

## Preparation of Papers for IFAC Conferences & Symposia: Use Title Case for Paper Title

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**Abstract:** High insulin euglycemia therapy (HIET) is a supra-physiological insulin dosing protocol used in acute cardiac failure to reduce dependency on inotropes to augment or generate cardiac output, and is based on the inotropic effects of insulin at high doses up to 45-250x normal daily dose. Such high insulin doses are managed using intravenous glucose infusion to control glycemia and prevent hypoglycemia. However, both insulin dosing and glycemic control in these patients is managed ad-hoc. This research examines a selection of clinical data to determine the effect of high insulin dosing on renal clearance and insulin sensitivity, to assess the feasibility of using model-based methods to control and guide these protocols. The results show that the model and, in particular, the modeled renal clearance constant are adequate and capture measured data well, although not perfectly. Equally, insulin sensitivity over time is similar to broader critical care cohorts in level and variability, and these results are the first time they have been presented for this cohort. While more data is needed to confirm and further specify these results, it is clear that the model used is adequate for controlling HIET in a model-based framework.

**Keywords:** renal clearance, HIET, cardiac failure, critically ill, model-based, control, insulin sensitivity

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### 1. INTRODUCTION

Insulin has beneficial effects on cardiac function in very high doses (Ouwens and Diamant 2007; Massion and Preiser 2010). Hyper-Insulinemia Euglycemia Therapy (HIET) combines these insulin effects to treat patients with postoperative cardiogenic shock. In particular, high dosing of insulin of ~1 U/kg/hour, which for an 80kg individual is ~45x the normal daily dose, has shown significant inotropic action in reducing the need for inotropes and reinstating cardiac function in cases of severe cardiac failure [REF].

Such high doses of insulin are managed via exogenous glucose infusions, to avoid severe hypoglycemia. However, insulin dosing protocols or rules during HIET are still empirical, as effect varies. Doses have been recommended between 0.5-6.0U/kg/hour [REFS]. However, all of these levels are very high and significantly hypoglycemic. Thus, there is a need for a careful protocol to administer insulin to titrate inotropic effect while safely managing BG levels via exogenous glucose infusion, where it should be noted that glucose infusions that are too high can also have negative effect over 30-50 g/hour delivered [REF]. Hence, the problem is one of dosing insulin for one outcome and controlling glycemia with a peak limited infusion of exogenous glucose.

This work aims to develop a model-based glycemic controller to capture the patient-specific response and safely optimize

HIET interventions. Such model-based controllers have shown significant success in controlling glycemia in highly insulin resistant critically ill patients [REFS]. Importantly, several of these controllers use both insulin and nutrition to control glycemia, where nutritional control elements are critical to this problem [REF].

Notably such high insulin doses can be controlled without significant increase in nutrition rate [REF]. Typically, for 40-50x the normal daily dose of insulin, glucose administration increases only approximately to 2x normal. Hence, there is evidence of significant insulin saturation effects, which have also been observed in critically ill glycemic control and other normal individuals [REFS].

The first step is to determine whether a validated glucose-insulin system model (Lin, Razak et al. 2011) has to be adapted for the very high insulin doses (~1UI/kg/h) in HIET. Specifically, do such large doses have different apparent kinetics. The characterization of patient-specific renal clearance is also an essential feature for an accurate physiological understanding of insulin kinetics at this dosing level. Finally, insulin sensitivity varies significantly in the critically ill, both inter-patient and, over 30-60 minutes, intra-patient [REFS], and the time course of insulin sensitivity at these dosing levels and for these patients has never been reported previously, which will also aid understanding of the physiological mechanisms.

Specifically, the research presented thus tries to answer 3 main questions:

- Is the glucose-insulin system model able to capture HIET patient behaviour?
- Should the insulin clearance modelling be modified for high insulin doses? In particular, renal clearance may be nonlinear at very high concentration as other renal clearance mechanisms can occur.
- Is the insulin sensitivity of HIET patients physiological or affected by modelling of high insulin doses?

In developing these answers, the research examines unique clinical data developed from two initial patients on an HIET protocol. The data includes full insulin and BG data to enable model-based analysis of all these questions. The main goal is to derive a first understanding of the answers to these questions to drive and inform future patients and studies.

## 2. METHODS

### 2.1 Patients and Data

This overview analysis is based on clinical data from 2 patients included in a HIET protocol from January 2011 in the intensive care units (ICU) at the Center Hospitalier Universitaire (CHU) de Liège, Belgium. Ethical approval was obtained from **XXXX**.

Clinical data measurements are blood glucose (BG) levels, exogenous insulin infusions, plasma insulin concentrations and exogenous glucose inputs (enteral and parenteral nutrition, medications and glucocorticoids). BG levels measurements were made using Accu-Check Inform (Roche Diagnostics, Mannheim, Germany) glucometers and plasma insulin concentrations were measured using the hexokinase method (Modular P, Roche Diagnostics, Mannheim, Germany).

The general characteristics of the two first patients who received HIET are summarized in Table 1.

Table 1: Characteristics of HIET patients.

	Patient 1 (P1)	Patient 2 (P3)
<b>Sex</b>	F	F
<b>Date of birth</b>	16/04/1963	13/06/1949
<b>Weight (kg)</b>	72	56
<b>Diagnosis</b>	Aortic valve replacement	Coronary Artery Bypass Graft Surgery Mitral valve replacement
<b>Diabetic status</b>	No	No
<b>ICU day when HIET started</b>	1	2
<b>Length HIET, in min (in hours)</b>	2880 (48h)	3120 (52h)
<b>Number of BG measurements</b>	36	25
<b>Initial BG (mg/dL)</b>	151	174
<b>Median BG</b>	119.5 [99.5 -	130.0 [114.8 - 152.0]

<b>[IQR] (mg/dL)</b>	139.5]	
<b>% BG within 80-140 mg/dL</b>	66.7	72
<b>% BG &lt; 80 mg/dL</b>	8.3	0
<b>% BG &lt; 72 mg/dL</b>	0.0	0.0
<b>Median insulin rate [IQR] (U/h)</b>	35.0 [35.0 - 70.0]	30.0 [30.0 - 59.0]
<b>Max insulin rate (U/h)</b>	70.4	60.0
<b>Median dextrose rate [IQR] (g/h)</b>	25.0 [25.0 - 25.0]	26.0 [20.0 - 26.0]

### 2.2 Glucose-insulin system model

The glucose-insulin system model used is defined by Equations (1)-(5) (Lin, Razak et al. 2011).

$$\dot{G} = -p_G \cdot G - S_I \cdot G \cdot \frac{Q}{1 + \alpha_G Q} + \frac{\min(d_2 P_2, P_{\max}) + EGP_b - CNS + PN}{V_G} \quad (1)$$

$$\dot{I} = -\frac{n_L I}{1 + \alpha_I I} - n_K I - (I - Q)n_I + \frac{u_{ex}(t)}{V_I} + (1 - x_L) \frac{u_{en}(G)}{V_I} \quad (2)$$

where

Non-diabetic

$$u_{en} = \min(\max(16.7, (14.9 * G - 49.9)), 266.7)$$

Type I diabetes

$$u_{en} = \min(\max(16.7, (0.0 * G + 16.7)), 266.7)$$

Type II diabetes

$$u_{en} = \min(\max(16.7, (4.9 * G - 27.4)), 266.7)$$

$$\dot{Q} = (I - Q)n_I - n_C \frac{Q}{1 + \alpha_G Q} \quad (3)$$

$$\dot{P}_1 = -d_1 P_1 + P(t) \quad (4)$$

$$\dot{P}_2 = -\min(d_2 P_2, P_{\max}) + d_1 P_1 \quad (5)$$

$G(t)$  and  $I(t)$  [mU/L] is the plasma insulin, exogenous insulin input is represented by  $u(t)$  [mU/min]. Interstitial insulin is represented by  $Q(t)$  [mU/L], with  $n_I$  [1/min] accounting for the rate of transport between plasma and interstitial insulin compartments. Endogenous insulin production is estimated with  $u_{en}$  [mU/min] modeled as a function of blood glucose concentration determined from critical care patients with a minimum pancreatic output of 1U/hr. First-pass hepatic insulin clearance is represented by  $x_L$ . Patient endogenous glucose clearance and insulin sensitivity are  $p_G$  [1/min] and  $S_I$  [L/(mU.min)], respectively. The parameter  $V_I$  [L] is the insulin distribution volume and  $n_K$  [1/min] and  $n_L$  [1/min] represent the clearance of insulin from plasma via renal and hepatic routes respectively. Basal endogenous glucose production unsuppressed by glucose and insulin concentration is denoted by  $EGP_b$  [mmol/min] and  $V_G$  [L] represents the glucose distribution volume.  $CNS$  [mmol/min] represents non-insulin mediated glucose uptake by the central

nervous system. Michaelis-Menten functions are used to model saturation, with  $\alpha_I$  [L/mU] used for the saturation of plasma insulin clearance by the liver, and  $\alpha_G$  [L/mU] for the saturation of insulin-dependent glucose clearance and receptor-bound insulin clearance from the interstitium.  $P_1$  [mmol] represents the glucose in the stomach and  $P_2$  [mmol] represents glucose in the gut. The rate of transfer between the stomach and gut is represented by  $d_1$  [1/min], and the rate of transfer from the gut to the bloodstream is  $d_2$  [1/min]. Enteral glucose input is denoted  $P(t)$  [mmol/min], and  $P_{max}$  represents the maximum disposal rate from the gut. The constants used in (1) to (5) are shown in Table 2.

Table 2: Numerical values of model parameters

Model variable	Numerical value (or typical range of values)
$p_G$	$0.006 \text{ min}^{-1}$
$S_I$	$[1 \times 10^{-7} - 1 \times 10^{-2}] \text{ L/(mU.min)}$
$\alpha_G$	$1/65 \text{ L/mU}$
$d_1$	$-\ln(0.5)/20$
$d_2$	$-\ln(0.5)/100$
$P_{max}$	$6.11 \text{ mmol/min}$
$EGP_b$	$1.16 \text{ mmol/min typically}$
$CNS$	$0.3 \text{ mmol/min}$
$V_G$	$13.3 \text{ L}$
$n_I, n_C$	$0.006 \text{ min}^{-1}$
$\alpha_I$	$1.7 \times 10^{-3} \text{ L/mU}$
$V_I$	$4.0 \text{ L}$
$x_I$	$0.67$
$n_K$	$0.0542 \text{ min}^{-1}$
$n_r$	$0.1578 \text{ min}^{-1}$

### 2.3 Evolution of renal insulin clearance over time

Hepatic insulin clearance saturates at high insulin doses whereas renal insulin clearance does not (Koschorreck and Gilles 2008). Therefore, it is hypothesised that only renal clearance processes can be modified or different for HIET patients. More specifically, only renal clearance has the ability to become large enough to potentially affect clearance and plasma insulin levels at such large doses.

This modification implies a change of the  $n_K$  parameter value in Equation (2). To study the possible change of renal clearance, the relationship between  $n_K$  and insulin data (plasma  $I$ , interstitial  $Q$  and exogenous  $u_{ext}$  insulin) can be derived. This relation can be obtained by rearranging Equation (2) to read:

$$n_K = \frac{\left( -I(t) - \frac{n_I \cdot I(t)}{1 + \alpha_I \cdot I(t)} - (I(t) - Q(t)) \cdot n_I + \frac{u_{ext}(t)}{V_I} + (1 - x_I) \cdot \frac{u_{en}(G)}{V_I} \right)}{I(t)} \quad (6)$$

Approximations (piecewise linear interpolation) of  $G(t)$ ,  $u_{en}(G)$ ,  $u_{ext}(t)$ ,  $I(t)$ ,  $\dot{I}(t)$ ,  $Q(t)$  can be obtained from clinical data using the approach outlined in Figure 1, and are used to calculate  $n_K(t)$ , using Equation (6). Equation (7) is used to define  $u_{en}(G)$ :

$$u_{en}(t) = \min(\max(16.7, (14.9 \cdot G(t) - 49.9)), 266.7) \quad (7)$$

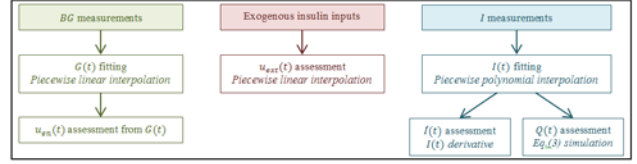


Figure 1: Determination of model variables from clinical data.

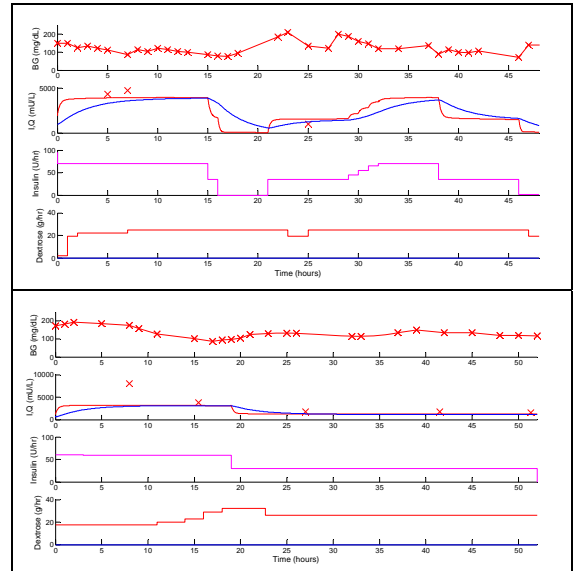
### 2.4 Analysis

From patient clinical data,  $G(t)$  can be approximated using piecewise linear interpolation and Equations (2) and (3) of the model can be solved to simulate the evolution of plasma  $I(t)$  and interstitial  $Q(t)$  insulin concentrations. Simulated  $I(t)$  evolution can then be compared to clinical plasma insulin measurements to assess model accuracy and the need for greater or lesser renal clearance.

Insulin sensitivity (SI) in the model accounts for evolving physiological patient condition and intra-patient variability. It is an overall measure of whole body insulin sensitivity and metabolic balance. Patient specific profiles of insulin sensitivity (SI) can be obtained using the method of Hann et al [REF]. These profiles can be compared to clinical results over 371 critically ill patients of all types [REFS] to ascertain whether they are within normal bounds or affected by the supra-physiological dosing used here.

## 3. RESULTS and DISCUSSION

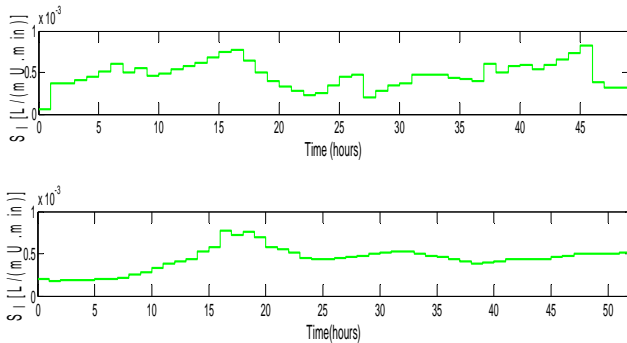
Measured and simulated plasma insulin concentration seems to correspond well for Patients 1 and 2 with median BG error of 0.2% and 0.5%, respectively, and median plasma insulin error of XX% and XX%, respectively. These results are presented in Figure 2 for both patients.



**Figure 2: Results of insulin-glucose simulation for patients 1 (top) and 2 (bottom).** For each patient, from top to bottom graphs: first panel = BG measurements (crosses) and linear fitting (mg/dL); second panel = measured  $I$  (crosses), and simulated  $I(t)$  (in red) and  $Q(t)$  (in blue) (mU/L); third panel = insulin infusions (U/h); last panel = exogenous dextrose inputs (g/h), enteral (in blue) and parenteral (in red) nutrition.

These results indicate that the model is able to reproduce insulin kinetics for HIET patients and doses. Patient 2 presents a relatively high plasma insulin concentration at  $t=8h$ , which is likely erroneous given the dosing and surrounding measurements.

Figure 3 shows that patient insulin sensitivity is quite variable over HIET as might be expected (Lin, Lee et al. 2008). These levels are within normal levels observed in the critically ill. The variability is also within observed boundaries. Hence, the insulin sensitivity profiles are not affected by the supra-physiological dosing used, which is also a further validation of the models and methods.



**Figure 3: Results of model simulation and insulin sensitivity (L/mU.min) identification for Patients 1 (top) and 2 (bottom).**

Analysis of the renal clearance parameter,  $n_K$ , is mixed. Patient 1 results seem to indicate that the default  $n_K$  value under-estimates insulin clearance, whereas Patient 3 results appear to indicate that the default  $n_K$  value over-estimates insulin clearance. These results are outlined in Figure 4. Note that the default renal clearance value is set at an approximate glomerular filtration rate (GFR) for renal clearance and does not account for supra-physiological levels or added clearance from tubule excretion [REF].

What is interesting to note is that the constant rate at an approximate GFR is largely accurate for both patients over much of their stay. However, at some insulin dosing levels it appears that GFR can be underestimated by a factor of 2. Similarly, the model-based analysis, also for Patient 2, shows a shorter period of overestimation of 100%. Similarly, Patient 3 consistently is consistently overestimated by 20-50%, or a factor of 0.5-0.8x lower than the default GFR value.

Overall, these results suggest two main outcomes for the analysis of renal clearance at supra-physiological insulin dosing levels for these patients:

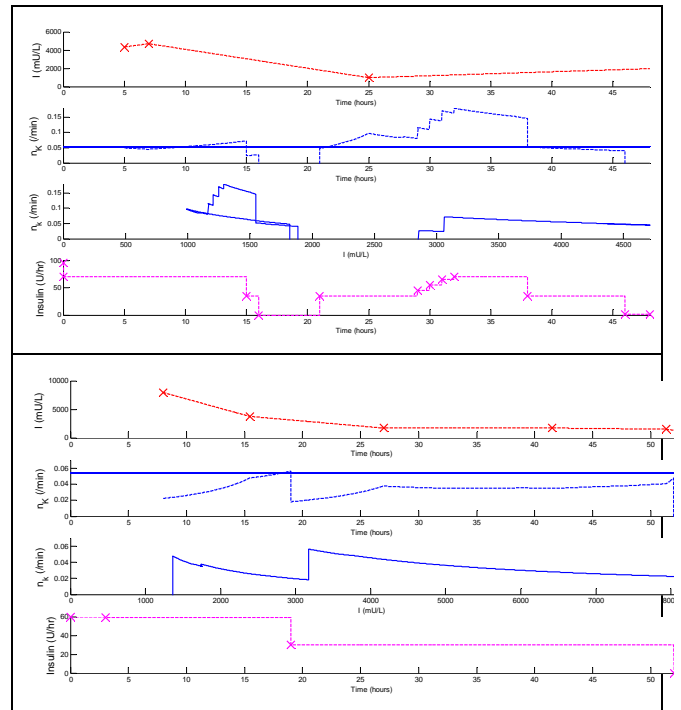
- The GFR approximation is not significantly in error, or at least, that very high insulin doses do not affect

renal clearance enough that it should be significantly modified based on this limited data and analysis

- Renal clearance appears to be time varying in nature in these patients. This outcome is not at all unexpected as renal clearance and failure are very common in critically ill patients [REFS]. Thus, a time varying value is not unexpected

Overall, these results are supportive of the current value until further patients and data are collected. Certainly, there is no reason to change the value in modeling insulin levels in these patients using the ICING model of Equations 1-5 [REF].

Given that renal clearance is not readily identifiable at the bedside in real time and that typical creatinine clearance methods and formulas have very high errors [REFS], the current assumptions may not be perfect. However, clinically, for application in a model-based protocol the results are indicative that the model is acceptable for this purpose going forward with more patients and creating a model-based protocol.



**Figure 4: Results of renal clearance parameter for Patients 1 (top) and 2 (bottom).** For each patient, from top to bottom graphs: first panel = BG measurements and linear piece-wise interpolation (mg/dL); second panel =  $n_K$  evolution over time (dashed line) and  $n_K$  default value (0.0542) ( $min^{-1}$ ); third panel =  $n_K$  as a function of  $I$ ; last panel = exogenous insulin infusions (U/h).

Thus, the answers to the main questions posed have all been answered in this initial study. Specifically:

- The glucose-insulin ICING system model of Equations 1-5 is well able to capture HIET patient behaviour and dynamics of both glucose and insulin at supra-physiological dosing levels

- The insulin clearance modelling and constant do not need to be modified for high insulin doses. This result is perhaps surprising and should be confirmed by further patients. However, it will provide much more certainty in protocol design and model-based analysis. However, it does appear that this clearance may be nonlinear or at least time-varying, as expected in critically ill cohorts.

The insulin sensitivity profile of HIET patients was the same or similar to those observed in broader cohorts of critically ill patients in both level and variability.

All these results validate the overall methods and models taken to start this research into HIET patients and protocols, as well as acting as further specific validation of the ICING metabolic system model.

#### 4. CONCLUSIONS

The model of the glucose-insulin system is able to reproduce insulin kinetics for HIET patients and high insulin doses. Renal insulin clearance modeling appears adequate but requires further data to confirm this result. Overall, the models and methods presented are further validated for the primary goal of creating model-based methods of managing this treatment and these patients. The results and outcomes also provide unique results and insight into the metabolic behaviour of patients who have severe cardiac failure and are supra-physiologically dosed with insulin.

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