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# Continuous Monitoring of Blood Glucose

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## Key Words

Continuous glucose monitoring · Glucose sensor · Diabetes mellitus

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## Abstract

Continuous blood glucose monitoring aims to: better evaluate glycaemic variations; better detect hypoglycaemia; and, ultimately, automatize insulin delivery (artificial  $\beta$  cell). The sensors can be fully implantable, with the challenge of constructing durable systems to avoid repeated implantations. In-dwelling needle-like electrodes and microdialysis fibres with a pump that brings the dialysate to the glucose sensor are inserted in the subcutaneous tissue through the skin. The GlucoWatch is an almost non-invasive technique that extracts the extracellular fluid by iontophoresis. In these systems, the glucose oxidase generates the electrical signal, proportional to the glucose concentration. Non-invasive techniques aim at measuring the glucose concentration without breaching the skin, using absorption of light in the infrared spectrum. These techniques have not reached the necessary reliability for use as glycaemic alarms, and even less as artificial  $\beta$  cells. Currently, glucose sensors are mainly used as glycaemic holters to help in the management of insulin therapy.

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## Introduction

Intensive insulin therapy requires several blood glucose measurements per day in order to adjust the insulin doses. Even with intensive monitoring, the number of glucose measurements is limited and can miss some important information, such as postprandial hyperglycaemia and nocturnal hypoglycaemia. Continuous glucose monitoring can act as a: glycaemic holter for more adequate insulin adjustment; a warning system for better detection of hypoglycaemia; and, ultimately, an automatic closed-loop insulin delivery system (artificial  $\beta$  cell) [1].

The concept of continuous glucose monitoring was developed in the mid-1970s [2]. However, even the mobile version of the Biostator could hardly be regarded as a home glucose monitor. It is interesting to recall the Biostator, because many of the problems being discussed with the newer glucose sensors were encountered with this early technique. How these difficulties are dealt with will be crucial for the future application of glucose sensors in ambulatory patients.

The glucose sensors now being tested in patients are based on principles that are very similar to those of the Biostator [3], which was itself derived from the Yellow Spring glucose analyser used in biochemistry. The method is founded on the glucose oxidase enzymatic reaction, which converts glucose into gluconic acid with the production of hydrogen peroxide, which then liberates electrons at the contact of a polarized electrode. The enzyme

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is enclosed in a membrane that is selective for certain blood substrates and reaction products. The electrode detects an electrical current, which is converted into a glucose concentration.

This sensor has some interesting characteristics. Very small changes in glucose concentration are detectable. The correlation between the glucose concentration and the electrical signal is linear for a wide range of physiological levels, making calibration possible. The enzymatic membrane is less stable when it is in contact with blood than with pure glucose. In particular, the electrical signal is not stable during the first hours of functioning, making calibration necessary several times a day. The calibration procedure recommended by the manufacturer is quite complex, but it can be simplified if repeated. In any case, the experimental measurement has to be checked against a reference method using a glucose analyser.

The initial publications on the clinical application of the Biostator raised issues similar to many reports today [4]: detection of postprandial hyperglycaemia and nocturnal hypoglycaemia, help in adjusting the insulin regimen, patient education, etc. The Biostator, however, is now employed mainly as a useful tool for clinical metabolic research.

## Glucose Sensors

The new glucose sensors should have positive clinical implications thanks to their two major advantages over older continuous monitoring techniques: they are less invasive and they allow monitoring of ambulatory patients.

Several new continuous glucose monitoring methods have been developed. Some are invasive, such as enzymatic sensors – which can be fully implanted or transcutaneous – or the transcutaneous microdialysis technique. Others are non- (or almost non-) invasive, such as the iontophoretic or the optical techniques.

### *Fully Implanted Sensors*

A fully implanted sensor has the main advantage that there is no transcutaneous material. However, many problems still remain, whether the implantation site is in a blood vessel – with the risk of blood clotting – or in the subcutaneous tissue [5]. The subcutaneous tissue seems an appropriate site because it is relatively surgically accessible, but the reliability and the duration of functioning of a sensor positioned here are very limited. These obstacles are defining the future of the technique. Indeed, most sub-

cutaneously implanted glucose sensors are not capable of monitoring glucose for more than a few hours because of a major drift in electrical signal. The removed sensors function properly in vitro, demonstrating that the biological environment plays a crucial role in the difficulties faced with implanted sensors. A very recent study reports that the addition of an interfacing angiogenesis membrane, to stimulate the development of capillaries around the sensor, shortened the early period of inconsistent monitoring and improved sensor longevity [6]. It shows that it is possible to monitor glucose in subcutaneous tissue for long periods of time: the mean lifetime of the sensors was > 100 days.

Some authors consider that there are fewer outstanding problems with intravascular than with subcutaneous sensors [5], and clinical trials have now been started with intravascular glucose sensors.

### *Transcutaneous Devices*

A transcutaneous electroenzymatic glucose sensor was designed about 20 years ago [7]. The glucose oxidase inside the membrane was positioned at the tip of a needle-like electrode. Recently, an electrode such as this has been made commercially available by Minimed [8]: mass production has permitted access to a relatively cheap glucose sensor, which can be implanted for about 3 days in the subcutaneous tissue. The sensor's electrical signal drops markedly in the hours after implantation and drifts over the subsequent days, making calibration necessary several times a day with the patient's own blood glucose. The monitor displays only the electrical current on its screen and the results can be interpreted only after all the recording has been transferred onto a computer. Thus, in its present form, the system is a glycaemic holter secondarily interpreted by the physician, but new versions should make the blood glucose concentration directly available to the patient.

Microdialysis has been used to measure metabolites continuously in human subcutaneous tissue [9]. It involves a double lumen catheter and a small hollow fibre inserted under the skin with microholes that allow the passive transfer of substances. A buffer is circulated and returned to an external glucose analyser. Drawbacks to this system include a lag time of 20–30 min between tissue sampling and glucose measurement due to the length of the tubing and the very slow flow rate.

### *Non-Invasive Sensors*

Iontophoresis is a technique whereby a low-density electric current is passed through the skin between an

anode and a cathode [10]. The current is carried primarily by the migration of sodium ions toward the cathode. Uncharged molecules such as glucose are transported by electro-osmosis. The amount of glucose extracted at the cathode, measured by a glucose oxidase biosensor, is correlated with blood glucose. The GlucoWatch glucose oxidase biosensor, after calibration using a fingerstick blood glucose measurement and a 3-h equilibration period, provides readings every 20 minutes. It gives acceptable results from 40–400 mmol/l but causes some degree of local irritation and cannot be used during periods of increased sweating. Skin temperature and skin conductance sensors eliminate these confounding factors, and about 20% of all readings are passed over for these reasons.

Optical sensors use the principle that the absorption pattern of near-infrared light can be related to glucose concentration [11]. Light is beamed onto a relatively transparent region of tissue such as the fingertip. The transmitted or reflected light signal is processed by elaborate mathematical models to filter out the interferences from biological molecules, tissue structures and optical effects, and to maximize any aspects of the signal that may show some correlation with blood glucose. The main difficulty with this technique is the lack of selectivity for glucose, and research is needed to analyse the complex in vivo factors that affect the optical measurement of blood glucose.

## Utilization and Problems

### *Clinical Experience*

The stage of development of these various techniques makes it possible to establish a clear relationship between blood glucose and the device signal, even with near-infrared spectroscopy [11], which raises the most problems in terms of accuracy. Several of the techniques can be used as glycaemic holters in ambulatory patients, the results being evaluated either retrospectively (as with the present version of the Minimed system) or after about a 20-min delay (such as with GlucoWatch or microdialysis). This has permitted the detection of major postprandial hyperglycaemia or frequent nocturnal undetected hypoglycaemia, which, according to several studies, can be used to adjust treatment or educate the patient, with some positive impact on HbA<sub>1c</sub>. These reports are somewhat reminiscent of early publications on the clinical applications of the Biostator, and one might wonder whether its availability to a much greater number of physicians and to

ambulatory patients will make the destiny of this device different. The cost impact of the adjustment of treatment has still to be fully evaluated.

Significant problems still have to be solved for continuous monitoring to have a direct and dramatic impact on patients' treatment, with the introduction of hypoglycaemic alarm and, ultimately, the closed-loop insulin delivery system. Discrepancies are not uncommon between the sensor signal and the reference method, for two main reasons: the differences in glucose concentration between the blood and the subcutaneous tissue, and the calibration procedure.

### *Subcutaneous Monitoring*

Several studies have shown that, after a glucose load, the glucose concentration increases earlier in the blood than in the subcutaneous tissue, while it decreases earlier in the subcutaneous tissue than in the blood [12]. This can be explained by the differences in glucose fluxes between the blood, the interstitial fluid and the cells, when blood glucose increases or decreases. After a glucose load, glucose increases first in the blood before it is transferred to the interstitial fluid, where the sensor is located. When the cells dispose of glucose, the concentration decreases first in the interstitial fluid. These discrepancies may have implications for the calibration of the glucose sensor.

### *Sensor Calibration*

The calibration of the sensor is a key issue. In vivo calibration is required, as the sensitivity of the sensor is different in vitro and in vivo. For a hypoglycaemic alarm or, even more so, a closed-loop system, the electrical signal has to be converted, in real time, into an estimate of glucose concentration. It has been shown that a one-point calibration procedure yields accurate continuous glucose monitoring [unpublished data]. Surprisingly, this was better than with a two-point calibration procedure, which was explained by the fact that the variances of the two points are additive, the accuracy being altered to a greater extent by measurement errors. The results were slightly improved by performing the one-point calibration twice a day, with no benefit from a third calibration. The sensitivity of the sensor was not constant, making recalibration mandatory. Data were accurate only if calibration was performed when discrepancies between blood and interstitial fluid were absent or very low, such as before meals. The optimal timing of calibration certainly remains a major issue. This is again reminiscent of the Biostator experience, which started with a complex multipoint calibration procedure, but ended with a one-point calibration

a few times a day, which provided excellent closed-loop control of blood glucose if checked with an appropriate reference method.

The challenge today, however, is not to control blood glucose for one or two days under constant medical supervision, but to do so in the long-term in ambulatory patients. Obviously, the present sensors do not meet the criteria required for this, nor for hypoglycaemic alarms. Interesting data have been reported recently, using the GlucoWatch [10]. Setting a hypoglycaemic alarm at 3.9 mmol/l, in comparison with blood glucose measured with a glucose meter, showed the sensitivity (alarm with true hypoglycaemia) to be only 24%, with an equivalent num-

ber of false-positives (alarm without hypoglycaemia) and about three times as many false-negatives (hypoglycaemia without alarm). The number of hypoglycaemia events detected with continuous monitoring would probably be greater than with intermittent monitoring performed twice or four times a day. In addition, the accuracy of the glucose meters is poor at low glucose concentrations. Although recent advances in basic research and clinical applications in the field of continuous glucose monitoring are very encouraging for the future of this technique, the present results are not yet compatible with the use of continuous monitoring as hypoglycaemic alarm or artificial  $\beta$  cell.

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