Glucose Sensing in the Peritoneal Space Offers Faster Kinetics than Sensing in the Subcutaneous Space

Running Title (<48char): Glucose Sensing in the Peritoneal Space

Daniel R. Burnett¹, Lauren M. Huyett², Howard C. Zisser²,³, Francis J. Doyle, III², and Brett D. Mensh¹

Author Affiliations: ¹Theranova, LLC, San Francisco, California; ²University of California Santa Barbara, Santa Barbara, California; ³Sansum Diabetes Research Institute, Santa Barbara, California

Corresponding Author:
Brett D. Mensh, MD, PhD
Theranova, LLC
101 Mississippi St.
San Francisco, CA  94107
Fax:  801-407-2649
Phone:  415-315-9848
bmensh@theranova.com

Number of Figures:  5

Word Count:  2502

Number of Tables:  0
Abstract

The paramount goal in the treatment of type 1 diabetes is the maintenance of normoglycemia. Continuous glucose monitoring (CGM) technologies enable frequent sensing of glucose to inform exogenous insulin delivery timing and dosages. The most commonly available CGMs are limited by the physiology of the subcutaneous (SQ) space in which they reside. The very same advantages of this minimally invasive approach are disadvantages with respect to speed. Because SQ blood flow is sensitive to local fluctuations (e.g., temperature, mechanical pressure), SQ sensing can be slow and variable. We propose the use of a more central, physiologically stable body space for CGM: the intraperitoneal space (IP). We compared the temporal response characteristics of simultaneously placed SQ and IP sensors during intravenous (IV) glucose tolerance tests in eight swine. Using compartmental modeling based on simultaneous IV sensing, blood draws, and intra-arterial sensing, we found that IP kinetics were more than twice as fast as SQ kinetics (mean time constant of 5.6 min IP vs. 12.4 min for SQ). Combined with the known faster kinetics of IP insulin delivery over SQ delivery, our findings suggest that artificial pancreas technologies may be optimized by both sensing glucose and delivering insulin in the IP space.
Tight glycemic control is critical to preventing the devastating long-term sequelae suffered by patients with type 1 diabetes (1). Historically, patients with type 1 diabetes assess their blood glucose (BG) ~2-4 times daily with capillary blood measurements and then administer subcutaneous (SQ) insulin with the short- and long-term goal of reducing overall glycemia. Modern efforts are aimed at mimicking the intact pancreas by increasing the frequency of the measure-and-deliver process, with the goal being to eventually operate in real time and automatically as in an artificial pancreas (AP). The goal in this case is to maintain strict normoglycemia around the clock.

Key to improved glycemic control is the ability to track blood glucose rapidly and accurately, which is the goal of continuous glucose monitoring (CGM) devices. Sensor development efforts all face the paramount design consideration of where in the body to place the sensor. This decision faces a tradeoff between access to the central vasculature and invasiveness-related complications. For example, CGMs in the intravenous (IV) space (2; 3) provide very fast (real-time) information about BG, but indwelling IV devices have an unacceptable safety profile. At the other extreme, non-invasive transcutaneous sensing technologies have been challenged by the presence of myriad anatomical and physiological barriers and confounds between the site of sensing and the bloodstream.

Using the subcutaneous space for glucose sensing provides good proximity to the vasculature while still being minimally invasive and, as such, has become the mainstay of CGM. Overall, SQ sensors are improving, largely due to improved manufacturing and data filtering, but SQ sensing has several limitations. First, the SQ space generates a robust inflammatory response which results in biofouling and encapsulation, in many cases >1mm thick within 3 weeks (4). This consideration limits sensor life to ~2 weeks, according to most manufacturer instructions.
Breakthroughs in biocompatible materials will be required to extend this limitation. Secondly, SQ sensing is susceptible to mechanical pressure applied to the sensors (5). This is especially vexing during sleep, since sleeping on SQ sensors can cause large inaccuracies (6), and sleeping patients are at high risk for hypoglycemic complications (6-16). Thirdly, subcutaneous kinetics have been variably reported to be moderately slow (17-25) and likely worsen with implantation time as the encapsulation develops (26; 27). A recent study has found that radiolabeled glucose could be detected in freshly-implanted sensors in the SQ space within 5-6 minutes after IV injection (28). This degree of delay could enable reasonably fast meal-detection by freshly-implanted sensors. However, in AP applications, the algorithms which guide insulin administration also depend on the kinetic time constant between the vasculature and the site of sensing, which provides a measure of equilibration time and thus is longer than the detection-delay alone. Further, all measure of SQ kinetics are expected to worsen over implantation time, and SQ sensor performance has been shown to be susceptible to decreases in peripheral perfusion (29; 30).

The peritoneal cavity has a number of physiologically advantageous features that lead us to hypothesize that the fluid in the intraperitoneal (IP) space may track blood glucose changes more closely than the interstitial space does. For example, the blood flow to the vessels lining the peritoneal cavity is copious and robust to changes in temperature and cardiac output. While this hypothesis is supported by the physiology literature, which demonstrates preservation of peritoneal transport even in the setting of reduced blood flow (31-33), early studies on the topic were inconclusive (34; 35). Further, the relative foreign-body tolerance of the IP space in humans (36-38) enables chronic implantation of indwelling medical devices (e.g., peritoneal dialysis catheters).
Additional features of the IP space make it worth investigating as a potential site for CGMs. IP glucose kinetics are expected to exhibit robustness to the physiological fluctuations that occur during daily life. During exercise, exposure to extreme outdoor temperatures, or sleep, the IP space is relatively thermally and mechanically protected. By contrast, SQ blood flow is susceptible to these perturbations. For example, in a human sleep study, we recently reported large inaccuracies in SQ sensing that occurred partially as a result of subjects sleeping on the side of sensor placement, reported as a compression effect (6). Yet, no direct quantitative comparison between SQ and IP glucose kinetics has been reported.

In this study, we measured the glucose kinetics of the IP and SQ spaces in anesthetized pigs and found the IP space to be more than twice as fast at tracking changes in blood glucose than the SQ space. The implications of the observed differences for insulin-replacement approaches in diabetes are discussed, including potential challenges of using the IP space for CGM.

**Research Design and Methods**

**Overview of Animal Experiments.** Experiments were conducted under an IACUC-approved protocol. Multiple sensors (described below) were placed in the subcutaneous, intraperitoneal, intravenous, and intra-arterial (IA) spaces of eight anesthetized nondiabetic juvenile female Yorkshire pigs weighing between 60 and 90kg. After allowing several hours for sensor wetting and baseline measures, intravenous hyperglycemia challenges similar to a glucose tolerance test (IVGTT) were administered, consisting of 250 mg/kg of D50 pushed over 2 minutes intravenously by an infusion pump. Venous samples were drawn at frequent intervals post-injection and analyzed by glucometer and YSI (YSI Inc., Yellow Springs, OH) assay. In several
animals, an additional IVGTT was administered, separated from the first challenge by at least 90 minutes.

**Sensors and Placement.** The sensors used in the SQ space were commercially available Dexcom Seven (DEXCOM, San Diego, CA) sensors placed in the pre-abdominal subcutaneous tissue using standard technique for sensor placement per manufacturer instructions. The sensors used in the intravenous and intra-arterial spaces were modified Dexcom Seven sensors, lengthened by attaching 30-gauge wires to the silver and platinum electrodes using conductive silver epoxy, and encapsulating these joints with epoxy to prevent shorts due to fluid intrusion. The IA and IV sensors were placed through introducers after cut-downs to the femoral or jugular vessels. The sensors used in the IP space were modified Dexcom Seven sensors, lengthened in the same manner as the IA/IV sensors and splinted to a short length of Teflon-coated coaxial wire with silicone o-rings in order to prevent the sensors from bending excessively or perforating intraperitoneal tissues. IP sensors were placed in the peritoneal cavity via the Hassan technique. The signal from all sensors was captured with custom potentiostat electronics and read into LabVIEW via an analog-to-digital converter. Prior to all analyses, sensor data was smoothed using a 60-s sliding window average. Some of the data logging for experimental manipulations was done using a clock with 1-minute resolution; since this could introduce a +/- 30-second “error” relative to the sensor board (which recorded at 1-second resolution). Smoothing the sensor data at 60-s, as described above, correspondingly reduced the resolution of the measures to 1-minute.

**Data Analysis: Response Time.** Response characteristics for each sensor were initially quantified using two simple measures on each sensor waveform during the IVGTT. First, to quantify latency between rapid increases in blood glucose and extravascular sensor measures, we
calculated the time to half-maximum (from beginning of IVGTT). Second, to quantify how rapidly the extravascular measures recover toward baseline glucose levels after the bolus, we calculated the percentage by which each sensor reading returned (from its maximum) to baseline at 35 minutes post-glucose-injection.

**Data Analysis: Compartmental Modeling.** To determine the dynamic response characteristics of each space, the IP and SQ sensor signals were modeled for each IVGTT challenge as a function of the vascular glucose concentration. The Systems Identification Toolbox in MATLAB (The MathWorks Inc., Natick, MA) was used to numerically fit the data to a first-order transfer function with time delay using least-squares regression. This type of two-compartment model has been used in previous studies to approximate the transport of glucose between the vascular compartment and the SQ compartment (39-43). The time-domain version of the model is described by the following pair of equations:

\[
\frac{dV_m(t)}{dt} = \frac{1}{\tau} (KV_V(t - \theta) - V_m(t))
\]

where \(V_V(t)\) is the vascular glucose concentration at time \(t\), \(V_m(t)\) is the signal of the sensor being modeled, \(K\) is the model gain, \(\tau\) is the model time constant, and \(\theta\) is the time delay. The time delay quantifies the amount of time it takes for the SQ or IP sensor signal to begin to respond to a change in the vascular glucose. The time constant represents the amount of time it would take for the IP or SQ signal to reach 63% of the vascular glucose concentration if a step change in vascular glucose were applied.

The models were initially fit using glucometer measurements of venous blood to represent the glucose concentration in the vascular compartment \((V_V(t))\), while either the IP or SQ sensor
signal was used for $V_m(t)$. The normalized root-mean-square error fitness value was used to quantify the goodness of fit of the model. This quantity is given by the following equation:

$$F = 100 \left( 1 - \frac{\|y - \hat{y}\|}{\|y - \bar{y}\|} \right)$$

where $y$ is the experimental data (in this case, the sensor signal), $\hat{y}$ is the output of the fitted model, $\bar{y}$ is the mean of $y$, and $F$ is the goodness of fit (%).

If more than one sensor was placed in a particular space during a challenge, the resulting model parameters were averaged. The robustness of the result was subsequently bolstered by comparing model parameters using the following additional data sources as $V_{IV}(t)$ in the model: signal from an indwelling IV sensor and signal from an indwelling IA sensor. In all cases, the parameters generated by compartmental modeling (most importantly the time-constant) are a model-specific measure.

**Data Analysis: Statistics.** 13 IVGGT challenges in 8 animals were successfully carried out. In general, the null hypothesis for the study was that SQ and IP sensor performance is equal. For each set of data in which we asked whether the null hypothesis was rejected, we carried out two statistical tests: one in which we assumed that the challenges were independent even when performed in the same animal (thus, $n=13$), and one in which we assumed that challenges performed in the same animal were completely dependent (thus, $n=8$). In both cases we used the binomial test, which is an exact, non-parametric test of the significance of deviations from a theoretically expected distribution of observations into two categories. The expected distribution according to the null hypothesis is that there is a 50% chance that for a given challenge (or animal) that IP will be faster than SQ, and vice-versa.

**Results**
Figure 1A shows raw sensor current data from a hyperglycemia challenge. Of note are the rapid rise and fall of the intravascular (IA and IV) sensors, and the less rapid waveforms from the extravascular (IP and SQ) sensors. Figure 1B illustrates the response-time analysis described above, in which latency (a measure of how rapidly the tissue glucose increases after a vascular bolus) and recovery (a measure of how rapidly the tissue glucose decreases as the vascular glucose decreases over 35 minutes post-bolus) were read from each sensor curve.

Figure 2A compares the latency between sensors in the SQ and IP spaces for the 13 IVGTT challenges (across eight animals) that were successfully carried out. On this plot, each challenge is depicted as a single point in which the IP latency (y-axis) is plotted against the SQ latency (x-axis) for the same challenge. For each space, latency was calculated as the mean time to half-maximum for all sensors in that space for that challenge. SQ latency was in the 4-8 minute range, consistent with the faster end of the range from prior published results (see Introduction). A diagonal line of identity is included in the plot, which illustrates that for all 13 challenges in all 8 animals, IP latency was shorter than SQ latency (p<0.001 for challenges, p<0.01 for animals). To assess whether wetting time might influence the results, two of the 13 challenges were conducted using SQ sensors that had been wetted overnight instead of for several hours on the morning of the experiments. The results from these sensors were in the middle of the range of the overall results, suggesting that overnight wetting does not have a large effect on SQ response times. However, because we only performed this on two sensors, we do not have the statistical power to quantify small influences.

Figure 2B compares the post-glucose-bolus recovery between the two sensor spaces, in a plot similar to Figure 2A. The average recovery for the SQ space was 33%, compared to 59% for the IP space. For all challenges, the IP space showed more complete return to pre-challenge baseline
glucose levels than the SQ space (all points above diagonal identity line, \( p < 0.001 \) for challenges, \( p < 0.01 \) for animals). Finally, we quantified the glucose kinetics of the SQ and IP spaces using compartmental modeling, in which the glucometer measurements served as an input function and the transport of glucose into the body spaces was modeled with a first-order transfer function. The glucometer measurements were used in place of the YSI measurements because the YSI data was too sparse to use as a model input. This approach yielded excellent fits to the data, as illustrated in Figure 3; across all challenges the mean goodness of fit was 75.6\% (SD 8.5\%) for the IP sensor data and 83.2\% (SD 8.9\%) for the SQ sensor data. The \textit{a posteriori} identifiability of all model parameters was confirmed (data not shown). The uncertainty of the parameters as determined from the covariance matrix was so small as to be negligible (standard deviations on the order of 1\% of fitted values).

As illustrated in Figure 4, IP glucose kinetics during IVGTT were an average of 2.3 times faster than SQ (range: 1.2 to 4.1, standard deviation: 1). The mean time constant was 5.6 (SD 2.9) minutes for the IP space and 12.4 (SD 3.6) minutes for the SQ space. The difference between the SQ and IP time constants was statistically significant, with the IP time constant smaller than that of SQ for all 13 challenges (by paired t-test, \( p < 0.001 \); by binomial test \( p < 0.001 \) for challenges, \( p < 0.01 \) for animals). The mean time delays were 0.68 (SD 0.58) minutes and 1.4 (SD 0.90) minutes for IP and SQ sensors, respectively, although there was an estimated tolerance of 30 seconds to account for potential differences in clock synchronization. Still, the delay for the IP sensor was significantly smaller than the SQ delay (by paired t-test, \( p = 0.019 \)). The addition of second-order dynamics did not improve the model fit (data not shown).

In order to demonstrate the robustness of the finding that IP kinetics are more than twice as fast as SQ kinetics, we repeated the modeling analysis using additional sources of data to represent
the vascular glucose concentration in the model ($V_{IV}(t)$ in Equation 1). For the challenges that had usable indwelling IA and/or IV sensors, the readings from those sensors were used as the input for modeling. Thus, the kinetics were modeled using the following three representations of the blood glucose concentration, unless a viable signal was not available: indwelling IV sensor, indwelling IA sensor, and glucometer measurements of venous blood. Figure 5 demonstrates that the >twofold speed increase for IP over SQ is independent of input-function source.

**Discussion**

In summary, we show that glucose kinetics between the bloodstream and the IP space are substantially faster than between the bloodstream and the SQ space, demonstrating the suitability of the intraperitoneal space for more rapidly measuring changes in BG. This is likely due to the robustness of peritoneal transport, which is, for example, why this space is effectively used for dialysis in patients with renal failure.

The performance difference between sensing in the IP and SQ spaces is of particular importance when considered in the context of closed-loop artificial pancreas (AP) implementations. After a glycemic meal, an ideal AP system would bring plasma glucose levels back to baseline nearly as quickly as an endogenous pancreas; however, with long return-to-baseline delays in CGM devices and slow SQ insulin kinetics, the algorithm must either delay insulin administration (forgoing tight glycemic control) or risk overshooting into hypoglycemia. Reduction of delays in the feedback loop for the AP has been shown to provide quantitative improvements in controller performance (44). In parallel work, we are using the mathematical model for glucose sensing kinetics developed in this study to inform an *in silico* evaluation of the benefits of IP sensors for closed-loop control with an artificial pancreas in combination with IP insulin delivery.
As described in the introduction, the decision of where to place CGM sensors involves a tradeoff between rapid access to plasma glucose, durability with respect to avoidance of tissue effects and invasiveness-related complications. The IP space may optimize this tradeoff, as previous work has shown that the IP space has an excellent safety profile, with no peritonitis across 63 patients over 381 patient years of implantation (36). While the safety risk profile will not be identical, since the sensor does not deliver a hormone with growth like properties, we do expect a sensor to have a nearly identical safety risk profile. Furthermore, unlike catheters placed in the central vasculature which have been found to occlude in up to 36% of patients within 1-2 years (45), peritoneal dialysis catheters have been found to have a mechanical failure rate of only 0.5% over 21 months when the catheter is placed in the true pelvis beyond the reach of the omentum (46). In addition, while this space would have very little, if any, inherent lag, central venous catheters place patients at risk for long-term vascular complications related to catheter-related thrombosis which occurs in up to 50% of children and 66% of adults with a long-term central venous catheterization (45).

However, tissue effects are still a potential problem, particularly with catheters placed in the upper quadrants of the peritoneal cavity. Haveman also showed that in the absence of a mechanism to prevent encapsulation, 49 re-operations were required in 63 patients over 381 patient years for catheter clogging (36). Thus, although the development of encapsulation in the IP space is much slower than in the SQ space, it is still an issue that needs to be contended with, in order to realize the goal of a long-term, fully-implanted, durable artificial pancreas. Additionally, although the IP space is more mechanically protected than the SQ space (by virtue of being further from intrusion by objects in the environment), the IP space does experience
mechanical motion and pressure fluctuations during normal activities such as breathing and peristalsis which may impact signal stability.

Acknowledgements
We gratefully acknowledge support from the National Institutes of Health (specifically the National Institute of Diabetes, Digestive, and Kidney Diseases, NIDDK), the Juvenile Diabetes Research Foundation, and the Helmsley Charitable Trust. This work was also supported by the National Science Foundation Graduate Research Fellowship Program. We also express our gratitude to Dr. Eyal Dassau for contributions to discussions and comments on the manuscript.

D.R.B. and B.D.M. designed and conducted experiments, analyzed data, and wrote and revised the manuscript. L.M.H. performed data modeling and analysis, and wrote and revised the manuscript. H.Z. designed and conducted experiments, and also revised the manuscript. F.J.D. analyzed data, contributed to discussion, and revised the manuscript.

D.R.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity.

Both D.R.B. and B.D.M. have proprietary interest in artificial pancreas technologies including sensing in the peritoneal space.
References

1. The Diabetes Control and Complications Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-986
2. Clemens AH, Chang PH, Myers RW: The development of biostator, a glucose controlled insulin infusion system (GCIIS). Horm Metab Res 1977;Suppl 7:23-33
3. Albisser AM, Leibel BS, Ewart TG, Davidovac Z, Botz CK, Zingg W: An artificial endocrine pancreas. Diabetes 1974;23:389-396
4. Gough DA, Kumosa LS, Routh TL, Lin JT, Lucisano JY: Function of an implanted tissue glucose sensor for more than 1 year in animals. Sci Transl Med 2010;2:42ra53
5. Helton KL, Ratner BD, Wisniewski NA: Biomechanics of the sensor-tissue interface-effects of motion, pressure, and design on sensor performance and foreign body response-part II: examples and application. J Diabetes Sci Technol 2011;5:647-656
6. Mensh BD, Wisniewski NA, Neil BM, Burnett DR: Susceptibility of interstitial continuous glucose monitor performance to sleeping position. J Diabetes Sci Technol 2013;7:863-870
7. Group The Diabetes Control and Complications Research Group: Hypoglycemia in the diabetes control and complications trial. Diabetes 1997;46:271-286
8. Banarer S, Cryer PE: Sleep-related hypoglycemia-associated autonomic failure in type 1 diabetes: reduced awakening from sleep during hypoglycemia. Diabetes 2003;52:1195-1203
9. Cryer PE: The barrier of hypoglycemia in diabetes. Diabetes 2008;57:3169-3176
10. DeVries JH, Wentholt IM, Masurel N, Mantel I, Poscia A, Maran A, Heine RJ: Nocturnal hypoglycaemia in type 1 diabetes--consequences and assessment. Diabetes Metab Res Rev 2004;20 Suppl 2:S43-46

11. Fanelli CG, Paramore DS, Hershey T, Terkamp C, Ovalle F, Craft S, Cryer PE: Impact of nocturnal hypoglycemia on hypoglycemic cognitive dysfunction in type 1 diabetes. Diabetes 1998;47:1920-1927

12. Guillod L, Comte-Perret S, Monbaron D, Gaillard RC, Ruiz J: Nocturnal hypoglycaemias in type 1 diabetic patients: what can we learn with continuous glucose monitoring? Diabetes Metab 2007;33:360-365

13. Jones TW, Porter P, Sherwin RS, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV: Decreased epinephrine responses to hypoglycemia during sleep. N Engl J Med 1998;338:1657-1662

14. McGowan K, Thomas W, Moran A: Spurious reporting of nocturnal hypoglycemia by CGMS in patients with tightly controlled type 1 diabetes. Diabetes Care 2002;25:1499-1503

15. Porter PA, Keating B, Byrne G, Jones TW: Incidence and predictive criteria of nocturnal hypoglycemia in young children with insulin-dependent diabetes mellitus. J Pediatr 1997;130:366-372

16. Tanenberg RJ, Newton CA, Drake AJ: Confirmation of hypoglycemia in the "dead-in-bed" syndrome, as captured by a retrospective continuous glucose monitoring system. Endocr Pract 2010;16:244-248

17. Boyne MS, Silver DM, Kaplan J, Saudek CD: Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. Diabetes 2003;52:2790-2794
18. Davey RJ, Low C, Jones TW, Fournier PA: Contribution of an intrinsic lag of continuous glucose monitoring systems to differences in measured and actual glucose concentrations changing at variable rates in vitro. J Diabetes Sci Technol 2010;4:1393-1399

19. Dye L, Mansfield M, Lasikiewicz N, Mahawish L, Schnell R, Talbot D, Chauhan H, Croden F, Lawton C: Correspondence of continuous interstitial glucose measurement against arterialised and capillary glucose following an oral glucose tolerance test in healthy volunteers. Br J Nutr 2010;103:134-140

20. Hullegie LM, Lutgers HL, Dullaart RP, Sluiter WJ, Wientjes KJ, Schoonen AJ, Hoogenberg K: Effects of glucose and insulin levels on adipose tissue glucose measurement by microdialysis probes retained for three weeks in type 1 diabetic patients. Neth J Med 2000;57:13-19

21. Jungheim K, Wientjes KJ, Heinemann L, Lodwig V, Koschinsky T, Schoonen AJ: Subcutaneous continuous glucose monitoring: feasibility of a new microdialysis-based glucose sensor system. Diabetes Care 2001;24:1696-1697

22. Lutgers HL, Hullegie LM, Hoogenberg K, Sluiter WJ, Dullaart RP, Wientjes KJ, Schoonen AJ: Microdialysis measurement of glucose in subcutaneous adipose tissue up to three weeks in type 1 diabetic patients. Neth J Med 2000;57:7-12

23. Schoonen AJ, Wientjes KJ: A model for transport of glucose in adipose tissue to a microdialysis probe. Diabetes Technol Ther 2003;5:589-598

24. Wientjes KJ, Schoonen AJ: Determination of time delay between blood and interstitial adipose tissue glucose concentration change by microdialysis in healthy volunteers. Int J Artif Organs 2001;24:884-889
25. Wientjes KJ, Vonk P, Vonk-van Klei Y, Schoonen AJ, Kossen NW: Microdialysis of glucose in subcutaneous adipose tissue up to 3 weeks in healthy volunteers. Diabetes Care 1998;21:1481-1488

26. Wisniewski N, Reichert M: Methods for reducing biosensor membrane biofouling. Colloids Surf B Biointerfaces 2000;18:197-219

27. Wolpert HA: Use of continuous glucose monitoring in the detection and prevention of hypoglycemia. J Diabetes Sci Technol 2007;1:146-150

28. Basu A, Dube S, Slama M, Errazuriz I, Amezcuja JC, Kudva YC, Peyser T, Carter RE, Cobelli C, Basu R: Time lag of glucose from intravascular to interstitial compartment in humans. Diabetes 2013;

29. Cengiz E, Tamborlane WV: A tale of two compartments: interstitial versus blood glucose monitoring. Diabetes Technol Ther 2009;11 Suppl 1:S11-16

30. Stout PJ, Racchini JR, Hilgers ME: A novel approach to mitigating the physiological lag between blood and interstitial fluid glucose measurements. Diabetes Technol Ther 2004;6:635-644

31. Boquist L, Lernmark A: Effects on the endocrine pancreas in Chinese hamsters fed zinc deficient diets. Acta Pathol Microbiol Scand 1969;76:215-228

32. Flessner MF, Lofthouse J: Blood flow does not limit peritoneal transport. Perit Dial Int 1999;19 Suppl 2:S102-105

33. Ungerstedt J, Nowak G, Ericzon BG, Ungerstedt U: Intraperitoneal microdialysis (IPM): a new technique for monitoring intestinal ischemia studied in a porcine model. Shock 2003;20:91-96
34. Velho G, Froguel P, Reach G: Determination of peritoneal glucose kinetics in rats: implications for the peritoneal implantation of closed-loop insulin delivery systems. Diabetologia 1989;32:331-336

35. Wolfson SK, Jr., Tokarsky JF, Yao SJ, Krupper MA: Glucose concentration at possible sensor tissue implant sites. Diabetes Care 1982;5:162-165

36. Haveman JW, Logtenberg SJ, Kleefstra N, Groenier KH, Bilo HJ, Blomme AM: Surgical aspects and complications of continuous intraperitoneal insulin infusion with an implantable pump. Langenbecks Arch Surg 2010;395:65-71

37. Klossner J, Kivisaari J, Niinikoski J: Oxygen and carbon dioxide tensions in the abdominal cavity and colonic wall of the rabbit. Am J Surg 1974;127:711-715

38. Renvall S, Niinikoski J: Intraperitoneal oxygen and carbon dioxide tensions in experimental adhesion disease and peritonitis. Am J Surg 1975;130:286-292

39. Breton M, Kovatchev B: Analysis, modeling, and simulation of the accuracy of continuous glucose sensors. J Diabetes Sci Technol 2008;2:853-862

40. Keenan DB, Mastrototaro JJ, Voskanyan G, Steil GM: Delays in minimally invasive continuous glucose monitoring devices: a review of current technology. J Diabetes Sci Technol 2009;3:1207-1214

41. King C, Anderson SM, Breton M, Clarke WL, Kovatchev BP: Modeling of calibration effectiveness and blood-to-interstitial glucose dynamics as potential confounders of the accuracy of continuous glucose sensors during hyperinsulinemic clamp. J Diabetes Sci Technol 2007;1:317-322

42. Rebrin K, Steil GM: Can interstitial glucose assessment replace blood glucose measurements? Diabetes Technol Ther 2000;2:461-472
43. Steil GM, Rebrin K, Hariri F, Jinagonda S, Tadros S, Darwin C, Saad MF: Interstitial fluid glucose dynamics during insulin-induced hypoglycaemia. Diabetologia 2005;48:1833-1840

44. Lee JJ, Dassau E, Zisser H, Weinzimer S, Tamborlane WV, Doyle III FJ: Impact of pharmacokinetics and pharmacodynamics on the closed-loop artificial pancreas. In Proceedings of Conference on Decision and Control Florence, Italy, 2013

45. Baskin BL, Pui CH, Reiss U, Wilimas J, Metzger ML, Ribiero RC, Howard, SC: Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. Lancet. 2009 July 11; 374(9684), 1-23.

46. Crabtree JH, Fishman A: A Laparoscopic Method for Optimal Peritoneal Dialysis Access. The American Surgeon. 2005 Feb vol. 71, 135-43.
FIGURE LEGENDS

Figure 1. (A) Sample raw data from an intravenous glucose challenge in one pig. Unfiltered data were collected every second (1 Hz). (B) Calculation of latency (time-to-half-maximum) and recovery (percent return-to-baseline at 35 minutes) for a sample IP trace. Data are filtered using a 1-minute sliding window average. Baseline is determined by the average reading for the 3 minutes prior to onset of glucose challenge. As with baseline, the value at 35 minutes is also determined by a 3-minute average (33.5 to 36.5 minutes).

Figure 2. Comparison of response speed between IP and SQ sensors. (A) Latency (time to half-maximum) is plotted for IP vs. SQ for all 13 challenges across eight pigs. The diagonal line represents IP=SQ; thus points below the line indicate IP faster than SQ. (B) Recovery (Percent return to baseline at 35 minutes, see Figure 1B for definition) is plotted for IP vs. SQ for all 13 challenges across eight pigs. The diagonal line of identity represents IP=SQ; thus points above the line indicate IP sensor readings returning to baseline by a greater amount than SQ sensors returned to baseline for the same IVGTT challenge.

Figure 3. Sample of compartmental modeling fit to data. This plot shows an example of the model fitting process for a single challenge, using glucometer measurements as the input (black circles). Shown on the plot are the experimental measurements made by the IP and SQ sensors (white triangles and white squares, respectively), as well as the model predicted output for each sensor (solid line and dashed line). The goodness of fit values for the IP and SQ models shown were 89% and 90%, with time constants of 1.7 min. and 13.1 min., respectively.
Figure 4. Comparison of kinetic-modeling-based response speed between IP and SQ sensors for all 13 challenges. The diagonal line represents IP=SQ; thus points below the line indicate IP time constants smaller (faster) than SQ.

Figure 5. Comparison of kinetic time constants between subcutaneous and intraperitoneal sensors from models fit using three different input sources for vascular glucose concentration. The average ratio is shown, with error bars indicating the standard error. The number above the bar specifies the number of challenges that had a usable signal from that particular type of input. For each type of input, the average IP time constant was less than half of the SQ time constant from the same challenge.
Figure 1. (A) Sample raw data from an intravenous glucose challenge in one pig. Unfiltered data were collected every second (1 Hz). (B) Calculation of latency (time-to-half-maximum) and recovery (percent return-to-baseline at 35 minutes) for a sample IP trace. Data are filtered using a 1-minute sliding window average. Baseline is determined by the average reading for the 3 minutes prior to onset of glucose challenge. As with baseline, the value at 35 minutes is also determined by a 3-minute average (33.5 to 36.5 minutes).
Figure 2. Comparison of response speed between IP and SQ sensors. (A) Latency (time to half-maximum) is plotted for IP vs. SQ for all 13 challenges across eight pigs. The diagonal line represents IP=SQ; thus points below the line indicate IP faster than SQ. (B) Recovery (Percent return to baseline at 35 minutes, see Figure 1B for definition) is plotted for IP vs. SQ for all 13 challenges across eight pigs. The diagonal line of identity represents IP=SQ; thus points above the line indicate IP sensor readings returning to baseline by a greater amount than SQ sensors returned to baseline for the same IVGTT challenge.
Figure 3. Sample of compartmental modeling fit to data. This plot shows an example of the model fitting process for a single challenge, using glucometer measurements as the input (black circles). Shown on the plot are the experimental measurements made by the IP and SQ sensors (white triangles and white squares, respectively), as well as the model predicted output for each sensor (solid line and dashed line). The goodness of fit values for the IP and SQ models shown were 89% and 90%, with time constants of 1.7 min. and 13.1 min., respectively.

99x55mm (300 x 300 DPI)
Figure 4. Comparison of kinetic-modeling-based response speed between IP and SQ sensors for all 13 challenges. The diagonal line represents IP=SQ; thus points below the line indicate IP time constants smaller (faster) than SQ.
Figure 5. Comparison of kinetic time constants between subcutaneous and intraperitoneal sensors from models fit using three different input sources for vascular glucose concentration. The average ratio is shown, with error bars indicating the standard error. The number above the bar specifies the number of challenges that had a usable signal from that particular type of input. For each type of input, the average IP time constant was less than half of the SQ time constant from the same challenge.