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Development and Evaluation of a Single-Site device for conjoined Glucose Sensing and Insulin Infusion in Diabetes Patients

DOCTORAL THESIS

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The Work described in this Thesis was performed at the Medical University of Graz and the Graz University of Technology.

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1.) M. Tschaikner et al., “Development of a single-site device for conjoined glucose sensing and insulin delivery in type 1 diabetes patients,” IEEE Trans. Biomed. Eng., May 2019. doi: 10.1109/TBME.2019.2919234.

2.) M. Tschaikner et al., “Novel single-site device for conjoined glucose sensing and insulin infusion: Performance evaluation in diabetes patients during home-use,” IEEE Trans. Biomed. Eng., Jun. 2019. doi: 10.1109/TBME.2019.2925434.

3.) M. Tschaikner et al., “Zusammenlegung von Insulingabe und Glukosemessung im Fettgewebe zur Verbesserung der Therapie von Diabetes,” in Proc. Annu. Meeting Austrian Soc. Biomed. Eng., Hall, Austria, 2014, pp. 77–78.

Some chapters of this thesis are partly or completely taken as published and eventually adapted from the original manuscripts when it appeared to be necessary.

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Wenn einer, der mit Mühe kaum,
geklettert ist auf einen Baum,
schon meint,
dass er ein Vöglein wär,
so irrt sich der.

(Wilhelm Busch)

ABSTRACT

Goal: Diabetes patients are increasingly using a continuous glucose sensor to monitor blood glucose and an insulin pump connected to an infusion cannula to administer insulin. Applying these devices requires two separate insertion sites, one for the sensor and one for the cannula. Integrating sensor with cannula to perform glucose sensing and insulin infusion through a single insertion site would significantly simplify and improve diabetes treatment by reducing the overall system size and the number of necessary needle pricks. Presently, several research groups are pursuing the development of combined glucose sensing and insulin infusion devices, termed single-port devices, by integrating sensing and infusion technologies created from scratch. **Methods**: Instead of creating the device from scratch, we utilized already existing technologies and introduced three design concepts of integrating commercial glucose sensors and infusion cannulas. We prototyped and evaluated each concept according to design simplicity, ease of insertion, and sensing accuracy. The best single-port prototype was then used in two clinical trials. The first trial was performed to inform final refinements in device assembly, insertion, and sensor operation techniques. The second trial was performed to ascertain the accuracy of the glucose sensing with the single-port device and to assess the feasibility of using the single-port device in combination with an algorithm to automatically control the blood glucose in diabetes patients. **Results:** We found that the best single-port device is the one in which a Dexcom sensor is housed inside a Medtronic cannula so that its glucose sensitive part protrudes from the cannula tip. Glucose sensing performed with this single-port device was found to be accurate and reliable - the average mean absolute relative deviation from blood glucose concentrations obtained for the sensor of the device was low (median, 13.0%; interquartile range, 10.5–16.7%; n= 10) and did not differ from that of the additionally worn glucose sensor (versus 13.9%; 11.9–15.3%; P= 0.922). Furthermore, insulin delivery with the single-port device was reliable and safe during home use and, when performed in combination with the control algorithm, was adequate to achieve and maintain near normoglycemia. **Conclusion:** Results from these studies indicate the feasibility of combining commercial glucose sensing and insulin delivery technologies to realize a functional single-port device. **Significance:** Our development approach

may be generally useful to provide patients with innovative medical devices faster and at reduced costs.

KEYWORDS

artificial pancreas,
electrochemical glucose sensor,
insulin infusion set,
insulin pump,
medical device development,
single-port device

ZUSAMMENFASSUNG

Ziel: Immer mehr Diabetespatienten verwenden kontinuierlich messende Glukosesensoren um ihren Blutzuckerspiegel zu überwachen und Insulinpumpen mit angeschlossenen Infusionskanülen, um sich Insulin zu verabreichen. Die Verwendung dieser Medizingeräte erfordert zwei separate Hauteinstichstellen, eine für den Sensor, die andere für die Infusionskanüle. Das Vereinen von Sensor und Infusionskanüle zur Durchführung von Glukosemessung und Insulininfusion über eine einzelne Hauteinstichstelle würde die Diabetestherapie deutlich vereinfachen und verbessern, da eine Reduzierung der für die Therapie benötigten Nadelstiche und eine Verkleinerung der Gerätebaugröße erreicht werden kann. Gegenwärtig versuchen mehrere Forschungsgruppen ein Gerät zur vereinten Glukosemessung und Insulinverabreichung, ein sogenanntes Single-Port-Gerät, von Grund auf neu zu entwickeln. **Methoden:** Im Gegensatz zu einer kompletten Neuentwicklung haben wir auf bereits bestehende Technologien zurückgegriffen und drei Konzepte des Vereinens von am Markt erhältlichen Glukosesensoren und Infusionskanülen erarbeitet. Auf Basis dieser Konzepte wurden Prototypen gebaut und mittels Kriterien wie Einfachheit des Designs, Einfachheit des Einstechvorgangs und Genauigkeit der Glukosemessung bewertet. Der beste Single-Port-Prototyp wurde dann in zwei klinischen Studien eingesetzt und getestet. Im Laufe der ersten Studie wurde der Zusammenbauvorgang, der Einstechvorgang und die Sensorhandhabung weiter verbessert. Die zweite Studie wurde durchgeführt, um die Sensorgenauigkeit des Single-Port Gerätes mit der von herkömmlichen Sensoren zu vergleichen und um das Gerät in Kombination mit einem Closed-Loop-Algorithmus zur automatischen Regulierung des Blutzuckerspiegels von Diabetespatienten zu testen. **Ergebnisse:** Die Bewertung der Prototypen ergab nun, dass das beste Single-Port-Gerät eines ist, bei dem ein Sensor der Firma Dexcom so im Inneren einer Infusionskanüle der Firma Medtronic platziert wird, dass die Glukose-sensitive Sensorspitze ein kurzes Stück über das Ende der Kanüle hinausragt. Die durchgeführten klinischen Studien zeigten, dass das Glukosemessen mit dem entwickelten Single-Port-Gerät zuverlässig und genau war – die mittlere absolute relative Abweichung von der Blutglukosekonzentration war niedrig (median, 13.0%; Interquartilbereich, 10.5–16.7%; n= 10) und nicht unterschiedlich von der eines zusätzlich getragenen

Kontrollsensors (versus 13.9%; 11.9–15.3%; P= 0.922). Weiters war die Insulinverabreichung während der Heimanwendung des Gerätes verlässlich und sicher. Darüber hinaus konnte gezeigt werden, dass wenn das Gerät zusammen mit dem Closed-Loop-Algorithmus betrieben wurde, die Blutzuckerkonzentrationen der Patienten nahe an den optimalen Blutzuckerwerten zu liegen kamen. **Schlussfolgerungen:** Unsere Studienergebnisse haben gezeigt, dass mithilfe des gewählten Entwicklungsweges ein verlässlich funktionierendes Single-Port-Gerät realisiert werden kann. Das so entwickelte Gerät könnte daher das erste Single-Port-Gerät sein, das marktreife erlangt und zu einer Vereinfachung und Verbesserung der Diabetestherapie führt. Der von uns erfolgreich beschrittene Entwicklungsweg könnte auch auf andere Geräteentwicklungen übertragen werden, um Patienten neue, innovative Medizingeräte schneller und günstiger zur Verfügung zu stellen.

Schlüsselwörter

Künstliche Bauchspeicheldrüse
Elektrochemischer Glukosesensor
Insulin Infusionsset
Insulinpumpe
Medizingeräteentwicklung
Single-Port Gerät

CONTENTS

LIST OF FIGURES

ABBREVIATIONS

(ARD)	Absolute Relative Difference
(AP)	Artificial Pancreas
(BMI)	Body Mass Index
(CRC)	Clinical Research Center
(CL)	Closed-Loop
(CGM)	Continuous Glucose Monitor
(CSII)	Continuous Subcutaneous Insulin Infusion
(CS)	Control Sensor
(CC)	Correlation Coefficient
(TR)	Hydraulic Tissue Resistance
(ISF)	Interstitial Fluid
(IQR)	Interquartile Range
(MPC)	Model Predictive Control
(MDI)	Multiple Daily Injections
(OL)	Open-Loop
(OGTT)	Oral Glucose Tolerance Test
(PARD)	Precision Absolute Relative Difference
(SP)	Single-Port
(SD)	Standard Deviation
(TTR)	Time spent in the Target Range

1. INTRODUCTION

1.1. Type 1 diabetes

Patients with type 1 diabetes are unable to produce insulin due to the autoimmune destruction of the B-cells in the pancreas [1]. As a consequence, type 1 diabetes patients require insulin replacement therapy to survive. The goal of the therapy is to avoid short-term, metabolic (dangerously low or high blood glucose concentration) and long-term, vascular (renal failure, blindness, nerve damage, and myocardial infarction) complications of the disease by replicating the insulin secretion of healthy individuals as closely as possible [2].

1.2. Current type 1 diabetes treatment forms

The majority of type 1 diabetes patients administer insulin in the form of multiple daily subcutaneous injections. However, an increasing number of patients are recently switching to the insulin pump therapy. Compared to the insulin injections, the insulin pump therapy has been shown to improve clinical outcomes by continuously administering insulin via a subcutaneous cannula.[3], [4] To adjust the insulin dosage, all forms of insulin therapy require that patients use a blood glucose meter to frequently self-monitor the glucose concentration in the blood, typically obtained by finger-pricking. However, since finger-pricking cannot be performed often enough to detect the early changes in the glucose concentration and carry out immediate corrective action, the blood glucose meters are increasingly being replaced by continuous glucose monitors (CGMs) as those provide continuous, real-time data throughout the day [5]. Much of the current focus in the pursuit of better clinical outcomes in diabetes patients [6], [7] is on designing smarter insulin pumps, developing more accurate CGMs, and coupling the state-of-the-art insulin pumps and CGMs to create an artificial pancreas (AP).

1.3. Artificial pancreas approaches

Over the past 50 years, a great deal of effort has been devoted to the development of a closed-loop insulin delivery system, or artificial pancreas, that is suitable to automatically control the blood glucose of individuals with type 1 diabetes [8]–[10]. Various approaches to realizing such a system have been adopted, including techniques based upon polymer-encapsulated islets (a so-called bioartificial AP; [9], [11]), insulin-releasing polymers (a fully synthetic AP; [10], [12]), and the combined use of an insulin pump, glucose sensor and control algorithm (an electromechanical AP; [8], [13]). Currently, owing to the advent of reliable glucose sensors that operate continuously in the subcutaneous space, the electromechanical approach employing the subcutaneous route for both glucose sensing and insulin delivery is considered most promising for widespread clinical use [6], [8]–[10]. Indeed, a considerable number of studies have demonstrated safety and effectiveness of such AP systems both in the clinical research center (CRC) and the outpatient environment [6], [14]–[16]. However, while there is now little doubt that such AP systems are technically feasible, it remains less clear that they will be widely adopted by the patients [17]–[19]. So far a number of factors have been reported which may hinder widespread future adoption of such an AP [19]–[21]. Of these, a critically important factor appears to be the size of the AP. For example, a recent survey-based study ascertained the expectations of diabetes patients and parents of children with diabetes with regard to the potential future use of an AP and found ‘small size’ and ‘discreet appearance’, followed by ‘being effective’, as the most favored attributes of an AP [21]. In addition, many participants in this survey expect the future AP to be an all-in-one device that is similar in size to an insulin pump [21]. Unfortunately, current clinically tested AP systems fall short in meeting these expectations. They all require the patient to wear one to two pumps, each with an infusion cannula inserted into the patient’s subcutaneous tissue, and one to two needle-type sensors with sensor tips inserted at separate subcutaneous tissue sites (Fig. 1a). Therefore, in order to broaden the appeal of the AP and increase the likelihood of achieving high adoption rates, it is desirable to integrate all components of the AP into one unit and reduce its size to approximately the size of a current insulin pump.

1.4. Improving mechanical artificial pancreas systems

One disadvantage of the current mechanical AP systems (Fig. 1a) is that the glucose sensing and the insulin delivery are performed by stand-alone components which require separate insertion sites (dual-port AP). Due to the spatial separation, these components need individual communication and power supply units, resulting in a bulky AP system. Furthermore, having to insert the glucose sensor and the insulin infusion cannula at two different subcutaneous tissue sites causes unnecessary pain, increases the risk of infection or skin problems [22], [23], and leads to impaired freedom of movement. In clinical studies performed to overcome these limitations [24]–[26], we have previously shown that glucose concentrations measured at the site of subcutaneous insulin infusion closely reflect the glucose levels in blood, thereby demonstrating the feasibility of conjoining glucose sensing and insulin delivery at a single subcutaneous tissue site. Integrating the glucose sensing and the insulin delivery components of an AP to perform sensing and infusion at a single tissue site (single-port AP) would allow a significant reduction in the overall system size since the number of the required system parts, such as power supply and communication units, could be decreased or some of the parts altogether eliminated. In addition, integrating the two components would also allow reducing the necessary number of treatment-related pinpricks to a minimum. Finally, managing diabetes with a single-port, as opposed to a dual-port AP (Fig. 1a,b) may result in improved patient convenience which in turn could lead to greater treatment acceptance.

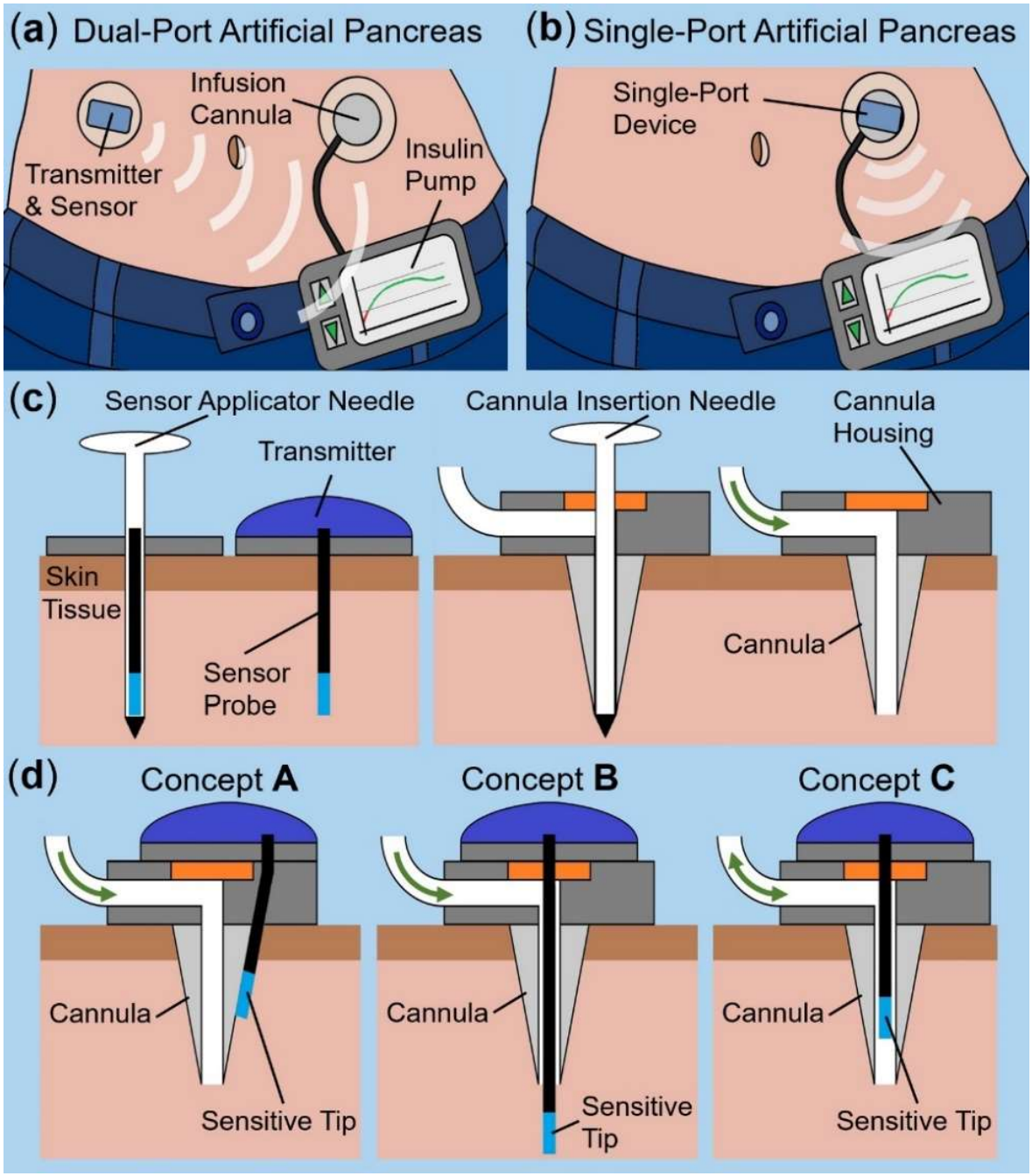

Fig. 1. *Dual-port and single-port artificial pancreas (AP) systems and their constituent parts:* ***(a)*** *Schematic representation of a dual-port AP.* ***(b)*** *Schematic representation of a single-port AP.* ***(c)*** *Schematic cross-sectional view of commercially available needle-type continuous glucose monitors and insulin infusion sets commonly used in dual-port APs.* ***(d)*** *Schematic cross-sectional view of the single-port device design Concepts A, B, and C: Concept A: the sensor-probe is affixed to the outer cannula wall; Concept B: the sensor-probe is placed inside the cannula lumen so that the glucose-sensitive probe tip protrudes from the cannula tip; Concept C: the sensor-probe is placed inside the lumen of the cannula housing so that the glucose-sensitive probe tip resides in the cannula lumen.*

1.5. Integrating completely new sensor and infusion technologies

Several academic and industrial research groups are therefore working on devices that enable conjoined glucose sensing and insulin delivery at a single subcutaneous tissue site (single-port device). For example, the group from Medtronic [27], and the group from Pacific Diabetes Technologies [28] are each developing a device which consists of an electrochemical glucose sensor integrated into the infusion cannula wall. Furthermore, the group from Johanneum Research and Graz University of Technology is working on a device in which an optical glucose biosensor is applied as a coating onto the infusion cannula wall and coupled to a read-out unit used to detect the glucose responsive changes in sensor fluorescence emission [29]. Finally, the group from Sensile Medical is developing a device consisting of a porous membrane that contains a glucose responsive hydrogel and a pressure sensor which measures the glucose responsive changes in fluidic resistance while insulin is being delivered through the membrane into the subcutaneous tissue [30]. All of these research groups share in common that their device development approaches are based on integrating new glucose sensor and insulin infusion technologies created from scratch. However, creating a medical device from scratch comes with high costs and risks since every stage of the highly regulated, multi-stage medical device development pathway has to be completed before a device can be brought to the market [31], [32].

1.6. Our approach: Integrating already existing technologies

Here we describe an alternative development approach that is more time- and cost-effective since it allows skipping some of these development stages. Our approach to the development of a single-port device is based on the integration of already existing glucose sensing and insulin delivery technologies. Thus, instead of creating the device from scratch, we performed a detailed analysis of the commercially available glucose sensing and insulin infusion technologies and introduced three design concepts of integrating commercial glucose sensors and infusion cannulas. Then, we built several prototypes of each concept and evaluated them according to design simplicity, ease of insertion, and sensing accuracy. Lastly, we assessed the best single-port device prototype in humans under real-use conditions.

This developed single-port device (Fig. 6) can be easily assembled and the device's cannula-sensor unit be inserted into the tissue without modification of its commercially available constituent parts. Furthermore, the device can be connected to a conventional insulin pump and used to perform glucose sensing and insulin delivery in an open-loop manner. Moreover, the device may also be used in combination with an algorithm to perform closed-loop glucose control (single-port AP; Fig. 1b, Fig. 11).

2. Development of the single-port device

2.1. Development methods

2.1.1. Candidate glucose sensing & insulin delivery components for the single-port device

The clinically useful state-of-the-art CGMs offered by Abbott, Dexcom and Medtronic [33]–[35] were considered as single-port device glucose sensing components. These CGMs track the glucose levels of the patients by measuring the glucose concentration in the interstitial fluid (ISF) of the subcutaneous tissue. They all consist of a subcutaneous needle-type sensor-probe which is secured in a plastic housing, a transmitter, and a receiver (Fig. 1c). Although the commercially available CGMs differ in shape, size, and insertion depth of the sensor-probe (5.5-14 mm), they share in common that the sensor-probe is inserted into the subcutaneous tissue with an applicator needle designed to protect it from the friction forces generated during insertion. Once inserted, the sensor-probe is operated with a transmitter which wirelessly sends the measured glucose concentration data to a receiver (Fig. 1c).

The commercially available insulin infusion sets with soft Teflon cannulas were considered as the insulin delivery component for the single-port device, since they are more commonly used than the infusion sets with steel cannulas [36]. Infusion sets with soft cannulas consist of a subcutaneous Teflon cannula secured in a plastic housing and a tube emerging from the cannula housing (Fig. 1c). The soft cannulas are designed for either slanted or straight insertion and come in different cannula lengths (6-17 mm) as well as different cannula diameters (28-27 gauge) [37]. To

insert them into the subcutaneous tissue an O-profiled steel needle housed inside the cannula is used (“over the needle insertion”). After insertion, the needle is withdrawn and the inserted cannula connected to an insulin pump.

2.1.2. Single-port design concepts

Following the detailed analysis of the commercially available devices, we introduced three design concepts of integrating a needle-type CGM sensor-probe with a soft infusion cannula (Fig. 1d). The first concept involves affixing the sensor-probe to the outer cannula wall. The second concept involves placing the sensor-probe into the cannula lumen so that the glucose sensitive probe tip protrudes from the cannula tip. The third concept involves placing the sensor-probe into the cannula housing so that the glucose sensitive probe tip resides in the cannula lumen. Unlike the first two concepts, this concept requires a push/pull-style pump which supports infusion and withdrawal. When in push mode, the pump facilitates insulin delivery by transporting the insulin solution to the subcutaneous tissue and, when in pull mode, it facilitates glucose sensing by transporting the ISF from the subcutaneous tissue to the glucose sensitive sensor-probe tip.

2.1.3. Building the single-port prototypes

Using commercially available CGMs and insulin infusion sets, we built several single-port device prototypes according to each concept. To build the prototypes, the CGM and the infusion set components were extracted in a laminar flow (HERAsave KS; Thermo Fisher Scientific, Massachusetts, USA) using scalpels, forceps, or scissors (Aesculap Surgical Instruments; B.Braun, Melsungen, GER), and subsequently integrated by press passing or gluing with biocompatible UV-curable glue (Vitralit-UV; Panacol-Elosol GmbH, Steinbach, GER). Prior to integrating the components, the infusion cannulas were adapted when necessary using an excimer laser (Laser Center Hanover, Hanover, GER) or a custom-made thermal embossing device which comprised a heating element from Hasco (Cartdrige Heater; Hasco Austria Ges.m.b.H, Guntramsdorf, AUT). Finally, if necessary, custom-made components were fabricated by CNC-machining polycarbonate (KBG Kunststoff-Bearbeitung s

Ges.m.b.H, Spielberg, AUT) and sterilized in an autoclave (Autoclave FVA-3; Fedegari Autoclavi SPA, Pavia, ITA) at high temperatures in pre-vacuum.

2.1.4. Criteria to select the optimal single-port prototype

In the development of the single-port device, we placed high priority on achieving low development costs, improved patient convenience, and high sensing accuracy during insulin delivery. We therefore introduced several criteria which reflect these priorities and desired performance characteristics. The best single-port device prototype was then selected according to these criteria. The used criteria were as follows:

2.1.4.1. Glucose sensor function when exposed to insulin solution:

By integrating a glucose sensor with an insulin infusion cannula (Fig.1d), the glucose sensor-probe may be exposed to the infused insulin solution during insulin delivery. Therefore, several in vitro experiments were performed to determine whether the candidate commercially available CGMs are affected by insulin or the phenol and metacresol preservatives [38] contained in the rapid-acting insulin formulations commonly used in insulin pump treatment (Aspart: 100 U/ml, Aspart; Novo Nordisk, Bagsvaerd, DNK or Lispro: 100 U/ml Lispro; Eli Lilly, Indianapolis, USA). For these experiments, each CGM sensor-probe was slid into one end of an infusion set tube, while the other end was connected to a syringe filled with an insulin solution spiked with glucose (10%, Glucosteril; Fresenius Kabi GmbH, Bad Homburg, GER). After attaching the syringe to a pump (Pico Plus Elite; Harvard Apparatus, Holliston, USA) and placing the infusion set tube in a thermoregulated box (37°C, Hotbox; Med. Universität Graz, Graz, AUT), the tube was perfused with the glucose-spiked insulin solution at a constant rate. Two sets of experiments were performed. In the first set of experiments, the stability of the sensors under long-term exposure was tested by continuously exposing the sensor-probes (for 12 h) to an insulin solution containing glucose at a concentration of 200 mg/dl. In the second set of experiments, the linearity and sensitivity of the sensors under exposure to the insulin solutions was tested by sequentially exposing the sensor-probes to insulin solutions containing glucose at concentrations of 100, 50, 200, and 0 mg/dl (each for 45 min).

When using the transmitters and receivers of the sensor manufacturers to perform these experiments, we noticed that the CGM software frequently misinterpreted the induced sudden changes in the glucose concentration (e.g., the change from 200 to 0 mg/dl) as sensor errors. The consequence of such “false” sensor errors was that the CGM receiver did not display and store the glucose values for up to two hours. To circumvent this problem of interrupted data logging, a potentiostat (PalmSens Handheld Potentiostat/ Galvanostat, Palm Instruments BV, Houten, NL; Fig. 2d) was used instead of the transmitters and receivers of the sensor manufacturers. This potentiostat was connected to the sensor electrodes via cable and custom-made contact plates (Fig. 2a-c). During the sequential exposure of the sensors to the glucose-containing solutions, the potentials applied to the sensors’ working- and counter electrode were maintained constant (0 mV for Abbott, 600 mV for Dexcom and 400 mV for Medtronic) and the sensor currents continuously recorded using a laptop connected to the potentiostat (Fig. 2d). In the beginning of the experiments, the recording of the sensor current was only started after the current signal had reached a steady state. At the end of the experiments, the recorded sensor currents were transformed into glucose concentrations. To this purpose, the slope and intercept of the sensor response curve were determined by first calculating the mean values of the current signal observed during each exposure period (e.g., Fig. 2e), and then regressing the obtained mean values against the glucose concentrations contained in the employed insulin solutions (e.g., Fig. 2f).

2.1.4.2. Degree of required component modification:

To keep the development costs low, the sensor-probe and the cannula should be integrated in the simplest possible way. The prototypes were therefore rated with respect to the degree of modification required to integrate the two components.

2.1.4.3. Feasibility of one-step device insertion:

To improve patient convenience, it is desirable to insert sensor and cannula of the single-port device in one step. Moreover, it would be advantageous to perform this one-step insertion with the existing CGM or cannula insertion instruments. Therefore, each prototype was rated depending on whether the design concept allows a one-step insertion with existing insertion instruments or a completely new insertion technique is needed.

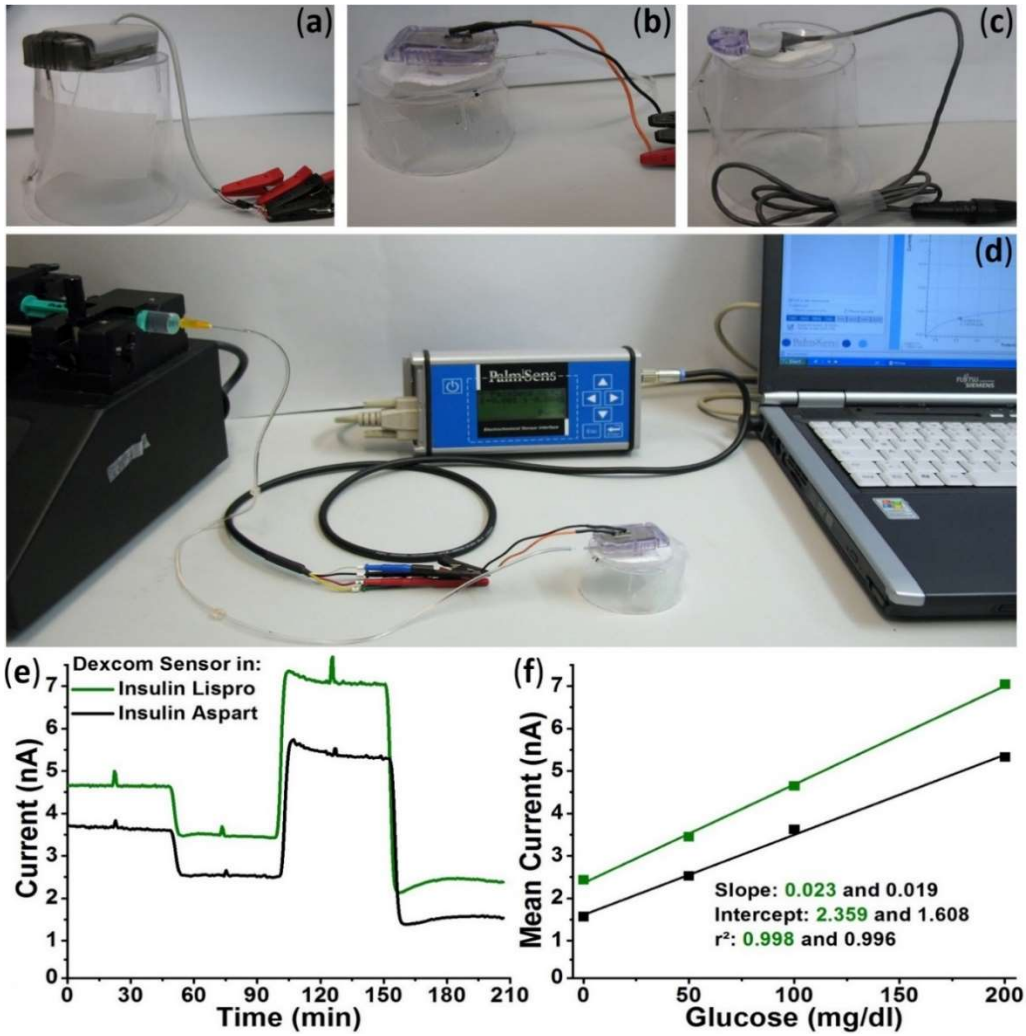

Fig. 2. *Operating the glucose sensors using a potentiostat: The sensors from Abbott* ***(a)****, Dexcom* ***(b)****, and Medtronic* ***(c)*** *were each connected to the potentiostat via cable and custom-made contact plates.* ***(d)*** *The potentiostat and a laptop PC were used to apply a constant potential difference between the working- and the counter electrode of the sensors, and to measure the resulting current while the sensor probes were exposed to different glucose-spiked insulin solutions.* ***(e)*** *Representative time courses of the current signal of a Dexcom sensor operated with the potentiostat.* ***(f)*** *Regression between the mean values of the current signal and the glucose levels of the insulin solutions. © 2019 IEEE*

2.1.4.4. Ease of obtaining reliable glucose measurements during insulin delivery:

As mentioned above, a CGM tracks the glucose levels of the patients by measuring the glucose concentration in the ISF. By performing glucose sensing and insulin infusion at the same tissue site, the infused insulin solution may temporarily dilute the ISF surrounding the glucose-sensitive sensor-probe tip, resulting in a temporary decline of the local glucose concentration [25] and in measurements that do not reflect the blood glucose concentration of the patient. The single-port prototypes were therefore rated regarding the ease of preventing glucose sensing in diluted ISF.

2.1.5. First clinical trial, performed to inform final device refinements

The objectives of this trial were to inform final refinements in device assembly, insertion, and sensor operation techniques.

2.1.5.1. Study subjects of the first clinical trial

Fifteen subjects were included in the study. They were of both sexes, in the age group of 18-65 years and diagnosed with type 1 diabetes. They had to have HbA1C values of <10%, and had to be treated with continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI). Subjects were excluded if they had evidence of clinically overt diabetic complications, or had plasma C-peptide levels >30pmol/l. Each subject signed a written consent form prior to any study-related procedures. The study was approved by the ethics committee of the Medical University of Graz and the Austrian Agency for Health and Food Safety.

2.1.5.2. Study protocol of the first clinical trial

The subjects were admitted to the clinical research center (CRC) at about 20:00. Subjects treated with MDI had been instructed to leave out the injection of long-acting insulin on the evening of the study. On admission to the CRC, subjects with CSII treatment were asked to disconnect their own insulin pump. At 20:30, an intravenous catheter was inserted into an arm vein for blood withdrawal during the night. After catheter insertion, the single-port device prototype was placed into the

subcutaneous adipose tissue as described in Figure 7. Next, a Dexcom sensor (G4 Platinum Sensor; Dexcom Inc., San Diego, CA, USA) was placed into the subcutaneous tissue at a distance >100 mm from the single-port device and used as a control sensor. Afterwards, the insulin infusion via the single-port device was started. The insulin infusion rate was adjusted on the basis of frequent plasma glucose measurements to slowly achieve and maintain normoglycemia overnight. Two hours after insertion, the single-port device sensor and the control sensor were calibrated against a plasma glucose value and the continuous glucose monitoring started. The plasma glucose concentrations were measured at the bedside using a laboratory instrument (Super GL 2; Dr. Müller Gerätebau GmbH, Freital, Germany). The subjects were asked to fast overnight. On the next day, at ~ 7:00, a hand or forearm vein was cannulated to allow blood withdrawal during the subsequent oral glucose tolerance test (OGTT) phase of the experiment. The forearm with this catheter (18-gauge) was then placed in a thermoregulated box (55°C) to arterialize the venous blood. At 9:00 the subjects the subjects ingested ~ 75 g glucose dissolved in 300 ml of water. Twenty minutes before glucose ingestion, an insulin bolus was administered via the single-port device. The amount of insulin administered as a bolus was determined by using medical records on the subject's insulin sensitivity factor (i.e., subject's insulin-to-carbohydrate ratio). After administration of the insulin bolus, the basal insulin delivery was continued and periodically adjusted so as to reestablish normal plasma. During the night period and during the 8-h OGTT phase, plasma glucose concentrations were determined every 5-30 min. If during experiments the plasma glucose levels decreased below 60 mg/dl, the subjects were asked to ingest additional glucose.

2.2. Development results

2.2.1. Selecting the optimal single-port prototype

Each single-port prototype was rated according to the criteria outlined in the material and methods section. The prototype with the highest score across all criteria was then selected for the human study.

2.2.1.1. Glucose sensor function is not impaired by contact with insulin

Prior to the integration of the sensors of the candidate CGMs with the candidate insulin infusion cannulas, it was tested whether exposure of the sensors to rapid-acting insulin solutions impairs the sensor function. Figure 3 shows the glucose concentrations obtained during continuous and sequential sensor exposure to glucose-spiked rapid-acting insulin solutions. As can be seen, during the continuous exposure, stable signals were observed over a 12-hour period for all three sensors (Fig. 3, right column). Furthermore, during the sequential exposure, each sensor signal attained steady-state values proportional to the glucose concentrations contained in the insulin solutions (Fig. 3, left column). Taken together, these results suggest that none of the glucose sensors was impaired when exposed to insulin itself or the preservatives contained in the insulin formulations. Therefore, the maximum rating was assigned to all single-port prototypes regardless of whether they are realized with a sensor from Abbott, Dexcom or Medtronic (Tab. 1).

2.2.1.2. Degree of required component modification varies among prototypes

The degree of component modification required to realize a certain prototype is depending on the chosen design concept (Fig. 1d). Representative prototypes built according to each of the three concepts are shown in Figure 4. As can be seen, realizing a prototype according to Concept A (Fig. 4a) requires extensive component modifications since affixing the sensor-probe to the outer cannula wall involves carving a grove into the cannula wall and gluing the sensor-probe into the grove. In contrast, realizing a Concept B prototype (Fig. 4b) requires almost no component modifications since the sensor-probe is simply inserted into the self-sealing septum

of the cannula housing and guided through the cannula lumen until it protrudes from the cannula tip. Similarly, Concept C prototypes (Fig. 4c) are also built by inserting a sensor-probe into the self-sealing septum of the cannula housing. However, here the sensor-probe is entirely placed inside the cannula lumen, making it necessary to perforate the cannula to aid transport of the ISF to the sensitive portion of the probe. Thus, Concept C prototypes still require more component modifications than Concept B prototypes. We therefore rated the single-port prototypes built applying design Concept C lower than those built applying Concept B, but higher than those built applying design Concept A (Tab. 1).

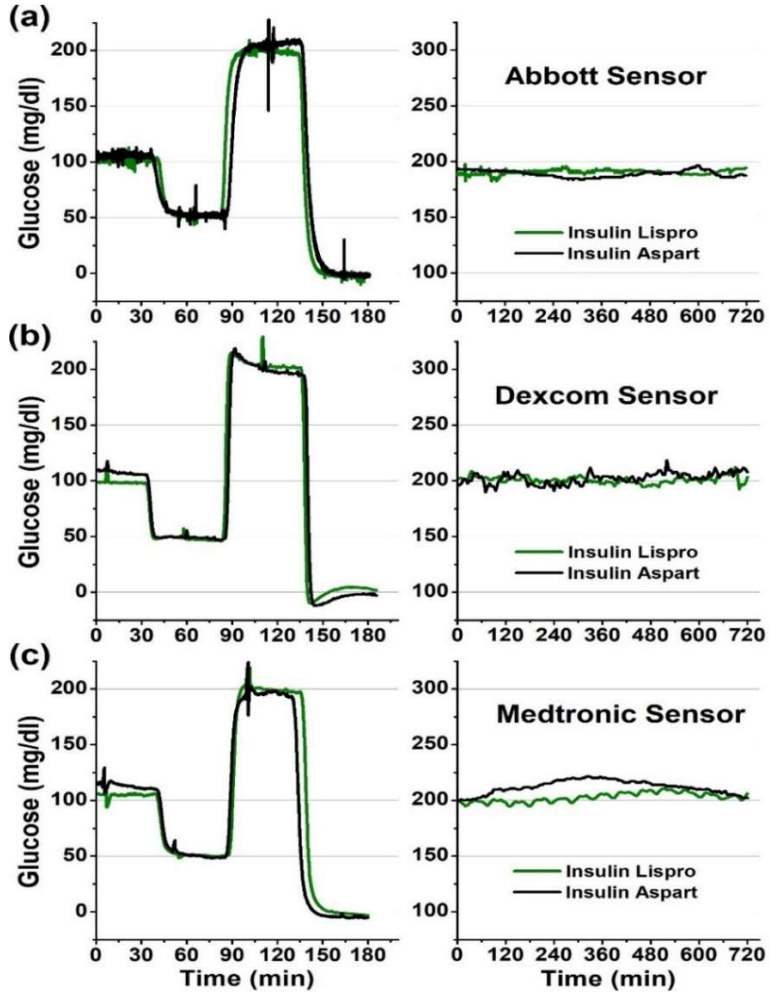

Fig. 3. *Glucose concentration time courses obtained during exposing the sensors from* ***(a)*** *Abbott,* ***(b)*** *Dexcom and* ***(c)*** *Medtronic to rapid-acting insulin solutions (Lispro and Aspart) spiked with glucose. The left column shows the time courses obtained during sensor exposure to a sequence of insulin solutions containing glucose at concentrations of 100, 50, 200, and 0 mg/dl, whereas the right column depicts the time courses obtained during continuous sensor exposure to insulin solutions containing glucose at a concentration of 200 mg/dl.*

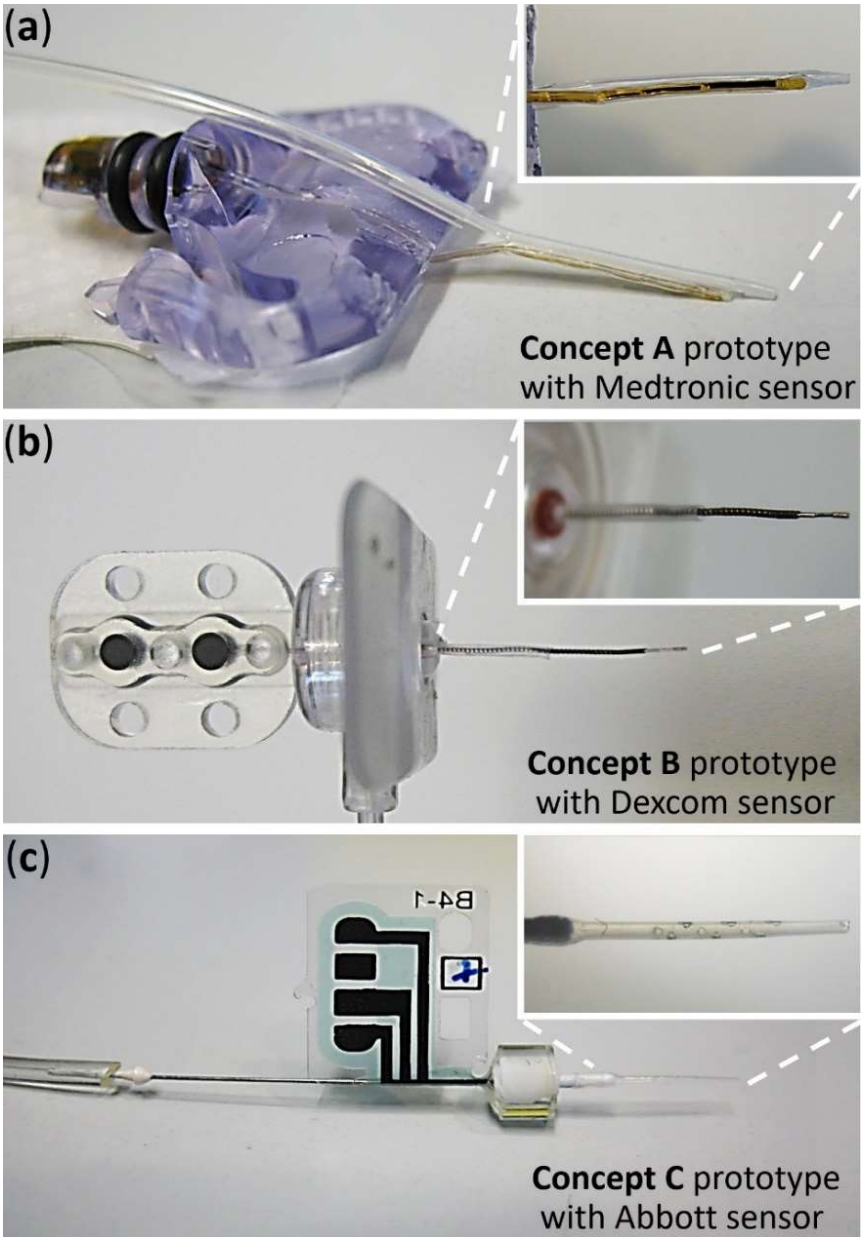

Fig. 4. *Representative single-port prototypes built using each design concept:* ***(a)*** *A Concept A prototype with the Medtronic CGM sensor-probe affixed to the outer cannula wall. To affix the probe, a groove was carved in the outer cannula wall and the probe was glued into the carved groove.* ***(b)*** *A Concept B prototype with a Dexcom CGM sensor-probe protruding from the cannula tip. To house the sensor-probe inside the cannula so that its glucose sensitive tip protrudes from the cannula tip, the probe was inserted into the self-sealing septum of the cannula housing and guided through the cannula lumen until it protruded from the cannula tip.* ***(c)*** *A Concept C prototype with an Abbott CGM sensor-probe residing in the cannula lumen. To house the entire sensor-probe inside the cannula, the probe was inserted into the self-sealing septum of the cannula housing and placed inside the cannula lumen. Prior to placing the sensor-probe inside the cannula, the cannula was perforated with a laser to aid transport of the ISF to the sensor-probe.*

2.2.1.3. One-step device insertion is feasible for certain prototypes

Basically all three concepts may allow a one-step insertion with an existing insertion instrument. For example, similar to an infusion cannula, Concept A prototypes (Fig. 1d) can be inserted using a cannula insertion needle. This cannula insertion needle resides in the lumen of the single-port cannula that has the sensor-probe affixed to its outer wall. When inserting the needle into the tissue, cannula and sensor-probe of the prototype are then following the needle through the same perforation. However, during this insertion process, the sensor-probe is directly exposed to friction forces which may then cause damage to it. Thus, protecting the sensor-probe against the friction forces generated during the insertion process would require further design refinements, such as creating an additional lumen for the probe, which would result in increased development and manufacturing costs. In contrast, when the sensor-probe and cannula are integrated applying design Concept B or C, no further design refinement is necessary to protect the sensor since here the one-step insertion can be carried out using the sensor-containing applicator needle. To insert such a single-port device the cannula insertion needle is first replaced by the sensor applicator needle (Fig. 5a,b). Then, the applicator needle is guided into the tissue with the cannula following the needle through the same perforation. However, the cannula insertion needle can only be replaced by the sensor applicator needle if they are the same size and shape. So far, all commercially available insulin infusion sets come with an O-shaped insertion needle. However, among the commercially available CGMs, only the Dexcom CGM comes with an O-shaped sensor applicator needle. Applicator needles from the other CGM manufacturers (Abbott and Medtronic) are either V- or C-shaped. When comparing the O-shaped sensor applicator needle from Dexcom with insertion needles of commercial infusion cannulas, we found that the Dexcom applicator needle perfectly matches the cannula insertion needle of a Medtronic infusion set (Sof-Set Micro QR, cannula length: 6 mm, tube length: 610 mm; Medtronic MiniMed, Northridge, CA, USA) and thus can be used to replace it (Fig. 4a,b,c). In view of these considerations, we rated prototypes with design Concepts B and C higher than those with design Concept A as they require no additional design modifications to protect the sensor-probe during insertion.

Furthermore, since only the O-shaped sensor applicator needle from Dexcom can be used for the one-step insertion, we rated Concept B and C prototypes realized with a Dexcom CGM higher than those realized with Abbott or Medtronic CGMs (Tab. 1).

2.2.1.4. Bringing the sensor in contact with ISF not diluted by insulin solution is possible

To measure the glucose concentration correctly, the sensor of the single-port device has to be in contact with ISF that is not diluted by the infused insulin solution. To avoid measuring the glucose concentration in diluted ISF, the sensitive probe tip and the cannula tip of Concept A or B prototypes were positioned at the maximum possible distance from each other. In Concept A prototypes, this was achieved by integrating a long cannula and a short sensor-probe, while in Concept B prototypes the maximum distance between the two was ensured by integrating a short cannula and a long sensor-probe, like the one from Dexcom (Fig. 5d). In contrast, since in Concept C prototypes the sensor is located inside the cannula, bringing the sensitive probe tip of these prototypes in contact with undiluted ISF requires switching the insulin pump to the withdrawal mode and operating it in this mode until the fluid surrounding the probe tip is free of insulin. However, the current insulin pumps would first have to be adapted to allow bidirectional flow, thus employing concept C would render a single-port device more costly than employing one of the other two concepts. Consequently, Concept A and B prototypes were rated higher than Concept C prototypes since they do not require a push/pull-style pump to obtain reliable glucose measurements. In Concept A and B prototypes, however, a long distance between the sensitive probe tip and the cannula tip is required to avoid measuring in diluted ISF. While this can be achieved with all sensor-probes in Concept A prototypes, Concept B prototypes can only be realized with the long sensor-probe from Dexcom. Therefore, only the Concept B prototypes with a Dexcom CGM scored equally high as the Concept A prototypes (Tab. 1).

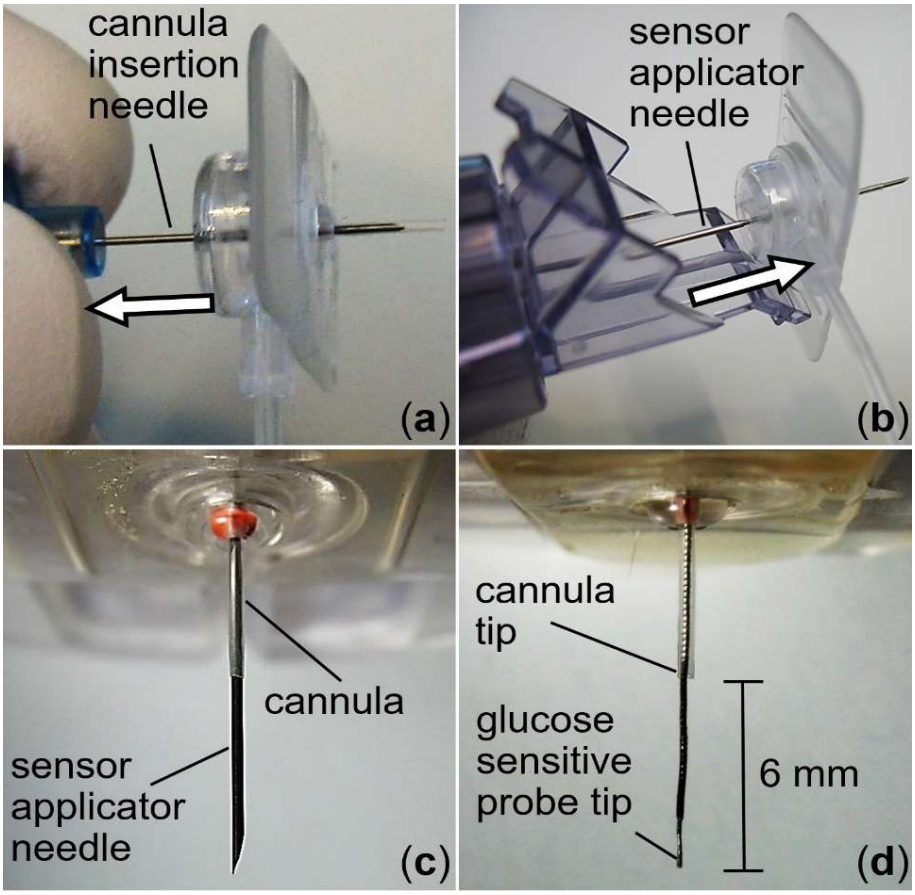

Fig. 5. *Achieving the maximum distance between the sensor-probe tip and the cannula tip in a Concept B prototype:* ***(a)*** *The Medtronic cannula insertion needle is removed from the cannula lumen.* ***(b)*** *The Dexcom applicator needle is inserted through the self-sealing septum of the cannula housing,* ***(c)*** *and placed in the cannula lumen so that it protrudes from the cannula tip.* ***(d)*** *Following insertion, the sensor-probe tip is positioned at the maximum distance from the cannula tip. © 2019 IEEE*

2.2.1.5. The single-port prototype evaluation summary

Table 1 summarizes the rating of the single-port prototypes. For each of the established selection criteria, points were assigned to the prototypes: 2 for good, 1 for fair, and 0 for poor. With a sum of 8 points across all criteria a Concept B prototype built using the Dexcom sensor and the Medtronic infusion cannula was found to be the most suitable single-port prototype. This prototype is described in more detail below.

Table 1 The single-port concept evaluation summary*.

Selection Criteria	Concept A			Concept B			Concept C		
	ABB	**DEX**	**MED**	**ABB**	**DEX**	**MED**	**ABB**	**DEX**	**MED**
Glucose sensor function when exposed to insulin solution	2	2	2	2	2	2	2	2	2
Degree of required component modification	0	0	0	2	2	2	1	1	1
Feasibility of one-step device insertion	0	0	0	1	2	1	1	2	1
Ease of obtaining reliable glucose measurements during insulin delivery	2	2	2	1	2	1	0	0	0
Total	4	4	4	6	8	6	4	5	4

*ABB = Abbott; DEX = Dexcom; MED = Medtronic

2.2.2. The final single-port prototype

The selected single-port prototype consists of a Dexcom G4-Platinum CGM (G4-Platinum, Dexcom Inc., San Diego, USA; Fig. 6a), a Medtronic Sof-Set insulin infusion set (Sof-Set Micro QR, cannula length: 6 mm, tube length: 610 mm; Medtronic MiniMed, Northridge, CA, USA; Fig. 6b), and a custom-made transition piece (CNC-machined from polycarbonate; 4A engineering GmbH, Traboch, Austria; Fig. 6c). The sensor-probe of the Dexcom CGM is positioned inside the cannula of the Medtronic infusion set in such a way that the glucose sensitive probe tip protrudes 6 mm from the cannula tip (Fig. 6 e-f). The transition piece is used to mount the G4 sensor housing onto the top of the cannula, and to provide a secure attachment of the prototype to the patient's skin (Fig. 6d). Cannula and sensor of the prototype can be inserted in one step with a Dexcom sensor applicator (Fig. 7b). Furthermore, a conventional insulin pump can be used to deliver insulin via the single-port prototype (Fig. 6d)

2.2.2.1. Assembling and inserting the final single-port prototype:

The assembly of the single-port prototype is performed in a laminar flow hood under sterile conditions prior to each experiment. First, the cannula insertion needle of the Medtronic Sof-Set is removed and the cannula housing pressed into the custom-made transition piece (Fig. 7a). Next, an insulin pump (Animas-Vibe Insulin Pump; Animas Corp., West Chester, USA) is connected to the infusion set and the tube filled with a glucose-spiked insulin solution. After the two are connected, the sensor housing of the Dexcom CGM is removed from the sensor applicator and the sensor-containing applicator needle inserted through the self-sealing septum of the cannula housing and guided through the cannula until it extends 6 mm beyond the cannula tip (Fig. 7b). The thus assembled single-port device is then inserted into the subcutaneous tissue in one step (Fig. 7c). After the applicator needle has been removed, the Dexcom transmitter is connected to the sensor-probe, making the single-port device ready for use.

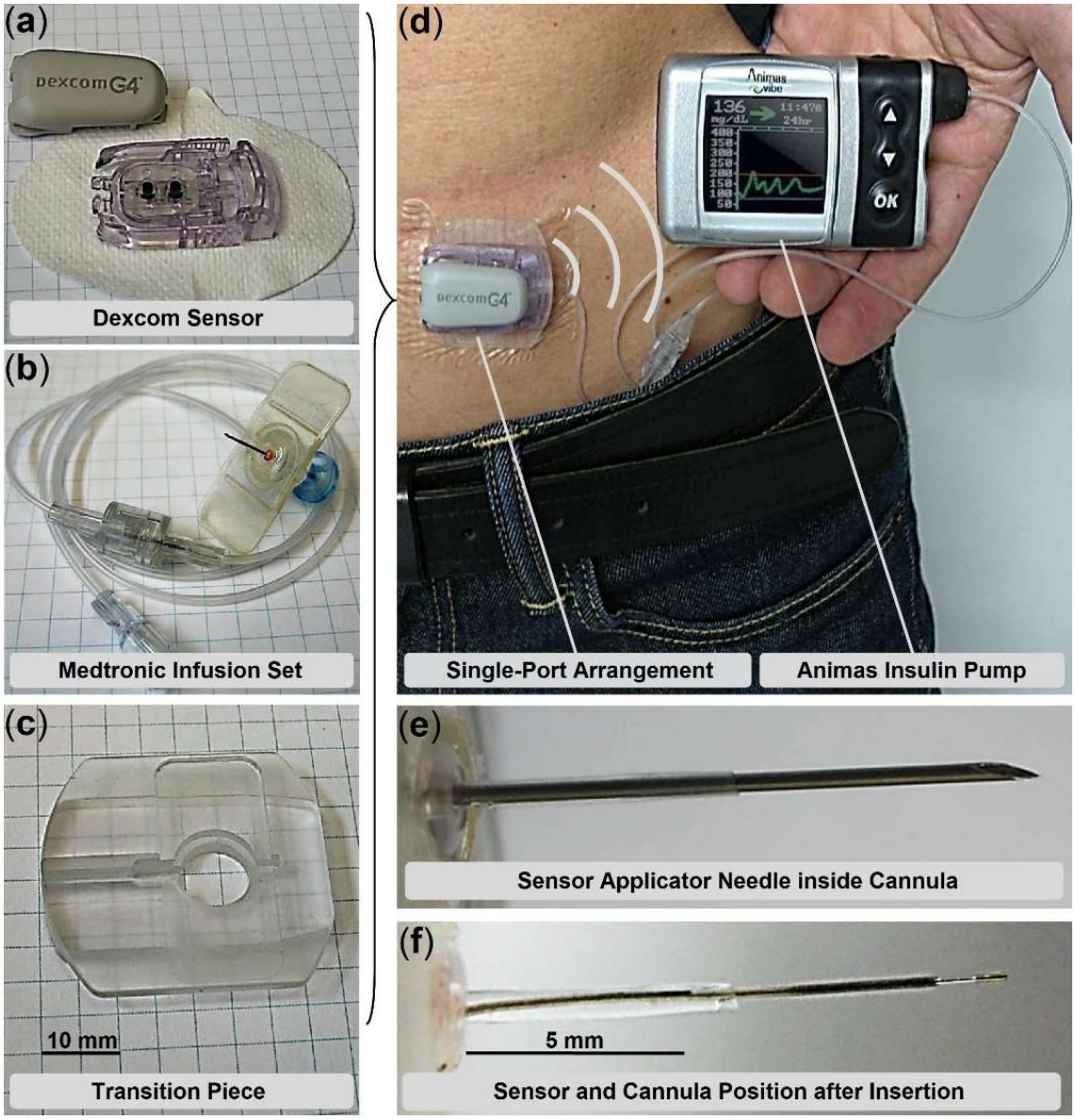

Fig. 6. *Final single-port prototype: The prototype consists of a commercial glucose sensor from Dexcom (Dexcom G4 Platinum Sensor; Dexcom Inc., San Diego, CA, USA)* ***(a)****, a commercial insulin infusion cannula from Medtronic (cannula length: 6 mm, tube length: 610 mm, SOF-Set Micro QR; Medtronic MiniMed, Northridge, CA, USA)* ***(b)****, and a custom–made transition piece (CNC-machined from polycarbonate; 4A engineering GmbH, Traboch, Austria)* ***(c)****. Since the applied infusion cannula from Medtronic exactly fits the introducer needle of the sensor applicator from Dexcom* ***(e)****, it is possible to use the applicator to simultaneously insert cannula and sensor into the subcutaneous tissue of the subjects. When inserted, the glucose-sensitive sensor portion extends about 6 mm beyond the cannula end* ***(f)****. Following insertion, the sensor is connected with a transmitter from Dexcom and the infusion cannula connected to an insulin pump from Animas via an infusion set tube from Medtronic* ***(d)****. The pump delivers the insulin and displays the measured glucose values. © 2019 IEEE*

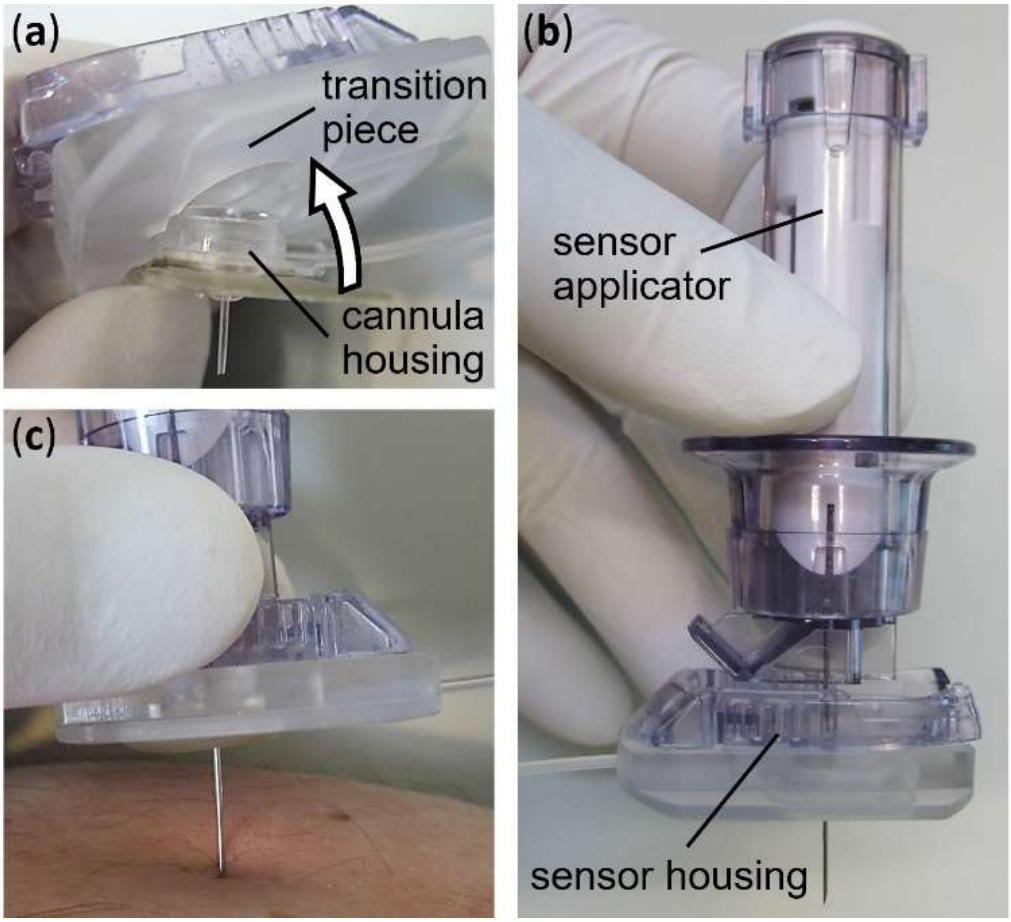

Fig. 7. *Assembling and inserting the final single-port prototype:* ***(a)*** *The Dexcom CGM housing is mounted onto the Medtronic infusion cannula housing using a custom-made transition piece.* ***(b)*** *The Dexcom sensor applicator needle is inserted through the cannula housing septum and guided through the cannula until it extends 6 mm beyond the cannula tip.* ***(c)*** *The assembled single-port device is inserted into the subcutaneous tissue in one step.* ***(d)*** *After the applicator needle is removed, the Dexcom CGM transmitter is connected to the sensor-probe, making the single-port device ready for use. © 2019 IEEE*

2.2.2.2. Connecting the transmitter to the sensor-probe of the prototype

In our final prototype, the sensor-probe of the Dexcom CGM is positioned inside the cannula of the Medtronic infusion set in such a way that the glucose sensitive probe tip protrudes 6 mm from the cannula tip (Fig. 6f). After the insertion of cannula and sensor of the single-port device and the removal of the applicator needle, the free probe end extends 6.5 mm from the septum of the cannula housing into the air (Fig. 8a). Since this length is too short to connect the sensor probe with the Dexcom Transmitter in the usual way, we devised a novel method to connect the two. The

method involves the following steps: First, the Dexcom CGM contact plate is pierced (Fig. 8b,c) with a sterile hypodermic needle (Medoject 0.5 x 25 mm; Chirana T. Injecta, Stará Turá, SVK). Then, the needle is passed over the free probe end (Fig. 8d) until the plate contacts (the black cylinders) are aligned with the sensor-probe electrodes. In the next step the needle is removed, while the contact plate is held in place (Fig. 8e). Finally, the Dexcom transmitter is connected to the sensor-probe by pressing it into the sensor housing (Fig. 8f).

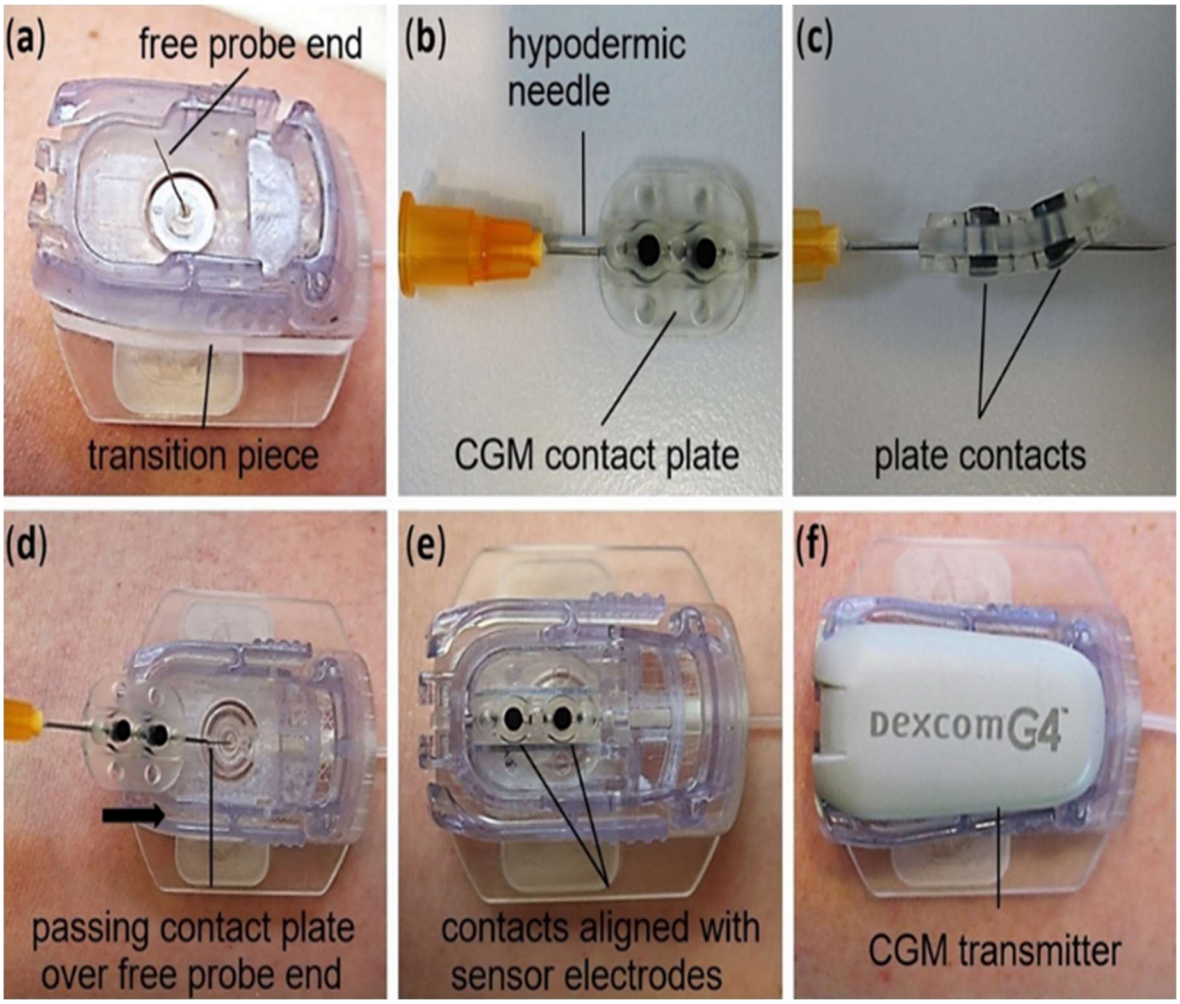

Fig. 8. *Devised method of connecting the sensor-probe of the single-port device to the Dexcom transmitter: After inserting cannula and sensor of the single-port device, the free probe end extends 6.5 mm from the septum of the cannula housing* ***(a)****. To connect this short probe end with the transmitter, the CGM contact plate is pierced with a hypodermic needle* ***(b-c)****, which is then passed over the free probe end until its contacts are aligned with the electrodes of the sensor-probe* ***(d)****. Following needle removal (e) the transmitter is connected to the sensor by pressing it into the sensor housing* ***(f)****. © 2019 IEEE*

2.2.3. Results from the first clinical trial

2.2.3.1. Avoiding "false" sensor errors during bolus insulin delivery:

During our first in vivo study with the single-port device, we found that when insulin is administered at a high infusion rate (bolus delivery), it may dilute the ISF surrounding the glucose sensitive probe tip even when the probe tip is positioned at the maximum distance from the cannula tip (Fig. 5d). Usually it takes only about 15 min until the insulin fluid has been absorbed and the ISF is again undiluted. However, the sudden drop in the glucose concentration that results from the ISF being diluted can be misinterpreted as sensor error by the CGM software.

The consequence of such "false" sensor errors is that the glucose values are not being displayed by the CGM receiver for up to two hours (Fig. 9a, white lines). The simplest way to avoid these "false" sensor errors involves instructing the CGM software to ignore the glucose sensor signal for about 15 minutes after an insulin bolus has been delivered. However, since we had no access to the source code of the CGM device, we initially avoided potential sensor errors by using the extended instead of the normal bolus delivery mode of the Animas insulin pump (Fig. 6d). In the extended bolus mode, the bolus delivery duration is increased but the insulin infusion rate decreased [3], [4]. Insulin delivered at this decreased rate did not dilute the ISF surrounding the glucose sensitive probe tip, thus no "false" sensor errors occurred (Fig. 9b). However, the extended bolus comes at a price of slower insulin absorption and consequently delays the re-establishment of the patients' normal blood glucose concentration. Therefore, we continued with using the regular bolus, but prevented the sudden drops in the ISF glucose concentration that caused "false" sensor errors by adding a small amount of glucose (200 mg/dl; a concentration typically measured in diabetes patients) to the administered insulin solutions. Now when a bolus was delivered, and the ISF got diluted for a short time, the glucose concentration measured by the sensor never dropped to zero and "false" sensor errors were prevented (Fig. 9c).

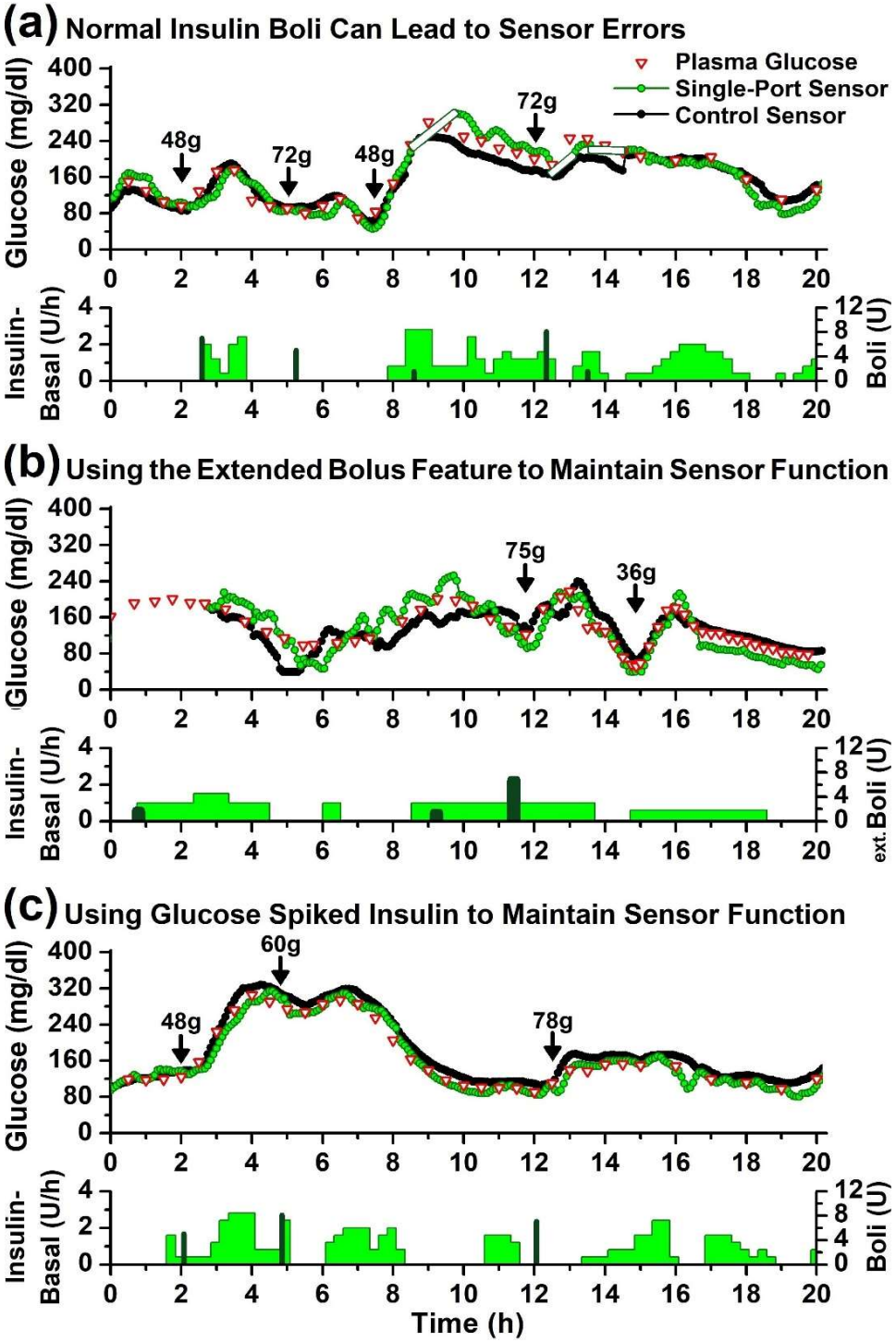

Fig. 9. *Avoidance of "false" sensor errors during bolus delivery: Shown are the glucose concentration time courses obtained with the single-port device (green dots), the glucose concentration time courses obtained with the control CGM (black dots), the reference blood glucose concentrations (red triangles), the carbohydrate intake (black arrows), the basal insulin infusion rates (green bars), and the delivered insulin boli amounts (dark green bars).* ***(a)*** *The occasional sensor error (white lines) that may occur following normal bolus delivery can be prevented* ***(b)*** *by using the extended bolus mode or* ***(c)*** *by spiking the infused insulin with small amounts of glucose. © 2019 IEEE*

3. Evaluation of the single-port device

3.1. Evaluation methods

3.1.1. Second clinical trial, performed to test efficiency and safety of the developed single-port device

The objectives of this trial were to ascertain the accuracy of the glucose sensing with the developed single-port device and to assess the feasibility of the single-port device, when combined with an algorithm, to automatically control the blood glucose in diabetes patients.

3.1.1.1. Study subjects

Ten subjects were included in the study. They were of both sexes, in the age group of 18 – 65 years and diagnosed with type 1 diabetes. They had to have HbA1C values of <10%, and had to be treated with continuous subcutaneous insulin infusion. Subjects were excluded if they had evidence of clinically overt diabetic complications, or had plasma C-peptide levels >30pmol/l. Each subject signed a written consent form prior to any study-related procedures. The study was approved by the ethics committee of the Medical University of Graz and the Austrian Agency for Health and Food Safety (Clinical Trials registration no. NCT02359617).

3.1.1.2. Study protocol

Eligible subjects were studied over a period of up to 7 days (Fig. 10). On study day 1, subjects were admitted to the CRC in the morning at 08:00. Upon arrival, the single-port device was assembled in a laminar flow under sterile conditions and the sensor-cannula unit of the single-port device placed into the subject's subcutaneous tissue in a standardized fashion (Fig. 7). Following insertion, the single-port device was fixed to the skin using a hypoallergenic adhesive tape (i.e., the one included in the SOF-Set Micro QR; Medtronic MiniMed, Northridge, CA, USA). After fixating the device to the skin, a Dexcom sensor (G4 Platinum Sensor; Dexcom Inc., San Diego, CA, USA) was placed into the subcutaneous abdominal tissue at a distance >100

mm from the single-port device and used as a control sensor. Afterwards, the Animas pump connected to the single-port device (Fig. 6d) was programmed with the same basal insulin infusion profile that had been used by the subject prior to the study period. The subject's own insulin pump was then removed and the insulin infusion via the single-port device started. Subsequently, transmitters (G4 Transmitter Kit; Dexcom Inc.) were attached to the single-port and control sensor. To display and store the sensor readings, the transmitter connected to the single-port sensor was paired to the receiver on the Animas pump (Fig. 6d), and the transmitter attached to the control sensor was paired with a handheld receiver (G4 Receiver Kit-mg/dl; Dexcom Inc.). Following a 2-h run-in period, both sensors were calibrated and the continuous glucose monitoring started. Calibration of the sensors was performed using capillary blood glucose measurements obtained with a blood glucose meter (FreeStyle Freedom Lite; Abbott Diabetes Care, Alameda, CA, USA). During the sensor run-in period, the subjects were trained in handling of the treatment devices. At ~12:30, the subjects received a standard meal (60g carbohydrates). Shortly before the meal, an insulin bolus was administered via the infusion cannula of the single-port device using the Animas pump. The size of the insulin bolus administered was calculated using medical records on each subject's insulin-to-carbohydrate ratio. At ~14:00, the subjects were allowed to leave the CRC. In the evening of study day 1 and during study day 2, the subjects were encouraged to continue their usual activities in their home/work environment and continue with their usual diabetes treatment, but to use the single-port device to administer insulin. In addition, they were asked to perform at least 7 blood glucose measurements per day using the Abbott glucose meter and to keep a written diary containing the estimated carbohydrate intake, the insulin bolus amounts, results of the blood glucose measurements as well as the time of meals, bolus administrations, and glucose measurements.

On study day 3 (Fig. 10), at ~0700, the subjects were admitted to the CRC for performing closed-loop insulin delivery. Upon arrival, a catheter (20-gauge, Vasofix® Safety; B. Braun, Melsungen, Germany) was inserted into a vein of the subject's forearm for blood sampling. The forearm with the sampling catheter was then placed under a heating blanked (P10; Beurer GmbH, Ulm, Germany) and maintained at ~55°C to ensure arterialization of the venous blood. Blood samples were taken every

10–30 min during day time and every 20–60 min during night. To assure consistency in the performance comparison between the single-port device and control sensor, finger capillary punctures were additionally performed for determining the blood glucose concentrations using the Abbott glucose meter. After insertion of the blood sampling catheter, the AP@Home closed-loop platform was connected to the single-port device as described in Figure 11. Closed-loop glucose control was then commenced at 09:30 and continued until the morning of the next day. During the study day, the subjects were given breakfast (50g carbohydrates) at 10:00, lunch (60g carbohydrates) at 13:00, snack (20g carbohydrates) at 16:00, and dinner (80g carbohydrates) at 20:00. An insulin bolus was administered manually via the single-port device cannula before each meal, with the exception of the snack at 16:00, where insulin was delivered automatically. In the afternoon, the subjects were encouraged to mimic their usual day such as to work on a computer, watch television or to walk inside the hospital premises. On the next morning, at 07:30, a breakfast (50g carbohydrates) was given accompanied by a manually administered prandial insulin bolus. Following breakfast, the closed-loop platform was disconnected and the Animas pump reconnected to the single-port device. Afterwards, the subjects were allowed to go home. On the study days 4 to 7 (Fig. 10), the subjects continued with the use of the single-port device in their home/work environment. In addition, subjects were asked to report daily whether they experienced an infection at the sensor/cannula insertion site, whether they experienced uncorrectable hyperglycemia or whether they observed a significant difference between the amount of administered insulin and the amount of insulin usually needed to keep their blood glucose concentration normal. After study day 7, or when an insertion site infection or a blood glucose deterioration occurred, or when a significant increase in the amount of insulin above the amount usually needed was observed, the subjects removed the single-port device and continued the treatment using their own insulin pump. The subjects were asked to come to the CRC on the subsequent day, where all study-related equipment was collected and a final physical examination performed.

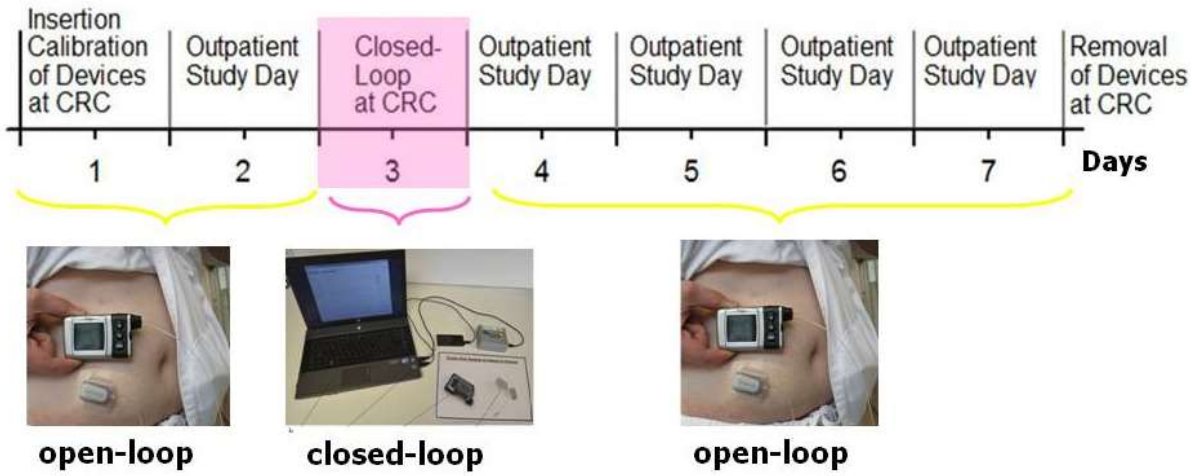

Fig. 10. *Timeline of the second clinical trial: The study protocol involved the use of the single-port device in an open-loop manner at the patient's home (up to 6 days) and, together with the AP@home closed-loop platform, in a closed-loop fashion at the CRC (day 3).*

3.1.1.3. Analytical procedures

The plasma glucose concentrations were measured at the CRC by the glucose oxidase method on a bench-top laboratory analyzer (Super GL 2; Dr. Müller Gerätebau GmbH, Freital, Germany) with a coefficient of variation of <2%. In order to maintain the function of the single-port device sensor during insulin bolus delivery (see Fig. 9), the insulin solution was spiked with small amounts of a 20%-glucose solution (20% Glucosteril; Fresenius Kabi, Bad Homburg, Germany) to obtain a glucose concentration of approximately 200 mg/dl. The plasma C-peptide concentrations were determined by a two-site sandwich chemiluminescent immunoassay using an ADVIA Centaur platform (Siemens AG, Erlangen, Germany) with a lower limit of quantification of 20 pmol/l. HbA1C was measured by high-performance liquid chromatography (HA-8160; Menarini Diagnostics, Florence, Italy).

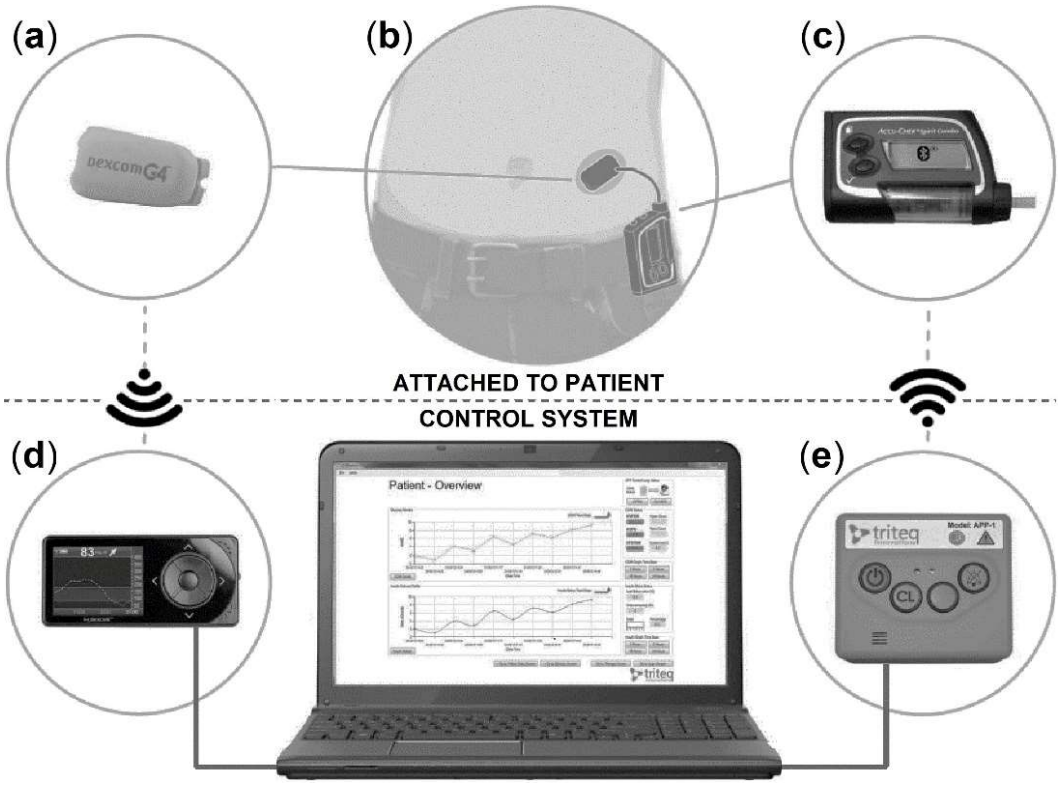

Fig. 11. *Closed-loop glucose control with the single-port device: To utilize the single-port device* ***(b)*** *for closed-loop insulin delivery, it was connected to the AP@Home closed-loop platform. This platform is comprised of a control unit (App-1 Unit; Triteq, Hungerford, UK) running a model predictive control (MPC)-based algorithm (Cambridge University Algorithm; University of Cambridge, Cambridge, UK)* ***(e)*** *and a data acquisition and processing software running on a laptop pc. The control unit is capable of receiving the glucose readings from a Dexcom receiver kit* ***(d)****, and controlling the insulin infusion rate of an insulin pump from Roche (Accu-Chek Spirit Combo; Roche Diabetes Care, Burgdorf, Switzerland)* ***(c)****. On the closed-loop study day at the CRC, the Animas pump, which was previously used for open-loop insulin delivery, was replaced by the insulin pump from Roche* ***(b–c)****, and the Dexcom receiver* ***(d)*** *was set to receive the glucose readings from the transmitter attached to the single-port device sensor* ***(a, b)****. Based on the glucose readings received from the single-port device, the control unit determined the basal insulin infusion rates and set them automatically on the Roche pump* ***(c–e)****. Insulin boli were administered manually prior to each meal. Each time, the information of the bolus dose, the time of the bolus delivery, the time of the meal ingestion, and the carbohydrate content of the meal was provided to the control unit running the algorithm. Additionally, the control unit was initialized with the subject's weight, age, total insulin dose, and the basal insulin infusion profile previously used by the subject.*

3.1.1.4. Data analysis

The agreement between the glucose concentrations obtained with single-port device and control sensor and that determined with the glucose meter from Abbott was assessed for each subject by using the median and mean absolute relative difference (ARD), as well as the precision absolute relative difference (PARD) and applying the correlation and error grid analysis and the method of residuals [40]–[43]. The median ARD (medARD) and mean ARD (MARD) were calculated as the average (median or mean) of the absolute value of the percentage difference between each paired sensor and glucose meter reading, with the glucose meter reading as the reference. Correlation analysis was performed using Pearson's product-momentum correlation coefficient (CC). The PARD was calculated as the mean (or median) of the absolute value of the percentage difference between a single-port device sensor reading and the time-matched control sensor reading, with the mean of the two sensor readings as the reference [43]. When calculating the MARD, medARD and CC only a small portion of the glucose sensor data was used (i.e., the sensor readings for which corresponding blood glucose meter readings were available). In order to examine if this portion of sensor data used to calculate such agreement indexes was representative for the whole set of sensor data, PARD values were calculated for those sensor readings for which corresponding blood glucose meter readings were obtained (PARDREF) and for those for which no corresponding blood glucose readings were available (PARDnoREF). To assess the feasibility of closed-loop insulin delivery with the single-port device, the proportion of time, that the glucose level – as measured by the single-port device sensor – is in the target range of 70 – 140.0 mg/dl (TTR), was determined both for the closed-loop insulin delivery period at the CRC and for the open-loop insulin delivery period in the patients' home environment. To determine the accuracy and precision of the glucose meter used by the patients for performing capillary blood glucose measurements (Abbott FreeStyle Freedom Lite), venous blood samples (n = 69) were additionally analyzed on the glucose meter, and the results were compared with plasma glucose concentrations obtained with the laboratory instrument used at the CRC. The MARD, medARD, residual mean and residual 2SD values obtained for the glucose meter were 5.1%, 4.0%, -3.3%, and 11.8%, respectively.

The ARD, CC, PARD and TTR data as well as the agreement index data obtained from the application of the method of residuals and error grid analysis were examined with the Wilcoxon´s signed-rank test and the paired Student's t test. A P value below 0.05 was considered to indicate statistically significant differences. The analysis of the data was performed using an OriginLab software package (Version 8.5; OriginLab Corp. Northampton, MA, USA).

3.2. Evaluation results

3.2.1. Subject characteristics

Eleven subjects were invited to take part in the study. One patient was excluded due to a screening error (HbA1C >10%). The ten subjects completing the study (3 females and 7 males) had an average age of 32.8 ± 10.9 years (mean ± SD; range 21 – 54 years) and an average BMI of 25.2 ± 2.7 kg/m2, (range 21.4 – 29.4). Their mean duration of diabetes was 22 ± 9.2 years (range 5 – 36) and their percent HbA1C averaged 8.0 ± 0.8% (63.8 ± 8.6 mmol/mol) [range 6.6 – 9.0% (49 – 75 mmol/mol), normal range 4.3 – 5.9% (23.5 – 41.0 mmol/mol)].

3.2.2. Insertion and wear time of the single-port device

The time taken to perform the assembling and subcutaneous insertion of the single-port device (Fig. 7) was 15–20 min. Insertion of the single-port device was successful on the first attempt in each of the ten subjects. Similarly, there were no failed attempts at inserting the control sensor. Furthermore, after inserting the single-port device and control sensor, in no one of the subjects did any sensor failure occur. Five of the ten studied subjects wore the single-port device for the full seven days, another four for six days, and one subject wore the device for five days. Overall, the mean wear time of the device was 6.4 days (Fig. 12). The reason for study termination prior to day 7 was, in each case, the increase in the amount of insulin above the amount usually needed to keep the blood glucose concentration normal.

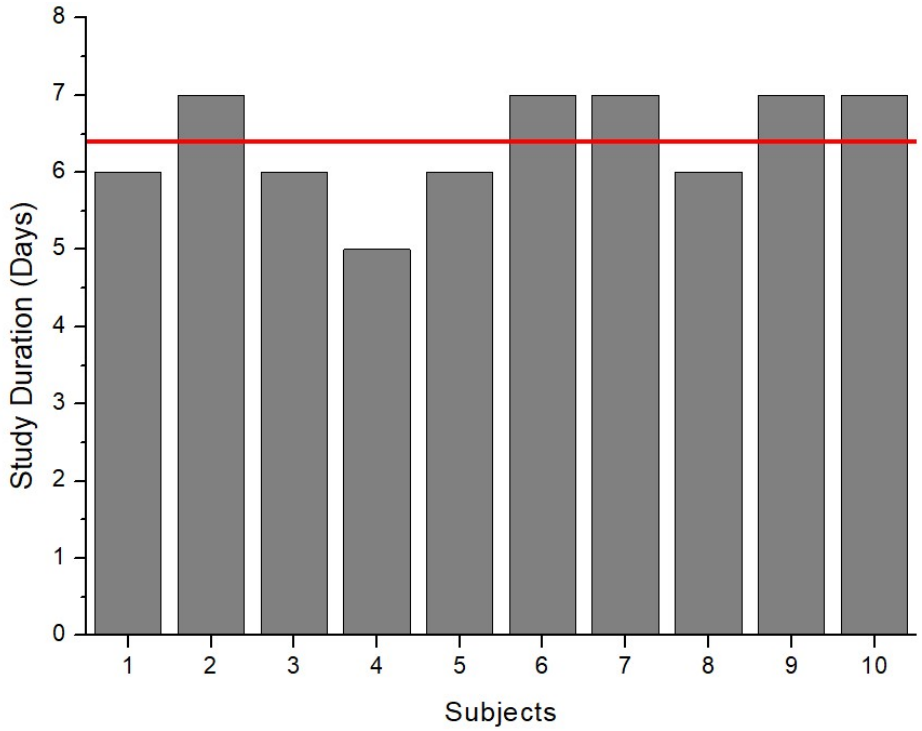

Fig. 12. *Wear time of the single-port device: Shown are the individual wear times of the single-port device for each subject (grey bars), and the overall mean wear time of 6.4 days (red line).*

3.2.3. Glucose monitoring with the single-port device

The glucose concentration time courses obtained with the single-port sensor were similar to those measured with the control sensor. In addition, the glucose concentrations obtained with the two sensors agreed well with the blood glucose levels determined with the blood glucose meter. Time courses of the sensor and blood glucose concentration as well as insulin infusion rate from a representative subject are shown in Figure 13 (data for all subjects are given in Fig. S1 of the Supplementary Material). For each, the single-port device sensor as well as the control sensor, 632 paired sensor and blood glucose values were obtained from the experiments. Error grid and residual plots for all collected data pairs are shown in Fig. 14a,b and Fig. 14c,d. Agreement indexes obtained for each individual subject from the application of the error grid analysis and method of residuals are given in Tables 2 and 3. Error grid analysis indicated that the average percentage number of sensor readings that fall into the clinically acceptable range (zones A and B) is high for the single-port device (median: 98.2%; interquartile range: 97.7 – 98.9%) and

comparable to that obtained for the control sensor (vs. 97.6%; 96.4 – 98.8%; P=0.063 with Wilcoxon signed rank test). Furthermore, applying the method of residuals, the average residual 2 SD obtained for the single-port device (37.3%; 29.2 – 47.2%) was similar to that calculated for the control sensor (vs. 38.5%; 34.2 – 40.7%; P=0.695 with Wilcoxon signed rank test). The ARD and CC values obtained for the single-port device and control sensor of each subject are given in Table 4. The average medARD obtained for the single-port device was found to be low (8.9%; 7.3 – 11.3%; n=10) and did not differ from that for the control sensor (vs. 9.8%; 8.9 – 11.5%; P=0.232 with Wilcoxon signed rank test). Similarly, the average MARD calculated for the single-port device (13.0%; 10.5 – 16.7%) was comparable to that of the control sensor (vs. 13.9%; 11.9 – 15.3%; P=0.922 with Wilcoxon signed rank test; Fig. 15). Moreover, on each day of wear the average MARD values obtained for the single-port device sensor were similar to those obtained for the control sensor (Fig. 15). Furthermore, there was no difference between the average CC calculated for the single-port device (0.94; 0.91 – 0.95) and that calculated for the control sensor (vs. 0.92; 0.91 – 0.95; P=0.322 with Wilcoxon signed rank test). The PARD values obtained for the sensor data of each subject are given in Table 5. The average median PARD calculated for the sensor readings for which corresponding glucose meter readings were obtained (11.2%; 10.0 – 12.4%; n=10) did not differ from that calculated for the sensor readings for which no corresponding glucose meter readings were available (vs. 11.3%; 9.4 – 12.5%; P=0.695 with Wilcoxon signed rank test). Similarly, the average mean PARD obtained for the sensor readings for which corresponding meter readings were available (16.0%; 13.7 – 16.6%) was comparable to that calculated for the sensor readings for which no corresponding meter readings were obtained (vs. 14.5%; 13.3 – 16.5%; P=0.846 with Wilcoxon signed rank test).

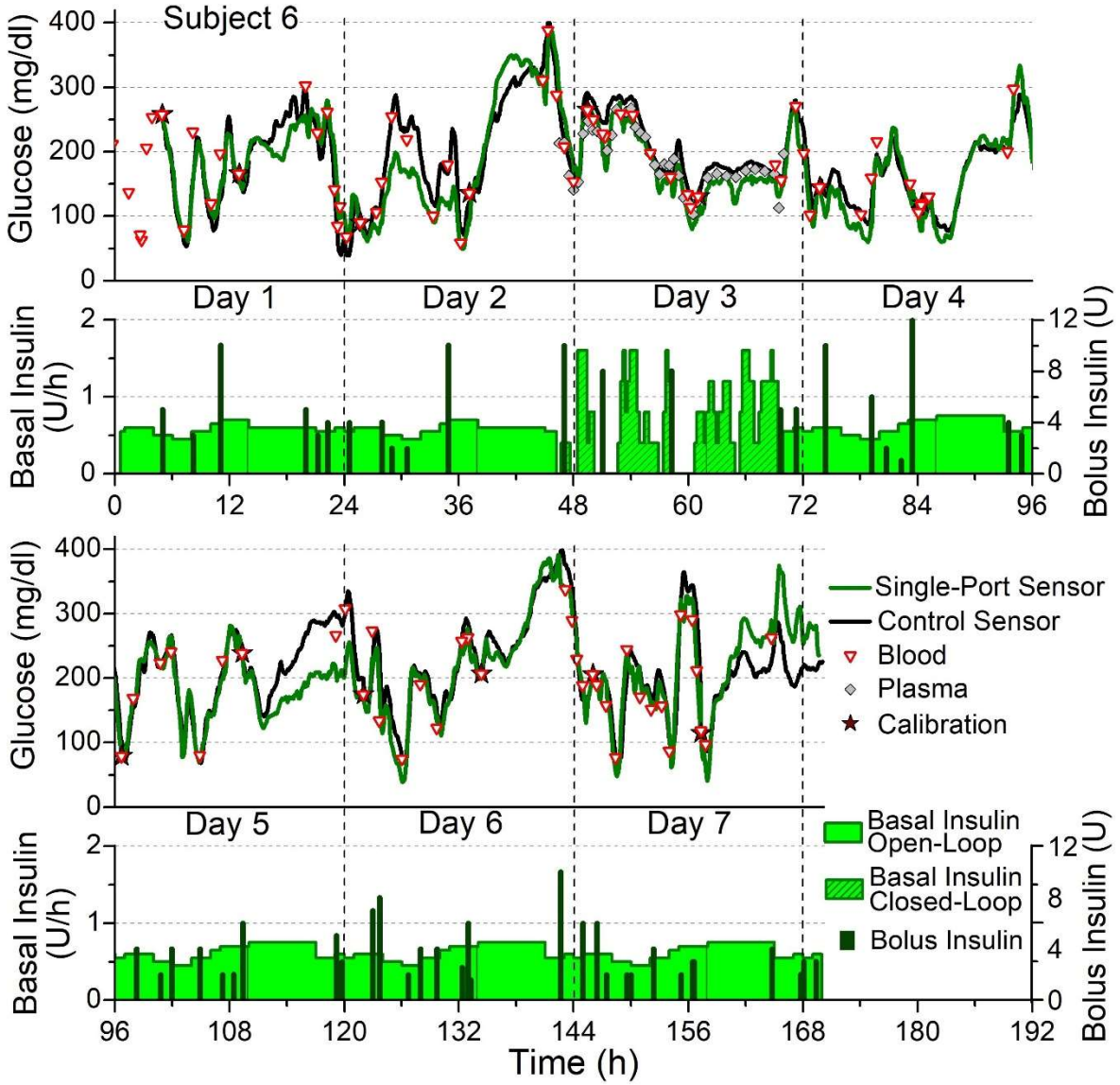

Fig. 13. *Glucose concentration time courses from a representative diabetes patient (subject 6) observed during open- and closed-loop insulin delivery with the single-port device: Shown are the glucose readings of the single-port device sensor (green solid line), readings of the control sensor (black solid line) as well as capillary blood glucose concentrations (red triangles) and plasma glucose concentrations (grey diamonds) observed over the 7-day treatment period. Also shown are the rates of insulin delivery (open and hashed green bars for basal rate & dark green bars for bolus delivery). On study day 3 the basal insulin infusion (hashed green bars) was controlled by the closed-loop algorithm.*

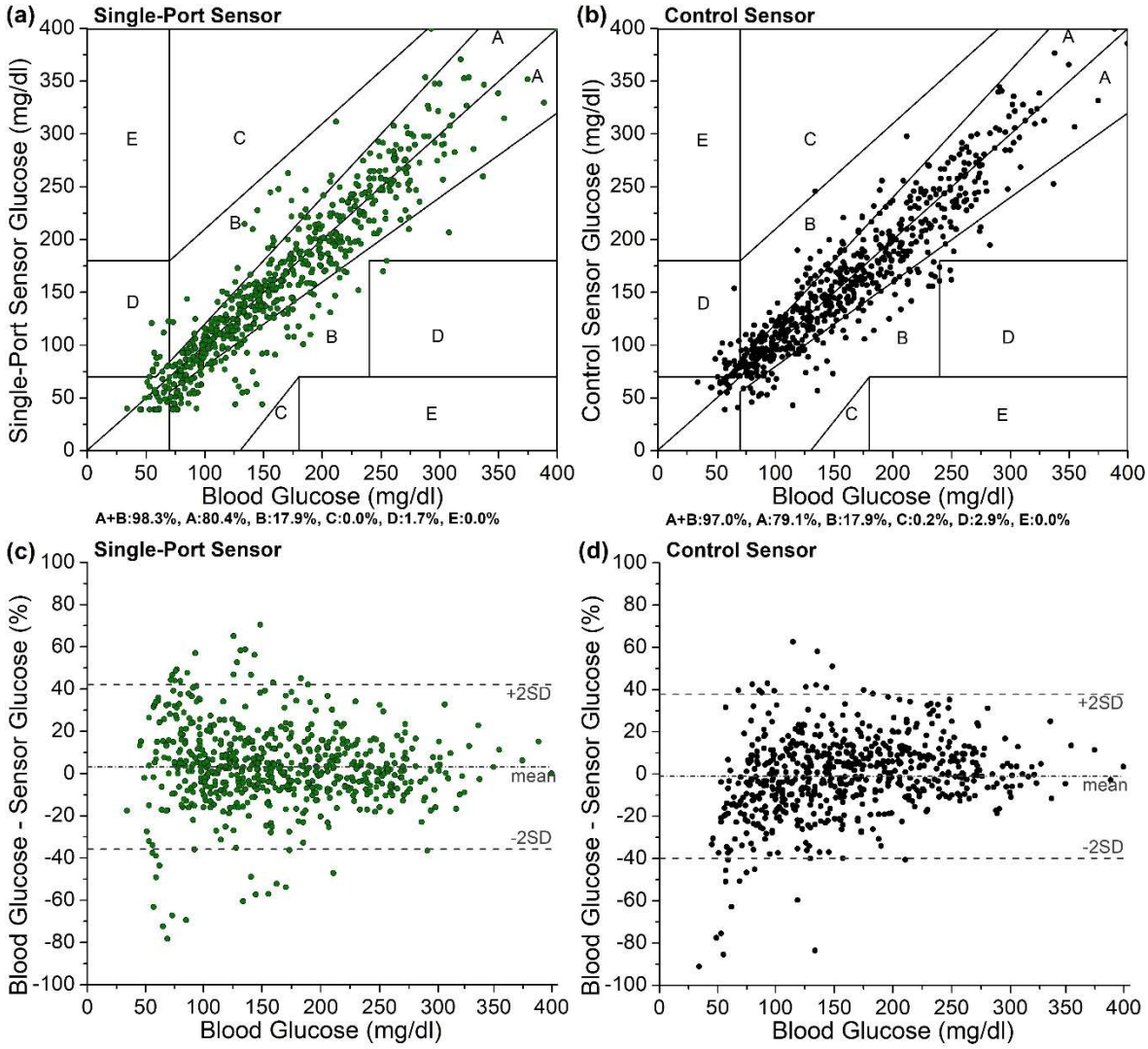

Fig. 14. *Assessing agreement between sensor glucose readings and capillary blood glucose measurements by use of the error grid analysis and the method of residuals:* ***(a)*** *Error grid analysis results for the single-port device sensor. Of the 632 data pairs, 621 (98.3%) fell within the clinically acceptable zone A or B of the error grid, with 508 (80.4%) in zone A and 113 (17.9%) in zone B. Eleven data points (1.7%) fell within zone D.* ***(b)*** *Error grid analysis results for the control sensor. Of the 632 data pairs, 613 (97.0%) fell within the clinically acceptable zone A or B of the error grid, with 500 (79.1%) in zone A and 113 (17.9%) in zone B. One (0.2%) data point fell within zone C, and 18 (2.9%) within zone D.* ***(c–d)*** *Results of applying the method of residuals. Percentage differences between sensor readings and capillary blood glucose measurements (residuals, y-axis) are plotted against capillary blood glucose measurements (x-axis). Short dashed line represents the residual mean, and long dashed lines represent the residual mean plus minus 2 times the residual SD. The mean differences for the single-port device sensor* ***(c)*** *and the control sensor* ***(d)*** *were 3.14% and -1.08%, respectively. The 2SD values for the single-port device sensor* ***(c)*** *and the control sensor* ***(d)*** *were 39.0% and 38.8%, respectively.*

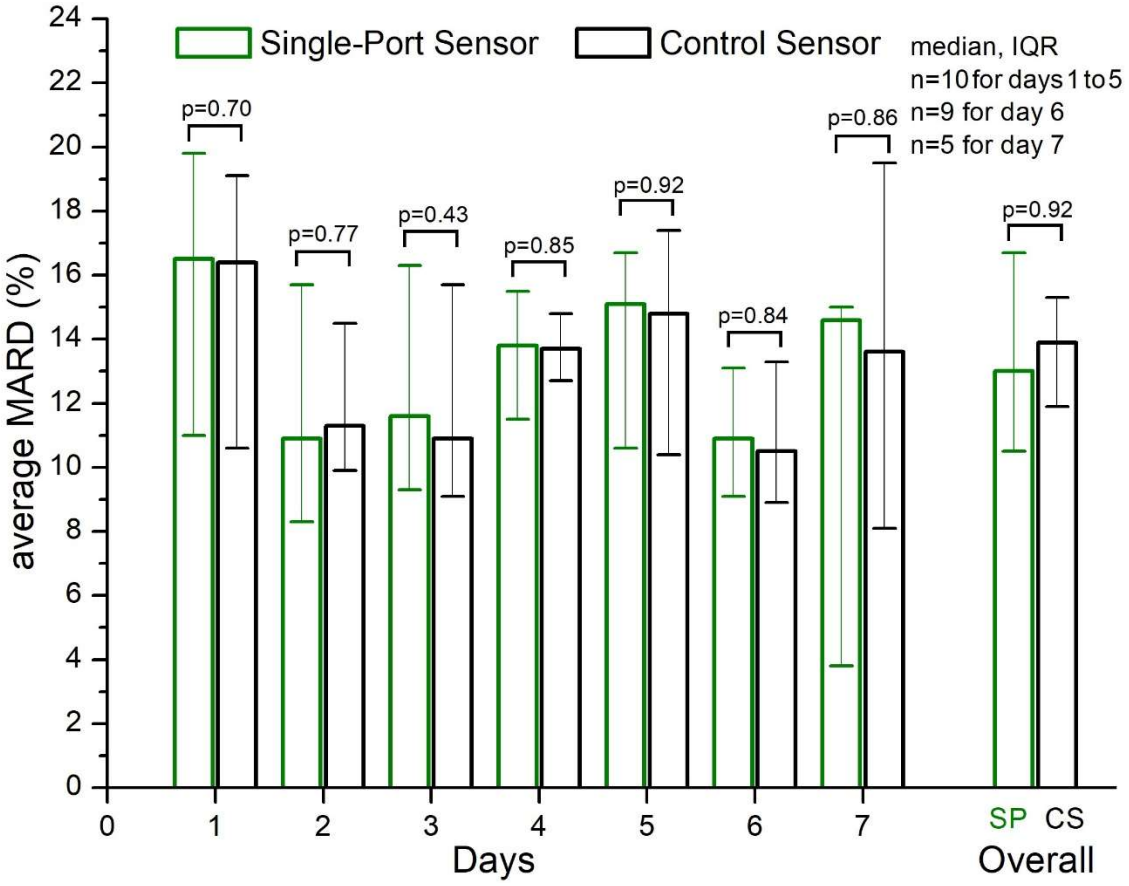

Fig. 15. *Average MARDs (median, IQR) of glucose readings from single-port sensor (green) and control sensor (black) for each day of wear and for the full 7-day period of wear. The MARD values obtained for the single-port sensor were similar to that of the control sensor (P > 0.43; with Wilcoxon signed rank test).*

3.2.4. Closed-loop and open-loop insulin delivery with the single-port device

Insulin delivery with the single-port device was found to be reliable during both the closed-loop glucose control period at the CRC and the treatment period in the patients' home/working environment. No cannula occlusion, cannula dislodgement or insulin leakage was observed in any of the subjects. The average time courses of the glucose concentration and the insulin delivery rate observed during closed-loop glucose control period are shown in Fig. 16. As can be seen, the closed-loop insulin delivery, using the single-port device in combination with the AP@home platform, was adequate to achieve and maintain near normoglycemia during the study day. The TTR values obtained for each subject are given in Table 6.

The average TTR was found to be significantly higher during the closed-loop glucose control period (70.4%; 58.1 – 87.3%) than during the home phase of the study (vs. 54.8%; 45.9 – 61.0%; P=0.002 with Wilcoxon signed rank test).

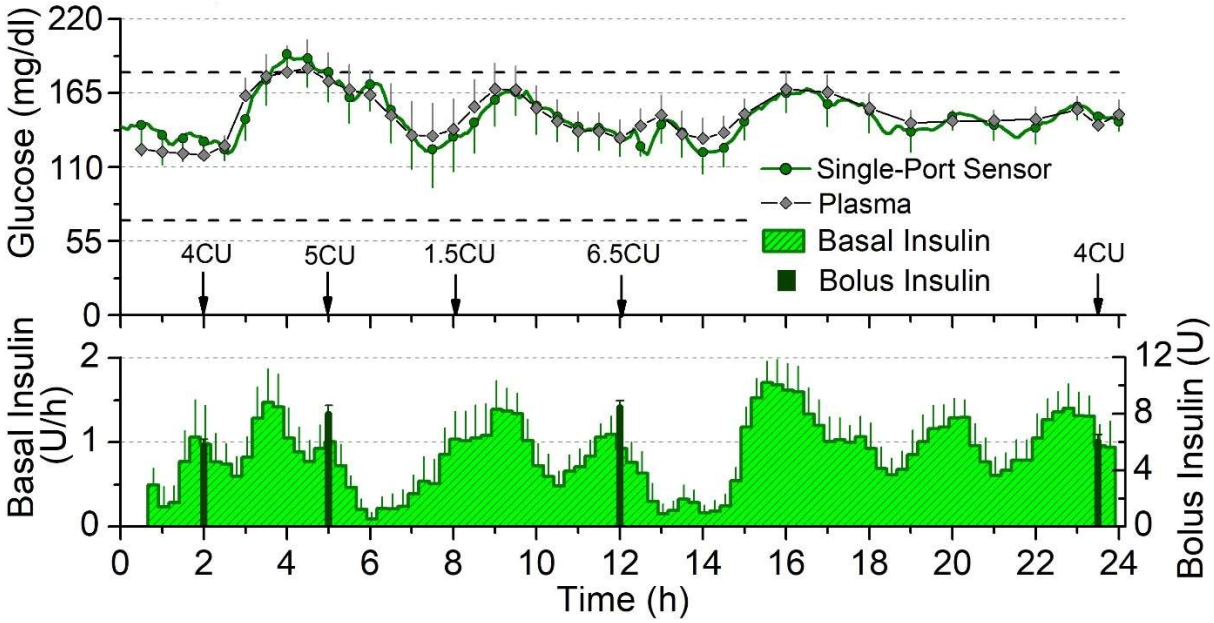

Fig. 16. *Mean glucose readings of the single-port device sensor (n = 10, means ± SE; green circles) and mean plasma glucose concentrations (grey diamonds) observed during closed-loop insulin delivery on study day 3. Also shown are the mean amount of bolus insulin administered via the cannula of the single-port device before each meal (dark green bars) as well as the mean rates of basal insulin infusion, which were calculated by the closed-loop algorithm and automatically infused via the cannula of the single-port device (green hashed bars). During the closed-loop insulin delivery the median percentage of the time spent in the target glucose range of 70 – 180 mg/dl (dashed lines) was 70.4 %.*

Table 2 Error grid analysis results - Shown are the percentage numbers of the single-port device (SP) and control sensor (CS) readings falling into each zone of the Clarke error grid. Also shown are the percentage numbers of the readings in the clinically acceptable range (zones A+B). © 2019 IEEE

Subject	Single-Port Sensor						Control Sensor					
No.	$A+B_{SP}$	A_{SP}	B_{SP}	C_{SP}	D_{SP}	E_{SP}	$A+B_{CS}$	A_{CS}	B_{CS}	C_{CS}	D_{CS}	E_{CS}
01	98.21	71.43	26.79	0.00	1.79	0.00	98.21	78.57	19.64	0.00	1.79	0.00
02	98.18	85.46	12.73	0.00	1.82	0.00	96.36	90.91	5.46	0.00	3.64	0.00
03	100	94.12	5.88	0.00	0.00	0.00	100	84.31	15.69	0.00	0.00	0.00
04	100	91.67	8.33	0.00	0.00	0.00	100	79.17	20.83	0.00	0.00	0.00
05	96.97	87.88	9.09	0.00	3.03	0.00	96.97	69.70	27.27	0.00	3.03	0.00
06	98.90	70.33	28.57	0.00	1.10	0.00	98.80	79.02	19.78	1.10	1.10	0.00
07	97.73	77.27	20.46	0.00	2.27	0.00	96.59	75.00	21.59	0.00	3.41	0.00
08	97.92	83.33	14.58	0.00	2.08	0.00	89.58	68.75	20.83	0.00	10.42	0.00
09	96.77	69.36	27.42	0.00	3.23	0.00	95.16	80.65	14.52	0.00	4.84	0.00
10	98.51	83.58	14.93	0.00	1.49	0.00	98.51	88.06	10.45	0.00	1.49	0.00
mean*	98.32	81.44	16.88	0.00	1.68	0.00	97.02	79.41	17.61	0.11	2.97	0.00
sem	0.35	2.82	2.67	0.00	0.35	0.00	0.97	2.26	1.98	0.11	0.97	0.00
median†	98.20	83.46	14.75	0.00	1.80	0.00	97.59	79.09	19.71	0.00	2.41	0.00
25th	97.73	71.43	9.09	0.00	1.10	0.00	96.36	75.00	14.52	0.00	1.10	0.00
75th	98.90	87.88	26.79	0.00	2.27	0.00	98.80	84.31	20.83	0.00	3.64	0.00
IQR‡	1.17	16.45	17.70	0.00	1.17	0.00	2.44	9.31	6.32	0.00	2.54	0.00

* no difference between mean A+BSP and mean A+BCP with Paired Sample t Test (P=0.145)
† no difference between median A+BSP and median A+BCP with Wilcoxon Signed Ranks Test (P=0.063)
‡ Interquartile range

Table 3 Method of residuals applied to sensor glucose and capillary blood glucose data – Shown are the Means and 2SD values of residuals obtained for the single-port device (SP) and control sensor (CS). © 2019 IEEE

Subject No.	Single-Port Sensor		Control Sensor	
	$Means_{SP}$ (%)	$\pm 2SD_{SP}$ (%)	$Means_{CS}$ (%)	$\pm 2SD_{CS}$ (%)
01	-0.93	47.01	0.07	35.34
02	3.14	34.33	-0.96	35.74
03	6.17	17.79	1.24	26.33
04	5.12	25.21	1.33	30.63
05	1.62	30.5	-7.91	40.05
06	3.12	41.3	-2.27	40.4
07	2.03	47.86	0.08	38.1
08	3.95	39.09	0.49	38.84
09	6.67	49.3	-2.85	49.88
10	1.95	35.56	1.75	41.74
mean[*†]	3.28	36.8	-0.90	37.7
sem	0.73	3.25	0.91	2.02
median[‡§]	3.13	37.33	0.07	38.47
25th	1.87	29.18	-2.41	34.16
75th	5.38	47.22	1.26	40.73
IQR	3.52	18.04	3.68	6.57

[*]difference between mean $Means_{SP}$ and mean $Means_{CS}$ with Paired Sample t Test (P=0.004)
[†]no difference between mean $2SD_{SP}$ and mean $2SD_{CS}$ with Paired Sample t Test (P=0.696)
[‡]difference between median $Means_{SP}$ and median $Means_{CS}$ with Wilcoxon Signed Ranks Test (P=0.006)
[§]no difference between median $2SD_{SP}$ and median $2SD_{CS}$ with Wilcoxon Signed Ranks Test (P=0.695)

Table 4 Mean and median absolute relative differences (MARD, medARD) as well as correlation coefficients (CC) derived for each single-port device (SP) and control sensor (CS). © 2019 IEEE

Subject No.	Single-Port Sensor			Control Sensor		
	$MARD_{SP}$ (%)	$medARD_{SP}$ (%)	CC_{SP}	$MARD_{CS}$ (%)	$medARD_{CS}$ (%)	CC_{CS}
01	17.11	10.04	0.89	13.46	10.99	0.91
02	12.82	9.14	0.95	11.66	8.93	0.95
03	8.65	7.33	0.98	10.12	7.69	0.95
04	9.41	6.52	0.95	12.05	9.66	0.92
05	10.90	7.15	0.93	17.73	15.28	0.88
06	15.21	11.34	0.90	14.30	9.43	0.92
07	17.32	11.64	0.92	15.01	13.02	0.93
08	13.17	8.07	0.95	14.60	10.27	0.90
09	16.58	11.27	0.93	16.15	9.88	0.95
10	12.86	8.61	0.96	11.98	8.75	0.94
mean[*†‡]	13.40	9.11	0.94	13.71	10.39	0.92
sem	0.99	0.60	0.01	0.73	0.71	0.01
median[§‖¶]	13.01	8.87	0.94	13.88	9.77	0.92
25th	10.53	7.28	0.91	11.90	8.88	0.91
75th	16.71	11.29	0.95	15.30	11.5	0.95
IQR	6.19	4.00	0.04	3.40	2.61	0.04

[*] no difference between mean $MARD_{SP}$ and mean $MARD_{CS}$ with Paired Sample t Test (P=0.753)
[†] no difference between mean $medARD_{SP}$ and mean $medARD_{CS}$ with Paired Sample t Test (P=0.189)
[‡] no difference between mean CC_{SP} and mean CC_{CS} with Paired Sample t Test (P=0.262)
[§] no difference between median $MARD_{SP}$ and median $MARD_{CS}$ with Wilcoxon Signed Ranks Test (P=0.922)
[‖] no difference between median $medARD_{SP}$ and median $medARD_{CS}$ with Wilcoxon Signed Ranks Test (P=0.232)
[¶] no difference between median CC_{SP} and median CC_{CS} with Wilcoxon Signed Ranks Test (P=0.322)

Table 5 Mean and median precision absolute relative differences (meanPARD, medPARD) calculated for sensor readings for which corresponding blood glucose meter readings were obtained (REF) and for sensor readings for which no corresponding blood glucose readings were available (noREF). © 2019 IEEE

Subject No.	**meanPARD$_{noREF}$ (%)**	**medPARD$_{noREF}$ (%)**	**meanPARD$_{REF}$ (%)**	**medPARD$_{REF}$ (%)**
01	17.82	15.95	16.84	12.08
02	17.99	12.78	15.33	12.27
03	12.27	9.4	10.35	7.73
04	13.74	11.4	12.6	9.28
05	16.05	11.83	15.88	12.62
06	14.74	11.11	16.45	10.68
07	12.88	9.25	16.12	10.26
08	15.66	12.39	17.44	12.81
09	13.42	9.25	16.38	10.71
10	14.26	11.08	14.07	11.63
mean[*†]	14.88	11.44	15.15	11.01
sem	0.62	0.64	0.7	0.51
median[‡§]	14.50	11.26	16.00	11.17
25th	13.28	9.36	13.7	10.02
75th	16.49	12.49	16.55	12.36
IQR	3.21	3.13	2.85	2.34

[*]no difference between mean meanPARD$_{noREF}$ and mean meanPARD$_{REF}$ with Paired Sample t Test (P=0.693)
[†]no difference between mean medPARD$_{noREF}$ and mean medPARD$_{REF}$ with Paired Sample t Test (P=0.429)
[‡]no difference between median meanPARD$_{noREF}$ and median meanPARD$_{REF}$ with Wilcoxon Signed Ranks Test (P=0.846)
[§]no difference between median medPARD$_{noREF}$ and median medPARD$_{REF}$ with Wilcoxon Signed Ranks Test (P=0.695)

Table 6 Percentage of time spent in the target range (TTR) during the closed-loop glucose control period (CL) and the open-loop insulin delivery period (OL). © 2019 IEEE

Subject No.	**Closed Loop TTR_{CL} (%)**	**Open Loop TTR_{OL} (%)**
01	54.86	56.14
02	59.23	50.49
03	77.00	60.72
04	65.85	47.90
05	90.89	62.25
06	59.58	39.50
07	75.00	62.03
08	91.29	53.55
09	86.06	39.96
10	45.30	56.68
mean*	70.51	52.92
sem	5.06	2.66
median†	70.43	54.84
25th	58.14	45.92
75th	87.27	61.05
IQR	29.13	15.13

* difference between mean TTR_{CL} and mean TTR_{OL} with Paired Sample t Test (P=0.010)

† difference between median TTR_{CL} and median TTR_{OL} with Wilcoxon Signed Ranks Test (P=0.002)

4. Discussion

The present report describes a simple and cost-effective realization of a diabetes treatment device for performing glucose sensing and insulin delivery through a single skin insertion site (the single-port device). In contrast to previous approaches based on the integration of glucose sensing and insulin infusion technologies created from scratch, we utilized already existing technologies and introduced several design concepts of integrating commercial glucose sensors and infusion cannulas. We prototyped and evaluated each concept according to design simplicity, ease of insertion, and sensing accuracy. We found that the best single-port prototype is the one in which a Dexcom G4-Platinum sensor-probe is inserted through the self-sealing septum of a Medtronic Sof-Set infusion cannula housing and subsequently placed in the cannula lumen so that its tip extends approximately 6 mm beyond the cannula tip. Owing to the low degree of component modification required to arrive at this configuration we were able to proceed directly to testing the final prototype in vivo in humans. Results from these human studies indicate the feasibility of integrating components of commercially available glucose sensing and insulin delivery technologies to realize a functional single-port device.

4.1. Single-port device safety and effectiveness

A single-port device, like any new treatment modality, must be proved safe and effective before regulatory authorities will approve it for marketing [44]. Since single-port devices integrate glucose sensing and insulin infusion technologies, approval for market introduction will require clinical data demonstrating that the devices' performance is at least equivalent to that of commercially available CGMs and insulin delivery devices. Thus, to prove safety and efficiency of a single-port device, the device's manufacturer will be required to conduct clinical trials to assess the performance characteristics of the single-port device and compare its performance to that of commercially available CGMs and insulin delivery devices.

4.1.1. Structural integrity of the single-port device

A performance characteristic that may be essential in the safe use of a single-port device is the maintenance of the device's structural integrity. Although potential issues with structural integrity may arise at any point in the single-port device lifespan, they are most likely to occur during insertion due to the device being exposed to high friction forces that arise between the tissue and the outer surface of the device. Currently, all research groups pursuing alternative approaches to the realization of a single-port device integrate the glucose sensor onto the outer wall of the infusion cannula. Hence, with such a design, high friction forces generated during the insertion process may increase the probability of sensor failure. For example, following insertion into adipose tissue of swine, Ward et al. observed fractures or short circuits in approximately one third of their electrochemical glucose sensors integrated onto the outer cannula walls [45]. To reduce the probability of experiencing such structural integrity issues Rumpler et al. pre-punctured the human skin with a large gauge needle prior to inserting the device [46]. However, a more permanent solution would require time- and cost-intensive single-port design refinements like creating an additional lumen for the sensor-probe, increasing the glucose sensor's mechanical robustness or developing completely new insertion techniques. In contrast to the integration of the sensor onto the outer wall of the infusion cannula, the sensor of the single-port device presented here is positioned in the lumen of the infusion cannula (Fig. 6f). Since the sensor applicator needle precisely fits into the lumen of the infusion cannula, both sensor and infusion cannula can be simultaneously inserted using the applicator needle (Fig. 6e, Fig. 7bc). During insertion, the sensor is encased by the applicator needle and so protected against the generated friction forces (Fig. 6f). Thus, with this design and mode of device insertion, sensor damage and subsequent sensor failure may be avoided. Indeed, following device insertion, in no one of the type 1 diabetes patients participating in the clinical trials was any sensor failure observed.

4.1.2. Accuracy and reliability of the glucose sensing with the single-port device

Besides the maintenance of the device's structural integrity, another important performance characteristic that has to be shown to be equivalent to that of commercial CGM devices is the accuracy and reliability of the glucose sensing with the single-port device. A common metric used to quantify the accuracy of commercial CGM devices is the MARD value, which is defined as the mean absolute relative difference between CGM measurements and matched reference blood glucose measurements [47]. Currently, commercial CGM devices already reach MARD values below 15% [48], [49] and are therefore considered accurate enough for the use in artificial pancreas systems [8]. To our knowledge, so far only two other research groups reported the in vivo assessment of the accuracy of the glucose sensing with their single-port devices. In a study conducted under hospital settings, the glucose sensing accuracy of the single-port device was evaluated in type 1 diabetes subjects without however administering any insulin via the device [46]. In other in vivo studies, the glucose sensing accuracy of the single-port devices was assessed in anesthetized swine during either constant basal insulin delivery [29], [50], [51] or following the administration of bolus insulin [45], [50]. The MARD values reported in these studies ranged from 13.5% to 22.5% [29], [45], [46]. Unfortunately, since a retrospective calibration method was used to convert the sensor currents into blood glucose concentrations, it is difficult to directly compare the reported MARD values with those of commercial CGM devices which typically employ a prospective calibration scheme [52]. Compared to the prospective calibration of commercial CGM devices, retrospective calibration of a glucose sensing device may result in an inflation of the accuracy measures that, in turn, may lead to an overly optimistic appraisal of the device's performance [52]–[54]. Furthermore, since in the retrospective calibration all paired sensor current values and reference glucose readings generated throughout the entire experiment are used to convert sensor currents into blood glucose concentrations, retrospective calibration is only performed at the completion of the experiment and, therefore, cannot be used for real-time display of blood glucose concentrations [52]. In comparison, during our home trials, the conversion of sensor current values into glucose concentrations was

carried out using the prospective calibration method incorporated in the data processing unit of the Animas pump.

The obtained glucose concentrations were then displayed in real time on the pump's display module (Fig. 6d). In order to assess the precision and accuracy of the Dexcom control sensor and the Dexcom sensor used in the single-port device, several agreement indexes, such as the MARD and the residual 2 SD, were calculated for each sensor (Tables 2 – 4). Values of the agreement indexes obtained for the single-port device sensor were similar to those obtained for the control sensor, which was worn at least 100 mm away from the single-port device and, thus, was most likely not affected by the infused insulin. Furthermore, the PARD value calculated for the sensor readings for which corresponding glucose meter readings were obtained was comparable to that calculated for the sensor readings for which no corresponding glucose meter readings were available (Table 5), thereby suggesting that the portion of the sensor data used to calculate the agreement indexes was representative for the whole set of sensor data. In addition, the obtained values of the agreement indexes were comparable to those recently reported for the same commercially available generation of Dexcom sensors (i.e., G4 Platinum sensor; [55], [56]). For example, studies assessing the accuracy of this generation of Dexcom sensors have observed average MARD values (range: 11 – 14%; [55]–[57]) that are similar to those obtained for the control and single-port device sensor in the present study (13.9 and 13.0%, respectively). Overall, these results indicate that the commercial glucose sensor incorporated into the single-port device maintained comparable accuracy to that of the same commercial sensor placed well apart from the tissue site of insulin delivery.

4.1.3. Accuracy and reliability of the insulin infusion with the single-port device

Another performance characteristic of the single-port device that has to be shown to be equivalent to that of the commercially available devices is the accuracy and reliability of the insulin infusion. During our first clinical trial and the 6-day home-use period of our second clinical trial the single-port device was used for open-loop insulin delivery. During these periods the insulin delivery was found to be reliable

and safe, suggesting that the delivery of insulin with the single-port device is equally reliable as with commercial stand-alone delivery devices. Furthermore, during the 1-day stay at the CRC of our second clinical trial the single-port device was used for closed-loop insulin delivery. To this purpose the single-port device was connected to the Roche insulin pump, which wirelessly communicated with the standalone Tritec control unit housing the Cambridge University Algorithm (Fig. 11). Based on the insulin dosing instructions sent by the control unit, the Roche insulin pump automatically adjusted the insulin delivery into the subcutaneous tissue. During the 24-h of closed-loop glucose control, the glucose levels of the patients were maintained within the target range of 40 – 180.0 mg/dl for a median of 70% of the time. In comparison, during the open-loop treatment period at home, the patients' glucose levels were within the target range for a medium of 55% of the time. This improvement in glycemic control achieved with the single-port AP is similar to that previously obtained with dual-port AP systems also using the Cambridge University Algorithm [16], [58]–[60] or other MPC-based algorithms [7], thereby indicating that the combining of insulin delivery and glucose sensing at the same tissue site may not compromise the AP's effectiveness in controlling patients' blood glucose levels.

4.2. Current limitations and next development steps

Given these promising clinical results, we are currently focusing on improving the usability of the single-port device to allow the performance of clinical trials in which the device is evaluated under unsupervised home-use conditions over treatment periods of several weeks.

4.2.1. Enabling automated insertion of the single-port device

Since the assembly and insertion of the current device have to be performed at the CRC and cannot be done by the patients themselves (Fig. 7), we are aiming to realize an automatic, spring-loaded insertion instrument [61] that facilitates easy insertion of the single-port device by the patients themselves (Fig.17a). The planned instrument consists of a re-usable and a disposable part (Fig. 17b). The re-usable part comprises a spring-operated piston which is cocked when the disposable part is pressed into the re-usable part. The disposable part comprises the single-port

housing and an insertion needle which contains the single-port sensor in its lumen and carries the single-port cannula on its surface. After pressing the disposable part into the re-usable part, the patients fixate the single-port housing onto their bodies using an adhesive tape.

After activating the release button on the re-usable part, the sensor and cannula of the single-port device are simultaneously inserted into the subcutaneous tissue of the patients and the insertion needle is automatically withdrawn. Finally, to make the single-port device ready for use, the patients connect the transmitter to the sensor and the insulin pump to the infusion cannula of the single-port device.

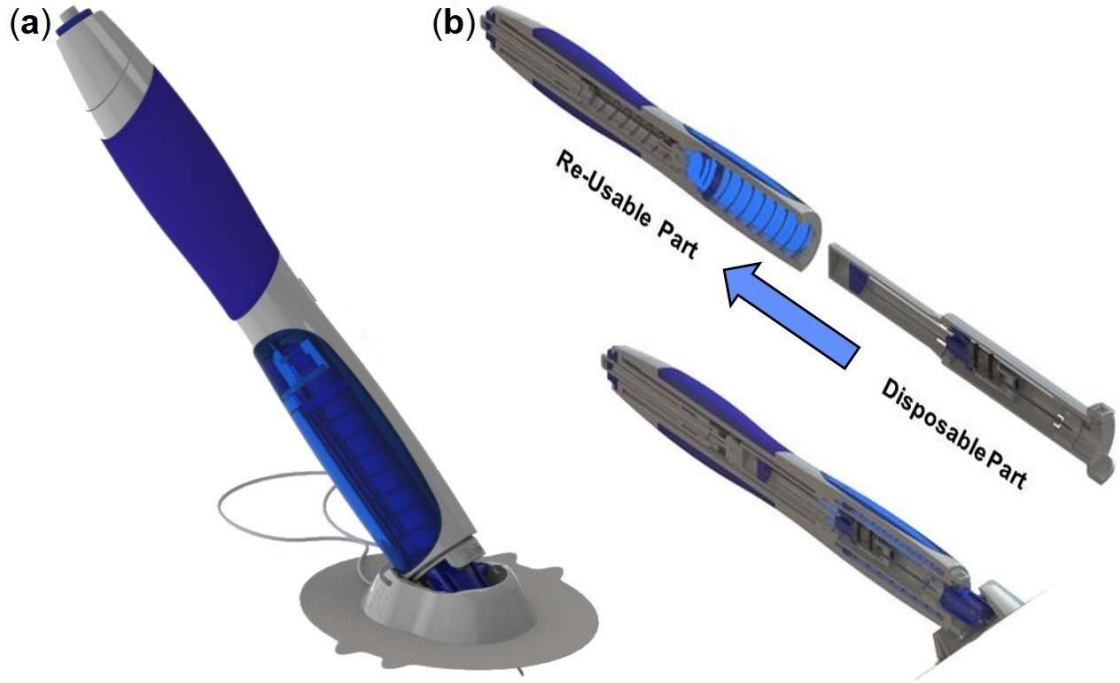

Fig. 17. *Automatic spring-loaded insertion instrument:* ***(a)*** *Schematic representation of the spring-loaded insertion instrument.* ***(b)*** *Schematic cross-sectional view of the re-usable and the disposable part of the automatic spring-loaded insertion instrument.*

4.2.2. Enabling device operation with standard insulin solutions

Currently, a small amount of glucose has to be added to the standard insulin solutions to avoid “false” glucose sensor errors caused by the rapid dilution of ISF following bolus insulin delivery (Fig. 9c). To overcome this shortcoming, we are evaluating alternative ways of avoiding the occurrence of these sensor errors. One way would be to simply instruct the device’s data processing unit to ignore the

measured glucose concentration for a short period of time after a bolus of insulin is administered (about 15 min). However, doing so may come at the price of not being able to display glucose values for a period of 15 min each time an insulin bolus is delivered. Another, more sophisticated way to avoid the occurrence of “false” sensor errors when boluses of insulin are delivered would be the application of the ionic reference technique [25], [26], [62]. This technique is based on the monitoring of the electrical conductivity in the ISF. When this fluid gets diluted by another fluid that has a different conductivity (e.g. insulin solutions have substantially lower conductivities than ISF), the degree to which the ISF has been diluted can be determined from the changes in the monitored conductivity. The glucose concentration in the undiluted ISF can then be calculated from the observed dilution degree and the glucose levels measured by the single-port sensor. Thus, integration of the ionic reference technique in the single-port device would allow glucose readings to be displayed also during the critical 15-min period following the bolus delivery of insulin. In addition, the ionic reference technique may be easily integrated into the single-port device, since the device's glucose sensor may additionally be used to monitor the electrical conductivity in its surrounding ISF. Both the use of the automatic insertion instrument and application of the ionic reference technique will allow the single-port device to be further evaluated under unsupervised home-use conditions and over longer periods of treatment.

4.2.3. Prolonging the wear-time of the single-port device

The Dexcom G4 sensor and the Medtronic SOF-Set infusion cannula employed in the single-port device differ considerably in their approved or recommended usage duration. Whereas the Dexcom G4 sensor is approved for 7 days of continuous use [43]–[45], [55], the Medtronic SOF-Set infusion cannula, like other commercial insulin infusion cannulas, is recommended to be replaced every 2-3 days [8], [56], [57]. It is well known that prolonged use of an insulin infusion cannula beyond the recommended 2–3 day period increases the risk for infection, scarring and lipodystrophy at the infusion site as well as deterioration of the blood glucose control due to reduced insulin absorption [8], [56], [57]. Therefore, during the open-loop treatment period at home, the subjects were instructed to stop using the single-port device when there were signs of infection at the sensor/cannula insertion site, when

correction boli failed to decrease the glucose levels, or when there was an increase in the amount of insulin above the amount usually needed to keep the glucose concentration normal. Owing to the occurrence of increases in the insulin amount above the amount usually needed, half of the studied subjects prematurely discontinued the device use – four subjects after 6 days and one after 5 days. However, the other half of the subjects wore the device for the full 7 days, as no insertion site infection, or uncorrectable hyperglycemia, or increase in the insulin amount occurred in any of these subjects. Overall, the mean wear time of the single-port device was 6.4 days.

These findings indicate that, in a large group of diabetes patients, the use of the single-port device may be safely prolonged beyond the 2–3 day period recommended for the use of insulin infusion sets. This conclusion is consistent with recent findings of Patel et al. [58], who assessed the effect of duration of use on infusion set function in diabetes patients. The authors observed that infusion sets were intact and properly functioning up to a median usage duration of 6.06 days. In order to increase the mean wear-time of the single-port device to at least 7 days, we plan to apply a novel method for determining the longest possible duration of use of an insulin infusion site [63]. This method is based on the monitoring of the hydraulic tissue resistance (TR) at the subcutaneous insulin infusion site (i.e., the resistance exerted by the subcutaneous tissue on the infused insulin solution) by using a pressure sensor. We previously observed that TR is generally decreasing during the first 2 to 3 days of infusion site use but is progressively increasing as the use of the infusion site is continued, and that there is a strong inverse relationship between TR and the efficiency of insulin absorption from the site of insulin infusion [63]. Thus, because of this relationship, a too high TR value observed during infusion site use may indicate that the maximum duration of its use is reached and that a new infusion site should be established. Therefore, integration of this method in the single-port device would allow the longest possible wear-time of the device to be determined. Furthermore, the method may be easily integrated into the single-port device, since the already existing occlusion detection sensor of the insulin pump may additionally be used to monitor the TR.

4.2.4. Creating an all-in-one single-port artificial pancreas

During the open-loop treatment period at the patients' home, the single-port device was attached to the Animas pump integrating a Dexcom sensor receiver which enabled it to be wirelessly connected to the single-port glucose sensor and to display and store the glucose readings received from the sensor (Fig. 6). However, to provide real-time insulin dosing decisions based on the received glucose readings, there would need to be an AP control algorithm implemented additionally into the insulin pump. Unfortunately, there is currently no insulin pump from Animas available that is integrated with an AP control algorithm. Advantageously, the combined integration of a control algorithm and wireless connectivity into an insulin pump, like the Animas pump, should not pose any technological obstacles nor increase the size of the insulin pump. Therefore, combining the single-port device with an insulin pump that houses both wireless connectivity and a control algorithm may lead to the commercial introduction of an AP device that readily fulfills the expectations of diabetes patients with regard to its shape (i.e., all-in-one device) and size (i.e., similar to an insulin pump) [21].

4.2.5. Performing a confirmatory study

Limitations of our second study include the lack of a closed-loop control arm in which a conventional dual-port AP system is used to control the patients' blood glucose levels in the CRC setting. Thus, a future parallel-arm study applying both the single-port and dual-port AP system will be needed to determine whether the performance of the single-port AP is equivalent to that of a dual-port AP. Since the improvement in glycemic control achieved with the single-port AP was comparable to that previously obtained with conventional dual-port AP systems, we anticipate that no difference in the performance of the two AP systems will be observed in such a study. Another limitation of our study may be that the glucose sensing accuracy of the single-port device and control sensor was evaluated against blood glucose meter instead of laboratory instrument readings. Generally, glucose meters have a lower level of accuracy than laboratory instruments and, thus, when comparisons are made between continuous glucose sensors and glucose meters, the limited accuracy of the glucose meters can influence the estimated accuracy of the glucose sensor (e.g., it

may increase the MARD value of the sensor [64]). The glucose meter used in the current study (Abbott FreeStyle Freedom Lite) was previously found to be one of the most accurate glucose test strip devices available [65], [66]. Thus, because of the relatively high level of accuracy of the used glucose meter (e.g., the MARD value determined for this meter is about 5%, see Materials and Methods or [66]), the impact on the estimated accuracy of the glucose sensing with the single-port device and control sensor may have been minimal [64]. Finally, the current study is a single-center study of a limited number of participants and, as such, provides only initial evidence that the quality and reliability of the glucose sensing and insulin infusion with the single-port device are equivalent to that with commercial stand-alone glucose monitoring and insulin delivery devices. Thus, in order to collect definitive evidence for equivalent performance, a future confirmatory study in a much larger sample size will be needed.

4.2.6. Fully implantable glucose sensors may not limit the market potential of the single-port device

Currently, most commercial CGM devices are using a subcutaneous needle-type sensor, except the novel CGM device from Senseonics, which employs a fully implantable glucose sensor [67]. It has been shown that this novel CGM device can be safely used for 90-180 days and its accuracy is comparable to that of current CGM devices using needle-type sensors [67]. Given these favorable performance features, it may seem possible that the CGM devices using fully implantable glucose sensors will replace needle-type glucose sensor devices in the near future, in which case the proposed single-port system (which integrates a needle-type sensor) may not gain substantial market traction. However, it may be argued that when a fully implantable glucose sensor device is used in combination with an insulin pump (e.g., within an AP system), the patient is still required to insert a new insulin infusion cannula every 2-3 days and surgically implant a new glucose sensor every 90-180 days. In comparison, when the single-port device is used to treat diabetes, the patient is only required to change the sensor-cannula arrangement on a weekly basis. Thus, diabetes treatment using a fully implantable glucose sensor device together with an insulin pump may still be more invasive than the treatment using the

single-port device. Therefore, the market introduction of CGM devices employing fully implantable glucose sensors may not limit the market potential of the single-port device.

5. Conclusion

In the present report, we describe a simple and cost-effective realization of a diabetes treatment device for performing glucose sensing and insulin delivery at a single subcutaneous tissue site (the single-port device). Instead of creating the device from scratch, we utilized already existing glucose sensing and insulin infusion technologies and introduced three design concepts of integrating commercial glucose sensors and infusion cannulas. We prototyped and evaluated each concept according to design simplicity, ease of insertion, and sensing accuracy. We found that the best single-port prototype is the one in which a Dexcom G4-Platinum sensor is housed inside a Medtronic Sof-Set cannula so that its glucose sensitive part protrudes from the cannula tip. Owing to the low degree of component modification required to build this single-port prototype, we were able to proceed directly to evaluate it in human studies. Results from these studies indicate the feasibility of integrating components of commercially available glucose sensing and insulin delivery technologies to realize a functional single-port device. Thus, using this development approach, skipping of some early stages of the medical device development pathway was possible. Skipping stages of the complicate and highly regulated medical device development pathway may significantly reduce development time and cost. Furthermore, performing a validation of a medical device under real-use conditions early on in the development pathway may help to avoid costly dead-end development paths and waste of resources. Therefore, our device development approach presented here may be generally useful to provide patients with innovative medical devices faster and at reduced costs.

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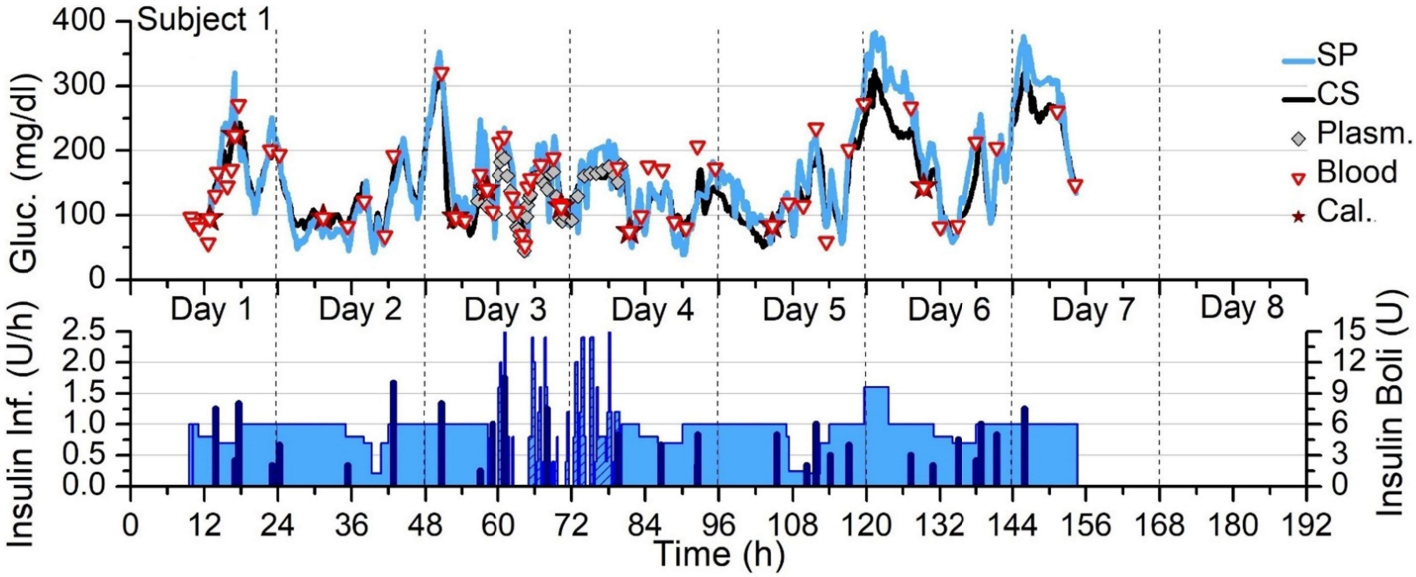


Fig. S1. *Glucose concentration time courses from all diabetes patients (subject 1-10) observed during open- and closed-loop insulin delivery with the single-port device: Shown are the glucose readings of the single- port device sensor (blue line), readings of the control sensor (black line) as well as capillary blood glucose concentrations (red triangles) and plasma glucose concentrations (grey diamonds) observed over the 7-day treatment period. Also shown are the rates of insulin delivery (blue bars for basal rate & dark blue bars for bolus delivery). On study day 3 the basal insulin infusion (blue hashed bars) was controlled by the closed-loop algorithm.*

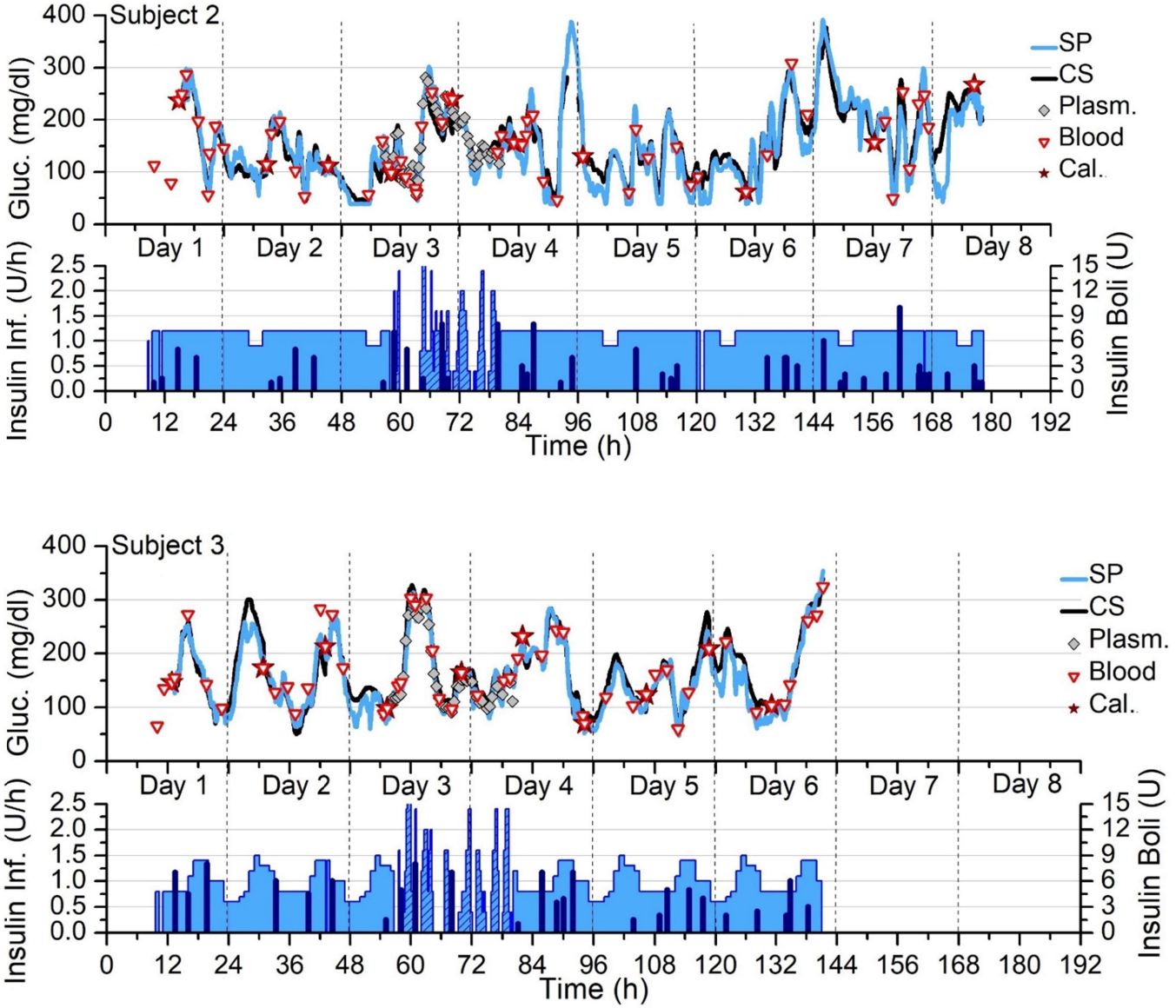
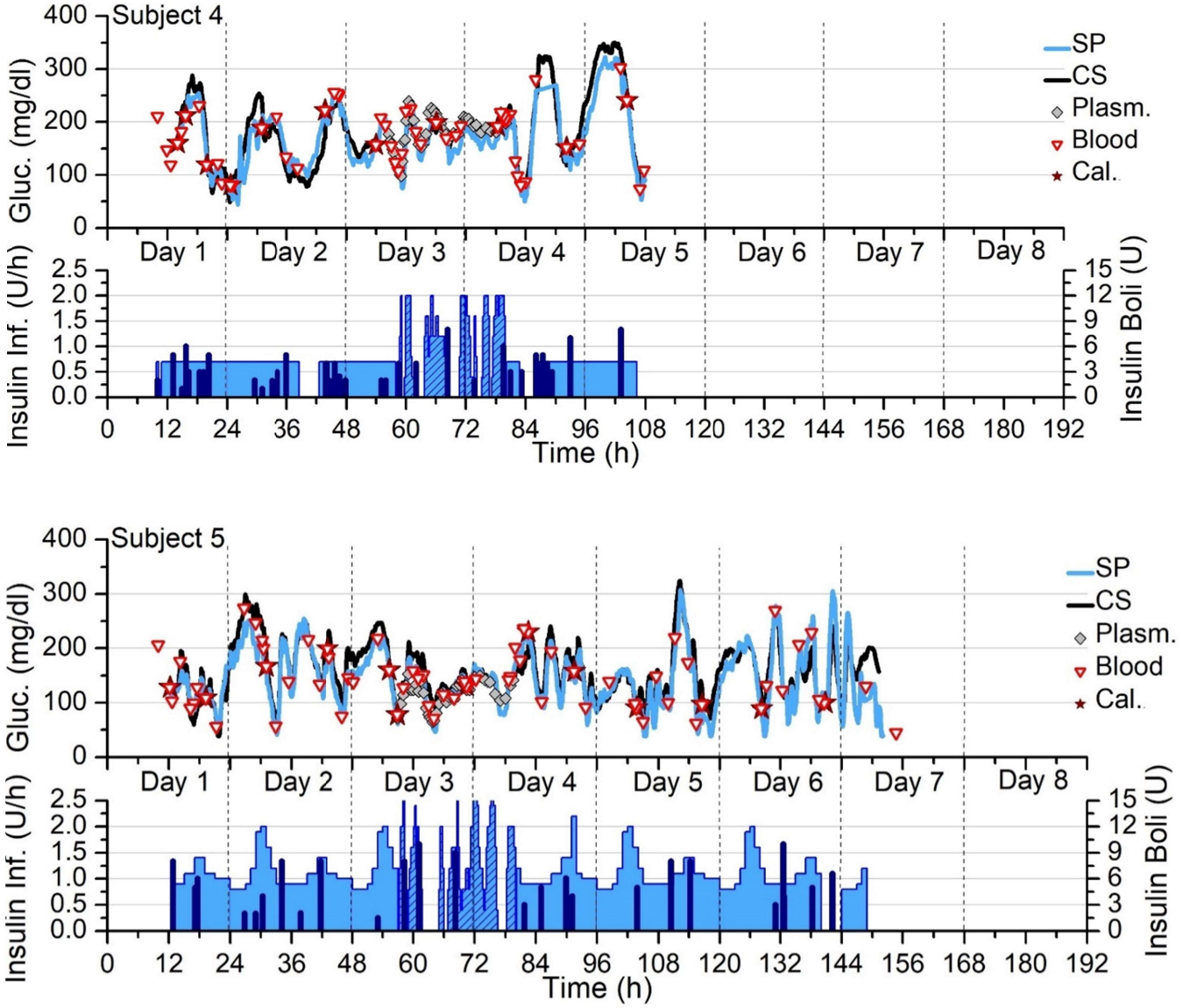


Fig. S1. *Continued*



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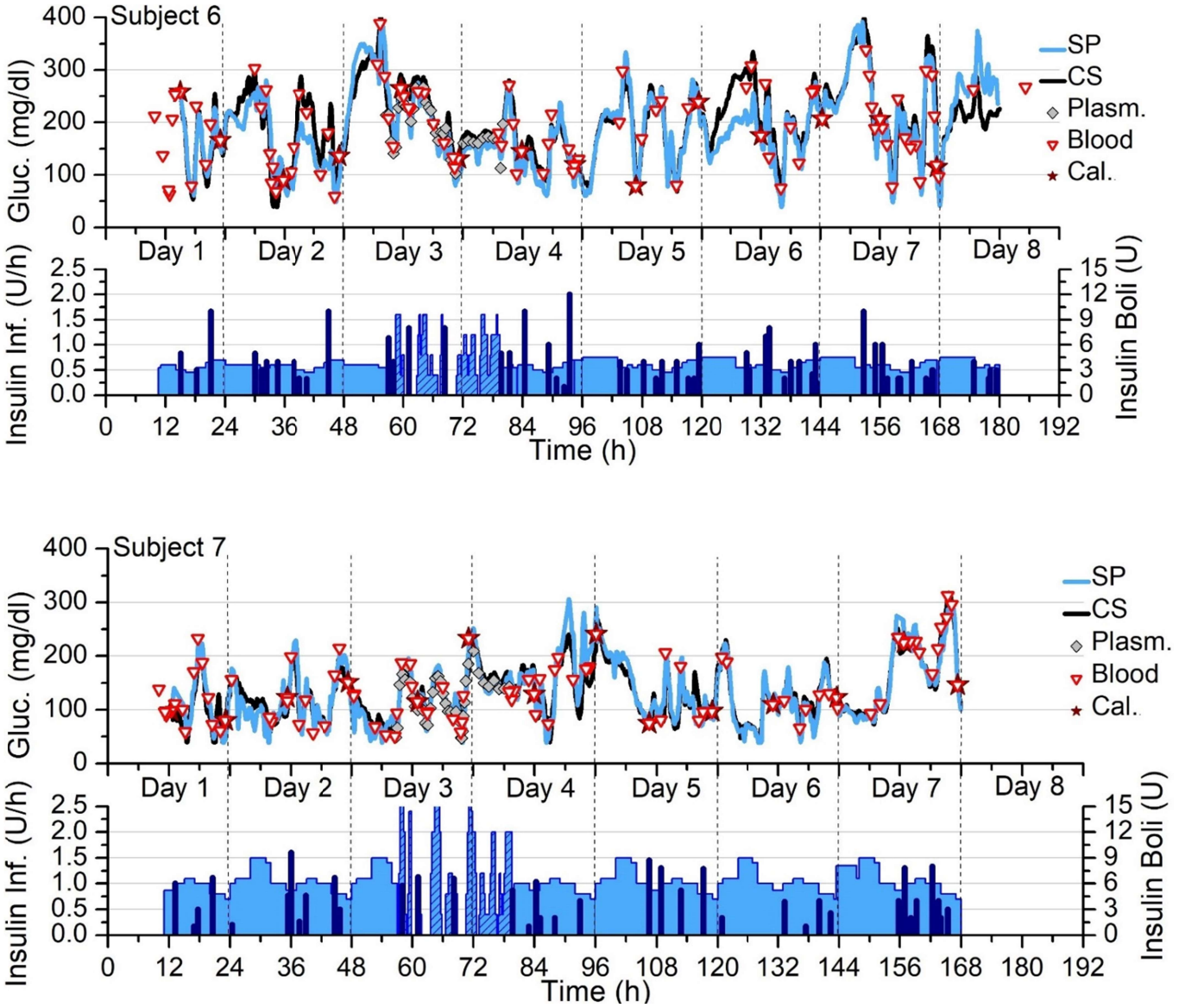

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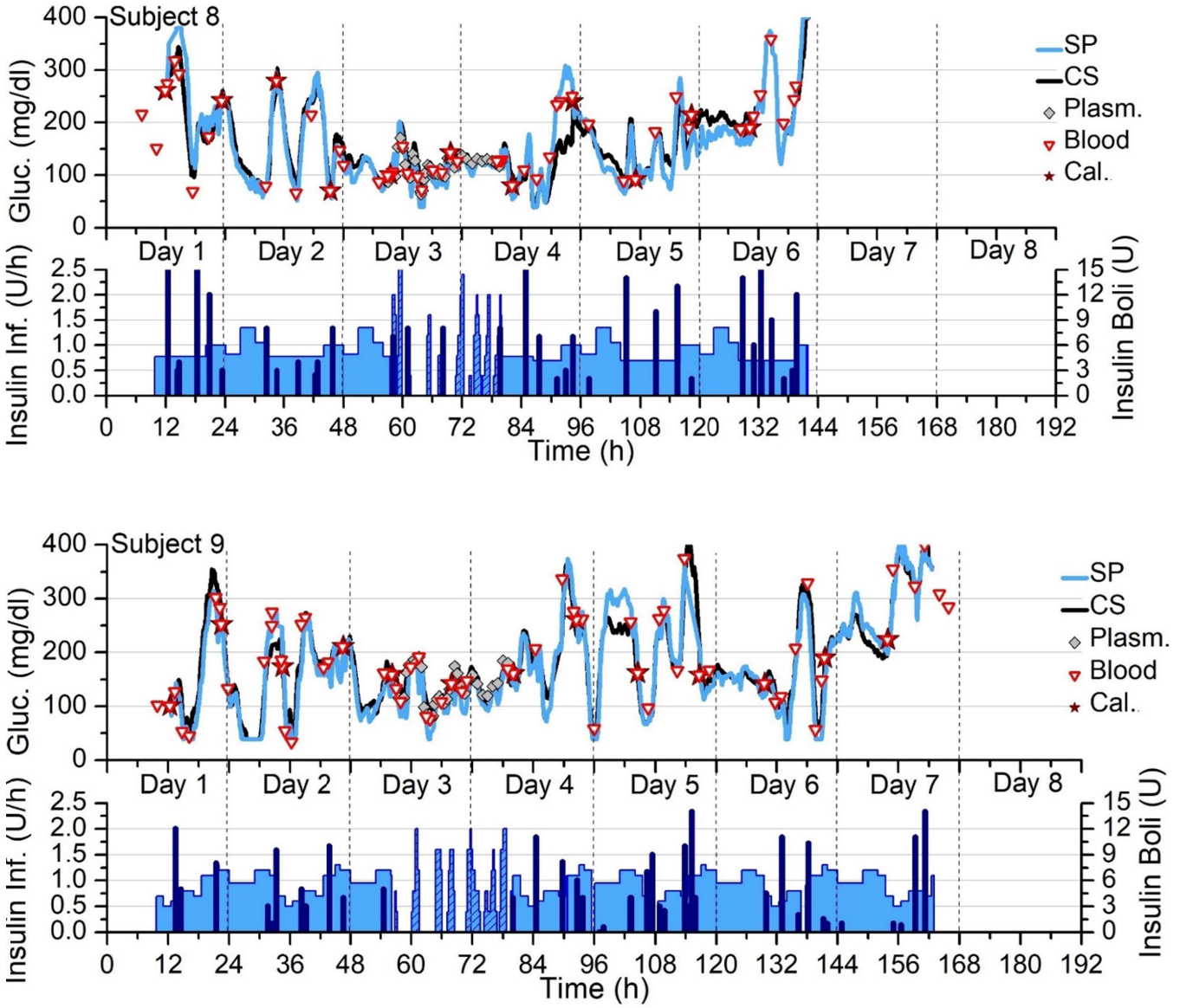

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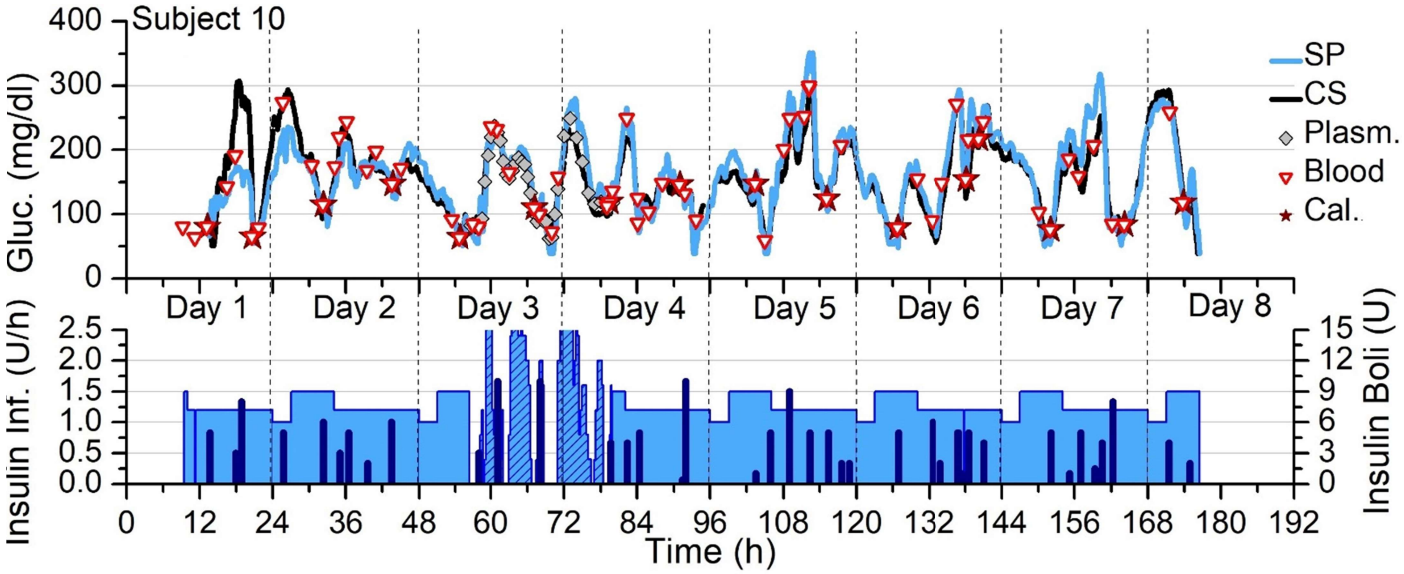

Fig. S1. *Continued*