

Closed-Loop Insulin Delivery Utilizing Pole Placement to Compensate for Delays in Subcutaneous Insulin Delivery

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Abstract

Background:

We have previously used insulin feedback (IFB) as a component of a closed-loop algorithm emulating the β cell. This was based on the observation that insulin secretion is inhibited by insulin concentration. We show here that the effect of IFB is to make a closed-loop system behave as if delays in the insulin pharmacokinetic (PK)/pharmacodynamic (PD) response are reduced. We examine whether the mechanism can be used to compensate for delays in the subcutaneous PK/PD insulin response.

Method:

Closed-loop insulin delivery was performed in seven diabetic dogs using a proportional-integral-derivative model of the β cell modified by model-predicted IFB. The level of IFB was set using pole placement. Meal responses were obtained on three occasions: without IFB (NONE), reference IFB (REF), and 2xREF, with experiments performed in random order. The ability of the insulin model to predict insulin concentration was evaluated by correlation with the measured profile and results reported as R^2 . The ability of IFB to improve the meal response was evaluated by comparing peak and nadir postprandial glucose and area under the curve (AUC; repeated measures analysis of variance with *post hoc* test for linear trend).

Results:

Insulin concentration was well predicted by the model (median $R^2 = 0.87, 0.79$, and 0.90 for NONE, REF, and 2xREF, respectively). Peak postprandial glucose ($294 \pm 15, 243 \pm 21$, and 247 ± 16 mg/dl) and AUC ($518.2 \pm 36.13, 353.5 \pm 45.04$, and 280.3 ± 39.37 mg/dl \cdot min) decreased with increasing IFB ($p < .05$, linear trend). Nadir glucose was not affected by IFB ($76 \pm 5.4, 68 \pm 7.3$, and 72 ± 4.3 mg/dl; $p = .63$).

Conclusions:

Insulin feedback provides an effective mechanism to compensate for delay in the insulin PK/PD profile.

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Abbreviations: (AUC) area under the curve, (DIR) daily insulin requirement, (IFB) insulin feedback, (IOB) insulin on board, (PD) pharmacodynamic, (PID) proportional integral derivative, (PK) pharmacokinetic, (REF) reference IFB, (SC) subcutaneous, (SG) sensor glucose, (T1DM) type 1 diabetes mellitus

Keywords: artificial β cell, closed-loop insulin delivery, continuous glucose monitoring, continuous subcutaneous insulin infusion

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