Photoacoustic blood glucose and tissue measurements based on optical scattering effect

Zuomin Zhao, Risto Myllylä

Department of Electrical Engineering and Infotech Oulu, University of Oulu, 90570 Oulu, Finland

Abstract

Non-invasive blood glucose determination has been investigated by more than 100 research groups all over the world during the past fifteen years. Many measurement methods are based on the capacity of near-infrared light to penetrate a few millimetres into human tissue where it interacts with glucose. A change of glucose concentration may change the optical parameters in tissue, with the result that its glucose concentration can be extracted by analysing the received optical (or other) signals. This paper applies a streak camera in conjunction with the photoacoustic (PA) technique to study glucose determination on the basis of optical scattering effect and on skin properties.

Keywords: photoacoustic, glucose, tissue, scattering effect

1. Introduction

Most non-invasive glucose sensors are based on optical or photoacoustic techniques, partly owing to the availability of low cost, sophisticated, lasers and detectors, partly because the techniques use non-ionising radiation that does not harm the tissue, do not require consumable reagents and have fast responses. Near-infrared light can penetrate a few millimetres into human skin to interact with glucose. It is well known that the water content in skin or blood could be more than 70%, making water the main absorbing substance. However, the optical absorption coefficient of glucose solution is similar to or smaller than that of water or blood in the near-infrared region, making the signal sensitivity of the absorption method very low at the physiological glucose level (< 0.7% / 33mM) [1]. However, some authors have predicted that glucose may correlate with the scattering coefficient of tissue [2-4]. Their results show that the reduced scattering coefficient may change about 3.3 % (tissue phantoms, Kohl. M), 3.6 ~ 11.2 % (clamping tests at abdomen, Bruulsemara J.T.), or even up 20 % (muscle at thigh, Marier J.S.) at the upper level of physiological glucose concentration (33 mM) in oral glucose tolerance test (OGTT). This means that measuring the scattering coefficient or quality relative to the scattering effect will improve the measure sensitivity.

2. Methods and experiments

The work reported here comprises three parts. First, we want to check whether glucose affects the scattering properties of tissue or not, and -if it does- how? Second, we shall use the PA method to measure the sensitivity of glucose in whole human blood and compare it with the value of distilled water to monitor the scattering effects of glucose. Third, we shall perform an in vivo PA skin test to obtain predictions for non-invasive glucose determination.

2.1 The glucose scattering effect

We started off by studying how increased glucose concentration in blood affects the scattering properties. To do this, we applied a picosecond pulsed near-infrared laser and a streak camera to study glucose in blood samples. The optical pulse has a width of 30 ps and a wavelength of 900 nm. Because whole blood is strongly absorbing and the light source is a laser diode operating with a relatively limited energy output, the blood sample was diluted to 3.7% in a buffer solution that is identical with blood content in skin. The sample was loaded in a cuvette with a thickness of 10 mm, and glucose was

* Correspondence: Email: zuomin@ee.oulu.fi; Telephone: +358-8-5532697; Fax: +358-8-5532700.
added to it. The initial results show that glucose causes a narrowing in the signal’s temporal width and precipitates its arrival, as seen in Figure 1. Both these effects indicate a reduction in the scattering capacity of the sample. Hence, glucose may directly decrease the reduced scattering coefficient of sample.

![Figure 1. Temporal dispersion curves of diluted blood samples in streak camera tests.](image)

**2.2 PA blood glucose measurement**

The PA generation mechanism can be described as follows. The exciting optical energy is first absorbed by the sample and turned into heat; then the thermal expansion in the heated region causes the generation of an acoustic wave. Thus, PA generation is an absorbing process. However, optical scattering may cause the redistribution of optical energy in the sample, probably changing the shape and intensity of the PA source\(^5\). This naturally produces a corresponding change in the PA signal.

We applied a near-infrared pulsed diode laser (with a wavelength of 905 nm) and a PZT transducer to study glucose in whole human blood. The typical parameters of laser are 160 ns of pulse width, 25 W of pulse power and 0.5 mm of beam diameter. The diameter and thickness of PZT disk are 4 mm and 3 mm respectively. The preamplifier has gain of 40 dB and bandwidth of 200 kHz ~ 2.3 MHz. The PA signal is averaged 1024 times to reduce random noise. Figure 2 displays the experimental apparatus, and Figure 3 shows the measurement results. It can be seen that the PA signal increases about 7% when the glucose concentration rises to 33mM. This value is much higher than that of glucose in water, where the concentration sensitivity is about 1 % / 33mM\(^6\).

![Figure 2. Experimental PA set-up.](image)

![Figure 3. Relationship between PA amplitude change and glucose concentration in fresh blood samples (the initial value was 88.2 mg/dl, 1mM = 18 mg/dl).](image)
2.3 PA skin tests

The purpose of the \textit{in vivo} PA skin tests was to get useful experience in non-invasive glucose measurements. The signal-to-noise ratio of the experimental apparatus exceeded 200, with the result that the PA amplitude drift was smaller than 0.5 % in distilled water. In skin tests, the test location was the right index finger. The laser beam incidented from the side of the finger and the transducer was in contact with a finger pad. During tests, the body, arm, hand and finger of the test person were naturally relaxed and kept as fixed as possible. The tests were carried out a few times in the course of several days. On some mornings, the test person fasted, on others he did not.

The initial results showed that changes in PA amplitudes varied almost irregularly during the day. The drift range was about 5 %. The contact pressure between transducer and finger may effect on the PA amplitude. Figure 4 shows a typical PA amplitude drift curve with time. The test person drank 300 ml of warm water at 20th minute. It seems that the PA signal increases in some degree after test person drank.

![Figure 4. Typical PA amplitude drift with time. The test person drank 300 ml of water at 20th minute.](image)

3 Discussion

In blood, the refractive indices between blood cells and plasma are unmatched, the former being 1.402 and the latter 1.333\cite{7}. The hydrophilic and osmotic properties of glucose may serve to decrease the mismatch by increasing the refractive index of plasma and decreasing that of blood cells. This produces a decrease in the scattering coefficient of blood. The same effect can be observed in other tissues as well.

It is well known that the PA amplitude is determined by the absorption coefficient and the thermal physical parameters of the sample. However, the contribution of the thermal physical parameters of glucose, being nearly identical to that of water\cite{8}, is much smaller than the corresponding value for blood\cite{7}. At the wavelength of 905 nm, also the optical absorption of glucose is smaller than that of blood. Both these effects result in a decrease in the PA amplitude. However, the experimental result shows that PA signal increases when glucose concentration rises in blood. We therefore think that the increase of PA amplitude is a result of dissolved glucose reducing the scattering coefficient of blood directly, as shown in section 2.1. The conclusion is corroborated by a comparison of the effects of glucose in water, which is not scattering effect and produces a smaller signal response.

The PA signal drift is apparently larger in the \textit{in vivo} skin tests than the signal-to-noise ratio of the experimental set-up. This finding can be explained by a variety of factors including physiological changes in skin, temperature drifts in the human body, motion artefacts, the heterogeneity of skin and a potential contact drift between the transducer and the test person's finger.

Usually, the scattering coefficient of the epidermis drifts due to a moisture uptake-release or a body fluid or blood composition shift. As a result, the scattering coefficient of the epidermis may drift up to
15% in just 20 minutes\textsuperscript{[9]}. If the contact between the transducer and the finger is tight, the PA amplitude tends to decrease with time. A corresponding amplitude increase can be brought about by a relaxation of the contact force. This shows that contact force has a direct effect on blood circulation. Thus, drinking water may increase the speed of blood circulation and expand blood capillaries, thereby causing an increase in the PA amplitude. Changes in the water content of skin may change its morphology, which, in turn, alters the optical scattering characteristics of skin and the contact with the transducer. As a result, it is possible that a change in the scattering coefficient caused directly by physiological glucose concentration is equal to or smaller than the drift in the scattering coefficient of skin. The main problem is that changes in scattering do not seem to correspond to specific compositions, such as glucose in skin. Consequently, this effect needs to be demonstrated by further research.

4. Conclusion

The scattering test by streak camera demonstrates that glucose may decrease the optical scattering properties of a tissue, as a result of the decrease in mismatching of refractive indices. The measurement sensitivity of PA glucose determination is about 7%/33mM in whole blood, much larger than that in pure water (1%/33mM). Hence, in the near-infrared region, the scattering change, rather than the change of absorption or thermal physical parameters of glucose dominates the PA response of glucose in whole blood. However, the skin \textit{in vivo} tests show that other factors, such as physiological change, blood circulation, water content, and body temperature drift, may interfere with PA response of glucose in non-invasive measurement. This is due to skin to be high scattering, neither homogeneous nor simply multi-layered, so that any change in its morphology will cause the scattering change in it.

In glucose measurements, PA technique has higher detection sensitivity than near infrared absorption method. The effect of glucose scattering can increase PA response. However, from the viewpoint of detection sensitivity, PA method is not the best choice for optical scattering measurement or non-invasive blood glucose determination based on the optical scattering effects, because PA mechanism is relative to the total effects of optical absorption and thermal expansion, rather than optical scattering directly. Future research work should focus on finding better scattering-related method or larger glucose-induced optical effects in tissue.

Reference

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