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

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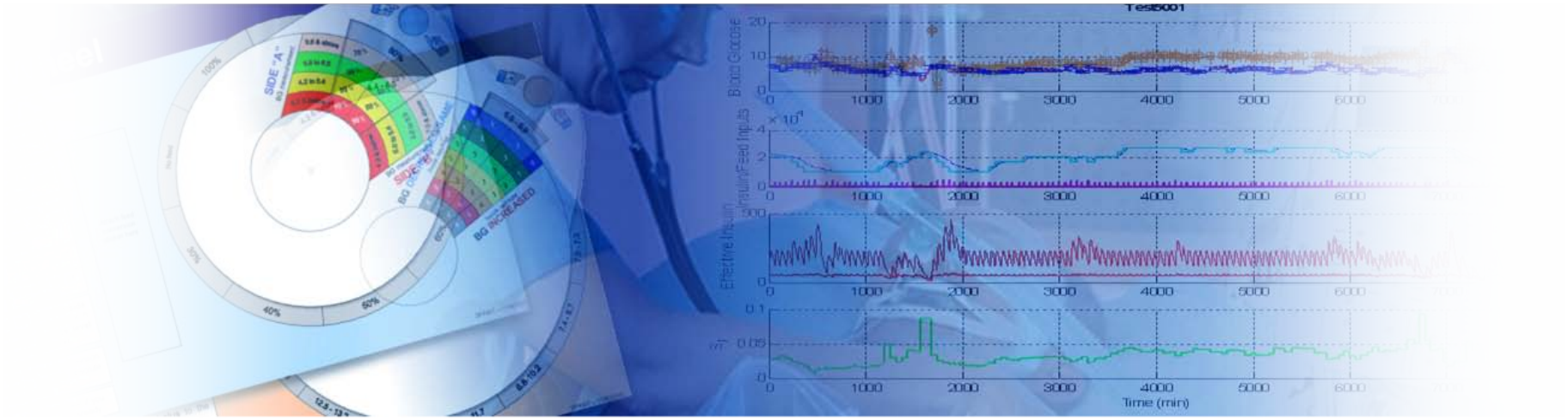

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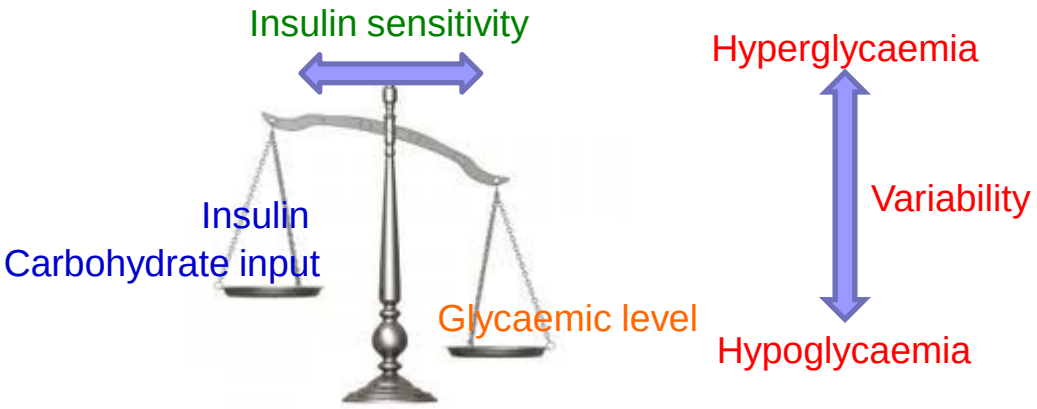
Introduction

- **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...

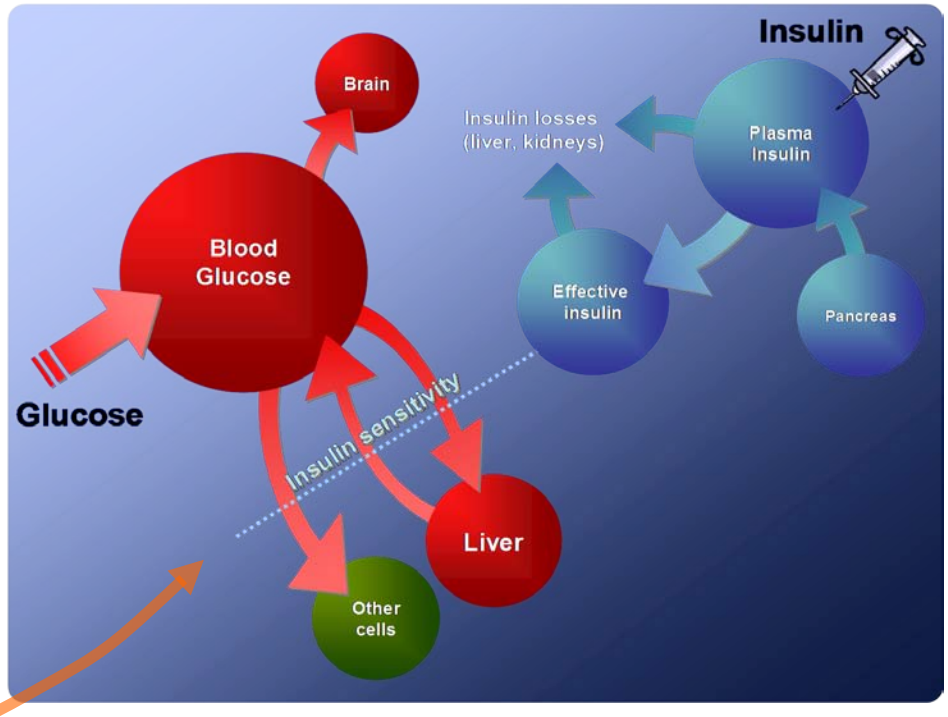


  - ... where the balance point keeps changing...
  - Insulin sensitivity (*SI*) defines the overall metabolic balance and response to exogenous insulin
  - Variability of *SI* is associated with the evolution of the stress response

- **Understanding the variability and evolution of insulin sensitivity is key to <u>safe, effective</u> TGC**

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**
  - ICING model [Lin 2010]

Key model equations

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

$$\dot{Q}(t) = -n_I(I(t) - Q(t)) - n_C\frac{Q(t)}{1+\alpha_G Q(t)}$$

$$\dot{I}(t) = -n_K I(t) - \frac{n_L I(t)}{1+\alpha_I I(t)} - n_I(I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (1-x_L)\frac{u_{en}}{V_I}$$

Study cohorts

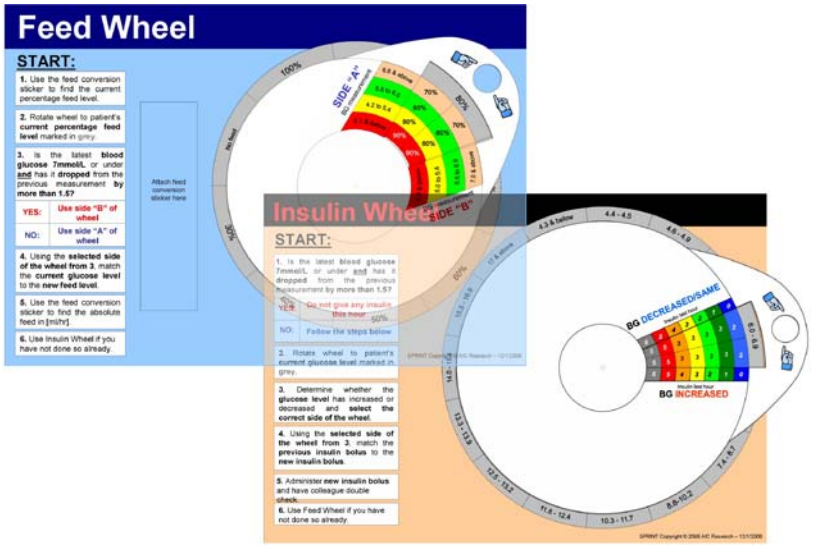
- **Patients**
  - Retrospective analysis of 219 patients from Christchurch Hospital ICU (Aug. 2005-May 2007)
  - Patients on the SPRINT glycaemic control protocol for at least 12 hours
  - Patients commenced SPRINT within 12 hours of ICU admission

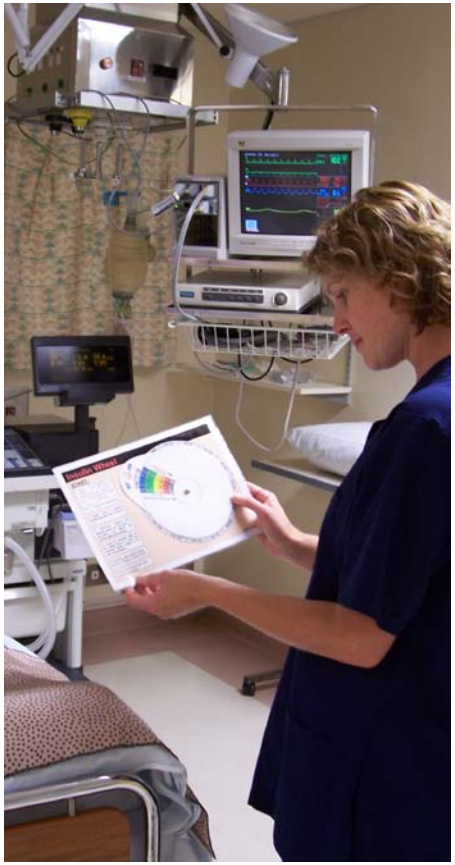
- **Diabetic patients**
  - Includes both type I and type II diabetics
  - Peripheral and hepatic insulin resistance is common to both forms of diabetes [DeFronzo 1982, Pang 2008]
  - Reduced insulin sensitivity (increased insulin resistance) may make TGC more difficult

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

SPRINT TGC

- **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



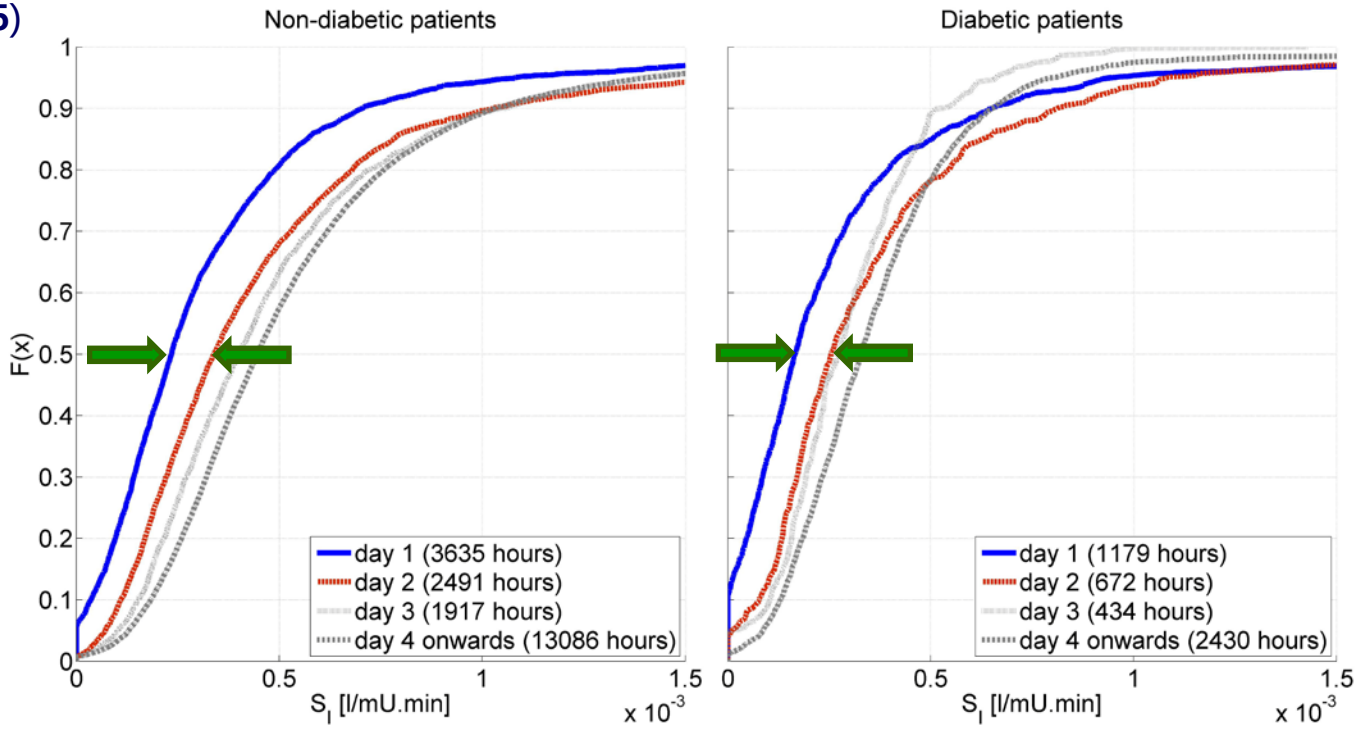


Results

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

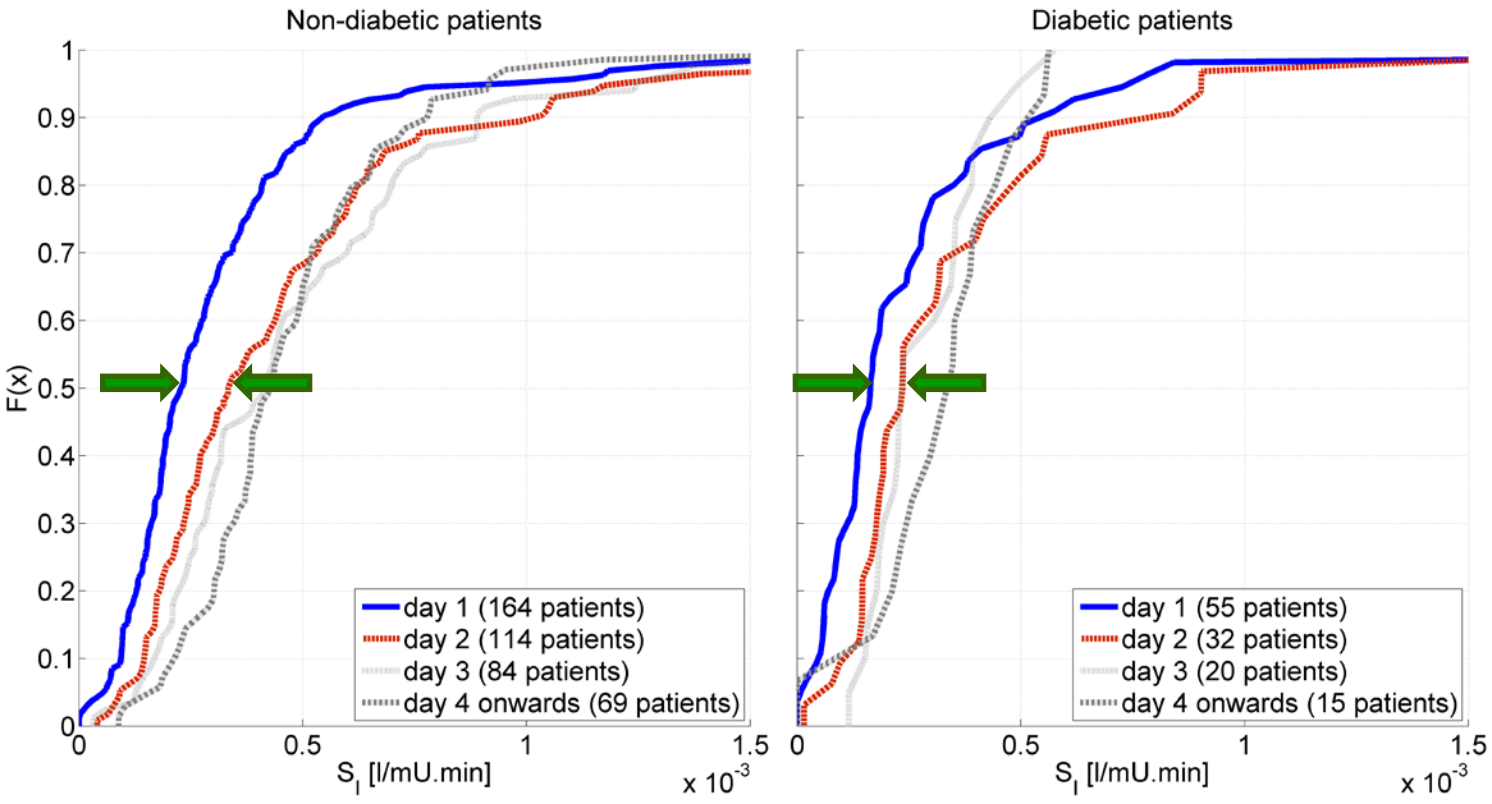
Cohort analysis	Non-diabetics		Diabetics	
	% Increase at median	p-value	% Increase at median	p-value
Days 1-2	45	**<0.0001**	53	**<0.0001**
Days 2-3	19	**<0.0001**	8	**0.9359**
Days 3-4+	11	**<0.0001**	20	**<0.0001**

Empirical cumulative distribution curves



Results

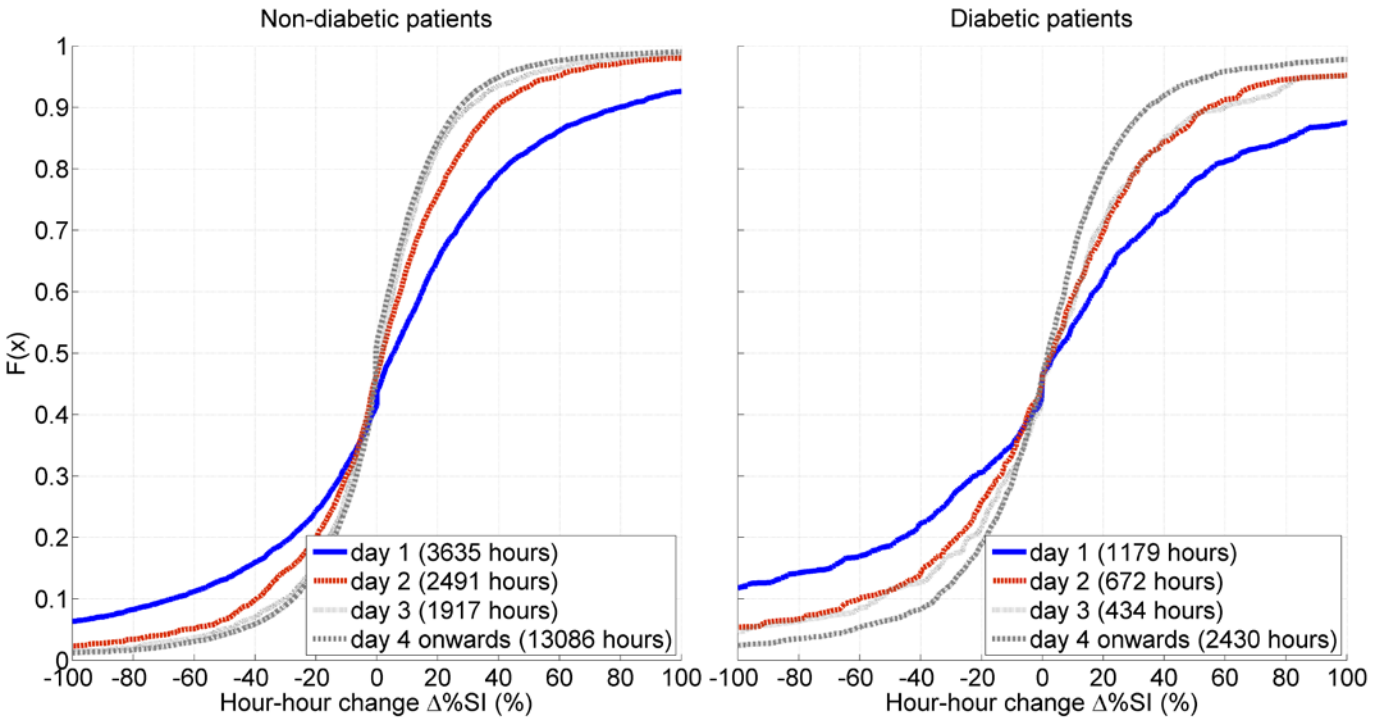
- **Patient median *SI* analysis:**
  - *SI* increases significantly over the first 24 hours (**p<0.02**).
  - For days 2-3, further increases are limited and not statistically significant
  - Median insulin sensitivity is 29-43% lower for diabetics compared to non-diabetics for days 1-3 (**p<0.05**)



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