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Computer Simulation of Glucose-insulin Kinetics During Intravenous Glucose Tolerance Test

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=Abstract=

A new quantitative method was developed for separation of three interactive physiological factors (hepatic glucose balance, peripheral tissue's insulin resistivity, and insulin secretion rate) influencing glucose intolerance in diabetic mellitus using an equivalent circuit model and the intravenous glucose tolerance test (IVGTT) in six dogs and twenty two humans.

The results show that the estimated model parameters of the above three factors are useful for evaluating different glucose-insulin kinetics in normal and diabetic subjects.

Ⅰ. INTRODUCTION

The three major physiological factors influencing glucose intolerance in diabetics are known as the hepatic glucose balance, the peripheral tissue's insulin resistivity (inverse of sensitivity), and the bata-cell insulin secretion rate. Since these factors are complicatedly related and interactive each other, it is difficult to evaluate individually the changes of these physiological factors for normal and diabetic subjects.

In the present paper, we have used an equivalent circuit model for the estimation of the peripheral tissue's insulin resistivity and the hepatic glucose sensitivty in normal and diabetic subjects. We have also obtained the fractional hepatic extraction ratio of insulin (FHER-I) and the secereton rate of insulin (SR-I) using C-peptide data[1, 2].

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Ⅱ. EXPERIMENTS AND ANALYSIS

Animal Experiments

Three normal and three diabetic dogs were used for the study. Diabetic condition was produced by Alloxan injection two days before experiments,and was checked by IVGTT results.

After twelve hours of overnight fasting, IVGTT experiments were performed. After intravenous glucose injection for two minutes (250mg/min/kg) through an antecubital vein, the blood samples were obtained through the contralateral vein. Arterial blood samples were obtained through a femoral artery. Hepatic and portal venous blood samples were collected

through the radio-opaque catheters inserted into the hepatic vein and the portal vein, respectively.

Whole blood glucose concentrations were immediately measured by YSI glucose Analyzer. The plasma insulin concentrations were determined using the double antibody radioimmunoassay technique. Hapatic blood flow was estimated at 10 min intervals by the clearance and extraction method of Bradley et al. using I^{131} labelled rose bengal as the extractable materials.[3]

Clinical Experiments

The normal and twelve diabetic subjects were studied after twelve hours of overnight fasting. After intravenous injectjon of 25gr(50%, 50ml) of glucose through an antecubital vein, the blood samples were obtained through the contralateral antecubitel vein.

In addition to the measurements of the whole blood glucose concentrations and the plasma insulin concentrtions as described above, the plasma C-peptide concentrations were also determined using the doube antibody radiommunoassay technique.

Equivalent Circuit Model

Fig. 1 shows the equivalent circuit model for the simulation of the changes of the glucose concentrations during IVGTT. In the model, the compartmental volumes are represented by electrical capacitances (Ci), and the net rate constants are represented by electrical resistances (Ri).

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

The equivalent circuit model includes most of the known physiological factors effective within one hour after glucose loading in IVG TT. G is the exogenous glucose loading. The tissue uptake is represented by a current flowing through the timevarying resistance, Rx, where Rx is directly related to the insulin resistivity parameter(Kr) and inversely related to the instantaneous insulin concentration in the slow pool of insulin kinetics model. [4,5,6] B is the glucose uptake at the brain, which is independent of glucose and insulin concentrations.[7] H is the hepatic glucose balance(uptake or output), represented by the equation of $H=H_0+H_1\ (V_2-V_{20})$ where H_1 is the hepatic glucose sensitivity parameter relating the changes of hepatic balance to the changes of the glucose concentrations from the basal level,

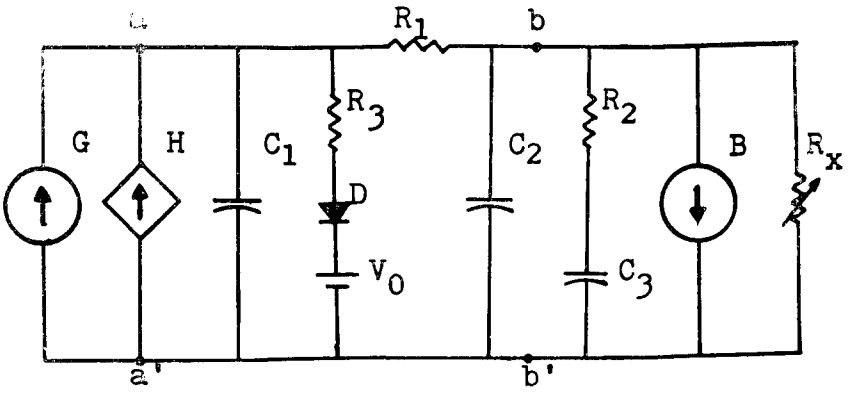


Fig. 1. Equivalent Circuit Model.

(V_2-V_{20}). When H is negative (uptake state), the circuit branch location is changed from a-a' to b-b'.[8,9] The renal glucose excretion rate occuring in hyperglycemia is represented by the current through the branch of a diode (D).[10] The details of the model can be found in our previous paper.[11]

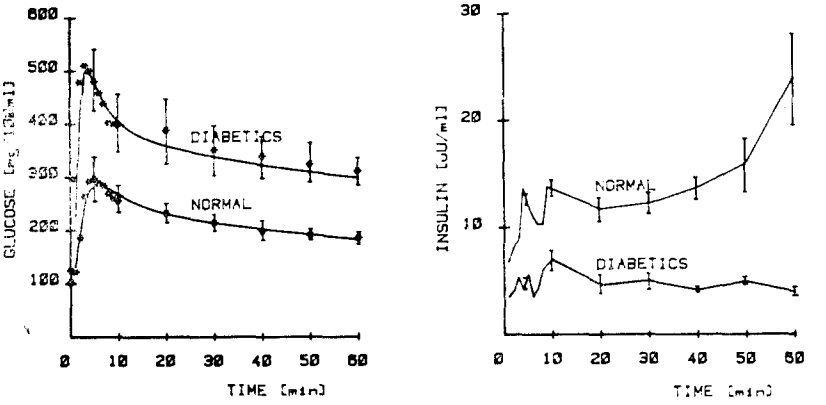
Computer Simulation

Three parameters (capillary-venous blood volume, C_2, hepatic glucose sensitivity, H_1, and insulin resistivity, K_r) were varied iteratively to provide the condition of the least squared error difference between the computed and the measured data.

For other physiological parameters of the model, we used the following reported values; In human's case, total blood volume is 75.6 ml/kg, slow pool volume (C_3) is 100ml/kg, B is 1.08mg/min/kg, the net hepatic glucose output at basal level (H_0) is 2mg/min/kg, the renal excretion threshold (V_0) is 220mg/dl, and the net rate constants R_1, R_2, R_3 are 0.026, 0.24, 0.79, respecitvely. In dog's case, B is 2.1mg/min/kg and H_0 is 2.8mg/min/kg.

Ⅲ. RESULTS

Fig. 2 shows the measured average values of the blood glucose and the plasma insulin concentrations during IVGTT for normal and diabetic dogs. It is shown that the changes of the glucose concentrations were closely simulated by the model. Fig.3 shows the changes of the hepatic glucose balance and the tissue uptake rate after glucose loading. Fig. 3 shows a good agreement of the hepatic glucose balance between the computed results and the measured hepatic balance data obtained from arterial, portal venous, and hepatic venous blood glucose concentration in normal and diabetics. The changes of the hepatic glucose balance and the tissue uptake rate after glucose loading are shown to be negligible in diabetics, as compared with significant changes in normal dogs.



Glucose Concentration
Durinc IVGTT (Mean+S.E.M)

Insulin Concentration
During IVGTT (Hmean+S.E.M)

Fig. 2. Dog experiement data of glucose and insulin concontrations during IVGTT. For the glucose concentration curves, the measured data are represented by -o- where* shows the mean values and I shows one standard error of mean values. And the simulation results are represented by the solid line.

Fig. 4 shows the measured changes of the blood glucose, plasma insluin, and plasma C-

peptide concentrations after glucose loading for normal and diabetic subjects in clinical experiments. In this clinical case also, the change of the glucose concentrations were closely simulated by the model. Fig. 5 shows the hepatic glucose balance and the tissue uptake rate during IVGTT in humans. Similarly to the animal experiment results, there is consi-

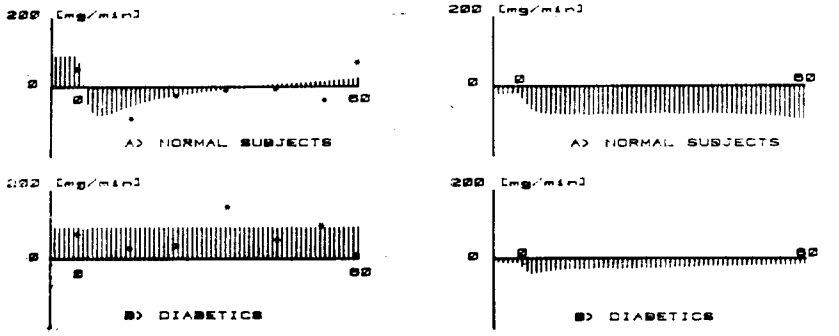


Fig. 3. Dog experiment data for the estimated changes of the hepatic glucose balance and the tissue uptake during IVGTT. The experimental data are shown by* mark. The positive values are for glucose output and the negative values are for glucose uptake.

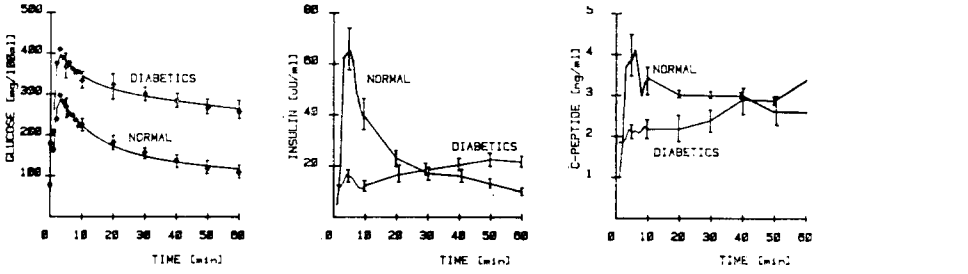


Fig. 4. Human experiment data of the glucose, insulin, and C-peptide concentrations during IVG TT. For the glucose concentration curves, the clinical data are represented by -o- where* shows the mean values and I shows one standard error of mean values. And the simulation results are represented by the solid line.

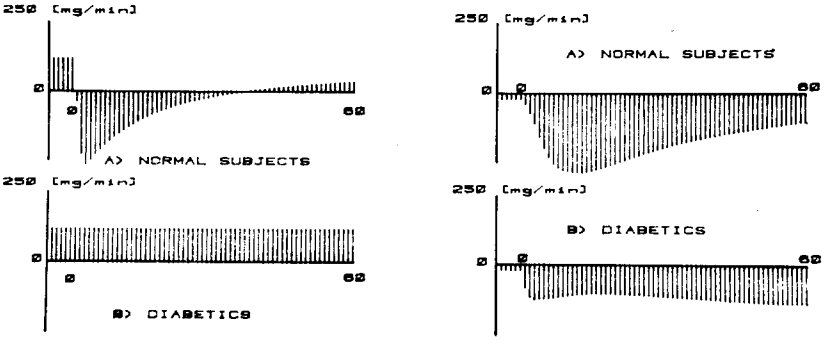


Fig. 5. Human experiment data for the estimated changes of the hepatic glucose balance and the tissue uptake during IVGTT. The positive values are for glucose output and the negative values are for glucose uptake.

Table 1. Dog experiment data for the estimated values of C_2(ml/kg), H_1, and K_r(mean± S.E.M.). E^2 is the residual mean square.

Parameters	Group		P-value
	Normal (3)	Diabetics (3)	
C_2	111.1±14.7	94.5±27.7	0.2
H_1	−1.1±0.1	0	0.05
K_r	36.1±4.5	94.3±5.9	0.025
E^2	0.73	1.04	

Table 2. Human experimant data for the estimated values of C_2(ml/kg), H_1, K_r, SR-I(ng/min), and FHER-I(mean±S.E. M.). E^2 is the residual mean square. P-values are *normal* vs. *diabetics (moderate+severe)*.

Parameters	Group			P-value
	Normal (10)	Moderate Diabeti(6)	Severe Diabetics(6)	
C_2	151.7±9.4	160.5±18.	5132.5±17.7	0.2
H_1	−1.9±0.2	−0.9±0.2	0	0.05
K_r	18.5±2.0	31.8±5.1	56.6±14.6	0.05
SR-I	1823.9 ±155	1569.1 ±332	1385±291	0.1
FHER-I	0.55±0.03	0.55±0.08	0.54±0.08	.N.S.
E^2	0.56	0.52	0.48	

derable differences in the hepatic glucose balance and the tissue uptake between normal and diabetic patients.

Table 1, 2 summarize the best fitted data of the capillary-venous blood volume (C_2), the hepatic glucose sensitivity (H_1), and the peripheral tissue's insulin resistivity (K_r), the insulin secretion rate (SR-I), and the fractional hepatic extraction ratio of insulin (FHER-I) for normal and diabetic dogs and three clinical groups. The clinical groups were classified based on Fujita et al's criteria.[12]

Ⅳ. DISCUSSION

In this paper we present a new quantitative method of estimating the peripheral tissue's insulin resistivity and the hepatic glucose sensitivity from the measured IVGTT data and the equivalent circuit model. It is shown in evaluation of our model that the changes of model-based sensitivity parameters between clinical groups agree with other clinical observations.[13,14] For example, the diminution of the sensitivity parameters becomes greater together with severity of diabetic condition. Also, the estimated hepatic balance in diabetic subjects agrees with the clinical observation[13], where the hepatic output in diabetics was shown to be not suppressed even with a rapid increase of glucose concentration after glucose loading. In other experimental study[14], the amount of the hepatic glucose balance was shown to have almost comparable magnitude as the glucose uptake amount at tissue sites, which is similar to our present estimated results.

In conclusion, the results show that the IVGTT data and the equivalent circuit model can provide a quantitative method for separation of the effects of the peripheral tissue's glucose uptake rate, the hepatic glucose balance, and the insulin secretion rate. It is also shown that these factors are useful in evaluating different insulin-glucose dynamics for clinical groups of normal and diabetic subjects.

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