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REVIEW ARTICLE

The Artificial Pancreas: Is It Important to Understand How the β Cell Controls Blood Glucose?

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Abstract

It has been more than 7 years since the first fully automated closed-loop insulin delivery system that linked subcutaneous insulin delivery and glucose sensing was published. Since the initial report, the physiologic insulin delivery (PID) algorithm used to emulate the β cell has been modified from the original *proportional-integral-derivative* terms needed to fit the β cell's biphasic response to a hyperglycemic clamp to include terms emulating cephalic phase insulin release and the effect of insulin *per se* to inhibit insulin secretion. In this article, we compare the closed-loop glucose profiles obtained as each new term has been added, reassess the ability of the revised PID model to describe the β cells' insulin response to a hyperglycemic clamp, and look for the first time at its ability to describe the response to a hypoglycemic clamp. We also consider changes that might be added to the model based on perfused pancreas data. We conclude that the changes introduced in the PID model have systematically improved the closed-loop meal response. We note that the changes made do not adversely affect the ability of the model to fit hyperglycemic clamp data but are necessary to fit the response to a hypoglycemic clamp. Finally, we note a number of β cell characteristics observed in the perfused pancreas have not been included in the model. We suggest that continuing the effort to understand and incorporate aspects of how the β cell achieves glucose control can provide valuable insights into how improvements in future artificial pancreas algorithms might be achieved.

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Introduction

Biphasic insulin release in response to rapid changes in glucose levels was first described 45 years ago using a completely *in vitro* perfused rat pancreas and fully defined media.[1] This and other characteristics of glucose-stimulated insulin release are illustrated in **Figures 1** and **2**. The first phase is a transient rapid rise in release, which ends in 3–5 min. This is followed by a rising second phase, where glucose progressively amplifies its signal. Higher glucose concentrations produce further amplification of both phases.

The progressively increasing second phase (**Figure 1**) has been modeled[2,3] as a glucose-stimulated, gradually accumulating potentiation signal. This dissipates at a slow rate (approximately 25 min for the rat pancreas) once the glucose level is reduced to the prestimulus level. Thus, the β cells retain some of the potentiation signal (**Figure 2**; response

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Abbreviations: (AP) artificial pancreas, (FFA) free fatty acids, (IFB) insulin feedback, (PID) physiologic insulin delivery, (SC) subcutaneous

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at minute 40 being greater than response at minute 20). This memory phenomenon has been called time-dependent potentiation[2,3] or priming.[4]

When glucose is rapidly stepped down to a lower, but still stimulating concentration (e.g., 500 to 150 mg/dl; **Figure 2**), a negative rate sensitivity occurs, reflected as a transient, negative spike undershoot (**Figure 2**; a lower value at minute 33 than minute 39).[3] Furthermore, islets at the end of the first phase are refractory so that their response to a second identical stimulus within the refractory period is reduced.[5] These phenomena were referred to as "signal-related feedback inhibition"[3] or "time-dependent inhibition."[6]

Based on these and other observations, several mathematical models of glucose-stimulated insulin secretion were described. These include compartmental models based on the assumption that insulin is stored in small labile compartments, which provide the insulin for first-phase release.[1–3,5–7] The concept of threshold sensitivity was incorporated to explain how different amounts of insulin are secreted from the labile compartment as glucose is increased, but with the same first phase temporal kinetics (**Figure 1**).[2,3] The concept proposes that insulin granules are released from the labile compartment in an all-or-nothing fashion when the glucose threshold of the granule is reached or exceeded, with the granules having

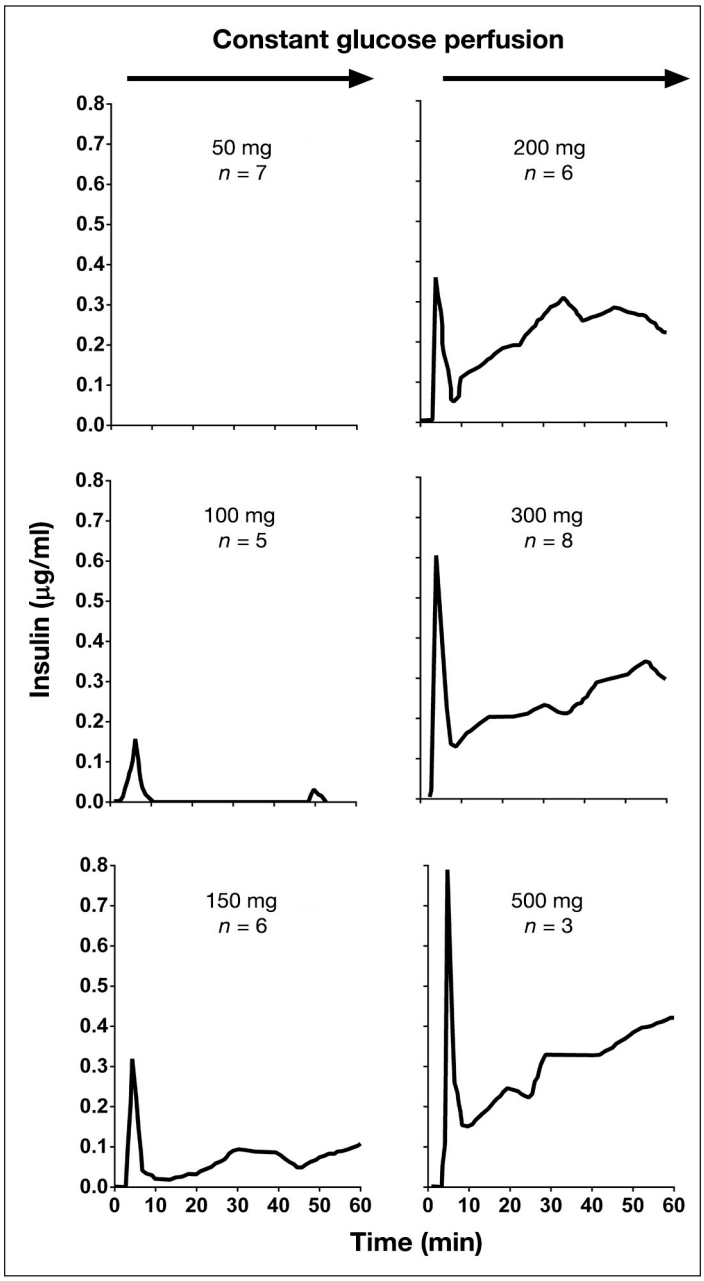

Figure 1. *In vitro* perfused pancreas dose response (adapted from Grodsky[2]).

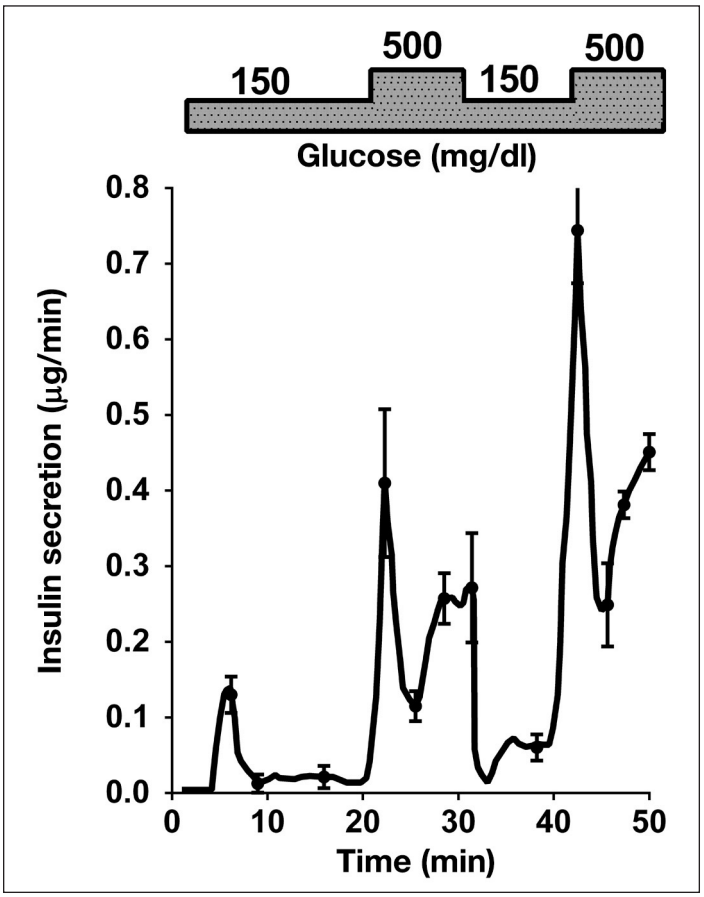

Figure 2. *In vitro* perfused pancreas showing refractory negative spike inhibition (~minute 33) and glucose potentiation (first phase at minute 40 > first phase at minute 20). Figure adapted from O'Connor and coauthors.[3]

a bell-shaped distribution of thresholds.[2] Thirty years later, the hypothesized labile compartment was confirmed by the observation that a pool of β cell granules is concentrated at the plasma membrane—the readily releasable pool—and depleted during first-phase secretion.[8–10] Second phase correlated, as predicted,[3] to additional granules being mobilized to the releasable pool from a larger pool of docked granules,[8] or newly matured granules mobilized from the cytosol.[11–13] Algorithms based on these compartmental models are now being investigated for use in the artificial pancreas (AP).[14,15]

As an alternate to the compartmental model, a signal-related feedback model was described in which the rise and fall of first-phase secretion was explained by glucose first inducing a rapid rise in an exciter, followed within minutes by a rise in an inhibitor, with the secretory signal being proportional to the difference between the two.[3] Mathematically, this approximates a derivative. The transient inhibition seen when glucose is reduced occurs when the exciter declines more rapidly than the inhibitor (**Figure 2**). The signal-related feedback model overcame an important limitation to compartmental models, which could describe the increase in insulin secretion to an increase in glucose concentration but did not describe the negative effect on secretion that was evident when glucose was rapidly lowered.[3] Subsequent studies confirmed that the β cell is sensitive to both positive and negative rates of change.[16] A replication of all the kinetic responses to glucose originally described in the perfused pancreas,[3] including the negative effects of lowering glucose, has been achieved using multiple inter-related glucose-sensitive insulin compartments.[17]

That the β cell model might serve as a guide for the design of a modern-day control algorithm for a closed-loop insulin delivery based on subcutaneous (SC) glucose sensing and SC insulin delivery was first advocated by Steil and coauthors[18] at Medtronic. That the β cell's first-phase response might serve the same role as the derivative component in a classical proportional-derivative controller[19] had previously been noted,[20] but the idea that the second-phase response might serve a role analogous to the integral component of a proportional-integral-derivative controller had not been pursued. Including an integral component as part of an AP algorithm was appealing in that the integral allows different basal rates to be maintained at the same steady-state target glucose level.[21] This was considered important, as many individuals with type 1 diabetes require different basal rates during or between days to maintain the same target.[22,23] The hypothesis that the β cell's second-phase response serves the same role as the integral in a proportional-integral-derivative controller is supported by observations made by Porte and Pupo[7] in 1969 that during prolonged 20 h glucose infusions, insulin secretion "paradoxically" increases as glucose levels decrease. Such a paradoxical increase is to be expected in any control algorithm with an integral component, as the integral will continue to increase *for the duration glucose is above target*. It can also explain how higher insulin levels are maintained in obese individuals who, despite being insulin resistant, have normal fasting glucose levels. This latter observation was first noted by Karam and coauthors[24] in 1963.

The hypothesis that β cells act like a proportional-integral-derivative controller was initially tested by fitting the insulin response obtained during a hyperglycemic clamp[21] to equations commonly used to describe the proportional-integral-derivative control response (**Figure 3**). The ability to fit the response does not prove the hypothesis that the β cell behaves like a proportional-integral-derivate controller, as other models have been shown to fit the response—notably, those proposed by Grodsky and coauthors[2,3] but also later models for estimating β cell indices of secretion from meals[25] (which somewhat surprisingly do not include the rate-effect of decreasing glucose levels to inhibit insulin secretion[26]). However, theoretical properties of the physiologic insulin delivery (PID) model[21] and its widespread use in other control applications[27] made it a logical starting point for developing the AP algorithm.

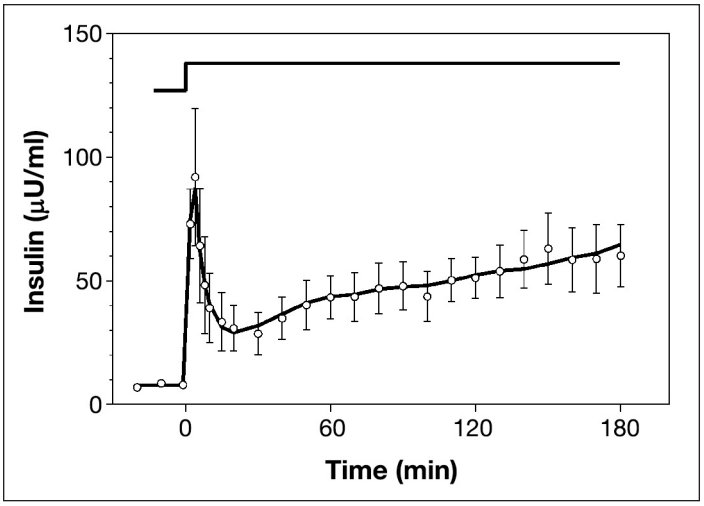

Figure 3. Physiologic insulin delivery fit of the β cell's response to a hyperglycemic clamp (adapted from Steil and coauthors[21]).

The decision to use a PID model of the β cell for a closed-loop AP system was not based on any of the well-known theoretical properties of the proportional-integral-derivative control algorithm *per se*[27] but on the belief that β cell response is inherently optimal for glucose control. This is supported by studies showing the product of first-phase insulin release and insulin sensitivity is constant in individuals who become insulin resistant but maintain normal glucose tolerance.[28,29] It is also supported by the observation that individuals who become more sensitive to insulin decrease secretion in proportion to an increase in insulin sensitivity[30] and that both first- and second-phase release decrease by a similar amount.[30–33] These observations suggest that the β cell has an optimal gain related to insulin sensitivity and an optimal ratio of first- and second-phase release.

There are arguments for not using a β cell model in a closed-loop system with SC insulin delivery. The β cell delivers insulin into the portal vein, creating a portal-peripheral insulin gradient putatively thought to effect a rapid change in net hepatic glucose balance.[34] Portal delivery also rapidly equilibrates within the circulation.[35] In contrast, SC insulin delivery cannot effect the high portal levels needed to suppress liver glucose production and is associated with much longer delays.[36] There are also arguments that the algorithm is not the underlying impediment to acheiving an AP system and that more focus needs to be placed on building better sensors and faster methods to deliver insulin. Improvements in the sensor and delivery of insulin are important; however, we argue that the choice of algorithm remains an important aspect of the design. To this end, we summarize β cell characteristics that have been added to the PID algorithm, how the algorithm can be modified to better account for differences between portal and SC delivery, and how the resulting closed-loop control has been affected by the changes that have been introduced.

Summary of Initial Physiologic Insulin Delivery Studies with Updated β Cell Modeling

The first study to attempt PID control using SC insulin delivery and SC glucose sensing (**Figure 4A**)[37] relied only on the *proportional integral derivative* components needed to characterize first- and second-phase insulin appearance during a hyperglycemic clamp (**Figure 3**).[21] This was not the first study to automate insulin delivery in humans; Biostator studies in the 1970s achieved that result using intravenous insulin and glucose infusion.[38] However, it was the first study to achieve even moderate control with SC insulin delivery and SC glucose sensing and to do so without meal announcement. The primary area of concern was the need to administer supplemental carbohydrate 4–5 h following breakfast.[37] Lunch and dinner responses were generally within two standard deviations of profiles obtained in healthy individuals consuming the same diet (**Figure 4**, shaded area). Fasting glucose (120 mg/dl) was higher than observed in healthy subjects (90 mg/dl), but the difference was attributed to the higher nighttime target glucose level (120 mg/dl) used by the closed-loop system. Target glucose was achieved.[37] Noteworthy is that the results were obtained without any attempt to optimize the PID configuration to account for delays introduced with the SC delivery site. To our knowledge, this remains the only published study to have used *subjects with no history of diabetes consuming the identical weight-maintenance diet* as the control group (grey shaded area, **Figure 4A**; reproduced in **Figure 4B** and **4C**).

Following the feasibility study,[37] the perception was that, if the peak breakfast response could be decreased by ~40 mg/dl and the postprandial nadir increased by ~20 mg/dl, it would be possible to automate control *with the existing sensor and insulin delivery technology*. It was first thought that a semi-closed-loop system in which an insulin bolus one-third of that normally taken by the subject but given 15 min in advance of the meal might achieve the desired peak and nadir values.[39] The bolus was argued to emulate the β cell's cephalic phase insulin release.[41] However, while the bolus reduced peak postprandial glucose, the rate of fall 3–4 h following breakfast suggested that had lunch not been given at noon, nadir hypoglycemia would still have occurred. Effectively, within 3 h of consuming breakfast, the glucose profiles with and without the added insulin bolus were identical.

The inability to stabilize the 3–4 h postprandial breakfast response at target suggested additional changes in the algorithm were needed. To this end, the effect of insulin *per se* to inhibit insulin secretion[32] [insulin feedback (IFB)] was added to the algorithm. The IFB effect was characterized from C-peptide data obtained from an earlier study of SC glucose kinetics during graded hypoglycemic clamps[42] (**Figure 5B, 5D,** and **5F**). The IFB effect is easily seen during the period when insulin is elevated and glucose is clamped at basal (labeled "insulin effect"; **Figure 5F**). Based on this observation, it was concluded that the decrease in C-peptide could not be fit with the proportional-integral-derivative

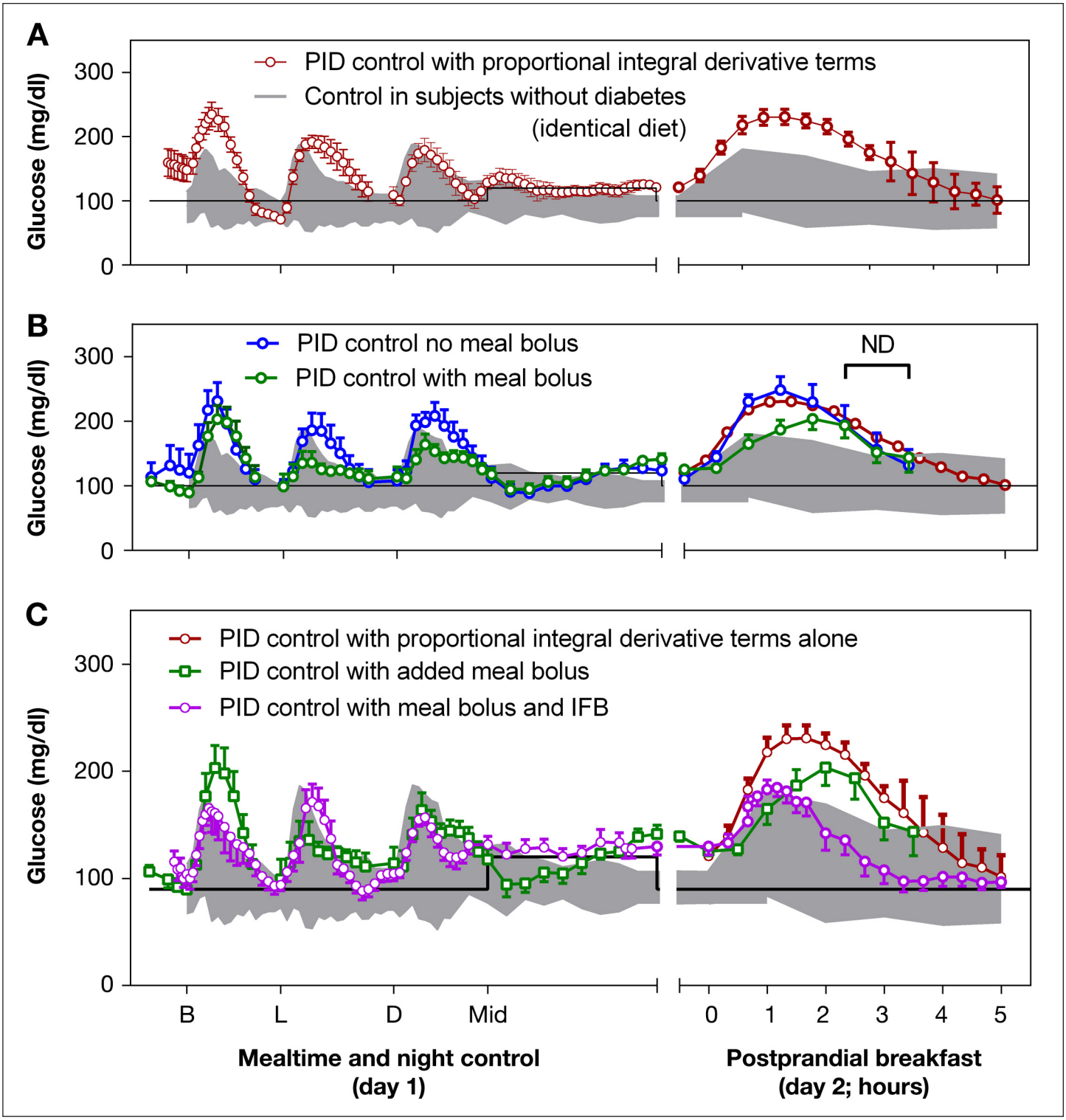

Figure 4. (A) Closed-loop control achieved using only proportional, integral, and derivate terms of a β cell model superimposed with control (±2 standard deviation) achieved by normal glucose-tolerant subjects consuming the identical weight maintenance diet (shaded area). **(B)** Physiologic insulin delivery control with and without a cephalic-phase-like meal insulin bolus (glucose rate of change 2.5–3.5 h following breakfast not different). **(C)** Improvements in control effected with the addition of IFB. Data adapted from References 37, 39, and 40. ND, not different.

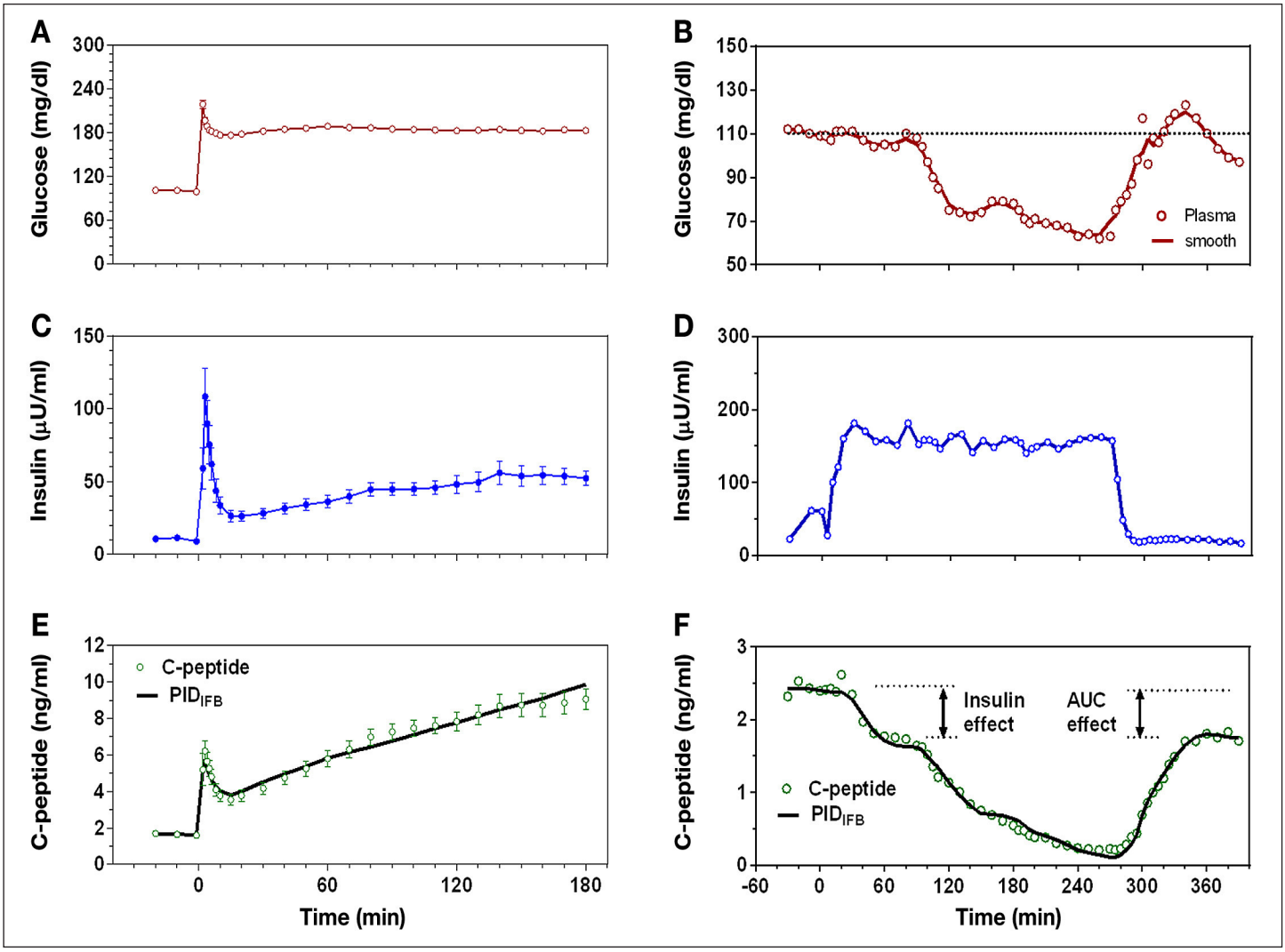

Figure 5. Updated model analysis of insulin profile shown in Figure 2 using (A,C,E) C-peptide together with model analysis of β-cell secretion during euglycemia–hyperinsulinemia followed by hypoglycemia and (B,D,F) recovery from hypoglycemia. Secretion model identified using standard nonlinear least squares (Mlab, Civilized Software Inc.). Data adapted from References 21 and 42. AUC, area under the curve of glucose below fasting (dashed line panel B).

model terms alone. Modifying the PID model to include IFB, but with delay, yielded good fits (black line, **Figure 5F**; fit obtained following methodology developed by Eaton and coauthors[43] with C-peptide parameters reported by Van Cauter and coauthors[44]). Here the delay was estimated to be ~35 min [0.0276 ± 0.0029 min^{-1} (mean ± standard error of the mean)]. Identifying the rate effect (first phase) as a ratio of proportional (U/h per mg/dl) and derivative (U/h per mg/dl per min) secretion yielded similar values for the two hypoglycemic periods (0–90 and 90–270 min) with the effect estimated as 37 ± 4 and 33 ± 6 min, respectively. No rate effect was observed during the recovery from hypoglycemia [270–390 min; ratio = 2.24 ± 2.28 (mean ± standard error of the mean) min, not different from zero by F-test]. The addition of IFB terms did not adversely affect the ability of the model to fit the hyperglycemic clamp (data of **Figure 2** refit using C-peptide; **Figure 5E**). Adding the effect to the model used for closed-loop control improved the meal response, with the breakfast on day 2 of closed-loop having a lower peak postprandial level and control stabilizing at target within ~3 h (**Figure 4C**).[40]

Discussion

As a control algorithm, the PID model was introduced with the expectation that terms other than the proportional, integral, and derivative components common to all "PID" algorithms might be needed to capture relevant β cell

characteristics.[18] In light of this, the control algorithm was not called proportional-integral-derivative *per se* but rather "physiologic insulin delivery."[37] That the breakfast response has improved as terms emulating cephalic phase insulin and IFB[40] were added supports the contention that the β cell can serve as a guide in the development of an AP control algorithm. The conclusion that IFB improves the meal response in **Figure 4** is based on a comparison of different studies. However, the benefit has been confirmed in a prospective randomized trial of human subjects[45] and determined to be essential in controlling glucose in children less than 7 years of age.[46] That IFB is an effective mechanism for contending with the added delays introduced by SC insulin delivery is supported by computer simulation studies[47] and by studies in canines.[48]

New analysis of the insulin secretion profile during insulin-induced hypoglycemia, presented here for the first time, revealed a number of additional β cell characteristics relevant to closed-loop glucose control. The observation that the *in vivo* effect of IFB was delayed by ~35 min suggests that the feedback might be compensating for the delay between insulin's appearance in blood and its appearance in interstitial fluid surrounding insulin-sensitive tissues. This delay has also been identified as ~35 min.[49] In contrast, the closed-loop control with IFB shown in **Figure 4** was obtained using feedback of model predicted *plasma insulin* levels.[40] Further improvements might therefor be achieved by including terms proportional to both insulin concentration and insulin effect. The ratio of proportional and derivative insulin secretion identified from the PID model was also ~35 min. That multiple signals seem to be affecting secretion with the same ~35 min delay suggests the signal may be mediated by an effect of insulin in peripheral tissue to reduce circulating secretagogues (free fatty acids or other). In any case, from a control theory perspective, setting the ratio of the proportional and derivative responses to be the same as a system delay can make it appear as if that delay does not exist (analogous to starting an infusion of a drug with a priming bolus where the ratio of the priming bolus to infusion rate equals the system delay). This is known in classical control theory as pole-zero cancelation.[19] In a similar manner, introducing feedback terms proportional to intermediate steps in the process being controlled can make the system behave identically to a system with shorter delays. This is referred to as pole placement in classical control theory[19,50] (poles determine the delay). Both mechanisms can be adapted for SC insulin delivery. In the first instance, no real change is needed, as the delay between an increase in plasma insulin and its subsequent effect in peripheral tissue is the same whether the insulin is delivered into the portal vein or SC site.

A direct effect of insulin to inhibit insulin secretion was not observed in the *in vitro* perfused pancreas,[51] suggesting that the effect is mediated by decreases in circulating insulin secretagogues, e.g., amino acids, potassium, or free fatty acids (FFAs). Elevating FFA levels during graded hyperglycemic clamps has been shown to increase secretion,[52] (and inhibit insulin's effect on the liver[53]) suggesting that the decrease in secretion observed here (**Figure 5**; $0 < t < 90$ min) may have been prevented had FFA levels also been clamped at basal. It remains to be seen whether AP algorithms can benefit from information pertaining to other secretagogues should sensors for these secretagogues become available.

The absence of a first-phase response during the recovery from hypoglycemia was an unexpected finding in this analysis (**Figure 5**). *In vitro*, the response is not present if glucose is stepped up to 50 mg/dl but is present if the glucose is stepped up to 100 mg/dl (**Figure 1**). *In vivo*, some subjects may not have surpassed the upper glucose threshold needed to effect first-phase release; however, at least some of the subjects surpassed what the model identified as target (**Figure 5**, dashed line). It is not clear if all the subjects would have returned to the same target glucose postclamp as preclamp and, if not, whether the target was affected by the area under the curve during the hypoglycemia (labeled AUC effect in **Figure 5F**) or indirectly related to a circadian signal that alters the β cell's desired target during the day.

That a first-phase response during recovery from insulin-induced hypoglycemia could not be identified (**Figure 5F**; time > 300 min) raises questions as to when the β cell reinitiates insulin delivery following insulin-induced hypoglycemia. Understanding when and how the β cell does this could potentially offer insight into how basal delivery should be restarted after the hypoglycemic-suspend feature available in some pumps is triggered.[54,55] Waiting too long to restart basal insulin delivery can be expected to result in rebound hyperglycemia.

Hyperglycemic clamp data do not allow the cephalic phase insulin release to be quantified; however, the response is *not* thought to be dose dependent or to commit a healthy individual to consuming the carbohydrates that triggered

the response. This differs from how the effect was initially implemented in the PID algorithm, which set the response in proportion to the expected amount of carbohydrate to be consumed. Although not tested, this likely committed the subjects to consuming at least some portion of the meal. Subsequent PID investigations have used either a fixed bolus (2 U; **Figure 3C**) or a lower bolus related to the subject's total daily dose of insulin (0.5, 1.0, and 1.5 U in subjects using <15, 15–30, and >30 U, respectively).[56] A study in children less than 7 years of age eliminated it altogether.[46] However, the bolus remains a popular option preferred by many patients and physicians, and algorithms using the mechanism will need to be assessed to ensure safety should the bolus be overestimated or the subject choose not to eat all of the meal.

Conclusions

One of the most common criticisms of the use of a β cell model for closed-loop control in an AP using SC delivery is the change of delivery site from the portal vein to the SC site. However, careful consideration of the β cell's secretory profile suggests that the β cell has put in place multiple mechanisms to contend with delay. While portal delivery allows rapid suppression of hepatic glucose output, insulin's effect to increase glucose uptake in peripheral tissue is well-known to be delayed by 30 to 60 min.[36] Evidence also exists that some of insulin's effect to lower hepatic glucose output is mediated by its effect to decrease circulating FFAs,[53,57–59] which is likewise delayed.[60] That first-phase insulin release and possible IFB are used to compensate for these delays is an attractive hypothesis, and both mechanisms are well-known from classical control literature.[19] That these same mechanisms can be adapted to different insulin delivery sites is supported by studies showing PID's effectiveness when used with intraperitoneal[61] or peripheral intravenous delivery [62,63]—the last study[63] having the lowest incidence of hypoglycemia of any published clinical trial of tight glycemic control in the intensive care setting.

Although the control achieved using SC insulin delivery has steadily improved as modifications to the PID control algorithm have been introduced to better reflect β cell secretion, the important question for individuals with type 1 diabetes is not how well new versions of the algorithm compare with previous versions, but rather how well the newest version compares with other putative optimal control approaches. We did not present here a comparison of the results obtained with PID with other approaches.[64–74] We believe a detailed comparison of the results obtained with all the different algorithms studied to date is needed but that the comparison should focus on the results obtained with different approaches more so than the method *per se*. That is, the review should focus on the peak and nadir glucose levels during meals, the average glucose values, and the overall incidence of hypoglycemia. If better control can be achieved with an alternative approach, it may not be important to have the algorithm behave "like the β cell."

Still, based on the improvements achieved to date in closed-loop control modeling the β cell, we suggest that continued efforts can provide important insights for future improvements. To this end, it is clear that much of what the β cell does has yet to be captured by the latest PID algorithm and that much of what has been captured has not been optimized for SC insulin delivery. Based on the results presented here, we conclude that the integral component will require modifications if it is to emulate the β cells' responses to sequential increases in glucose, that the magnitude of the IFB terms might better be optimized to reflect what the β cell is trying to achieve, and that the threshold for delivering first-phase insulin during recovery from hypoglycemia might be reduced. As faster-absorbing insulins become available, these changes can be more easily incorporated.

Disclosures:

Garry Steil serves on the medical advisory board for BD. No BD devices were use in the conduct of this study. Gerold Grodsky is a consultant for Medtronic.

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