

## Estimations of Insulin Sensitivity and Hepatic Glucose Balance in Diabetic Patients

Jang H. Youn, Byoung G. Min, Hong K. Lee\* and Hun K. Min\*

*Departments of Biomedical Engineering and Internal Medicine\*,  
College of Medicine, Seoul National University.*

### INTRODUCTION

A reduced peripheral insulin sensitivity is known as one major factor responsible for glucose intolerance in diabetes mellitus as well as the diminished beta cell sensitivity to glucose. Various methods have been used for quantitative estimation of the insulin sensitivity (Olefsky et al., 1973; Insel et al., 1975; Reaven et al., 1977; Cunningham et al., 1978; Bergman et al., 1979). Among these methods, simple and less invasive methods were based upon the compartmental models of the glucose kinetics, and they provided the estimated insulin sensitivity using the measured changes of glucose and insulin concentrations after intravenous glucose injection (Cunningham et al., 1978; Bergman et al., 1979). In the above methods, however, a minimal model was used (Bergman et al., 1979) or the hepatic glucose balance function was neglected (Cunningham et al., 1978). Thus, the neglected physiological factors of glucose kinetics could affect the accuracy in estimating the insulin sensitivity.

In the present paper, we have developed an equivalent circuit model of glucose kinetics which includes most of the known physiological factors effective within one hour after glucose loading in intravenous glucose tolerance test

(IVGTT). The we have used this equivalent circuit model for estimation of insulin sensitivity and hepatic glucose sensitivity in various clinical groups of normal and diabetic subjects.

In our best knowledge, there were no reported clinical results in which the model-based estimation of these two parameters (insulin sensitivity and hepatic glucose sensitivity) was used to evaluate different clinical groups of the diabetic patients.

### METHODS

#### A. Subjects and protocol

The present study was performed in the following three stages: (1) Derivation of equivalent circuit model, (2) Verification of the model and estimation of the two sensitivity parameters using clinical data reported by Fujita et al. (1975), (3) Clinical experiments of IVGTT and the parameter estimation for four subjects (Two nonobese normal, one nonobese moderate diabetic, and one patient with insulinoma).

All four subjects did not receive any previous medication which would alter carbohydrate metabolism. Also, they gave informed consent to the study. After twelve hours of overnight fasting, IVGTT experiments were performed at 9:00 A.M. After intravenous injection of 25gr glucose through an antecubital vein, the blood was sampled through the contralateral antecubital vein at every one minute for the first ten minutes and at every ten minutes for the next fifty minutes. Whole blood glucose concentrati-

\* Address: Byoung G. Min, Ph. D. Department of Biomedical Engineering, Seoul National University Hospital, 28, Yeongun-Dong, Chongro-Koo, Seoul, Korea, 110

ons were immediately measured by the glucose oxidase method (Robin et al., 1965) using a YSI Glucose Analyzer (Yellow Springs Instrument Co., Inc., Ohio.). The plasma insulin concentrations were measured with the double antibody method utilizing Dainabot Insulin Radioimmunoassay Kit (Dainabot Isotope Lab., Ltd., Japan).

### B. Equivalent Circuit Model

Fig. 1 shows the equivalent circuit model developed for simulation of the changes of glucose concentration during IVGTT. In the model, the compartmental volumes are represented by electrical capacitances ( $C_i$ ), the glucose quantities in the compartments represented by the charges in the capacitors, and the rate constants represented by electrical resistances ( $R_i$ ). Then, the glucose volume flow rates between compartments and the concentration in the compartments are analogous to the electrical currents and voltages of the equivalent circuit, respectively. The concentrations (represented by electrical voltages) are used as state variables in the circuit model instead of the quantities in the previous compartment model (Insel et al., 1975; Cunningham et al., 1978; Insel et al., 1978; Bergman et al., 1979).

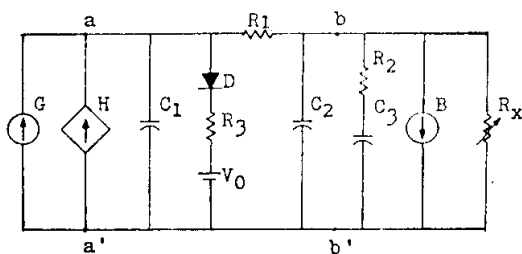


Fig. 1. Equivalent circuit model.

Using the above analogy, the circuit model elements of Fig. 1 represent the following physiological functions of glucose kinetics as reported by various investigators.

(a) **Glucose Pools and an exogenous glucose source:** Three glucose pools of arterial blood volume, capillary-venous-extravascular volume,

and slow pool volume (Long et al., 1971) are represented by three capacitors,  $C_1$ ,  $C_2$ , and  $C_3$ , respectively. The exogenous glucose source is represented by a current source,  $G$ .

(b) **Glucose uptake at tissue sites:** Glucose uptake rate at tissues was known to be proportional to both the glucose concentration and the insulin concentration at the cell surface. Also, it was known that this insulin concentration is the level in the slow insulin pool (Sherwin et al., 1974; Daniel et al., 1975). The effect of insulin on glucose utilization rate is different depending upon insulin sensitivity at tissues in normal and diabetics (Kimmerling et al., 1979; Wigand et al., 1979). In the model, the glucose uptake rate is represented by the current flowing in the time-varying resistance,  $R_x$ , where  $R_x$  is related as follows

$$R_x(t) = \frac{1}{K_s} \cdot \frac{1}{I_n(t)} \quad (1)$$

where  $K_s$  is the insulin sensitivity parameter and  $I_n(t)$  is the instantaneous insulin concentration in the slow pool of insulin kinetics model.

(c) **Glucose uptake at the brain:** As glucose uptake at the brain was known to be relatively constant and independent of glucose and insulin concentrations (Butterfield et al., 1966; Buschiazzo et al., 1970), it is represented by a current sink,  $B$ , separately from the glucose uptake at tissues.

(d) **Hepatic glucose balance:** The hepatic glucose balance (uptake or output) is represented by a voltage-controlled current source,  $H$ , in eq. (2), where this equation is based upon Bergman et al.'s experimental result (Bergman et al., 1974).

$$H = H_0 + H_1 (V_2 - V_{20}) \quad (2)$$

Where  $H_0$  is the hepatic glucose output at basal level,  $H_1$  is the hepatic sensitivity relating the changes of hepatic glucose balance to the changes of glucose concentration,

$V_2$  is the glucose concentration in capillary-venous space (voltage across capacitor  $C_2$ ) in the model,  $V_{20}$  is  $V_2$  at basal level.

(e) **Renal excretion:** The renal glucose excretion rate ( $I_r$ ) occurring in hyperglycemia is represented by current through the branch of a diode ( $D$ ), a resistance ( $R_3$ ), and a constant voltage source ( $V_0$ ), and computed as follows, using McPhaul et al.'s clinical data (McPhaul et al., 1968)

$$I_r = 0 \quad \text{When } V_1 < V_0$$

$$I_r = (V_1 - V_0) / R_3 \quad \text{When } V_1 > V_0$$

where  $V_0 = 220$  (mg/dl),  $R_3 = 0.79$  (1/dl).

(f) **Rate constants:** The resistance  $R_1$  which is related to the rate constant of glucose flow between arterial and venous blood pool, is computed using McGuire et al.'s data (McGuire et al., 1976) as follows;

$$R_1 = (A - V)_B / H_0 \quad (4)$$

where  $(A - V)_B$  is the difference of glucose concentrations between arterial and venous blood at basal level, and was reported to be  $3.1 \pm 0.6$  (mg/dl) by McGuire et al.

The resistance  $R_2$  value of 0.24 (1/dl) was used for computation, based upon Long et al.'s results (1971).  $R_2$  is related to the rate constant between the venous space and the slow pool.

### C. State Variable Equations

The voltages across the capacitors representing the glucose concentrations in the three compartments are used as the state variables in the following equations (5) and (6). Either equation is used depending upon the magnitudes of the computed hepatic glucose balance function,  $H$ . The liver absorbs glucose from the venous space ( $C_2$ ) with negative values of  $H$ , and it produces glucose into the arterial space ( $C_1$ ) with positive values of  $H$ . Thus, the circuit branch location of the hepatic balance function is changed from a-a' to b-b' in Fig.

1, as  $H$  becomes negative during IVGTT. Equation (5) represents the hepatic output state when  $H$  is positive, and the hepatic uptake state is represented by equation (6) with negative values of  $H$ .

(a) In the hepatic output condition ( $H > 0$ ):

$$\frac{dV_1}{dt} = -\frac{V_1}{R_1 C_1} + \left( H_1 + \frac{1}{R_1} \right) \frac{V_2}{C_1} +$$

$$(G - I_r + H_0 - H_1 V_{20}) \frac{1}{C_1}$$

$$\frac{dV_2}{dt} = \frac{V_1}{R_1 C_2} - \left( \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_2} \right) \frac{V_2}{C_2} +$$

$$\frac{1}{R_2 C_2} V_3 - \frac{B}{C_2} \quad \frac{dV_3}{dt} = \frac{V_2}{R_2 C_3} - \frac{1}{R_2 C_3} V_3$$

(5)

(b) In the hepatic uptake condition ( $H < 0$ ):

$$\frac{dV_1}{dt} = -\frac{V_1}{R_1 C_1} + \frac{V_2}{R_1 C_1} + (G - I_r) \frac{1}{C_1}$$

$$\frac{dV_2}{dt} = \frac{V_1}{R_1 C_2} + \left( H_1 - \frac{1}{R_1} - \frac{1}{R_2} - \frac{1}{R_2} \right) \times$$

$$\frac{V_2}{C_2} + \frac{V_3}{R_2 C_2} - (B - H_0 + H_1 V_{20}) \frac{1}{C_2}$$

$$\frac{dV_3}{dt} = \frac{V_2}{R_2 C_3} - \frac{V_3}{R_2 C_3} \quad (6)$$

where

$V_i$ : the glucose concentration (mg/dl) in the  $i$ -th compartment (voltage across capacitor)

$C_i$ : the  $i$ -th compartment volume (dl) (Capacitance)

$R_i$ : the inverse of the product of the rate constant and the compartment volume (min/dl) (resistances)

$H_0$ : the basal hepatic output rate (mg/min)

$H_1$ : the hepatic sensitivity to glucose level (dl/min)

$I_r$ : the rate of the renal glucose loss (mg/min)

$G$ : the glucose infusion rate (mg/min)

$B$ : the brain uptake rate (mg/min)

$V_{20}$ : the basal glucose concentration across  $C_2$  (mg/dl)

### D. Simulation methods

The following reported constants were used

for the simulation;

Total blood volume per body weight:

75.6ml/kg

Slow pool volume as given by Long et al.

(Long et al., 1971):

100ml/kg

Glucose uptake at the brain:

1.08mg/min/kg

Net hepatic glucose output at basal level:

2mg/min/kg

Glucose infusion rate:

250mg/min/kg in 2min. IVGTT

100mg/min/kg in 5min. IVGTT

Also, we assume initially that the arterial volume ( $C_1$ ) is approximately one third of the total volume and finally set at the value of 25 (ml/kg) during iterative computation. In calculating glucose space and glycuria, the glucose space of blood was taken as 0.86 liter per one liter of blood.

The time course of insulin concentration in the slow insulin pool was estimated from the plasma insulin concentration using the models of Insel et al. (1974) or Forst et al. (1973). Three parameters ( $C_2$ ,  $K_s$ , and  $H_1$ ) were varied iteratively to provide the condition of the least squared error difference between the computed and the measured venous glucose concentrations. In the verification part of the present study, the accuracy of fitting was compared by the following residual mean square (Cunningham et al., 1978)

$$E^2 = \sum_{i=2}^n W_i D_i^2 / DF$$

where  $E^2$  is the residual mean square

$D_i$  is the difference between the computed and the measured data at the  $i$ -th sample point

$W_i$  is the weighting factor for the  $i$ -th sample, as calculated by the inverse of the square of the standard deviation of the measured data at the  $i$ -th sample

$n$  is the number of data points

$DF$  is the degree of freedom, i.e.,  $n-1$

Since the present model does not include the delay effects of the glucose distribution from an injection site to a measuring sites, we do not include the first one minute data in the analysis.

All computations and simulations were carried out using a Digital Equipment Corporation MINC-11 computer.

## RESULTS

Evaluations of the present equivalent circuit model were performed using Fujita et al.'s IVGTT results of four clinical groups (nonobese normal, nonobese mild diabetics, obese mild diabetics, and nonobese moderate diabetics).

In Fig. 2 and 3 it is shown that the changes of glucose concentration after intravenous glucose injection were closely simulated by the model

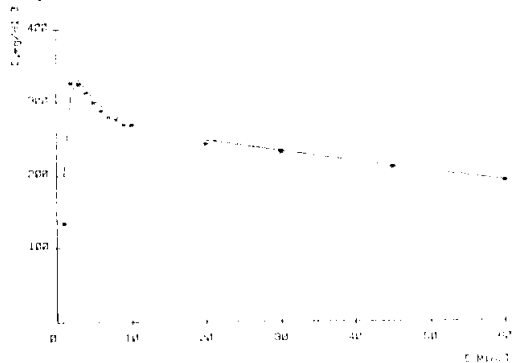


Fig. 2. Comparison of clinical data(\*) and simulation (—) in nonobese normal subjects.

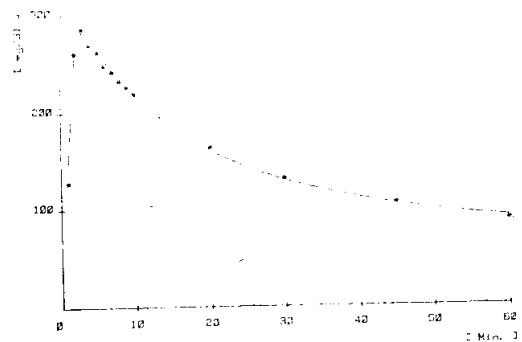


Fig. 3. Comparison of clinical data(\*) and simulation (—) in nonobese moderate diabetics.

**Table 1.** Estimated values of  $K_s$ ,  $H_1$ , and  $C_2$  (ml/kg) in the normal subjects

Infusion period	Insulin model	$K_s(\times 10^2)$	$H_1$	$C_2$	$E^2$	P value
2	Frost	5.72	-1.50	183.3	0.08	<0.001
	Insel	7.81	-1.90	180.0	0.05	<0.001
5	Frost	5.88	-1.60	193.3	0.54	<0.25
	Insel	8.85	-1.95	195.8	0.35	<0.025

**Table 2.** Estimated values of  $K_s$ ,  $H_1$ , and  $C_2$  (ml/kg) in the diabetic groups

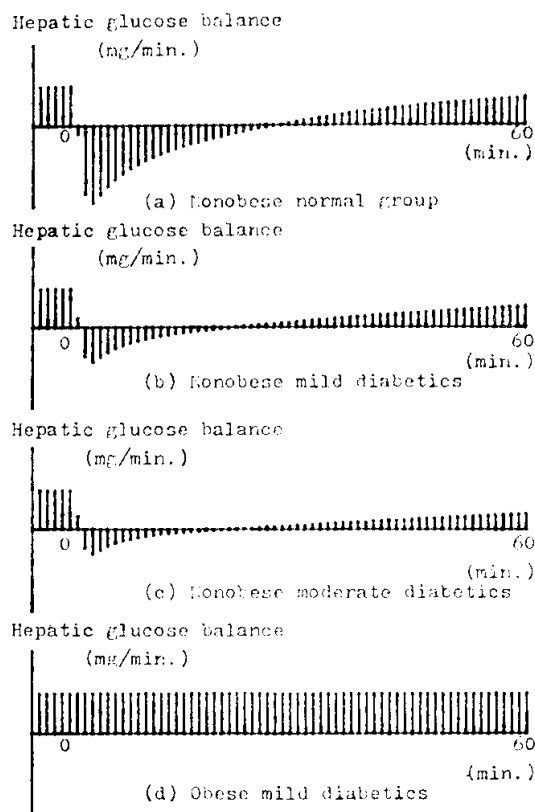
Group	$K_s(\times 10^2)$	$H_1$	$C_2$	$E^2$
Nonobese mild diabetics	3.85	-0.95	183.3	0.90
Nonobese moderate diabetics	3.40	-0.90	192.7	0.41
Obese mild diabetics	2.53	0	166.7	0.23

for normal subjects and nonobese moderate diabetics in two minute infusion period. These best fitted curves were obtained when the residual mean square ( $E^2$ ) of the glucose concentrations had the minimum value. Only the three parameters of  $K_s$ ,  $H_1$ , and  $C_2$  were used as the variables, since the variation of the other parameters did not contribute any significant changes in goodness of fitting, when they were varied within the physiological ranges. This result is comparable to Cunningham's model study where only two parameters, capillary-extravascular volume and  $K_{ins}$  (insulin sensitivity), were shown to be significant variables (Cunningham et al., 1978).

We studied the differences of the above three parameters among four clinical groups for both two minute and five minute glucose infusions. Also, we used two reported insulin models (Insel et al.'s and Frost et al.'s) in converting the time course of the plasma insulin concentration to that of the slow pool insulin concentration.

Table 1 summarizes the best fitted data of  $K_s$ ,  $H_1$  and  $C_2$  for normal subjects. Different values of  $K_s$  and  $H_1$  were computed depending upon which insulin models were used, as the slow pool insulin concentration profile was different in the two insulin models for the

same plasma insulin concentration. There was no significant changes in  $K_s$  and  $H_1$  values as the infusion period varied from two to five



**Fig. 4.** Hepatic glucose balance during IVGTT in four clinical groups (positive values for glucose output and negative for glucose uptake).

**Table 3.** Experimental data of four subjects (two nonobese normal, one nonobese moderate diabetic, and one patient with insulinoma)

Subject	H.S.		M.P.		J.Y.		S.L.	
Sex	M		M		M		F	
Age	40		53		37		59	
Weight(kg)	58		60		68		65	
Infusion(min.)	1		2		2		2	
Measurement Time(min.)	BG	IRI	BG	IRI	BG	IRI	BG	IRI
0	80	3.0	85	2.1	230	5.5	55	54.2
1	452	4.0	—	5.8	306	5.7	89	89.1
2	359	52.5	237	9.0	460	10.9	404	94.3
3	309	70.6	334	29.3	422	5.1	343	137.2
4	264	58.0	295	25.2	408	10.1	—	—
5	257	45.4	287	28.5	395	9.6	309	55.6
6	233	40.6	272	21.6	392	6.7	258	40.6
7	229	34.6	256	22.1	385	7.5	250	32.6
8	—	24.3	253	20.5	380	5.7	244	176.5
9	227	26.5	245	13.1	361	6.6	227	156.5
10	224	22.2	241	15.2	368	6.0	224	120.6
20	194	12.6	197	9.4	338	6.4	199	107.0
30	172	11.0	169	14.5	325	12.2	161	96.5
40	147	13.7	150	12.9	309	12.1	125	82.8
50	136	11.6	137	13.7	291	12.5	105	75.7
60	126	10.7	125	10.5	281	10.0	89	82.4

minutes.

Table 2 summarizes the  $K_s$ ,  $C_2$ , and  $H_1$  values for three diabetic groups, they were estimated from the two minute IVGTT data using the Frost et al.'s insulin kinetics model. The obese mild diabetic subjects are shown to have the minimum tissue insulin sensitivity as indicated by the lowest values of  $K_s$ . Also, this group had a zero  $H_1$  value indicating that the hepatic inhibition of glucose output was not effective during IVGTT. In the nonobese group, both  $H_1$  and  $K_s$  values were lower in the moderate diabetics than in the mild diabetics and the normal groups. As compared with these variations of  $K_s$  and  $H_1$ ,  $C_2$  was relatively constant for all three groups except the obese mild diabetics group which had a smaller value of  $C_2$ .

Fig. 4 shows the changes of the hepatic glu-

**Table 4.** Estimated values of  $K_s$ ,  $H_1$ ,  $C_2$ (ml/kg) for the four subjects: two nonobese normal subjects (H.S., M.P.), one nonobese moderate diabetic (J.Y.), one patient with insulinoma (S.L.)

Subject	$K_s(\times 10^2)$	$H_1$	$C_2$
H.S.	6.25	-1.7	155
M.P.	8.33	-1.7	157
J.Y.	3.51	-0.75	153
S.L.	2.38	0	102

cose balance after glucose infusion in four groups. The response of hepatic glucose balance is shown to become smaller with increasing severity of diabetic state.

Table 3 shows the summary of the measured IVGTT data on four subjects in our experiment. The first two experiments were performed on normal subjects, and the third subject was

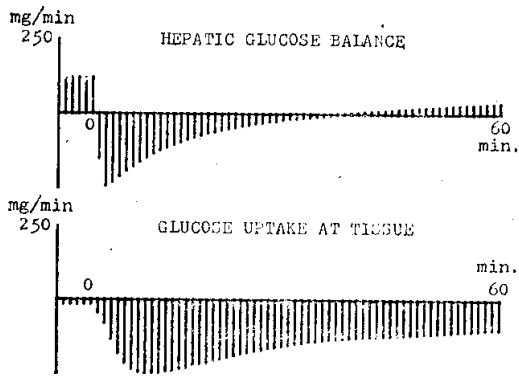


Fig. 5. Estimated changes of the hepatic glucose balance and the tissue uptake during IVGTT for a normal subject (H.S.).

nonobese diabetic, and the last patient had insulinoma. Table 4 is the summary of the estimated parameters for the above four patients.

As shown in Table 4, the estimated parameter values of the experiment are comparable to the parameters estimated using Fujita et al.'s data in normal and nonobese moderate diabetic subjects. For the insulinoma patient, the insulin sensitivity is lower, and the hepatic sensitivity is shown to be zero. Fig. 5 shows the estimated changes of the hepatic glucose balance and the tissue uptake during IVGTT for a normal subject in our experiment.

## DISCUSSION

In this paper we present a new quantitative method of estimating a specific subject's insulin sensitivity and hepatic glucose sensitivity from the measured IVGTT data. For the simulation of changes of glucose concentration during IVGTT, we have used equivalent circuit model which includes the well-known physiological factors determining the glucose disposal process, as complete as possible.

It is shown in performance evaluations of our model that the changes of model-based sensitivity parameters between clinical groups agree with

other clinical observations. For example, the diminution of the sensitivity parameters is greater in severe diabetics, and they are much lower in obese diabetics than in nonobese groups (Wigand et al., 1979). Also, the estimated hepatic balance in obese diabetics, shown in Fig. 4, agree with the clinical observation (Wahren et al., 1972) in which the hepatic output in untreated diabetic was shown not to be suppressed even with a rapid increase of glucose concentration after glucose infusion.

The lower values of the estimated glucose space in obese group also agree with other observations (Wigand et al., 1979). The estimated sensitivity parameters in our own experiments were comparable to the estimated values using Fujita et al.'s data. In a patient with insulinoma, the estimated insulin sensitivity was much lower than normal subject's value, and the hepatic sensitivity was estimated as zero value. These results are comparable with the measured changes of insulin resistance in hyperinsulinemia in general.

In other previous investigations (Bergman et al., 1979; Cunningham et al., 1978) of utilizing the system simulation methods for estimating insulin sensitivity, either the hepatic response was neglected (Cunningham et al., 1978) or a minimal model was used. (Bergman et al., 1979) Therefore, these neglected physiological factors could affect the accuracy of estimation. As an example, in Cunningham's model, the hepatic glucose output was assumed to be either in completely suppressed condition (zero hepatic output), or in sustained condition. Depending upon which assumption was used, two significantly different values of insulin sensitivity were estimated for the same diabetic group. Also, the neglect of the hepatic uptake led to over-estimation of insulin sensitivity in normal subjects, as suggested by the same investigators.

In Fig.5, the amount of the hepatic glucose

balance was estimated to have almost comparable magnitude as the estimated uptake amount at tissue sites, as reported in other measurements (Madison, 1969). Thus this result shows that the hepatic balance function is important in evaluation of the overall glucose kinetics, and should be included computation of insulin sensitivity as a major factor. In the present study of short-time effects of glucose concentration on the hepatic glucose balance was only considered, and the direct effect of insulin concentration on the hepatic glucose balance was neglected. While the long term effect of insulin on glucose metabolism in the liver is well known, the short term effect within one hour period is still controversial (Madison, 1969; Sacca et al., 1978; Liljenguist et al., 1979; Davidson et al., 1981). Any probable direct effects of insulin on hepatic glucose balance would be reflected as the peripheral glucose uptake in our model, as this term is related to the product of glucose and insulin concentrations (Bergman et al., 1979). In this case, our estimated insulin sensitivity parameters would reflect the combined insulin sensitivity of the peripheral tissue and the liver.

As we compare our results with Cunningham's compartmental results, the insulin sensitivity parameter is shown to be lower in our model. When Frost et al.'s insulin model was used, the insulin sensitivity was  $5.72 \times 10^{-2}$  in our study as compared with  $7.75 \times 10^{-2}$  in Cunningham's study. In the case of simulation using Insel et al.'s insulin model, it was  $7.81 \times 10^{-2}$  in our study, and  $11.79 \times 10^{-2}$  in Cunningham's study. Since both estimations were made based upon Fujita et al.'s clinical data, the above difference might be caused by the inclusion of hepatic uptake in our model. Also, when we convert Insel et al.'s rate constant of the first order insulin-independent glucose loss ( $L_{06}$ ) to our hepatic sensitivity ( $H_1$ ), using an equation of  $L_{06} \cdot (V_6 + V_7 + V_9) \cdot (M_7 + M_9) / (M_6 + M_7 + M_9)$

(Insel et al., 1975), their value of 1.4 is comparable to our estimated  $H_1$  value of 1.7.

In the equivalent circuit model, the glucose concentrations are used as the state variables of the system, as compared with the material amount as state variables in the compartmental model. Since the actual measurements are based on the concentration data, the circuit model approach may be more realistic and visible.

In conclusion, we have shown that the IVGTT data can provide a specific subject's insulin sensitivity and hepatic glucose sensitivity. Also, we have shown that these sensitivity parameters are useful in distinguishing clinical groups of normal and diabetic subjects.

## SUMMARY

A new quantitative method was developed for estimation of the insulin sensitivity and the hepatic glucose balance from intravenous glucose tolerance test (IVGTT) in humans. The method was based upon an equivalent circuit model of glucose kinetics, previously developed by our group. This model includes important physiological factors determining the glucose disposal process during IVGTT, such as the peripheral glucose utilization rate represented by electrical current in a time varying resistance represented by a voltage controlled current source. The estimated changes of the sensitivity parameters among four clinical groups were similar to other measured experimental results and these parameters were shown to be useful in distinguishing clinical groups of normal and diabetic subjects.



== 國文抄錄 ==

人體의 인슐린에 대한 敏感度와 간에서의  
葡萄糖 平衡에 관한 研究

尹長鉉\* · 閔丙九\* · 李弘揆\*\* · 閔獻基\*\*

서울 大學校 醫科大學  
醫工學科\* 및 內科學敎室\*\*

본 논문에서는 정맥내 당 부하 시험(IVGTT) 자료로부터 정상인과 당뇨병 환자의 조직에서의 인슐린 민감도와 간에서의 포도당 평형을 추정해 내는 새로운 정량적인 방법을 제시하였다. 본 방법은 저자들에게 의해 개발된 포도당 kinetics의 등가회로 모델에 기초를 두고 있다. 이 모델에서는 주변 조직에서의 포도당 이용도나 간에서의 포도당 평형동 IVGTT 중의 체내에서의 포도당 처리 과정에 관계되는 대부분의 중요한 생리적인 현상들을 고려하였다. 정상과 당뇨병 환자의 4 임상 그룹에 대하여 추정된 민감도 조변수들은 다른 연구자들에 의해 직접 측정된 실험 결과와 비슷하였으며 이들 조변수들이 정상 또는 당뇨병 환자의 여러 임상 그룹들을 분류하는데 유효하게 사용될 수 있음이 밝혀졌다.

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