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

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PHARMACOLOGY AND THERAPEUTICS

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 space in which they reside. The very same advantages of this minimally invasive approach are disadvantages with respect to speed. Because subcutaneous blood flow is sensitive to local fluctuations (e.g., temperature, mechanical pressure), subcutaneous sensing can be slow and variable. We propose the use of a more central, physiologically stable body space for CGM: the intraperitoneal space. We compared the temporal response characteristics of simultaneously placed subcutaneous and intraperitoneal sensors during intravenous glucose tolerance tests in eight swine. Using compartmental modeling based on simultaneous intravenous sensing, blood draws, and intraarterial sensing, we found that intraperitoneal kinetics were more than twice as fast as subcutaneous kinetics (mean time constant of 5.6 min for intraperitoneal vs. 12.4 min for subcutaneous). Combined with the known faster kinetics of intraperitoneal insulin delivery over subcutaneous delivery, our findings suggest that artificial pancreas technologies may be optimized by sensing glucose and delivering insulin in the intraperitoneal 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 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 BG 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 trade-off between access to the central vasculature and invasiveness-related complications. For example, CGMs in the intravenous space (2,3) provide very fast (real-time) information about BG, but indwelling intravenous devices have an unacceptable safety profile. At the other extreme, noninvasive 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, subcutaneous sensors are improving, largely due to improved manufacturing and data filtering, but subcutaneous sensing has several limitations. First, the subcutaneous space generates a robust inflammatory response that results in biofouling and encapsulation, in many cases >1-mm thick within

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3 weeks (4). This consideration limits sensor life to ~2 weeks, according to most manufacturer's instructions. Breakthroughs in biocompatible materials will be required to extend this limitation. Secondly, subcutaneous sensing is susceptible to mechanical pressure applied to the sensors (5). This is especially vexing during sleep, because sleeping on subcutaneous 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 subcutaneous space within 5–6 min after an intravenous injection (28). This degree of delay could enable reasonably fast meal detection by freshly implanted sensors. However, in AP applications, the algorithms that 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 measures of subcutaneous kinetics are expected to worsen over implantation time, and subcutaneous 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 space may track BG 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. Although 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 intraperitoneal space in humans (36–38) enables long-term implantation of indwelling medical devices (e.g., peritoneal dialysis catheters).

Additional features of the intraperitoneal space make it worth investigating as a potential site for CGMs. Intraperitoneal 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 intraperitoneal space is relatively thermally and mechanically protected. By contrast, subcutaneous blood flow is susceptible to these perturbations. In a human sleep study, for example, we recently reported large inaccuracies in subcutaneous 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 subcutaneous and intraperitoneal glucose kinetics has been reported.

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

RESEARCH DESIGN AND METHODS

Overview of Animal Experiments

Experiments were conducted under a protocol approved by the institutional animal care and use committee. Multiple sensors (described below) were placed in the subcutaneous, intraperitoneal, intravenous, and intraarterial spaces of eight anesthetized nondiabetic juvenile female Yorkshire pigs weighing between 60 and 90 kg. After allowing several hours for sensor wetting and baseline measures, intravenous hyperglycemia challenges similar to an intravenous glucose tolerance test (IVGTT) were administered, consisting of 250 mg/kg D50 pushed over 2 min intravenously by an infusion pump. Venous samples were drawn at frequent intervals postinjection 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 min.

Sensors and Placement

The sensors used in the subcutaneous space were commercially available Dexcom SEVEN (Dexcom, San Diego, CA) sensors placed in the preabdominal subcutaneous tissue using standard technique for sensor placement according to the manufacturer's instructions. The sensors used in the intravenous and intraarterial 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 intraarterial and intravenous sensors were placed through introducers after cutdowns to the femoral or jugular vessels. The sensors used in the intraperitoneal space were modified Dexcom SEVEN sensors, lengthened in the same manner as the intraarterial and intravenous sensors and splinted to a short length of Teflon-coated coaxial wire with silicone O rings to prevent the sensors from bending excessively or perforating intraperitoneal tissues. The intraperitoneal sensors were placed in the peritoneal cavity by the Hassan technique.

The signal from all sensors was captured with custom potentiostat electronics and read into LabVIEW by an analog-to-digital converter. Before all analyses, sensor data were smoothed using a 60-s sliding window average. Some of the data logging for experimental manipulations was done using a clock with 1-min resolution; this could introduce a ± 30-s "error" relative to the sensor board, which recorded at 1-s resolution. However, smoothing the sensor data at 60 s, as described above, correspondingly reduced the effective resolution of the measures to ~1 min.

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 BG and extravascular sensor measures, we calculated the time to half-maximum (from the beginning of the IVGTT). Second, to quantify how rapidly the extravascular measures recovered toward baseline glucose levels after the bolus, we calculated the percentage by which each sensor reading returned (from its maximum) to baseline at 35 min after the glucose injection.

Data Analysis: Compartmental Modeling

To determine the dynamic response characteristics of each space, the intraperitoneal and subcutaneous 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 subcutaneous compartment (39–43). The time-domain version of the model is described by the following pair of equations:

$$\frac{dV_m(t)}{dt} = \frac{1}{\tau}\ (KV_{IV}(t-\theta) - V_m(t)) \qquad (1)$$

where $V_{IV}(t)$ is the vascular glucose concentration at time t, $V_m(t)$ is the signal of the sensor being modeled, K is the model gain, τ is the model time constant, and θ is the time delay. The time delay quantifies the amount of time it takes for the subcutaneous or intraperitoneal 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 intraperitoneal or subcutaneous 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 [$V_{IV}(t)$], whereas the intraperitoneal or subcutaneous 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:

$$F = 100\left(1 - \frac{y-\hat{y}}{y-\bar{y}}\right) \qquad (2)$$

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 intravenous sensor and signal from an indwelling intraarterial sensor. In all cases, the parameters generated by compartmental modeling (most importantly the time constant) are a model-specific measure.

Data Analysis: Statistics

Thirteen IVGGT challenges in eight animals were successfully carried out. In general, the null hypothesis for the study was that subcutaneous and intraperitoneal sensor performance is equal. For each set of data in which we asked whether the null hypothesis was rejected, we performed 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, nonparametric 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 intraperitoneal will be faster than subcutaneous, and vice versa.

RESULTS

Figure 1*A* shows raw sensor current data from a hyperglycemia challenge. Of note are the rapid rise and fall of the intravascular (intraarterial and intravenous) sensors, and the less rapid waveforms from the extravascular (intraperitoneal and subcutaneous) sensors. Figure 1*B* 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 min postbolus) were read from each sensor curve.

Figure 2*A* compares the latency between sensors in the subcutaneous and intraperitoneal 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 intraperitoneal latency (y-axis) is plotted against the subcutaneous 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. Subcutaneous latency was in the 4–8 min 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 eight animals, intraperitoneal latency was shorter than subcutaneous latency ($P < 0.001$ for challenges, $P < 0.01$ for animals). To assess whether wetting time might influence the results, 2 of

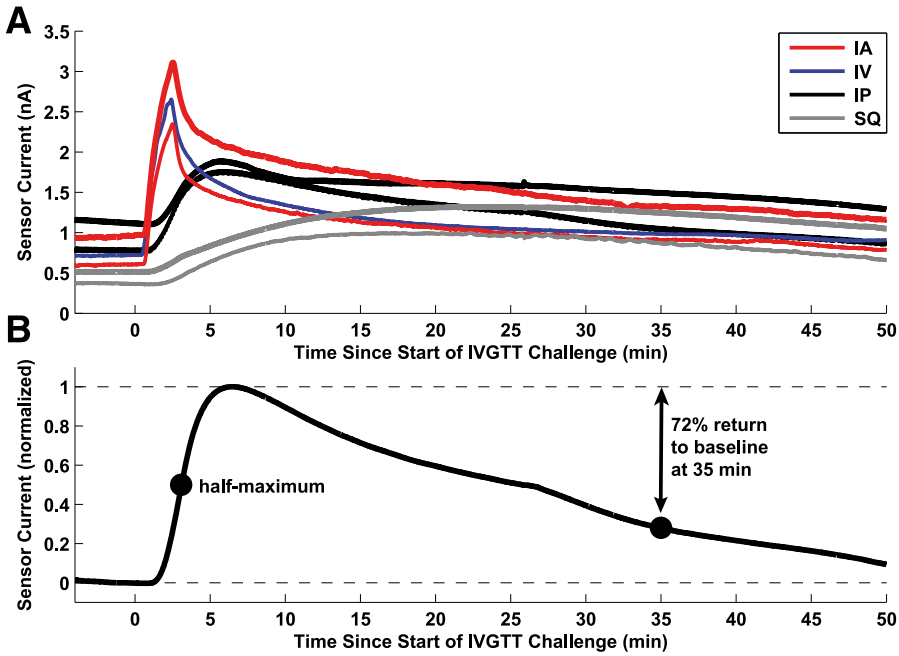

Figure 1—*A*: Sample raw data from an intravenous (IV) glucose challenge in one pig. Unfiltered data were collected every second (1 Hz). *B*: Calculation of latency (time to half-maximum) and recovery (percent return to baseline at 35 min) for a sample intraperitoneal (IP) trace. Data are filtered using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

the 13 challenges were conducted using subcutaneous 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 subcutaneous response times. However, because we only performed this on two sensors, we do not have the statistical power to quantify small influences.

Figure 2*B* compares the postglucose-bolus recovery between the two sensor spaces in a plot similar to Fig. 2*A*. The average recovery for the subcutaneous space was 33%, compared with 59% for the intraperitoneal space. For all challenges, the intraperitoneal space showed a more complete return to prechallenge baseline glucose levels than the subcutaneous 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 subcutaneous and

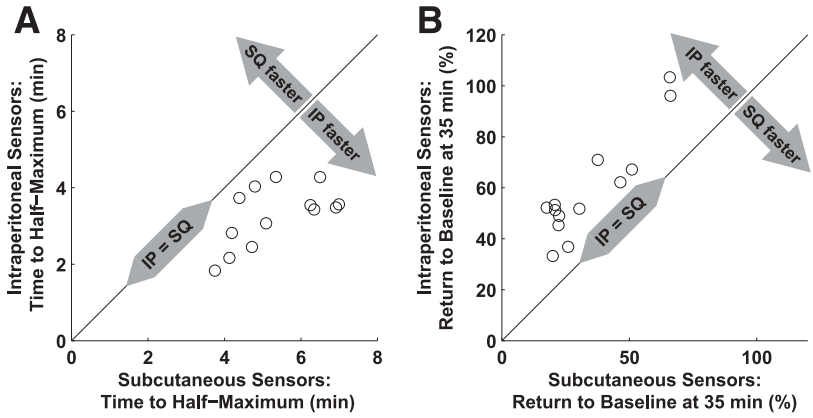

Figure 2—Comparison of response speed between intraperitoneal and subcutaneous sensors. *A*: Latency (time to half-maximum) is plotted for intraperitoneal (IP) vs. subcutaneous (SQ) for all 13 challenges across eight pigs. The diagonal line represents intraperitoneal = subcutaneous; thus, points below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

intraperitoneal 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 were too sparse to use as a model input. This approach yielded excellent fits to the data, as illustrated in Fig. 3; the mean goodness of fit across all challenges was 75.6% (SD 8.5%) for the intraperitoneal sensor data and 83.2% (SD 8.9%) for the subcutaneous sensor data. The 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 (SDs on the order of 1% of fitted values)

As illustrated in Fig. 4, intraperitoneal glucose kinetics during the IVGTT were an average of 2.3 times faster than subcutaneous (range 1.2–4.1, SD 1). The mean time constant was 5.6 (SD 2.9) min for the intraperitoneal space and 12.4 (SD 3.6) min for the subcutaneous space. The difference between the subcutaneous and intraperitoneal time constants was statistically significant, with the intraperitoneal time constant smaller than that of subcutaneous 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) min for intraperitoneal sensors and 1.4 (SD 0.90) min for subcutaneous sensors, although there was an estimated tolerance of 30 s to account for potential differences in clock synchronization (as described in RESEARCH DESIGN AND METHODS). Still, the delay for the intraperitoneal sensor was significantly smaller than for the subcutaneous delay (by paired t test, $P = 0.019$). The addition of second-order dynamics did not improve the model fit (data not shown).

To demonstrate the robustness of the finding that intraperitoneal kinetics are more than twice as fast as subcutaneous kinetics, we repeated the modeling analysis using additional sources of data to represent the vascular glucose concentration in the model [$V_{IV}(t)$ in Eq. 1]. For the challenges that had usable indwelling intraarterial and/or intravenous 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 BG concentration, unless a viable signal was not available: indwelling intravenous sensor, indwelling intraarterial sensor, and glucometer measurements of venous blood. Figure 5 demonstrates that the more than twofold speed increase for intraperitoneal over subcutaneous is independent of input-function source.

DISCUSSION

In summary, we show that glucose kinetics between the bloodstream and the intraperitoneal space are substantially faster than between the bloodstream and the subcutaneous 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 intraperitoneal and subcutaneous spaces is of particular importance when considered in the context of closed-loop 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 subcutaneous insulin kinetics, the algorithm must delay insulin administration (forgoing tight glycemic control) or risk overshooting into hypoglycemia. Reduction of delays

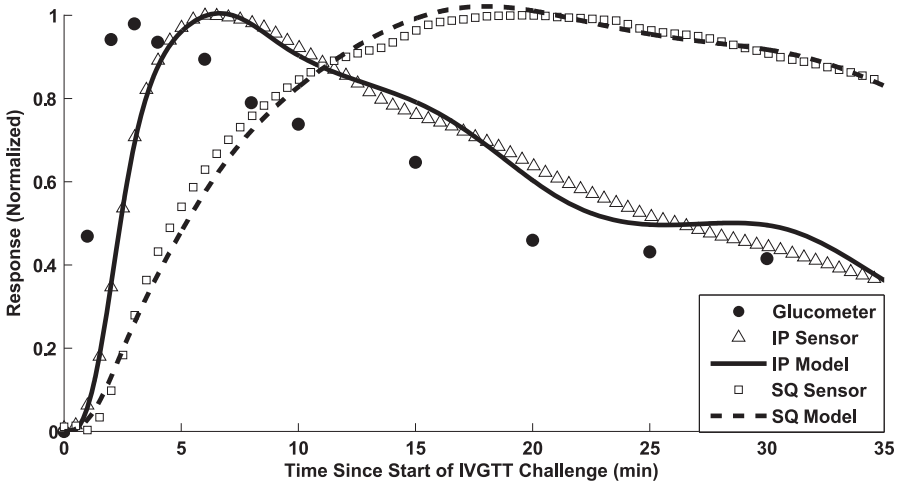

Figure 3—Sample of compartmental modeling fit to data. This plot shows an example of the model-fitting process for a single challenge, using glucometer measurements as the input. Shown on the plot are the experimental measurements made by the intraperitoneal (IP) and subcutaneous (SQ) sensors, as well as the model predicted output for each sensor model. The goodness-of-fit values for the intraperitoneal and subcutaneous models shown were 89% and 90%, with time constants of 1.7 and 13.1 min, respectively.

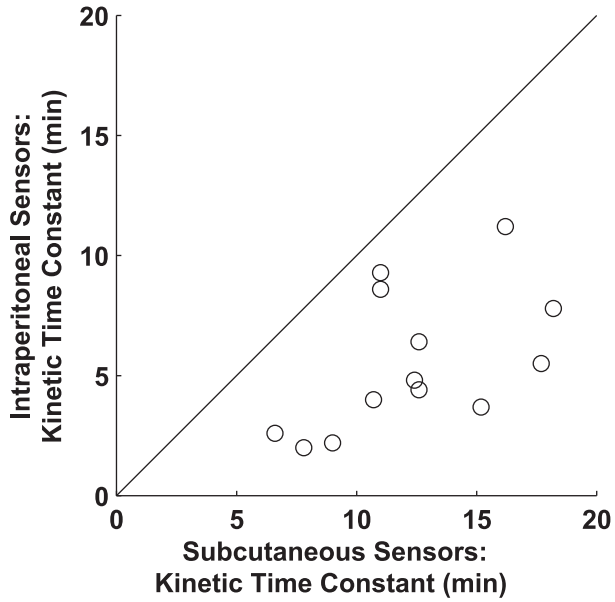

Figure 4—Comparison of kinetic modeling–based response speed between intraperitoneal and subcutaneous sensors for all 13 challenges. The diagonal line represents intraperitoneal = subcutaneous; thus, points below the line indicate intraperitoneal time constants smaller (faster) than subcutaneous.

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 intraperitoneal sensors for closed-loop control with an AP in combination with intraperitoneal insulin delivery.

As described in the Introduction, the decision of where to place CGM sensors involves a trade-off between rapid access to plasma glucose, durability with respect to avoidance of tissue effects, and invasiveness-related complications. The intraperitoneal space may optimize this trade-off, because previous work has shown that the intraperitoneal space has an excellent safety profile, with no peritonitis across 63 patients over 381 patient-years of implantation (36). Although the safety risk profile will not be identical, because 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, although 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 in 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

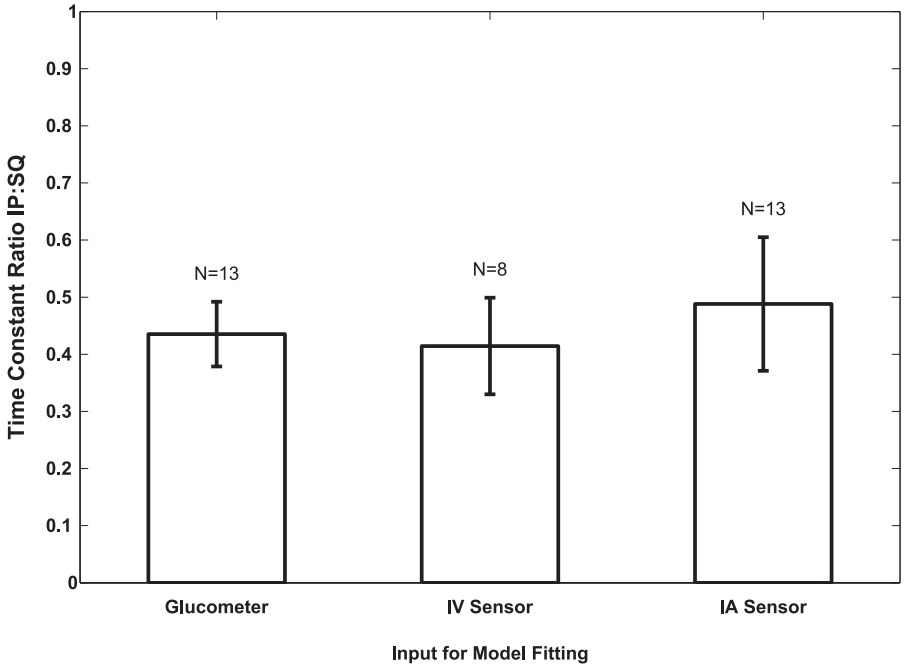

Figure 5—Comparison of kinetic time constants between subcutaneous (SQ) and intraperitoneal (IP) sensors from models fit using three different input sources for vascular glucose concentration. The average ratio is shown, with error bars indicating the standard error. The number above the bar specifies the number of challenges that had a usable signal from that particular type of input. For each type of input, the average intraperitoneal time constant was less than half of the subcutaneous time constant from the same challenge. IA, intraarterial; IV, intravenous.

of the peritoneal cavity. Haveman et al. (36) also showed that in the absence of a mechanism to prevent encapsulation, 49 reoperations were required in 63 patients over 381 patient-years for catheter clogging. Thus, although the development of encapsulation in the intraperitoneal space is much slower than in the subcutaneous space, it is still an issue that needs to be contended with to realize the goal of a long-term, fully implanted, durable AP. In addition, although the intraperitoneal space is more mechanically protected than the subcutaneous space (by virtue of being further from intrusion by objects in the environment), the intraperitoneal space does experience mechanical motion and pressure fluctuations during normal activities, such as breathing and peristalsis, which may affect signal stability.

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Duality of Interest. D.R.B. and B.D.M. have a proprietary interest in AP Technologies, including sensing in the peritoneal space. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. 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.C.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 of the data and the accuracy of the data analysis.

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