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Insulin Kinetics during Hyper-Insulinemia Euglycemia Therapy (HIET)

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Abstract: Hyper-insulinemia 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

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 (Boyer, Duic et al. 2002; Massion and Preiser 2010).

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 (Boyer, Duic et al. 2002; Massion and Preiser 2010). 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 (Ichai, Cariou *et al.* 2009). 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 (Plank, Blaha et al. 2006; Evans, Shaw et al. 2011; Penning, Le Compte et al. 2011). Importantly, several of these controllers use both insulin and nutrition to control glycemia, where nutritional control elements are critical to this problem (Chase, Shaw et al. 2008; Evans, Shaw et al. 2011; Penning, Le Compte et al. 2011).

Notably such high insulin doses can be controlled without significant increase in nutrition rate. 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 (Prigeon, Roder et al. 1996; Natali, Gastaldelli et al. 2000; Lin, Razak et al. 2011).

The first step is to determine whether a validated glucose-insulin system model (Chase, Suhaimi et al. 2010; 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 (Lin 2006; Lin, Lee et al. 2008), 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 Centre Hospitalier Universitaire (CHU) de Liège, Belgium. Ethical approval was obtained from the Ethics Committee of the Medical Faculty of the University of Liege (Belgium).

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)
Sex	F	F
Date of birth	16/04/1963	13/06/1949
Weight (kg)	72	56
Diagnosis	Aortic valve replacement	Coronary Artery Bypass Graft Surgery Mitral valve replacement
Diabetic status	No	No
ICU day when HIET started	1	2
Length HIET, in min (in hours)	2880 (48h)	3120 (52h)
Number of BG measurements	36	25
Initial BG (mg/dL)	151	174
Median BG [IQR] (mg/dL)	119.5 [99.5 - 139.5]	130.0 [114.8 - 152.0]
% BG within 80-140 mg/dL	66.7	72
% BG < 80 mg/dL	8.3	0
% BG < 72 mg/dL	0.0	0.0
Median insulin rate [IQR] (U/h)	35.0 [35.0 - 70.0]	30.0 [30.0 - 59.0]
Max insulin rate (U/h)	70.4	60.0
Median dextrose rate [IQR] (g/h)	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).

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

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

where (2)

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 α_I [L/mU] used for the saturation of plasma insulin clearance by the liver, and α_G [L/mU] for the