OBSERVATIONS

Pilot Studies of Wearable Outpatient Artificial Pancreas in Type 1 Diabetes

The artificial pancreas (AP) has been tested extensively in the hospital setting (1–5). Here we describe a next logical step in AP development—the first outpatient trials of a wearable AP based on a smartphone computational platform.

Following Ethical Committee approvals and ClinicalTrials.gov registration (NCT01447992 and NCT01447979), two simultaneous studies were conducted in Padova, Italy, and Montpellier, France, in October 2011, enrolling a 38-year-old female and a 52-year-old male, respectively; both were Caucasian, type 1 diabetic insulin pump users.

Day 1—At 17:00, the patients arrived at hotels located within 1 km from the emergency room. Subjects' pumps were replaced by Omnipod Insulin Management Systems. The APs were activated in open-loop mode implementing the patients' regular routines and remote monitoring was initiated. At 20:00, the patients had dinner at a local restaurant, without dietary restrictions and then spent the night in the hotel.

Day 2—At 7:00, the patients were admitted to the clinic and the APs were switched to automated closed-loop control and challenged by breakfast at 8:00 and lunch at 12:00. At 18:00, the patients moved back to the hotel; dinner was at 20:00 in a local restaurant, without dietary restrictions. Meal bolus was recommended by the APs and approved by the patients; basal rate and corrections were automatically delivered by the APs.

Day 3—At 8:00, the patients had breakfast at the hotel. At 11:00, they had low intensity exercise (30-min walk in town). Throughout the study, the clinical team remotely observed the system operation and reference blood glucose was measured using HemoCue (HemoCue AB, Ängelholm, Sweden) pre- and postmeals, at bedtime, and upon physician judgment.

The AP, developed at the University of Virginia, is based on the Sony Xperia smartphone; sensor and pump communications are handled by the University of California Santa Barbara/Sansum Artificial Pancreas System (APS) running on a communication box connected via Bluetooth to the phone (Fig. 1, *upper panel*). The control algorithm includes safety supervision responsible for the prevention of hypoglycemia and a range correction module delivering insulin corrections as needed (5). The patients interact with the system via touch-screen graphical user interface allowing for AP initialization with patient-specific characteristics, confirmation of meal boluses, and optional entries of exercise and hypoglycemia treatment. Every 5 min, sensor, insulin pump, and system technical data are sent via secured 3G connection to a remote server, which ensures continuous remote monitoring of the patient and the system. Phone calls, Internet browsing, and other features of the smartphone are disabled at the level of its operating system (Android).

The smartphone computational platform, the control algorithm, and the remote monitoring system performed as intended, without any functional or reliability issues. On two occasions the communication box malfunctioned requiring intervention by the study team. Although reaching near normoglycemia was not the objective of these pilot studies, glucose control results are presented in Fig. 1 (*lower panel*): the AP avoided hypoglycemia (<3.9 mmol/L) and major hyperglycemia (>15 mmol/L) in both cases. No adverse events were experienced by the patients; no ketone production was detected during the studies.

These first results indicate that a wearable AP is feasible and safe; therefore its continued testing and refinement for ambulatory use is warranted.

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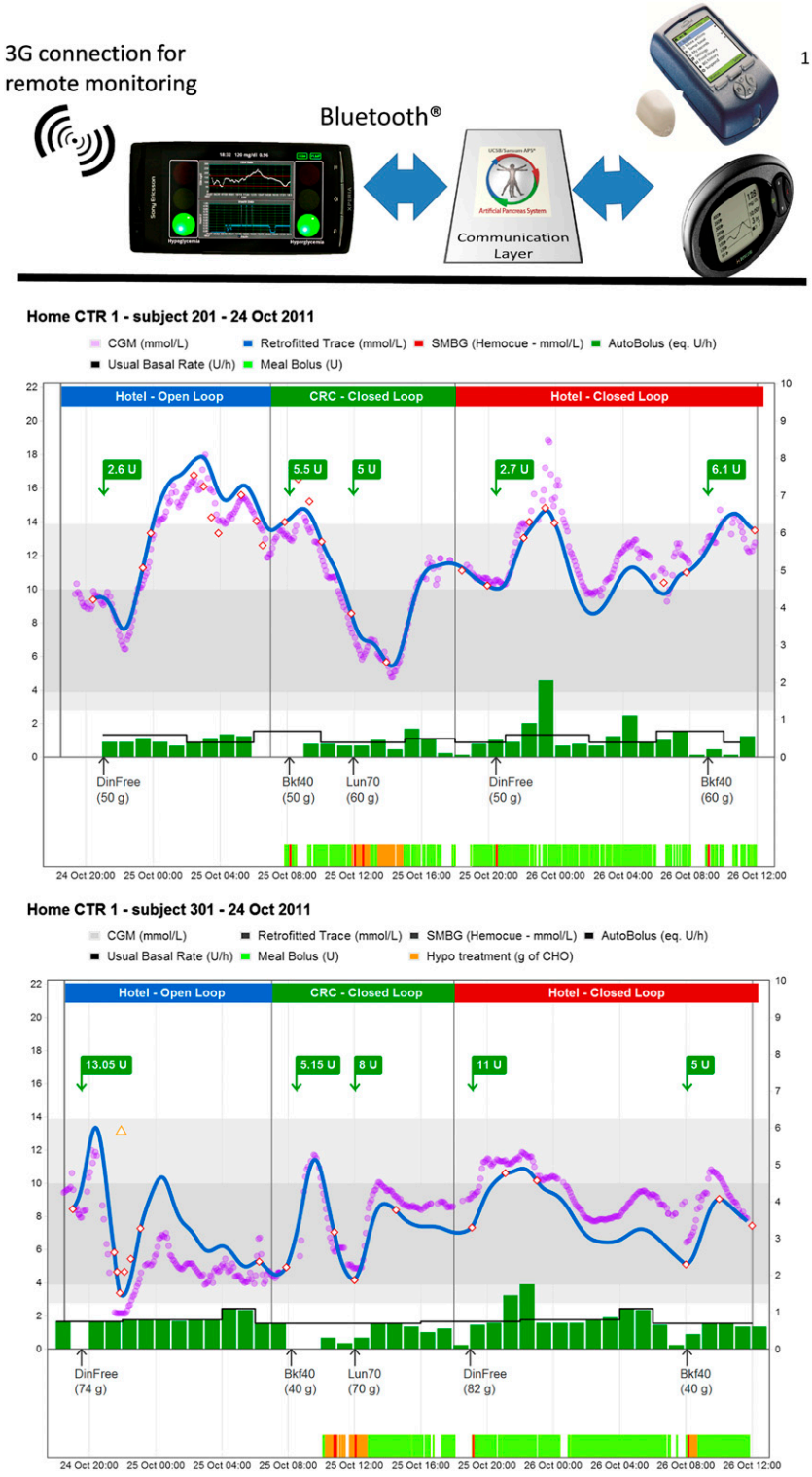

Figure 1—Upper panel: *Dual-layer structure of the APS used in this study*: 1) *the upper layer was a smartphone programmed to run the control algorithm, the user interface, and a one-way connection to a server for remote monitoring; and* 2) *the lower layer was a communication system transmitting data from the sensor to the smartphone and control commands to the insulin pump.* Lower panel: *Blood glucose and insulin delivery during two clinical experiments with a wearable AP in Padova, Italy (subject 201), and in Montpellier, France (subject 301). The three consecutive study phases are labeled as: open-loop control in the hotel, closed-loop control in the clinic, and closed-loop control in the hotel. Meals are marked by arrows with carbohydrate content in parentheses. Corresponding meal boluses are indicated as green flags. The blue line shows blood glucose levels as sensor trace retrofitted to HemoCue self-monitored blood glucose measurements (open red diamonds). The open purple circles indicate raw sensor values used by the control algorithm. Green bars at the bottom show the delivered insulin according to patient programming of the pump (open-loop) or algorithm-driven pump (closed-loop) rate. Bkf, breakfast; CGM, continuous glucose monitoring; CHO, carbohydrate; CRC, clinic; CTR, control to range; Din, dinner; Lun, lunch; SMGB, self-monitoring blood glucose.*

References

1. Cobelli C, Renard E, Kovatchev B. Artificial pancreas: past, present, future. Diabetes 2011;60:2672–2682
2. Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet 2010;375:743–751
3. El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER. A bihormonal closed-loop artificial pancreas for type 1 diabetes. Sci Transl Med 2010;2:27ra27
4. Kovatchev BP, Cobelli C, Renard E, et al. Multi-National Study of Subcutaneous Model-Predictive Closed-Loop Control in Type 1 Diabetes: summary of the results. J Diabetes Sci Technol 2010;4:1374–1381
5. Breton MD, Farret A, Bruttomesso D, et al. Fully integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia. Diabetes. 11 June 2012 [Epub ahead of print]