Accuracy and Optimization of a Subcutaneous Insulin Model for Less Acute Critical Care Patients

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INTRODUCTION

Extending safe, effective glycemic control to the general wards requires a simple approach using subcutaneous (SC) insulin. However, this approach can increase relative risk compared to intravenous insulin due to the increased variability of SC insulin appearance. This poster evaluates the accuracy of a SC plasma insulin model and optimizes its parameters.

METHODS

Subcutaneous Insulin Study Patients

A total of 6 patients enrolled in a prospective clinical trial studying a protocol for SC insulin delivery. Each patient had a set of blood samples assayed for insulin and C-peptide

TABLE I. SUMMARY OF SUBCUTANEOUS TRIAL PATIENT CHARACTERISTICS. DATA ARE SHOW AS MEDIAN [IQR] WHERE APPROPRIATE

Number (N)	6
Age (years)	58 [43-60]
Gender (M/F)	5/1
APACHE II score	18.5 [14.3-23.5]
Hospital mortality (L/D)	(6/0)

Model

$$\dot{x}_{dm} = U_{dm} + p_d\left(\frac{1}{3}x_h - Q\frac{x_{dm}^3}{V^2}\right) - k_{dm}x_{dm}$$

$$\dot{x}_h = U_h - p_d\left(\frac{1}{3}x_h - Q\frac{x_{dm}^3}{V^2}\right)$$

$$\dot{x}_i = k_{dm}x_{dm} - k_i x_i$$

$$U_{RI} = f_{RI}k_i x_i$$

TABLE II. FITTED VALUES OF SUBCUTANEOUS INSULIN MODEL CONSTANTS

Parameter	Value
k_i	4.60 x 10^{-2} min^{-1}
k_{dm}	1.20 x 10^{-2} min^{-1}
Q	5.02 x 10^{-10}
p_d	1
f_{RI}	0.597

Where x_h, are the total insulin mass in the hexameric (h), local interstitial, (i), and dimeric or monomeric, (dm), compartments, respectively [mU]. Transport parameters are denoted k_i and k_{dm} [min^{-1}], U_{dm} and U_h are the exogenous appearance rate [mUmin-1] as delivered by injection to the dimeric or monomeric and the hexameric compartment respectively. p_d is the hexameric dissociation rate [min^{-1}]. Exogenous insulin input is U_{RI} [$mU.min^{-1}$], where the unique scaling factor, f_{RI}, highlights the many currently unquantified processes at work during the absorption process.

Analysis Methods

Measured and modelled plasma insulin values were compared and residuals calculated:

$$Residual\ Error = I(t)_{measured} - I(t)_{modelled}$$

where $I(t)_{measured}$ is the plasma insulin measured during the 12 hour trials and $I(t)_{modelled}$ is the forward prediction of the plasma insulin using the model identified SI profile. An optimal value of the parameter, f_{RI} was identified by iteratively searching the range of 0.60 to 0.20 in steps of 0.01 to find the value of f_{RI} that generated the smallest residuals and the best model fit.

RESULTS

TABLE III. RESIDUAL ERROR OF SC MEASURED – MODELLED PLASMA INSULIN. DATA PRESENTED AS MEDIAN[IQR].

Residual Error	f_{RI} = 0.597		f_{RI} = 0.25	
	RMS	Median[IQR]	RMS	Median[IQR]
Patient 1	31.3	-31.6 [-36 -26]	8.90	0.144 [-4.9 7.8]
Patient 2	36.2	-36.5 [-44 -29]	21.7	-24.2 [-28 -12]
Patient 3	26.6	-17.8 [-35 -11]	13.0	10.6 [3.9 15]
Patient 4	24.9	-23.6 [-27 -19]	12.1	4.26 [-12 10]
Patient 5	31.1	-22.8 [-33 -9.9]	24.8	-7.58 [-14 25]
Patient 6	34.9	-30.8 [-38 -22]	18.5	-13.0 [-23 -8.0]
Overall	31.1	-28.3 [-37 -19]	17.4	-5.37 [-15 9.7]

Model fit improved by 20-70% for each patient by identifying f_{RI}.

The original model value for f_{RI} was found using data from 18 heathy male volunteers.

This change in f_{RI} thus reflects **a distinct difference in SC insulin kinetics between healthy volunteers and critical care patients**.

The reduction of f_{RI} suggests less of the injected SC insulin is appearing in critical care patients than would appear in a healthy individuals injected with the same SC insulin bolus.

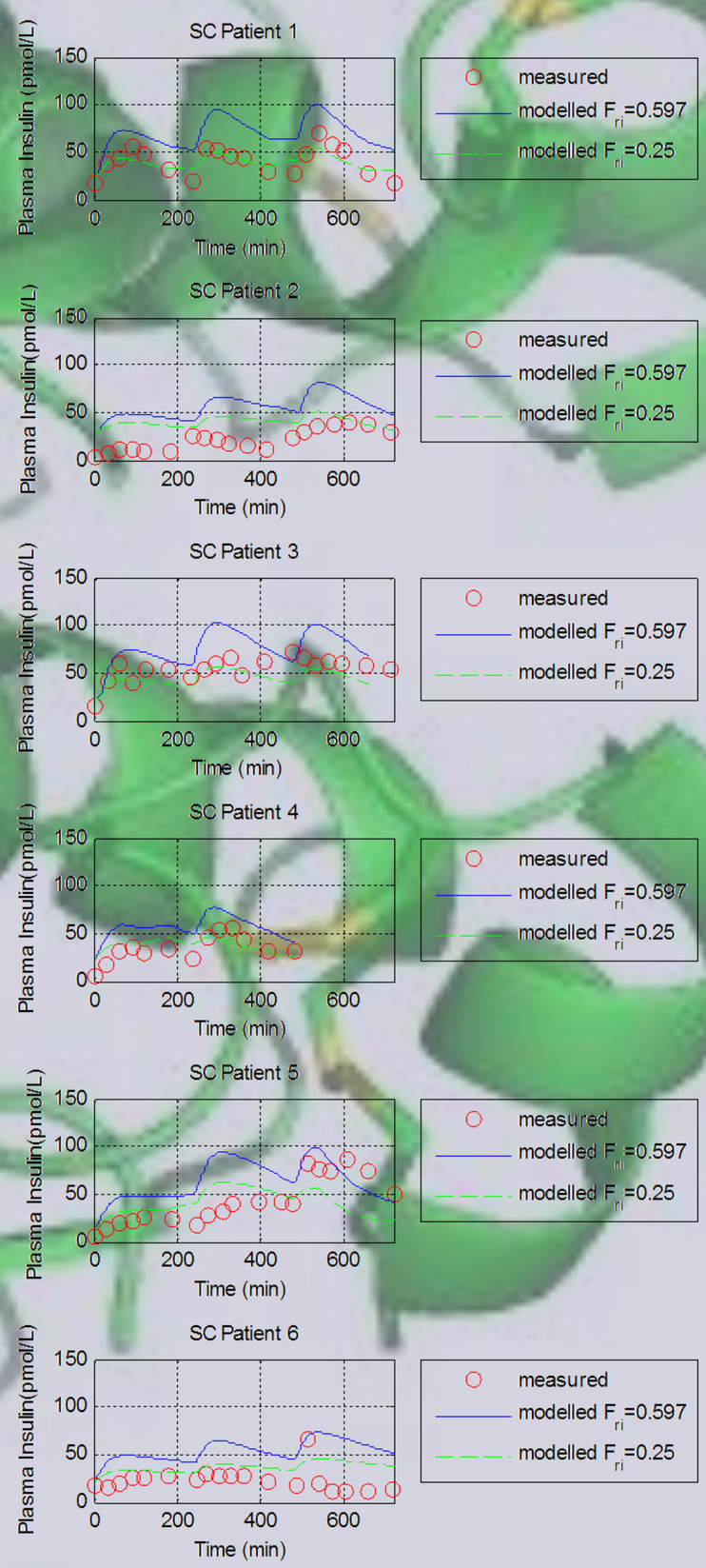

FIGURE I. MEASURED AND MODELLED PLASMA INSULIN DATA FOR SC INSULIN USING F_{RI} = 0.597AND F_{RI} = 0.25

CONCLUSION

The SC plasma insulin model used captures the dynamics of regular SC insulin well. However, there appears to be a positive bias leading to an overall median [IQR] residual error of -28.3 [-37 -19] mU/L. The optimized model reduced the RMS residual error by 20-70% for each patient with a median [IQR] residual error of -5.37 [-15 9.7] mU/L. The distinct inter- and intra- patient, and cohort variation seen in this data highlights the importance to of understanding how SC insulin appearance dynamics may be affected by the subject condition.

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