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Why intraperitoneal glucose sensing is sometimes surprisingly rapid and sometimes slow: A hypothesis

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A B S T R A C T

The artificial pancreas requires fast and reliable glucose measurements. The peritoneal space has shown promising results, and in one of our studies we detected glucose changes in the peritoneal space already at the same time as in the femoral artery. The peritoneal lining is highly vascularised, covered by a single layer of mesothelial cells and therefore easily accessible for proper sensor technology, e.g. optical technology. We hypothesize that the rapid intraperitoneal glucose dynamics observed in our study was possible because the sensors were located directly at the peritoneal lining, at the point where the glucose molecules entered the peritoneal space. Glucose travels slowly in fluids by diffusion, and a longer distance between the sensor and the peritoneal lining would consequently result in slower dynamics. We therefore propose to place the glucose sensor in an artificial pancreas as closely to the peritoneal lining as possible, or even utilize appropriate sensor technology to measure glucose in the peritoneal lining itself.

Introduction

Automatic closed-loop glucose control, i.e. an artificial pancreas (AP) system, has the ultimate aim of providing stable glucose control in the normal or near normal range and thereby improve the long-term outcomes for patient with diabetes mellitus type 1 (DM1). This requires precise, reliable glucose measurements as close to real time as possible. The intraperitoneal (IP) space is a possible site for real time glucose sensing in an AP, and animal studies indicate both superior and similar results compared to subcutaneous glucose sensing [1–3].

DM1 is a life-long disease in which the pancreas no longer produces insulin, resulting in loss of blood glucose (BG) regulation and increasing BG levels. Thus, these patients are dependent on external supply of insulin to control their BG levels. This is done almost exclusively by daily multiple subcutaneous (SC) injections or continuous SC infusion of insulin. Although the treatment of DM1 has seen incredible improvements over the last 100 years, and in particular during the last decades, the disease still leads to marked reduction in life expectancy and quality of life [4–6]. Several AP systems are under development and hold the promise of stabilizing BG levels in most patients with DM1. An AP consists of three major components; a glucose sensor, an insulin infusion pump and a controller that calculates the appropriate dose of insulin (and glucagon if a bi-hormonal approach is chosen) based on the continuous glucose sensor data. Fast glucose sensing dynamics, i.e. glucose levels measured as close to real time as possible, is crucial to achieve a fully automated and well-functioning AP. Almost all groups working with AP use what can be called the double SC approach, i.e. they both measure glucose and deliver insulin in SC tissue. However, slow glucose dynamics of the SC tissue imposes challenges to all these AP systems [7]. Investigating the peritoneal space as an alternative site for an AP, i.e. a double IP approach is therefore warranted.

Glucose sensing in the IP space has only been sparsely studied [1–3,8–12]. However, it has been demonstrated that IP glucose sensing can sometimes be surprisingly rapid; reacting to intravenous (IV) glucose boluses almost as fast as intra-arterial (IA) sensors (time delays of 0–26 s between IA and IP sensor locations) [1]. This study used interferometric sensors (GlucoSet AS, Trondheim, Norway) and the observed sensors gave varying results. This variance might be explained by the location of the sensor, the proximity to the peritoneal lining, and

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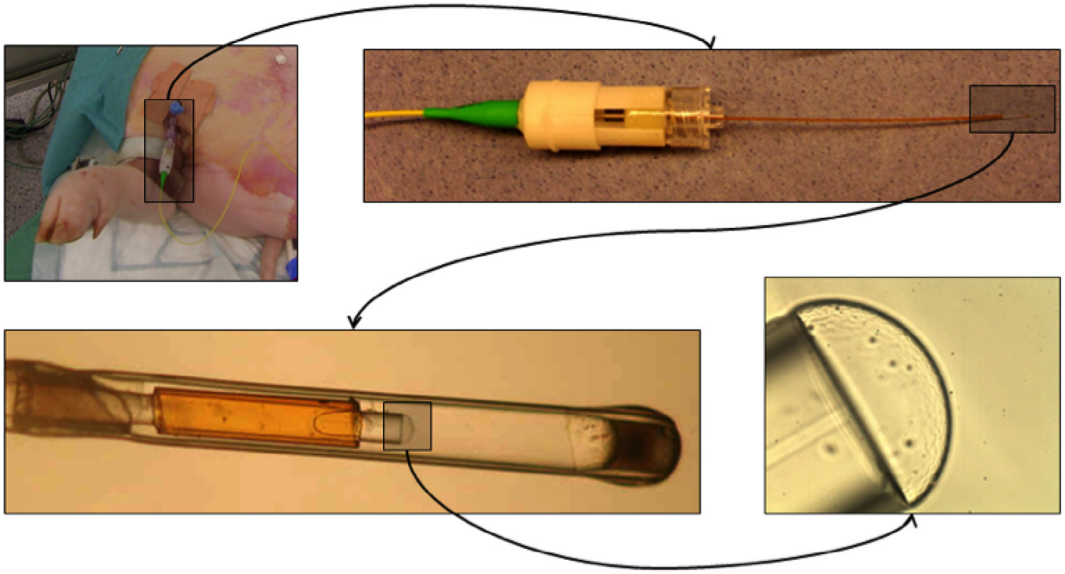

Fig. 1. The GlucoSet sensor at increasing magnification and its localisation in the femoral artery [1,14].

varying amounts of peritoneal fluid. This paper uses the definitions of time delay, time constant etc. as previously described by Stavdahl et al. [13].

The hypothesis

We hypothesize that glucose changes can be detected as quickly in the abdominal cavity as in arterial blood only by locating the glucose sensor at the surface of, and in direct contact with, the peritoneal lining.

Evaluation of the hypothesis

Studies on IP glucose sensing has only been performed on animals [1–3,8–12]. Three studies report dynamic parameters, such as time delay and time constants on IP glucose dynamics, and with differing results [1–3]. It is difficult to compare these studies due to the use of different sensor technologies and system identification methods, as well as the lack of information on sensor dynamics in two of the studies. We will therefore discuss the results from one of our pig studies in which we used an interferometric glucose sensor (Fig. 1) [1]. This sensor was developed for intravascular use [14,15]. Glucose reversibly binds to receptors in a sphere-shaped hydrogel on the tip of an optical fibre, causing the hydrogel to expand or contract depending on the glucose concentration. The change of the optical length of the hydrogel alters the reflection of light, which is then translated to glucose values. In the article, the sensor dynamics was identified and excluded, and only the dynamics from the intra-arterial to the IP space was reported [1]. The sensors were placed in different locations in the ventral parts of the peritoneal cavity of pigs. The nature and the histological structures of the surrounding peritoneal lining were unknown, and the sensors could have been positioned against the peritoneal lining or in a compartment of fluid (Fig. 2). Pigs lack the greater omentum which in humans covers the intestines, so the sensors could have been resting against the visceral peritoneal lining of the intestines or the parietal peritoneal lining of the inner abdominal wall.

The peritoneal lining is made up of a single layer of mesothelial cells (mesothelium) with an underlying layer of connective tissue embedded with capillaries, other blood vessels, nerves and lymphatic vessels (submesothelium) [16,17]. Glucose is a small molecule (180 Da, 8.6 Å × 8.4 Å), and passes easily through the small pores in the endothelium of the capillaries and into the peritoneal space and vice versa, mainly by diffusion [18,19]. Further transport of glucose in the peritoneal fluid will also be by diffusion, although there is some movement of peritoneal fluid [16,20,21]. Convection forces also contribute to the movement of glucose from the capillaries to the IP space [22], but are not included in our calculations.

The diffusion coefficient for glucose in peritoneal fluid is not known, but we can make a short-cut calculation based on the diffusion time of glucose in water (25 °C).

Fick's first law describes the diffusion flux J for a solute as a function of the concentration gradient of the solute in a medium:

$$J = -D(\delta c/\delta x) \quad (1)$$

where D is the diffusion coefficient, $\delta c/\delta x$ expresses the solutes change in concentration per unit of length in the diffusion direction. **Fick's second law** describes the time dependency of the change in concentration:

$$\delta c/\delta t = D\delta^2 c/\delta x^2 \quad (2)$$

where t is time. By combining Eqs. (1) and (2), it is possible to calculate the concentration as a function of time and position.

We are interested in an estimate of the time it takes a given molecule to diffuse an average distance in one direction. This diffusion time (t) can be approximated by [23]:

$$t \approx x^2/2D \quad (3)$$

This gives the following diffusion times ($D = 6.7 \times 10^{-6}$ $cm^2 s^{-1}$ for glucose in water at 25 °C [24]):

- For $x = 1$ mm; $\Rightarrow t_{25°C,1mm} \approx 750$ s
- For $x = 100\ \mu$m; $\Rightarrow t_{25°C,100\mu m} \approx 7.5$ s
- For $x = 10\ \mu$m; $\Rightarrow t_{25°C,10\mu m} \approx 750$ s

These calculations are indicative and based on the diffusion coefficient of glucose in water at 25 °C. According to the Stokes-Einstein equation [23] the diffusion coefficient may be estimated to be roughly 40% higher at 37 °C compared to the one at 25 °C due to increased thermal molecular motion and lower viscosity. Although the glucose diffusion coefficient in peritoneal fluid is unknown, and glucose probably will diffuse more rapidly in water due to its lower viscosity compared to that of IP fluid, we argue that it is likely that at 37 °C it will be of quite similar value to the one in water at 25 °C, given the apparent similarity of the fluids in this context.

For the IP sensors in our first study we estimated time delays between 0 and 26 s [1]. This implies a distance between the sensor and the

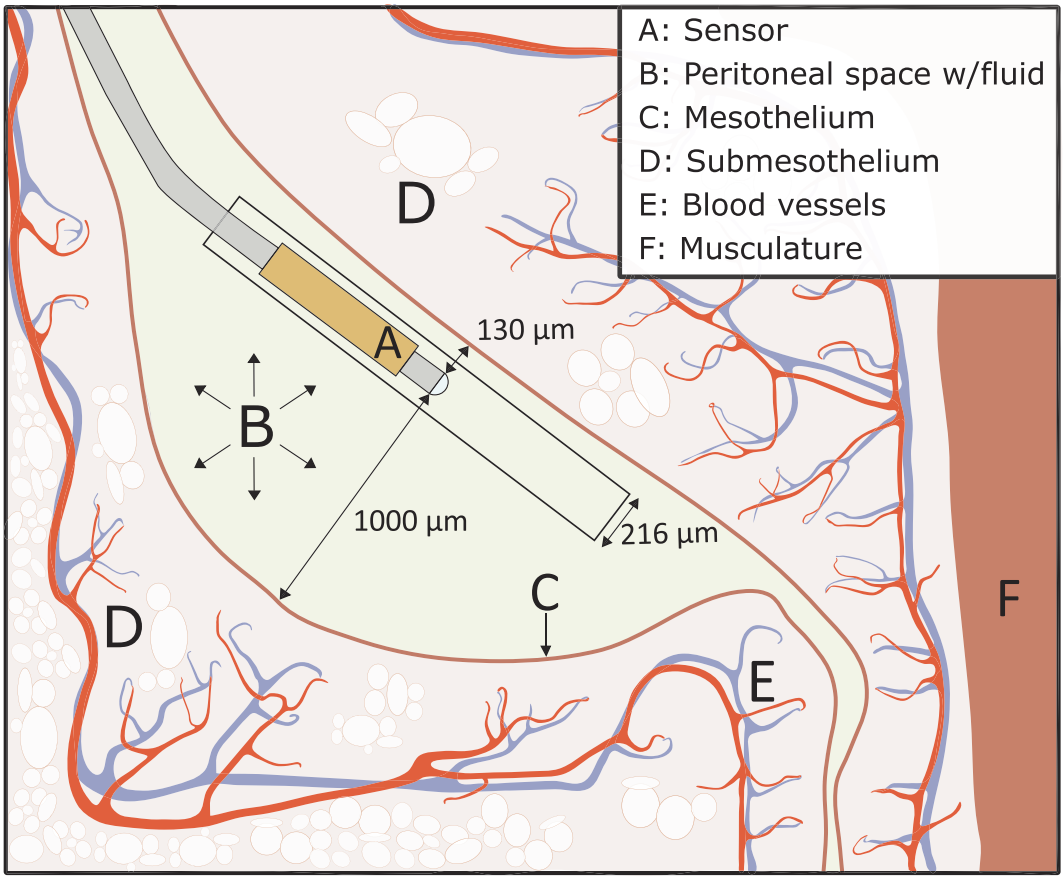

Fig. 2. Sketch of the mesothelium (A), submesothelium (D) with adipocytes and capillaries (E) and the GlucoSet sensor (A) in the peritoneal space (B) illustrating how different diffusion lengths between the sensor and the peritoneal lining/mesothelium could affect the glucose dynamics of intraperitoneal glucose sensing. Assuming Fickian diffusion, we estimate the glucose diffusion time to be approximately 13 s and 12.5 min for 130 µm and 1000 µm diffusion distances, respectively.

glucose source (capillaries) considerably less than 1 mm, under the prerequisite of mass transport being dominated by diffusion. A time delay of 26 s corresponds to a diffusion distance of approximately 190 µm.

The average IP lining area in adult humans is 1.5 m^2 [25], probably somewhat less for the pigs in our study. The large area of the peritoneal lining compared to the small volume of free IP-fluid justifies the assumption that diffusion is the dominant force on glucose transportation into the IP space. It is possible to assume that active convection would affect and give equally fast responses, but we do not know if such a mechanism was present in the conditions of our pig experiments. It is unlikely, however, that changes in convective fluid transport can explain the marked differences observed in time delays.

The outer diameter of the membrane was 216 µm, and the diameter of the fibre and hydrogel was 125 µm [15], resulting in an approximate distance from the membrane to the hydrogel of 45 µm.

Consequences of the hypothesis

Minimizing time delays and time constants in an AP might eliminate the need for patients to calculate and administer insulin meal boluses, achieving the aim of fully automatic glucose regulation.

Thus, if our hypothesis is confirmed, intraperitoneal glucose sensors should ideally measure glucose as close to the peritoneal lining as possible, or even in the capillary network immediately below the peritoneal lining, in the peritoneal lining itself or where glucose emerges from the lining but before it enters the peritoneal fluid. This can be achieved by choosing sensor technology that minimizes the distance between the peritoneal lining and the active sensor site (be it electrochemical, optical or any other sensing technology) and with membranes facilitating rapid diffusion of glucose. The latter is a well-known fact that all sensor manufacturers likely strive to achieve, but the relative importance of a suitable membrane increases as the other parts of the dynamics become faster.

Optical sensor technology might enable glucose sensing in or just below the peritoneal lining instead of in the peritoneal fluid, using mid-infrared (MIR), near-infrared (NIR) or Raman spectroscopy [26]. Transdermal, non-invasive optical glucose sensing using NIR spectroscopy has shown promising results in pre-clinical trials, but no products have made it to commercialization. The IP space should provide a more suitable environment for this type of sensor technology as the peritoneal lining is much thinner than the dermis and thus the capillary network is closer to the organ surface and in theory more accessible for glucose measurements. Less tissue between the sensor and the sensing site of glucose in the capillary network should also reduce the effect of interfering substances making the glucose sensing more reliable. By measuring into the capillary network rather than in the peritoneal fluid, real-time sensing can also be achieved. By measuring glucose in the peritoneal lining or below, one also avoids the effect of temperature variations, that may have a substantial influence on the subdermal blood flow and the SC glucose delays. Other epithelial or mesothelial surfaces in the human body might also be feasible for glucose sensing, as the capillaries are more accessible with optical sensing technology at these surfaces compared to the skin. Potential locations include, but are not limited to, the nasal mucosa, pleural cavity or the epithelium in the ear channel. Sensing glucose on, in or just below the peritoneal lining, will standardize the measured glucose dynamics within the peritoneal cavity as the differences in diffusion lengths are minimized. Reducing the diffusion length with only 0.5 mm will reduce the diffusion time by several minutes. Fixation of the sensor might be needed to ensure

glucose sensing in the proper environment, but exactly how this fixation of the sensor element is to be done, is yet to be determined. A possible solution might be to apply negative pressure to the area around the sensor element to both fixate the sensor and move any surrounding IP fluid.

Minimizing time delays and time constants is also important in insulin dynamics. The slow glucose lowering effect after SC insulin delivery, even with fast acting insulins [27], is considered the greatest challenge to a subcutaneous AP system. Delivering insulin in the IP space provides a faster effect compared to SC delivery [28], and resembles the normal physiologic situation when pancreas secretes insulin into the portal vein [29–32]. By moving both the glucose sensing and hormone delivery of the AP into the IP space, it is possible to improve both glucose sensing and insulin dynamics.

Conclusion

Research is still needed in the field of IP glucose sensing to determine glucose dynamics, the best location of the sensor and the optimal sensor technology. However, we hypothesize that measuring glucose directly on the surface or in the peritoneal lining, and not in the peritoneal fluid, is crucial to optimize glucose sensing for an IP artificial pancreas. This technological approach might hold the promise of near real-time glucose measurements which seem to be crucial to be able to achieve normal non-diabetic glucose levels by means of an AP in patients with DM1. Thereby long-term complications may be avoided, normal life expectancy established and adverse effect of DM1 on quality of life reversed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109318.

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