e^{-(\lambda_{in}(t))} I_B$$

RESULTS & OUTCOMES

The median insulin sensitivity for neonates was 0.68×10^{-3} L/(mU.min), compared to 0.24×10^{-3} L/(mU.min) for adults, and the 5%-95% data interval was $[0.17 - 1.70] \times 10^{-3}$ L/(mU.min) for neonates and $[0.06 - 0.79] \times 10^{-3}$ L/(mU.min) for adults respectively. In healthy Type II diabetes, median insulin sensitivity is $1-2 \times 10^{-3}$ L/(mU.min) for comparison.

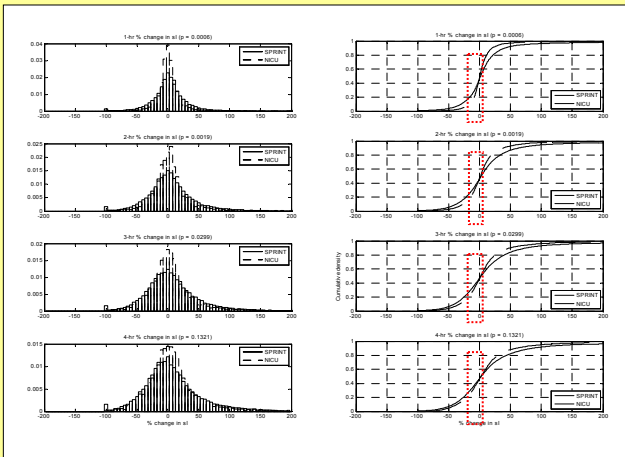


Figure 2. Temporal variation in insulin sensitivity for adult and neonatal cohorts. The left panel shows distribution of change in insulin sensitivity, and the right panel shows cumulative density functions for insulin sensitivity change for 1-4 hour intervals.

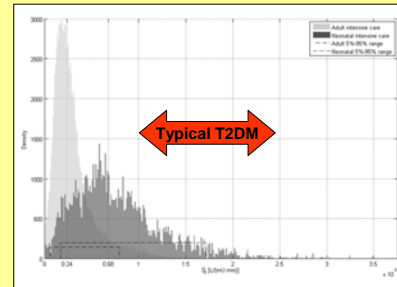


Figure 1: Empirical probability distribution function of model-fitted insulin sensitivity in adult critical care (light grey) and neonatal (dark grey) cohorts. The shaded area of each plot is equal to 1.0. The 5%-95% range of insulin sensitivity for adult and neonatal cohorts are shown by the dashed and dash-dot lines respectively.

The range and variation of model-fitted insulin sensitivity has been studied in adult critical care populations. **However, this research is the first time this form of modeling and analysis has been applied to a neonatal cohort.** Higher median insulin sensitivity in neonates may be due to higher glucose turnover and higher metabolic clearance of insulin resulting in lower plasma insulin concentrations.

The distribution of insulin sensitivity variation between adults and neonates, shown in Figure 2, is significantly different for intervals of 1-3 hours ($p < 0.05$, Mann-Whitney test). Additionally, the median values of ΔS_t are not significantly different to zero over any time interval for either cohort.

Thus, noting the wider insulin sensitivity spread in Figure 1, NICU patients exhibit less inter-patient variation and higher inter-patient variation compared to adults. However, as seen in Figure 2, adult patients exhibit very high intra-patient variability.

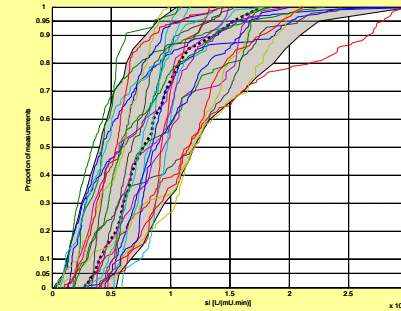


Figure 3: Per-patient empirical distribution of insulin sensitivity for the neonatal cohort. Each line represents a fitted insulin sensitivity profile for each of the 25 retrospective data sets. The overlaid dashed line shows the median and the shaded region represents the 5%-95% range of per-patient insulin sensitivity.

Finally, Figure 3 shows that each NICU patient has a uniquely identified insulin sensitivity profile, further highlighting the importance of accurate identification for tight control.

Overall, typical fixed insulin dosing protocols (e.g. sliding scales) will often fail to consistently provide effective glycemic control in both cohorts due to the significant intra- and inter- patient variability in insulin sensitivity observed in these cohorts.