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Noninvasive Measurement of Glucose by Metabolic Heat Conformation Method

Ok Kyung Cho,[1*] Yoon Ok Kim,[1] Hiroshi Mitsumaki,[2] and Katsuhiko Kuwa[3]

Background: **We developed a method, called the metabolic heat conformation (MHC) method, for the noninvasive measurement of blood glucose. The MHC method involves the measurement of physiologic indices related to metabolic heat generation and local oxygen supply, which correspond to the glucose concentration in the local blood supply.**

Methods: **We used noninvasive thermal and optical sensors on the fingertip of an individual to measure thermal generation, blood flow rate, hemoglobin (Hb) concentration, and oxyhemoglobin concentration. The calibration model incorporates mathematical procedures to convert signals from the sensor pickup to final glucose concentrations. The mathematical procedures are multivariate statistical analyses, involving values from sensor signals, polynomials from various values, regression analyses of individual patients, and cluster analyses of patient groups. The glucose value is calculated for each patient measurement, applying one of the clusters by discriminant analysis.**

Results: **Regression analysis was performed to compare the noninvasive method with the hexokinase method, using 127 data points (109 data points from diabetic patients, 18 data points from nondiabetic patients) with glucose concentrations ranging from 3.0 to 22.5 mmol/L (54–405 mg/dL). The correlation coefficient (*r*) was 0.91. Reproducibility was measured for healthy fasting persons; the CV was 6% at 5.56 mmol/L (100 mg/dL).**

Conclusions: **These data provide preliminary evidence that the MHC method can be used to estimate blood glucose concentrations noninvasively.**

Since its introduction in clinical practice, self-monitoring of blood glucose, which uses a combination of test strips and a measuring device, has been shown to be extremely useful in controlling blood glucose in patients with diabetes. However, considerable worldwide efforts have been sought to develop a noninvasive glucose monitoring technology to alleviate the pain and anxiety associated with the current fingerstick methods. Previously developed noninvasive methods, which mainly detect blood glucose molecules by spectroscopy, seem not able to achieve acceptable precision and accuracy because of the enormous complexity of matrix effects within the human body *(1–3)*.

We developed a new method for measuring blood glucose noninvasively, based on a method named metabolic heat conformation (MHC),[4] which takes into account these matrix effects. The principles (Fig. 1) underlying the MHC method are unique in that measurements are performed on indices associated with the oxidative metabolism of glucose. The metabolic oxidation of glucose in the human body provides most of the necessary energy for cellular activities. Body heat generated by glucose oxidation is based on the subtle balance of capillary glucose and oxygen supply to the cells. Hence, blood glucose can be estimated by measuring the body heat and the oxygen supply. Several authors have suggested the relationship between blood glucose concentration and physiologic indices relating to metabolism. To date, however, this phenomenon has not been used to calculate blood glucose concentration *(4–8)*.

The MHC method was derived from the observation that the homeostatic circadian rhythm of the human body is dependent on the interrelationship between metabolic heat, local oxygen supply, and glucose concentration and is based on the following conceptual equation:

$$[\mathrm{GLU}] = F(\text{heat generated, blood flow rate, Hb, } \mathrm{HbO_2})$$

[1] PhiScience GmbH, Schwerte, Germany.
[2] Hitachi Ltd., Tokyo, Japan.
[3] University of Tsukuba, Ibaraki, Japan.
*Address correspondence to this author at: PhiScience GmbH, Konrad-Zuse-Strasse 6, D-58239 Schwerte, Germany. Fax 49-2304-2528-131; e-mail cho-phiscience@versanet.de.

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[4] Nonstandard abbreviations: MHC, metabolic heat conformation; Hb, hemoglobin; HbO_2, oxyhemoglobin; and LED, light-emitting diode.

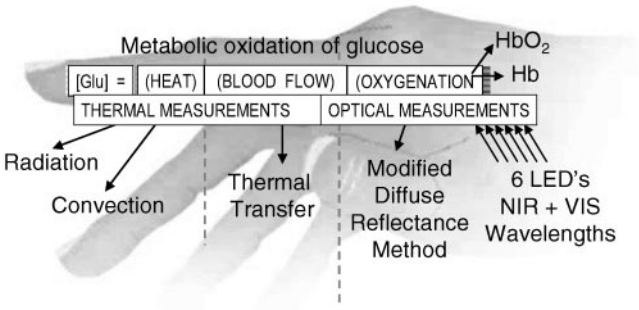

Fig. 1. Principles of the MHC method.

Glucose is derived by measuring heat generated, blood flow rate, and hemoglobin oxygenation in a person's fingertip.
NIR, near-infrared; *VIS*, visible.

where [GLU] represents the concentration of glucose, and F is a function of a set of interdependent and correlated metabolic variables, which can be measured in a person's fingertip. The variables in this model consist of heat generated, hemoglobin (Hb) concentration, oxyhemoglobin (HbO_2) concentration, and blood flow rate. All variables should be estimated after compensation for the appropriate environmental conditions.

The MHC device uses both thermal and optical sensors to measure these values simultaneously in an individual and, through statistical manipulations *(9–11)*, quantitatively derives the concentration of blood glucose. The various sensors used should enable correction for effects of different endogenous interferences.

Materials and Methods

MHC DEVICE

The MHC device was developed for the noninvasive determination of glucose concentration in human blood. A schematic block diagram of the MHC device is shown in Fig. 2. The measuring device consists of a sensor pickup and electronics integrated with a chip card. The sensor

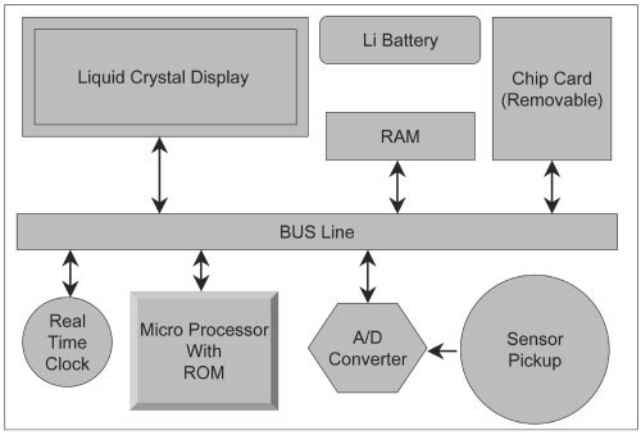

Fig. 2. Block diagram of the MHC device.

Raw data from sensor pickup are processed by a microprocessor. The results are displayed on a liquid crystal display and stored in a chip card.

Fig. 3. Outer shape of the MHC device.

Dimensions: 170 (width) × 115 (depth) × 63 (height) mm; weight, 600 g.

pickup contains various radiation sources and detectors, which interact with the human body when the finger is placed on it. Subsequently, the measured signals are directly converted into digital signals by means of 24-bit multichannel analog/digital converters. Operation of the device is controlled by the microcontroller, in which the data processing is done by means of the device software.

The device is simple to handle and portable (Fig. 3). No external power supply is necessary; a rechargeable battery supplies power to the MHC device for ~24 h. User information and the results of glucose measurements performed by the MHC device are stored in the chip card.

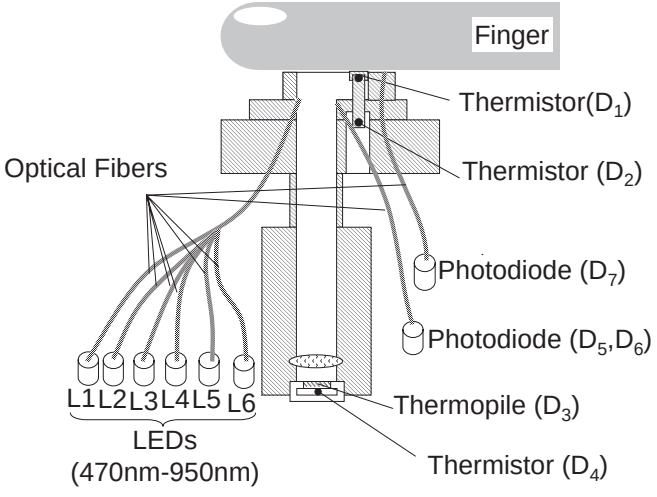

Fig. 4. Structure of sensor pickup.

Four thermal sensors (D_1–D_4) and three optical sensors (D_5–D_7) with six LEDs (*L1–L6*).

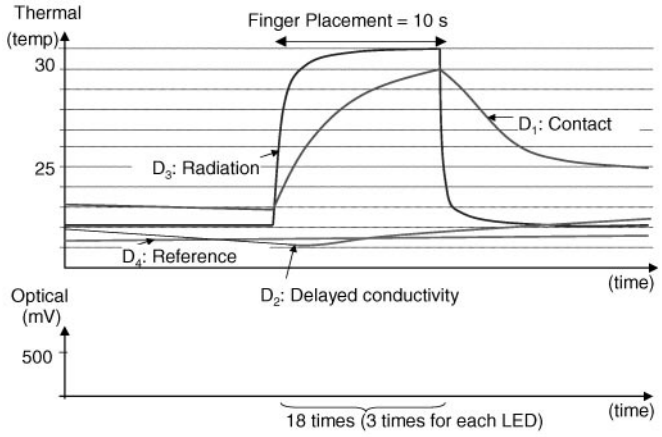

Fig. 5. Example of signals from the sensor pickup.

Thermal and optical signals are continuously collected before/after finger placement.

SENSOR PICKUP

A schematic diagram of the MHC device sensors and photodetectors is shown in Fig. 4. The sensor pickup uses several noninvasive thermal and optical sensors to measure the following physicochemical indices in an individual, such as thermal generation, heat balance, blood flow rate, and Hb and HbO_2 concentrations as well as several environmental conditions. The heat generated by glucose oxidation in the human body is measured by the principle of heat diffusion, which represents the sum of nonevaporative and evaporative heat loss. The heat diffused from the body of an individual in a resting state (nonperspiring), known as the thermo-neutral zone, is almost entirely nonevaporative. Nonevaporative heat loss can be quantified by measuring the thermal conduction, convection, and radiation produced by the body.

Consistent with the foregoing principles, the MHC device obtains temperature measurements from a fingertip surface by four temperature sensors (D1–D4). Three temperature measurements—surface finger temperature, ambient room temperature, and background radiation temperature—are derived from these four sensors and are used to measure conduction, convection, and radiation of heat from the fingertip, which is placed on the MHC device sensor pick-up for approximately 10 s.

Blood flow rate in the finger is directly proportional to and mainly determined by thermal conductivity of the skin *(12)*. The MHC device measures heat transferred from the fingertip to the two thermistors (D1 and D2) through the skin. If the skin has higher thermal conductivity, the heat will be transferred at a higher rate. If there is lower thermal conductivity, the heat will be transferred at a lower rate. The MHC device therefore estimates blood flow rate by monitoring the change in temperature for the contact duration between the contact (D1) and adjacent (D2) thermistors.

Optical measurements of the MHC device are based on the principles of diffuse reflectance. Briefly, under this theory, skin absorption of various wavelengths is determined by the total absorptive and scattering properties of the epidermis and the dermis. In the epidermis, melanocytes contribute to the majority of the absorptive properties, whereas the scattering properties are dependent on

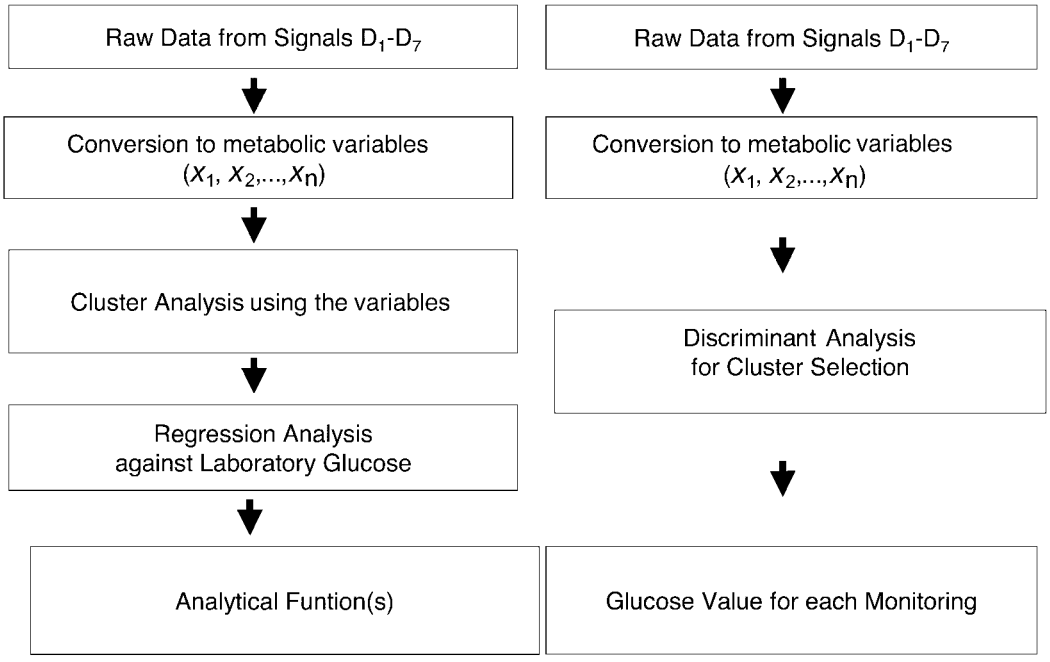

Fig. 6. Calibration process and estimation of glucose value.

Flow diagram depicting the calibration process (*left-hand side*) and glucose calculation (*right-hand side*).

the constituent keratin fibers. In the dermis, absorptive properties are largely dependent on oxy- and deoxyhemoglobin located in the dermal blood vessels/plexuses, whereas collagen fibers account for almost all of the light-scattering properties of the dermis.

The optical sensors use visible and near-infrared spectral reflectance, via a modified diffuse reflection method, to generate the metabolic values for the Hb and HbO_2 concentrations obtained from the fingertip. Multiwavelength spectroscopy is performed with six wavelengths (470, 535, 660, 810, 880, and 950 nm), which provides a reflectance spectrum for each of these measured substances and could then be converted to absorbance values via conversion formulas. These wavelengths are produced by six light-emitting diodes (LEDs; L1–L6) and measured by three photodiodes (D5, D6, and D7). Optical fibers lead light from the LEDs to the individual's fingertip and to the photodiodes. Photodiodes D5, D6, and D7 are arranged to measure the specular and the diffuse reflection on the top, just inside, and through the skin surface.

A total of 18 optical data points (combination of 6 LEDs with 3 photodiodes; Fig. 5) are obtained at each time point, and the concentrations of Hb and HbO_2 are calculated and corrected for individual skin color, surface characteristics (i.e., roughness), and skin diffusion factors (i.e., thickness). In diffused reflectance spectroscopy measurements, it is well established that light is partially absorbed and scattered depending on its interaction with the various tissue components and skin surface conditions. The MHC device must therefore take these factors into account and correct for their effects.

DEVELOPMENT OF CALIBRATION MODEL AND GLUCOSE CALCULATION

The calibration and glucose measurement processes are shown in Fig. 6. These processes are performed independently. The development of calibration process is shown on the left-hand side of Fig. 6, and the glucose calculation in the actual measurement process is shown on the right.

Because all of the sensor signals are somewhat interdependent, methods of multivariate statistical analysis were applied. Various signals from the sensor pickup were converted to physicochemical variables. Multivariate statistical analysis involving the variables from sensor signals, polynomial(s) from various variables, regression analysis of individual patients, and cluster analysis of patients group was then performed.

At the cluster analysis, patients were classified into clusters by use of the individual variables as well as their composites. The calibration function was then generated for each group. By comparing the values from the noninvasive measurement with the venous plasma glucose result from the same patient, we obtained the analytical functions for each patient.

As shown in the right diagram of Fig. 6, the discriminant analysis to select a proper cluster for each monitor-

Table 1. Demographics of patients in clinical trial.

Group	Diabetes, n	No diabetes, n	No. of measurements	Mean age, years	Weight, kg	Height, cm	Smoking	Insulin injections	Complications	Case history	Glucose, mmol/L (mg/dL)
Female	3	1	73	29	49–69	150–162	Yes (n = 2)	Yes (n = 3)	Yes (n = 1)	1 month–30 years	4.17–21.28 (75–383)
							No (n = 2)	No (n = 1)	No (n = 3)		
Male	3	1	54	76	57–87	169–176	Yes (n = 2)	Yes (n = 3)	Yes (n = 1)	3–29 years	3.0–22.5 (54–405)
							No (n = 2)	No (n = 1)	No (n = 3)		
Total	6	2	127	29–76	49–87	150–176	Yes (n = 4)	Yes (n = 6)	Yes (n = 2)	1 month–30 years[a]	3.0–22.5 (54–405)
							No (n = 4)[a]	No (n = 2)[a]	No (n = 3)[a]		

[a] For diabetes.

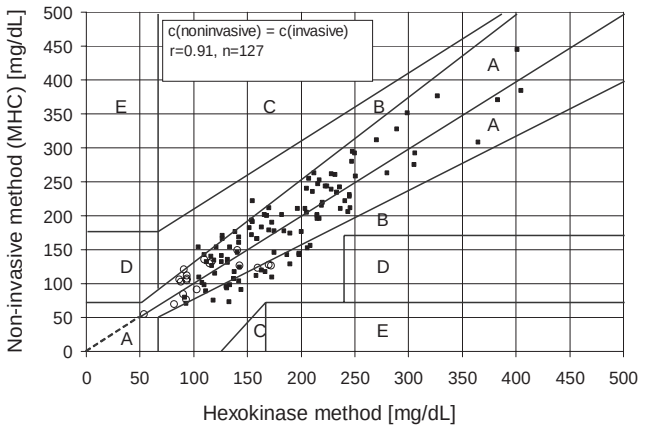

Fig. 7. Regression analysis on Clarke error grid.
■, patients with diabetes; ○, patients without diabetes.

ing or patient, respectively, was established, and then the glucose value was estimated. Clinical changes in each patient's metabolism are important variables that affect the values used to classify patients into clusters. In our opinion, the cluster assigned to a patient would be valid as long as the metabolic condition remains unchanged. This evaluation is in progress.

CLINICAL TRIAL

We measured blood glucose concentrations in 10 patients, 6 with diabetes (3 females and 3 males) and 2 without diabetes (1 male and 1 female), comparing results obtained with the MHC device with measurements obtained with the hexokinase method on a Hitachi 7170 automated analyzer for venous specimens obtained invasively (Table 1). The ages of the patients ranged from 29 to 76 years. Invasive and noninvasive measurements were temporally obtained as close to each other as possible. The mean glucose concentrations were 9.83 mmol/L (177 mg/dL) for the patients with diabetes and 5.28 mmol/L (95 mg/dL) for the patients without diabetes.

Results

Regression analysis (depicted on a Clarke error grid; Fig. 7) was performed to compare the noninvasive method with the hexokinase method, using 127 data points (109 data points from patients with diabetes and 18 data points from patients without diabetes) with glucose concentrations ranging from 3.0 to 22.5 mmol/L (54–405 mg/dL). The correlation coefficient (r) was 0.91.

Reproducibility was measured at five intervals over 20 min for fasting individuals without diabetes. The CV was 6% at the mean glucose concentration of 5.56 mmol/L (100 mg/dL). Reproducibility was measured in the normal glucose range because relatively stable glucose concentrations could be obtained only from fasting individuals without diabetes. We plan to evaluate the effects of interfering substances and the reproducibility at hypo- and hyperglycemic concentrations in successive study.

Discussion

We have developed a noninvasive process for the measurement of blood glucose by the MHC method. The physiologic indices of glucose oxidative metabolism can be thermally and optically measured by various sensing modalities, and blood glucose concentration can be derived by the methods of multivariate statistical analysis. This study shows that the MHC method provides a foundation for measuring blood glucose noninvasively. Clinical studies are currently ongoing to further characterize the performance of this technology as a valuable tool for home glucose monitoring. We plan to evaluate the device in a wide variety of clinical conditions and among various ethnic groups.

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