

## Computer Simulation of Optimal Insulin Profiles in Diabetic Patients

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### INTRODUCTION

Various types of the insulin delivery systems have been used for the treatment of diabetic patients to maintain the blood glucose level within normal range (Slama et al., 1974; Deckert et al., 1977; Genuth et al., 1977; Bojsen et al., 1978; Tambolane et al., 1979). In utilizing these systems, an optimal insulin infusion rates and its patterns after meals are determined by trial and error methods, as the required insulin patterns are different from one patient to another. In these empirical methods, the endogenous insulin delivery patterns of non-diabetic subjects have been used as an initial reference information. Then, by adjusting the insulin infusion rates every day and evaluating the blood glucose level, the final optimal insulin pattern is determined when the glucose level remains within normal range. This adjusting procedure usually takes about one week in our clinical experience, and other reported results (Genuth et al., 1977).

These results suggest that normal subject's insulin delivery pattern may not provide a satisfying reference information in determining the optimal insulin infusion pattern for diabetic patients. For example, the same amount of insulin has different effects on glucose control in normal and diabetic groups, since each group

has significantly different hepatic glucose balance function and insulin resistivity at tissue sites (Bergman et al., 1974; Kimmerling et al., 1976; Youn et al., 1981).

Therefore, it is desirable to develop a quantitative method of estimating the optimal insulin infusion pattern required to maintain glucose level within normal range for a specific subject. As a preliminary study of a new approach, we will present a computer simulation method in which the optimal plasma insulin concentration profile after intravenous glucose loading is computed from an analysis of the intravenous glucose tolerance test (IVGTT) based on the equivalent circuit model of the glucose kinetics (Youn et al., 1981).

### ANALYSIS

#### A. Equivalent Circuit Model

Our previously developed equivalent circuit model of glucose kinetics, as shown in Fig. 1, is used for the estimation of the optimal plasma insulin concentration profiles for diabetic subjects. In this section, a brief summary of the circuit model is presented.

In Fig. 1, the glucose distribution compartment volumes are represented by electrical capacitances, where three capacitances ( $C_1, C_2, C_3$ ) represent arterial, venous (capillary-venous-extra-vascular), and slow glucose pool volume, respectively. Also, the resistances ( $R_1$  and  $R_2$ ) are related to the rate constants between the

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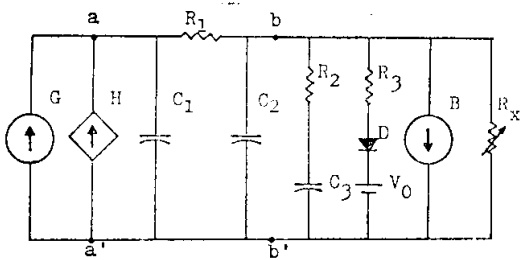


Fig. 1. Equivalent circuit model of glucose kinetics.

compartments. Then, the glucose volume flow rates between compartments and the concentrations inside the compartments are analogous to the electrical currents and voltages, respectively, of the equivalent circuit.

In the circuit model, the following physiological functions are included, the exogenous glucose input flow by a current source ( $G$ ), the brain's glucose uptake rate by a current sink ( $B$ ), and the renal glucose excretion rate by the current in the branch of diode ( $D$ )-resistance ( $R_3$ )-voltage source ( $V_0$ ).

The computer simulation study has shown that the computed physiological parameters (the tissue's insulin resistivity and hepatic sensitivity to glucose level) are important for separation of normal and diabetic groups. The tissue's glucose utilization rate is represented in Fig. 1 by the current,  $T(t)$ , flowing in a time-varying resistance,  $R_x$ , where  $R_x$  is related to the insulin level of the slow insulin pool,  $IN(t)$ , and the insulin resistivity at tissue sites,  $K_r$ , as follows;

$$R_x(t) = \frac{K_r}{IN(t)} \quad (1)$$

Thus, the tissue glucose utilization rate,  $T(t)$ , is related to the venous glucose concentration,  $V_2(t)$ , in eq.(2).

$$\begin{aligned} T(t) &= \frac{V_2(t)}{R_x} \\ &= \frac{1}{K_r} IN(t) \cdot V_2(t) \end{aligned} \quad (2)$$

The hepatic glucose uptake rate (or output rate), represented by a voltage-controlled current source ( $H$ ) in Fig. 1, is determined by the venous

glucose concentration ( $V_2$ ) and the hepatic sensitivity to glucose level,  $H_1$ , in Eq.3, based upon Bergman's result (Bergman et al., 1974).

$$H(t) = H_0 + H_1 (V_2(t) - V_{20}) \quad (3)$$

where  $H_0$  represents the basal level of the hepatic glucose output rate, and  $V_{20}$  is the basal level of the venous glucose concentration.

### B. Computed Optimal Plasma Insulin Concentration Profile

An optimal plasma insulin profile in diabetic subject after intravenous glucose loading is obtained using the equivalent circuit model by computing the plasma insulin concentrations which is required to maintain the changes of the venous glucose concentration in a diabetic subject equal to those of the nondiabetic group.

In Fig. 1, the venous glucose concentration can be evaluated by computing the instantaneous voltage,  $V_2$ , across the capacitor,  $C_2$ . The major factors contributing any different changes in  $V_2$  between normal and diabetic group after a pulse type of glucose loading are the glucose current from the hepatic source,  $H(t)$ , and the current to the tissue,  $T(t)$ .

Then, the above optimal condition can be expressed in Eq.4 by setting the change of the instantaneous capacitor voltage ( $V_2$ ) due to the current flows,  $H(t)$  and  $T(t)$ , in normal group to be equal to that of the diabetic group after glucose loading as follows:

$$\begin{aligned} & \frac{1}{C_n} \int_0^{t_m} [H_n(t) + T_n(t)] dt \\ &= \frac{1}{C_d} \int_0^{t_m} [H_d(t) + T_d(t)] dt \end{aligned} \quad (4)$$

where the subscript  $n$  represents normal group data, and  $d$  represents diabetic group data.

$H(t)$  is the hepatic glucose balance (Positive value for uptake, and negative value for output)

$T(t)$  is the glucose utilization rate at tissue sites

$t_m$  is the measurement time

$C$  is the equivalent capacitance for the glucose compartment volume  
 To satisfy Eq. 4 for all period of  $t_m$ , it is necessary that

$$\frac{1}{C_n} [H_n(t) + T_n(t)] = \frac{1}{C_d} [H_d(t) + T_d(t)] \quad (5)$$

Thus,  $T_d(t)$  can be computed as

$$T_d(t) = \frac{C_d}{C_n} [T_n(t) + H_n(t)] - H_d(t) \quad (6)$$

Then, the required insulin concentration for a diabetic subject,  $IN_d(t)$ , can be computed from Eqs. 2 and 6 as follows:

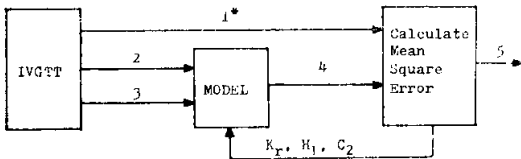
$$\begin{aligned} IN_d(t) &= K_{rd} \frac{T_d(t)}{V_{2d}(t)} \\ &= \frac{K_{rd}}{V_{2d}(t)} \left[ \frac{C_d}{C_n} [T_n(t) + H_n(t)] - H_d(t) \right] \end{aligned} \quad (7)$$

As the glucose level in diabetic subject,  $V_{2d}(t)$ , is set to be equal to the known glucose level in normal group,  $V_{2n}(t)$ , Eq. 7 becomes Eq. 8

$$\begin{aligned} IN(t) &= \frac{K_{rd}}{V_{2n}(t)} \\ &\left[ \frac{C_d}{C_n} [T_n(t) + H_n(t)] - H_d(t) \right] \end{aligned} \quad (8)$$

is used to compute the optimal insulin profile by the computer simulation method.

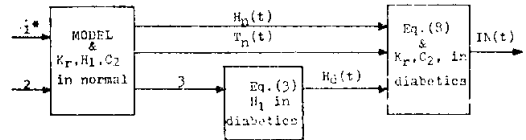
A summary of the computation is shown in two block diagrams of Figs. 2 and 3. In the initial step of Fig. 2, the three parameters ( $K_r, H_1, C_2$ ) of the circuit model are estimated for a diabetic patient using the data of IVGTT



- \*1. Measured glucose conc. profile during IVGTT
- 2. Measured insulin concentration profile during IVGTT
- 3. Glucose infusion pattern of IVGTT (pulse type)
- 4. Computed glucose profile from the model
- 5. Optimal parameter values ( $K_r, H_1, C_2$ )

**Fig. 2.** Estimation procedure of the model parameter for a specific diabetic patient.

by obtaining the best fit parameters which minimize the squared error difference between the computed and measured glucose concentration during IVGTT (Youn et al. 1981).



- \*1. An intravenous glucose loading pattern in normal
- 2. Measured insulin conc. profile after glucose loading in normal
- 3. Computed glucose conc. profile from simulation in normal

**Fig. 3.** Estimation procedure of optimal insulin profile.

These three parameters for normal groups were previously computed and used as the control values in computation. Fig. 3 shows the final step of computing the optimal insulin profile for a specific diabetic patient using Eq. 8. The variables ( $H_n(t), T_n(t), V_{2n}(t)$ ) can be obtained in the computer simulation of intravenous glucose loading in normal group.  $H_d(t)$  can be obtained from  $V_{2n}(t)$  and hepatic sensitivity parameter,  $H_1$ , of a diabetic patient in Eq. 3. The computed slow pool insulin profile,  $IN(t)$ , can be converted to the plasma insulin level using relations developed by Frost et al. (Frost et al., 1973).

### COMPUTER SIMULATION

Computer simulation was performed using Fujita et al.'s IVGTT data (Fujita et al., 1975) for normal and diabetic groups. The three characteristic parameters ( $K_r, H_1, C_2$ ) of normal and nonobese moderate diabetic groups were estimated from the two-minutes IVGTT data. Then, an optimal plasma insulin profile necessary to normalize the glucose concentrations of diabetic group in five-minutes glucose infusion

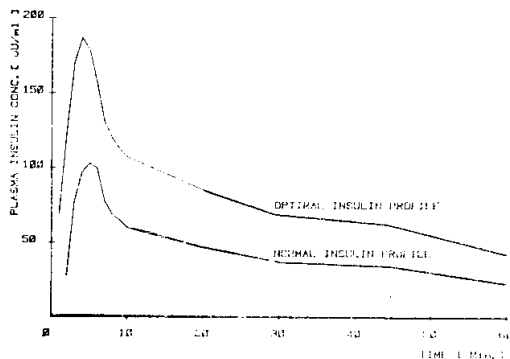


Fig. 4. The computed optimal plasma insulin profile (upper curve) for diabetic group and the normal group's plasma insulin profile(lower curve) in five minutes glucose loading.

was computed. Fig. 4 shows two insulin profiles; the lower one is from the Fujita et al.'s reported data of normal group in five-minutes glucose infusion, the other represents the computed optimal plasma insulin profile for diabetic group. It is shown in Fig. 4 that higher insulin level is required in diabetic group to normalize glucose level as compared with the normal group's insulin level due to higher insulin resistivity and lower hepatic sensitivity.

Fig. 5 shows the comparison of computer simulation in the changes of glucose concentration in diabetic group using two different mo-

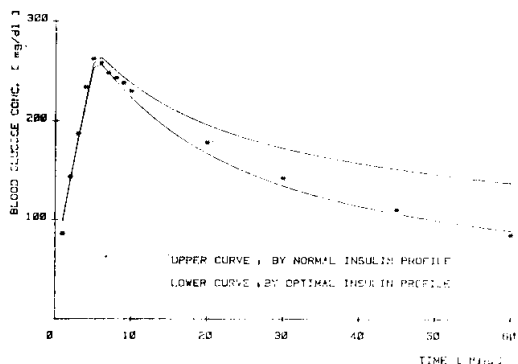


Fig. 5. Computer simulation showing the changes of blood glucose concentration in response to the normal insulin profile(upper curve) and the optimal insulin profile(lower curve). The points show the measured glucose changes in normal group in five minutes glucose loading.

des of insulin profiles in simulation; the upper curve is using the normal group's insulin profile, and the lower curve is using the computed optimal insulin profile.

As shown in Fig. 5, the optimal insulin profile has produced a glucose profile which is more closely matched to the measured normal glucose profile, as compared with the case of emulating normal insulin profile in diabetic group.

## DISCUSSION

The present computer simulation approach has provided a quantitative method of estimating an optimal insulin requirement from measured IVGTT data and equivalent circuit analysis of glucose kinetics. The basic goal of this approach is to obtain a plasma insulin profile necessary to maintain glucose concentration within normal range after glucose loading. Thus, this approach is different from other conventional approaches in which the insulin profile of nondiabetic group was used for the treatment of diabetic patients(Genuth et al., 1977).

The accuracy of the present analysis was evaluated by comparing changes of glucose concentration when we apply either computed or normal group's insulin profiles in diabetic patients. As shown in Fig. 5, an improved performance was obtained in maintaining normal glucose levels when we apply the computed insulin profile rather than using the normal group's insulin profile.

Also, the optimal insulin profile of diabetic group was shown to be twice higher than the normal group's endogenous insulin level. This simulation result can be explained by the differences of insulin resistivity and hepatic glucose sensitivity in normal and diabetic groups. In our previous study (Youn et al., 1981), the

insulin resisitivity was shown to be seventy percent higher and the hepatic sensitivity was fourty percent lower in diabetic group.

In applying the present computer simulation to the experimental and clinical trials, we need a kinetic relationship between plasma insulin level and intravenous (or subcutaneous) infusion rate. Pilo et al.'s report(Pilo et al., 1977) on this subject will provide a useful information on these pathways.

Once the experimental trial is performed, the computed optimal insulin profile will provide a new way of setting the initial insulin infusion protocols in the treatment of diabetic patients.

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—國文抄錄—

컴퓨터시뮬레이션 方法을 利用한 糖尿病 患者의 最適 인슐린 濃度變化 形態推定

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본 논문에서는 당뇨병 환자에게 정맥내 포도당 부하를 가했을 때 혈당농도를 정상화시키는 최적의 방법에 대해 연구하였다. 최적의 혈중 인슐린 농도변화 형태는 저자들이 개발한 "포도당 kinetics에 대한 등가회로 모델"을이용 하여 환자의 정맥내 당부하시험(IVGTT) 자료로부터 구하였다. 본 컴퓨터 시뮬레이션 방법에서는 포도당부하후 매순간 당뇨병환자의 포도당농도변화가 정상인의 농도변화와 같아지기 위해 당뇨병 환자에게 필요한 인슐린 농도를 계산하였다. 보고된 정상인과 당뇨병환자의 IVGTT 자료에 본 분석방법을 적용한 결과 당뇨병환자의 최적인슐린 변화형태는 정상인의 변화형태에 비교하여 2배정도의 높은 수준이 요구되었다. 계산된 최적인슐린 변화형태에 의한 당뇨병환자의 혈당조절상태를 시뮬레이션한 결과, 정상인의 인슐린변화 형태를 시뮬레이션에 사용한 결과에 비해 혈당농도조절 상태가 개선된 것을 보았다.

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