

What's the Time? Does the Artificial Pancreas Need to Know?

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The development of a closed-loop artificial pancreas (AP) represents a major technological effort that aims to improve glucose control, prevent complications, and decrease disease burden for patients with diabetes. An AP consists of three components: 1) a subcutaneous glucose monitor, 2) a subcutaneous insulin pump, and 3) an automated control algorithm (Fig. 1) (1,2). Until recently, clinical trials investigating AP function were limited to controlled, in-hospital settings (1,3). However, several recent studies showed that an AP can maintain (4) or even improve (5) glycemic control outside of the hospital.

Several types of control algorithms have been developed. On the one hand, proportional-integrative derivative algorithms use a classical feedback approach. On the other hand, model-predictive control (MPC) algorithms continuously update a strategic plan for glucose control. These MPC algorithms can possibly be further improved by taking the daily variation in insulin sensitivity into account. It has been known for a long time that glucose levels in type 1 diabetes show an increase in the early morning (the dawn phenomenon) (6), and *in silico* it is possible to incorporate a daily rhythm in basal insulin secretion into an MPC algorithm to deal with this difference in basal insulin requirement (7). The daily variation in meal responses may be a further opportunity for algorithm developers to improve MPC.

Glucose levels and glucose tolerance show clear 24-h rhythms that are induced by the circadian timing system. These consist of a central clock in the hypothalamic suprachiasmatic nucleus (8,9) and peripheral clocks in metabolic tissues such as liver, pancreas, and adipose tissue (10–12). In rodents and humans, the magnitude of glucose and insulin excursions after a meal depends on the time of the day (12). In healthy subjects, postprandial glucose excursions are lower in the morning than in the evening (6), which may be the result of the 24-h rhythm of insulin sensitivity with increased insulin sensitivity in the morning (13,14).

As reported previously in *Diabetes*, Saad et al. (15) used a triple tracer technique to disentangle the mechanisms underlying increased morning glucose tolerance in healthy individuals. Their work showed that, relative to lunch and dinner and under controlled conditions of identical mixed

meals and physical activity, increased breakfast glucose tolerance resulted from better β -cell responsiveness, a tendency toward better insulin action, and lower hepatic insulin extraction (15).

If only for the development of a control algorithm, these measurements had to be repeated in patients with type 1 diabetes. In a follow-up study presented in this issue of *Diabetes*, Hinshaw et al. (16) used exactly the same protocol with controlled conditions to determine diurnal changes in glucose excursions following meals in subjects with type 1 diabetes. Perhaps unexpectedly, they showed that on the whole, patterns of glucose appearance and disappearance and the insulin sensitivity index (S_i) were not significantly different between meals in people with type 1 diabetes.

The absence of one uniform daily pattern of insulin sensitivity for the type 1 diabetic population as a whole mainly results from large intersubject variability. This would argue against using mealtime as a factor in the AP control algorithm. Interestingly however, from the individual data on S_i reported in the article by Hinshaw et al., it appears that every patient showed his/her own specific pattern over the day, and the authors conclude that individual rhythms may need to be incorporated into AP control algorithms. However, since the authors only depict individual-level average S_i over three breakfasts, lunches, and dinners without providing a measure of dispersion, the consistency of these individual patterns remains unclear.

Thus, before individual patterns can be implemented in a control algorithm, it is first important to know the day-to-day variation of individual patients. For comparison, for overnight control the night-to-night insulin requirement varies between 50 and 200% within subjects (R. Hovorka, unpublished observations).

Second, an important question that arises from these data is whether individual patterns observed under controlled circumstances with three identical meals and controlled levels of physical activity are relevant to a real-life situation. In practice, the major determinants of plasma glucose in type 1 diabetes (meal composition, physical activity, stress) vary considerably during the day. Compared with an algorithm that only uses information on meals and physical activity, it remains to be determined whether the amplitude of the proposed daily rhythm in insulin sensitivity is so large that incorporating this daily rhythm into a control algorithm would improve performance.

In conclusion, the question of whether an AP control algorithm can be improved by accounting for a daily rhythm in insulin sensitivity remains to be resolved. Hinshaw et al. (16) convincingly showed that there is no general daily rhythm in insulin sensitivity in patients with type 1 diabetes. It is possible that incorporating individual daily rhythms in insulin sensitivity in the control algorithm may improve glucose control, but this will have to be verified in well-controlled clinical trials.

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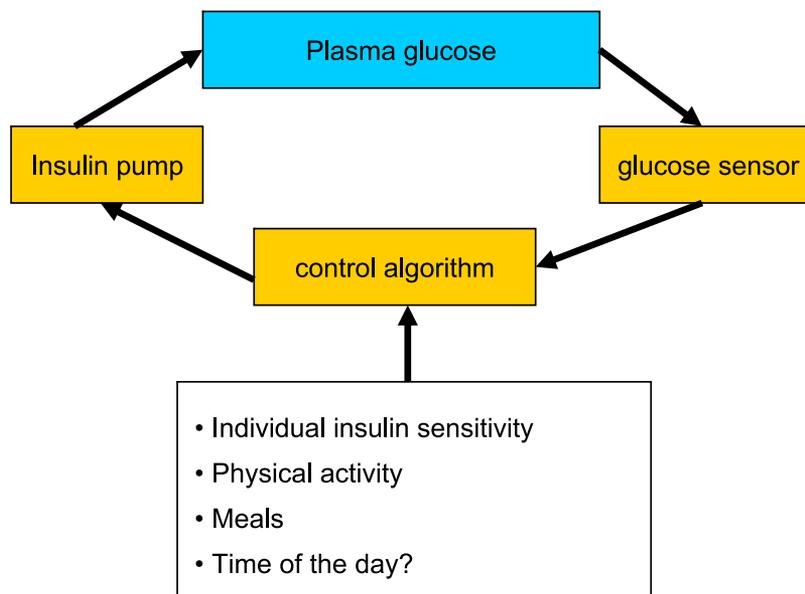


FIG. 1. Schematic overview of a closed-loop AP. A closed-loop AP consists of a glucose sensor, an insulin pump, and a control algorithm. The algorithm controls insulin infusion rate based on recent glucose values, recent insulin infusion, and individual-specific information on insulin sensitivity. The latter is often initially derived from body weight, and total and basal insulin doses. In addition, the algorithm needs information on physical activity and meal announcement. Incorporating individual diurnal insulin sensitivity patterns possibly may improve algorithm performance.

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