Reassessment of Glucose Effectiveness and Insulin Sensitivity From Minimal Model Analysis

A Theoretical Evaluation of the Single-Compartment Glucose Distribution Assumption

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Minimal model analysis with the frequently sampled intravenous glucose tolerance test provides an effective way to measure two important metabolic parameters in vivo under non–steady-state conditions: glucose effectiveness (S_G) and insulin sensitivity (S_I). Two questions regarding the validity of S_G and S_I have recently emerged. First, S_G from the minimal model is suspected to be overestimated. Second, the occurrence of S_I values indistinguishable from zero ("zero-S_I") is not negligible in large clinical studies, and its physiological meaning is uncertain. In this study, we examined the significance of the assumed single-compartment glucose distribution embedded in the minimal model on the estimation of S_G and S_I. A more accurate two-compartment model was constructed by incorporating insulin action on hepatic glucose output and uptake into a previously validated construction. The two-compartment results were compared with the one-compartment minimal model results. It was shown that the one-compartment assumption contributes to a systematic deviation of S_G (slope = 0.54, y-intercept = 0.014 min^{-1}; n = 195 simulations). However, S_G from the minimal model was linearly correlated to S_G determined from the two-compartment model (r = 0.996). The one-compartment assumption also contributed to the occurrence of zero S_I values for insulin-resistant subjects. A similar linear relationship was found between S_I estimated by both the minimal model and the two-compartment model (slope = 0.58, y-intercept = -0.57×10^{-4} min^{-1} per μU/ml, r = 0.998). In conclusion, S_G and S_I from the minimal model are not necessarily equivalent to values emanating from the more accurate two-compartment model. However, the very high correlation between one- and two-compartment results suggests that the minimal model–derived S_G and S_I are dependable indexes of in vivo glucose effectiveness and insulin sensitivity. Minimal model analysis' advantages of simplicity, minimal invasiveness, reasonable reflection of non–steady-state glucose kinetics, and cost-effectiveness could in many cases outweigh the structural bias introduced by the model simplification. *Diabetes* 46:1813–1821, 1997

The minimal model was developed to quantify whole-body glucose metabolism from the frequently sampled intravenous glucose tolerance test (FSIGT) (1). In vivo glucose tolerance is determined by both insulin-dependent and non–insulin-dependent processes. Two important metabolic parameters related to these two processes are estimated by the minimal model–insulin sensitivity (S_I), which characterizes insulin action on glucose kinetics, and glucose effectiveness (S_G), which characterizes non–insulin-dependent glucose kinetics at basal insulin.

Despite the potential advantages of minimal model analysis in studying glucose metabolism, including its cost-effectiveness and the fact that it is a single-test procedure, serious questions have unfolded over the years regarding its use in the measurement of S_I and S_G. In the early stage of the minimal model development, S_I was reported to correlate weakly with insulin sensitivity determined from glucose clamps (2). Adding an injection of tolbutamide or insulin during the FSIGT strengthened the correlation considerably (3,4). As a result, the use of S_I for measuring insulin sensitivity in vivo is widely accepted.

More recently, two questions have arisen about the use of minimal model analysis: the possible overestimation of S_G and the occurrence of S_I values indistinguishable from zero ("zero S_I"). The first question is related to the validation of minimal model–derived S_G, whose importance has been recently reemphasized (5). Quon et al. (6) proposed that S_G from the minimal model was overestimated in IDDM subjects compared with direct measurement of glucose effectiveness. There are several possibilities that might contribute to this discrepancy. One suggestion is that aggregation of hepatic and peripheral components of S_G into a single parameter (i.e., p_1 in the minimal model) might contribute to the overestimation of S_G (6,7). Alternatively, Finegood and Tzur (8) proposed that the estimation of S_G from the minimal model was not independent of the endogenous insulin secretory response. A third possible explanation, which is the main hypothesis tested in this paper, is the simplifying assumption of single-

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FSD, fractional standard deviation; FSIGT, frequently sampled intravenous glucose tolerance test; GINF, glucose infusion rate; HGO, hepatic glucose output; S_G, glucose effectiveness; S_I, insulin sensitivity.

compartment glucose distribution kinetics in the minimal model (9,10). This simplification was originally implemented so that the parameters of the model could be identified from a single, relatively simple experimental procedure. However, abundant evidence exists that glucose distribution is multicompartmental (11). The degree to which the single-compartment assumption affects S_G and S_I estimation has not been previously examined. The other serious question about minimal model analysis is the occurrence of zero S_I values (12). The meaning of a zero S_I value is not yet fully understood; whether it represents a physiologically relevant phenomenon or a manifestation of modeling deficiency remains to be examined. Because S_G and S_I are estimated simultaneously from an FSIGT, the single-compartment assumption that might affect estimation of S_G might also contribute to the occurrence of zero S_I. Therefore, in the present study, we used computer simulations to examine the impact of a single-compartment assumption on a multicompartmental distribution system of glucose. The goal was to examine the effects of this assumption on estimation of metabolic parameters S_I and S_G from minimal model analysis.

RESEARCH DESIGN AND METHODS

Model representations for in vivo glucose metabolism. To examine the effect of a single-compartment assumption on the estimation of parameters S_G and S_I, two models were used: a comprehensive model that represents glucose kinetics, and the minimal model. Known parameters were assigned to the comprehensive model based on known physiology; the ability to estimate them from the minimal model was then tested.

Two-compartment model (Model 2C). In this study we exploited a two-compartment model we previously introduced that accounts for the dynamics of tritium-labeled and unlabeled glucose in plasma after injection of both moieties (Fig. 1). Our model was slightly modified from previously published similar two-compartmental representations (13). The construction accounts for "cold" and "hot" glucose data without significant bias, yet it is structurally simple enough for precise parameter identification when both dynamic patterns are available (14). We previously validated the model with animal data in which the plasma insulin remained at basal levels (14). In the present study, the use of this model was extended to include a dynamic insulin response so that a typical FSIGT could be studied (13).

Schematic representation of Model 2C is presented in Fig. 1. Compartments of glucose distribution are as follows. Compartment G_1 (the fast compartment) consists of plasma and tissues that equilibrate rapidly with plasma; compartment G_2 (the slow compartment) represents the pool that equilibrates more slowly with plasma (11). Consistent with known physiology, glucose uptake from compartment G_1 is assumed to be noninsulin mediated. Glucose enhances glucose disappearance and suppresses glucose output in proportion to its concentration in the fast compartment. Uptake from compartment G_2 is considered insulin sensitive (13). Similar to the minimal model itself (1), plasma insulin must first move into the interstitial fluid (compartment "Ins") from which it exerts its actions to enhance glucose uptake from G_2, and suppress endogenous glucose production into G_1. Model 2C is characterized by the following equations:

$$\frac{dq_1(t)}{dt} = \text{HGO}(t) + k_{12}q_2(t) - [k_{01} + k_{21}]\,q_1(t);\ q_1(0) = q_{10} \quad [1]$$

$$\frac{dq_2(t)}{dt} = k_{21}q_1(t) - [k_{02} + k_{12} + (1 - f_{\text{HGO}})X]\,q_2(t);\ q_2(0) = q_{20} \quad [2]$$

$$\frac{dX(t)}{dt} = -k_a X(t) + k_b\,[I(t) - I_b];\ X(0) = 0 \quad [3]$$

$$g_1(t) = \frac{q_1(t)}{V_1} \quad [4]$$

where q_1 and q_2 are the masses of glucose in compartments G_1 and G_2, respectively. Variable g_1 is the glucose concentration in G_1 (representing plasma glucose concentration), and V_1 is the glucose distribution volume of compartment G_1. HGO is hepatic glucose output, which is time-dependent during the FSIGT. The relationship between HGO and glucose pool size in plasma (q_1) is represented by the following relation (14):

$$\text{HGO}(t) = \text{HGO}_0 - (k_L + f_{\text{HGO}} \cdot X)\,q_1(t) \quad [5]$$

where HGO_0 is the putative rate of hepatic glucose output when plasma glucose mass becomes zero, and k_L is the parameter describing the effect of plasma glucose on HGO. Variable f_{HGO} is the relative fraction of insulin action exerted on HGO, rather than glucose uptake. The dynamics of the effect of interstitial insulin (X) is defined by equation [3], in which k_b and k_a represent the transport of plasma insulin I (above basal insulin I_b) into compartment "Ins" and disappearance of the remote insulin effect, respectively. Representative values of these parameters are given in Table 1 (3,14).

Minimal model. The minimal model has been published in detail elsewhere; only a brief summary of this model is presented here (Fig. 2). The assumed single-compartment distribution kinetics of glucose is described by equation [6]. The effect of glucose per se on net glucose disappearance is characterized by p_1 (also termed S_G). The dynamics of interstitial insulin effect X is defined by equation [7], where p_3 and p_2 represent the transport of insulin into the interstitial compartment and disappearance of the interstitial insulin effect, respectively.

$$\frac{dG(t)}{dt} = p_1 G_b - [p_1 + X(t)]\,G(t);\ G(0) = G_0 \quad [6]$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3\,[I(t) - I_b];\ X(0) = 0 \quad [7]$$

Insulin sensitivity S_I is defined as p_3/p_2, and glucose effectiveness S_G is equal to p_1.

General approach. Throughout this paper, Model 2C was assumed to be a perfect representation of glucose metabolism in all simulated subjects. Each subject was assigned a set of parameters that characterized the glucose kinetics in all clinical experiments (i.e., glucose clamps and FSIGTs) performed on the subject. Two independent sample groups (case studies 1 and 2, described below) were constructed to determine the effect of the single-compartment assumption on either S_G or S_I estimated from minimal model analysis. Glucose clamps and FSIGTs were carried out on each subject. No random error was added to the simulated experiment data; this permitted us to evaluate the theoretical effect of the single-compartment assumption of minimal model analysis without the confounding effect of random measurement errors.

Case study 1: simulated group in which subjects have identical insulin sensitivity but varying glucose effectiveness. In this simulated sample group, insulin sensitivity was assumed to be the same for all individuals, whereas glucose effectiveness varied across the group according to a normal distribution. The purpose of choosing such a group was to investigate the correlation of glucose effectiveness obtained from different models. In a previous study, we showed that the major component of glucose effectiveness was k_{01}, and total glucose effectiveness was the algebraic sum of the peripheral component k_{01} and HGO component k_L (14). Therefore, for simplicity but without loss of generality, we generated a normal distribution of glucose effectiveness by varying k_{01} (n = 195) while keeping all other parameters constant. For each specific k_{01} value, glucose effectiveness ($S_{G(\text{Clamp})}$) and insulin sensitivity ($S_{I(\text{Clamp})}$) were determined by two separate glucose clamps (Eqs. A1–A9 in APPENDIX). The simulated FSIGT was also performed within the group, and the minimal model was applied to the FSIGT data to determine $S_{G(\text{MINMOD})}$ and $S_{I(\text{MINMOD})}$. In this case study, $S_{G(\text{Clamp})}$ was varied as a function of k_{01}, whereas $S_{I(\text{Clamp})}$ remained constant within the group.

Case study 2: simulated group in which subjects have identical glucose effectiveness but varying insulin sensitivity. In this second simulated sample group, glucose effectiveness was assumed to be identical throughout the group, but insulin sensitivity varied according to a normal distribution. We generated normal distributions of k_a and k_b (Fig. 1) simultaneously (n = 394). All other parameters in Model 2C again remained constant. For each specific k_b/k_a combination, both $S_{G(\text{Clamp})}$ and $S_{I(\text{Clamp})}$ were determined, and a simulated FSIGT was performed. Using the minimal model, $S_{G(\text{MINMOD})}$ and $S_{I(\text{MINMOD})}$ were then calculated. In this study, $S_{I(\text{Clamp})}$ was varied as a function of k_b/k_a, whereas $S_{G(\text{Clamp})}$ was the same for all subjects.

Glucose clamps. Two separate glucose clamps were required for the measure of glucose effectiveness and insulin sensitivity for each simulated subject (APPENDIX).

Glucose effectiveness from the glucose clamp. A stepwise hyperglycemic clamp at basal insulin (glucose level clamped at 150, 225, and 300 mg/dl) was simulated using Model 2C (Fig. 1) with glucose infused into G_1 (14). $S_{G(\text{Clamp})}$ was calculated as the slope of glucose infusion rate (GINF; mg/min) versus plasma glycemia (mg/dl), and was normalized to the volume of the accessible glucose pool (compartment G_1, dl) to convert its units to those of glucose effectiveness (minutes^{-1}).

Insulin sensitivity from the glucose clamp. A stepwise hyperinsulinemic, euglycemic clamp was simulated. Insulin was infused sequentially at 8 mU/m^2 per min (dose 1) and 16 mU/m^2 per min (dose 2) (3). $S_{I(\text{Clamp})}$ was defined at steady state as $\Delta\text{GINF}/(\text{G} \times \Delta\text{I})$, where GINF is the maintenance glucose infusion rate, G is the mean targeted plasma glucose, and ΔI is the increment of steady-state plasma insulin concentration between the two insulin infusion doses. For unit consistency, volume correction was again applied to $S_{I(\text{Clamp})}$ to obtain units similar to those of the minimal model (APPENDIX).

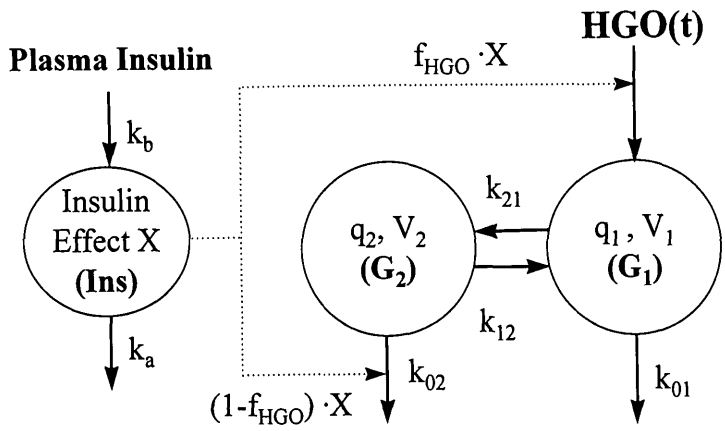

FIG. 1. Schematic representation of a two-compartment model for glucose distribution kinetics. Compartment 1 (G_1) represents the accessible pool, including plasma, into which glucose and tracer are injected, and endogenous HGO enters. Glucose disappearance from this compartment is considered to be independent of insulin, and includes uptake by tissues such as the central nervous system and liver. The second compartment (G_2) represents the remote, interstitial compartment, and is considered the primary site of insulin-stimulated glucose uptake (14). Plasma insulin enters the interstitial space (Ins) and exerts its effect (X) on both HGO and insulin-sensitive glucose uptake. Variable f_{HGO} represents the fraction of total insulin effect X that describes the suppression of HGO.

Tolbutamide-modified FSIGT. The second experiment was the FSIGT, carried out assuming a glucose injection of 300 mg/kg, followed 20 min later by an injection of tolbutamide. A known plasma insulin response profile was used (15) (Fig. 3*B*), as the β-cell response to glucose and tolbutamide was not simulated. A typical simulated FSIGT glucose profile using the representative kinetic parameters (Table 1) is shown in Fig. 3*A*. A full sampling schedule (26 samples over 180 min) was used in this study (15). The resultant predicted glucose data was subjected to analysis by the minimal model implemented using MLAB (Civilized Software, Bethesda, MD) to provide estimates of $S_{G(MINMOD)}$ and $S_{I(MINMOD)}$.

Numerical and statistical analysis. Simulated glucose clamps, FSIGTs, and minimal model analyses were carried out by MLAB implemented on a desktop computer. The Gaussian normal distributions for parameters in Model 2C (k_{01}, k_a, and k_b) were generated by MLAB's built-in random number generator. Parameters of the minimal model were identified by weighted nonlinear least-squares fitting using a Marquardt-Levenburg algorithm with inverse variance weights. Statistical properties and analyses were calculated by SPSS for Windows (SPSS, Chicago, IL). Data are presented as means ± SE unless otherwise stated.

RESULTS

Case study 1: correlation between $S_{G(MINMOD)}$ and $S_{G(Clamp)}$. A total number of 195 simulated subjects were generated in this study. Overall, k_{01} was normally distributed and had a mean value of 0.022 ± 0.01 min^{-1} (SD).

Glucose effectiveness was determined by either the glucose clamp [$S_{G(Clamp)}$] or the minimal model [$S_{G(MINMOD)}$]. The fractional standard deviation (FSD) for $S_{G(MINMOD)}$, which represents the precision of minimal model fitting, was 9.6 ± 0.3%. Linear regression between $S_{G(MINMOD)}$ and $S_{G(Clamp)}$ indicated a strong correlation between the two estimates of glucose effectiveness (r = 0.996) (Fig. 4*A*). Thus, on a theoretical basis, representing glucose distribution as an oversimplified one-compartment system (minimal model) yields a glucose effectiveness value ($S_{G[MINMOD]}$) that is closely related to that from a more complex representation ($S_{G[Clamp]}$). However, a positive intercept of 0.014 min^{-1} and a non-unity slope of 0.54 were also found. This result suggests that, despite a highly correlated relationship, $S_{G(MINMOD)}$ will not always be quantitatively equal to glucose effectiveness emanating from a more comprehensive multicompartment model. Despite the differences across certain ranges of S_G, the overall mean values for $S_{G(MINMOD)}$ and $S_{G(Clamp)}$ were not statistically different (0.0304 ± 0.00035 vs. 0.0308 ± 0.00065 min^{-1}, respectively; P = 0.187).

Similarly, insulin sensitivity was estimated by either the glucose clamp ($S_{I[Clamp]}$) or the minimal model ($S_{I[MINMOD]}$). $S_{I(Clamp)}$ was fixed at 4.66 × 10^{-4} min^{-1} per μU/ml for all subjects. The corresponding $S_{I(MINMOD)}$ values (FSD = 3.3 ± 0.1%) are shown in Fig. 4*B*. $S_{I(Clamp)}$ remained unchanged for all subjects across the entire spectrum of glucose effectiveness; $S_{I(MINMOD)}$ also remained relatively constant (2.08 ± 0.01 × 10^{-4} min^{-1} per μU/ml; P < 0.001 vs. $S_{I[Clamp]}$). This result suggests that variation in glucose effectiveness in different individuals has little effect on the calculation of S_I from minimal model analysis, although the mean value of $S_{I(MINMOD)}$ is only 44% of the reference $S_{I(Clamp)}$ when expressed in the same units.

Case study 2: correlation between $S_{I(MINMOD)}$ and $S_{I(Clamp)}$. In this study there were 394 simulated subjects in which glucose effectiveness remained constant but insulin sensitivity was varied. Parameters k_a and k_b were normally distributed and had mean values of 0.10 ± 0.0018 min^{-1} (SD) and 7.2 ± 0.31 × 10^{-5} min^{-2} per μU/ml (SD), respectively.

Insulin sensitivity was measured by two independent methods: the glucose clamp and minimal model analysis. The FSD for $S_{I(MINMOD)}$ was 6.5 ± 0.9%. Similar to the results with glucose effectiveness, we found a strong correlation between $S_{I(MINMOD)}$ and $S_{I(Clamp)}$ (r = 0.998) (Fig. 5*A*). A negative intercept of –0.57 and a slope of 0.58 were determined by linear regression analysis. Despite a strong correlation, $S_{I(MINMOD)}$ was quantitatively different from $S_{I(Clamp)}$ (2.10 ± 0.05 vs. 4.63 ± 0.09 × 10^{-4} min^{-1} per μU/ml, respectively; P < 0.001).

TABLE 1
Representative kinetic parameters from Ader et al. (14) and Beard et al. (3)

	Typical parameter value
k_{01}	0.0206 min^{-1}
k_{02}	0.0000 min^{-1}
k_{21}	0.1105 min^{-1}
k_{12}	0.1229 min^{-1}
k_L	0.00917 min^{-1}
k_a	0.10 min^{-1}
k_b	7.0 × 10^{-5} min^{-2}/[μU/ml]
f_{HGO}	0.15 (15%)
V_1	113.75 dl*
q_{bolus}	21,000 mg†
I_1	20.6 μU/ml
I_2	35.5 μU/ml

*Calculated for a 70-kg subject. Total distribution volume is estimated as 25% of body weight. Volume of accessible pool is 65% of total plasma volume. †Calculated for a 70-kg subject. Typical FSIGT glucose bolus is 300 mg/kg.

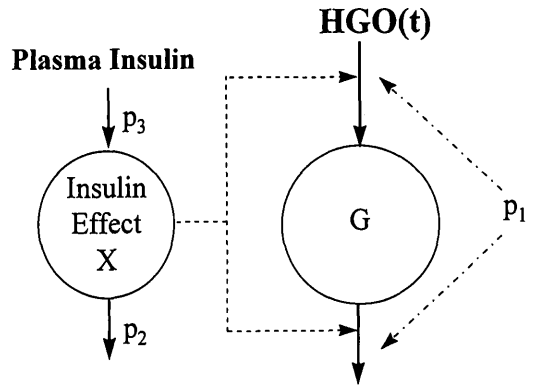

FIG. 2. Schematic representation of the minimal model for glucose distribution kinetics (1). Glucose was assumed to be distributed homogeneously into a single compartment. Plasma insulin enters the interstitial space and exerts its effect (X) on both HGO and insulin-sensitive glucose uptake.

In the low range of $S_{I(Clamp)}$ (less than ~1.0×10^{-4} min^{-1} per μU/ml), $S_{I(MINMOD)}$ approached zero faster than did $S_{I(Clamp)}$. Once $S_{I(MINMOD)}$ became zero, there was no correlation between the two parameters.

The profile of $S_{G(MINMOD)}$, determined from minimal model analysis for all subjects, is shown in Fig. 5*B*. The FSD for $S_{G(MINMOD)}$ is 8.9 ± 0.1%. Although $S_{G(Clamp)}$ for all subjects was fixed at 0.0296 min^{-1}, we observed a similar invariability of $S_{G(MINMOD)}$ across nearly the entire range of insulin sensitivity. However, once the $S_{I(MINMOD)}$ value was indistinguishable from zero, the corresponding $S_{G(MINMOD)}$ revealed a downward systematic deviation. This result suggests that S_G estimated from the minimal model is relatively unchanged for a constant $S_{G(Clamp)}$ population with non-zero-S_I. However in the zero S_I population, $S_{G(MINMOD)}$ became biased.

In the current minimal model analysis, insulin sensitivity was constrained to be non-negative. This restriction was based on the known physiology that elevated plasma insulin stimulates whole body glucose consumption. However, our simulation data indicated that insulin sensitivity from the minimal model might be an underestimation of insulin sensitivity measured from a more accurate multicompartment model. Under conditions where $S_{I(MINMOD)}$ is constrained to be positive, estimation of insulin sensitivity becomes problematic for insulin-resistant subjects. Thus we anticipate that, in the low S_I range, removing this constraint might result in not only a better correlation between $S_{I(MINMOD)}$ and $S_{I(Clamp)}$, but also less systematic deviation of $S_{G(MINMOD)}$ observed in this S_I range. We examined this hypothesis by repeating case study 2 with all conditions identical to the previous run (Table 1 and Fig. 5), except that negative S_I values were allowed to occur during minimal model analysis. The results are shown in Fig. 6. The overall correlation did not change (r = 0.999 vs. 0.998 with standard analysis) because of the relatively small proportion of zero S_I subjects (4.3%) in the entire sample group. The regression slope and intercept also failed to change significantly (intercept changed from –0.57 to –0.64 and slope, from 0.58 to 0.59). However, in the low $S_{I(Clamp)}$ region, we observed better correlation between $S_{I(MINMOD)}$ and $S_{I(Clamp)}$ (Figs. 5*A* and 6*A*). The systematic deviation of $S_{G(MINMOD)}$ was also partly corrected (Figs. 5*B* and 6*B*).

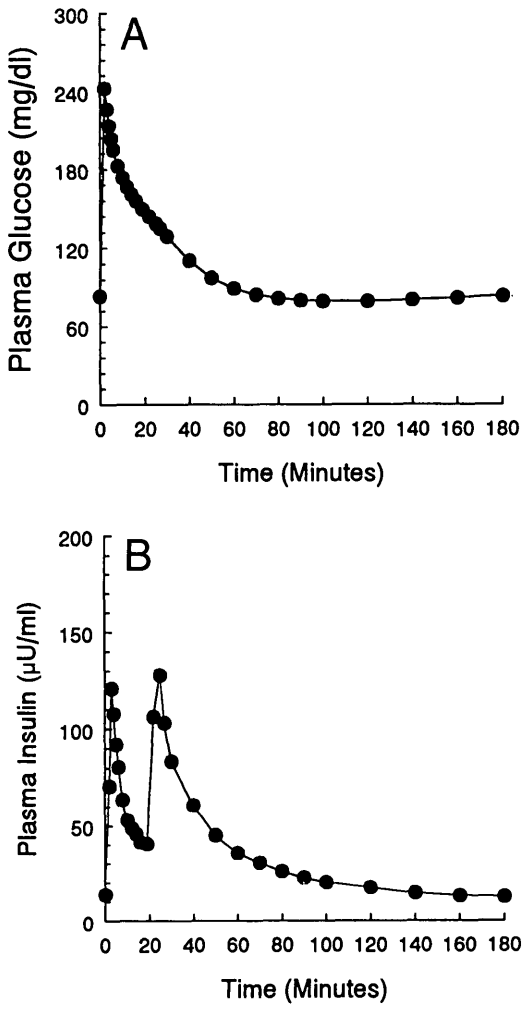

FIG. 3. Typical glucose and insulin profiles from a tolbutamide-modified FSIGT. *A*: glucose profile, generated by the two-compartment model (Fig. 1). *B*: insulin time course. Tolbutamide was assumed to be injected 20 min after glucose injection (15).

DISCUSSION

There are two potential advantages of minimal model analysis. First, it measures glucose action (S_G) and insulin action (S_I) simultaneously from a single FSIGT. In comparison, two separate glucose clamps must be performed to obtain similar information. It has become clear recently that both whole body characteristics may be risk factors for type 2 diabetes and other chronic ailments (12,17). Second, performing the FSIGT has proven to be less technically demanding and more cost-effective compared with equivalent glucose clamps, particularly in large epidemiological studies. Because of these perceived advantages, there is an increasing trend to apply minimal model analysis to the study of a wide variety of normal and pathological states (19). Validations of S_I are abundant in the literature (3,4), and attempts to validate S_G are increasing (5). Continued efforts to examine the characteristics and validity of this widely used methodology are therefore justified.

There are two major criticisms of minimal model analysis. First, Quon et al. (6) provided evidence that the minimal model overestimates the actual importance of glucose effectiveness. Secondly, several studies reported apparent zero val-

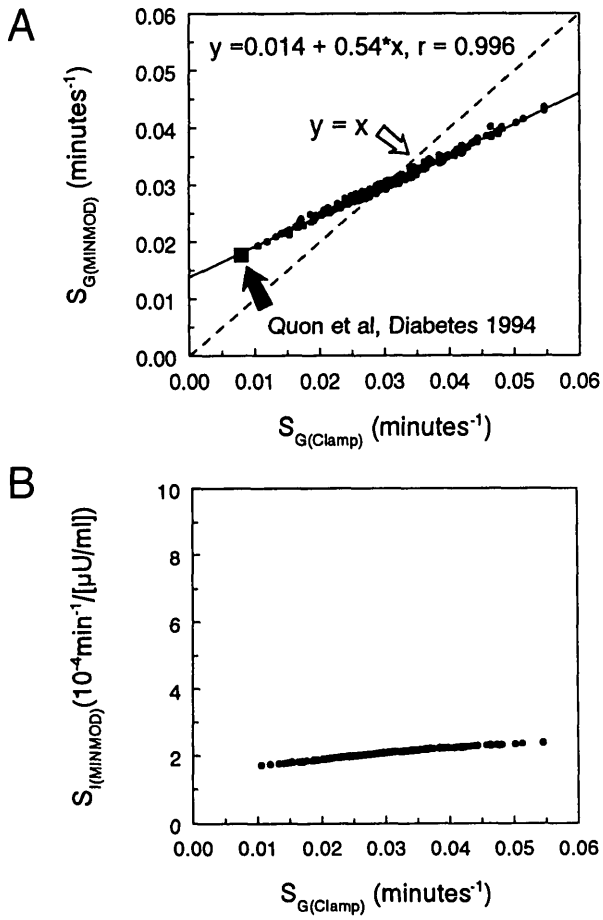

FIG. 4. Correlation of S_G values from two independent measurements (minimal model versus clamp-based measure) in a simulated group with constant S_I and varying S_G. *A*: correlation between $S_{G(MINMOD)}$ and $S_{G(Clamp)}$. The dashed line is the line of unity ($y = x$). Data above this line implies $S_{G(MINMOD)}$ overestimates $S_{G(Clamp)}$ ($y > x$); data below this line implies $S_{G(MINMOD)}$ underestimates $S_{G(Clamp)}$ ($y < x$). The average result from Quon et al. (6) is also presented here as a solid square. The single-compartment assumption of minimal model accounts for the observed overestimation of $S_{G(MINMOD)}$ reported in that paper (see DISCUSSION). *B*: corresponding $S_{I(MINMOD)}$ for all simulations in which S_G was varied. $S_{I(Clamp)}$ remained constant ($4.66 \times 10^{-4} \cdot min^{-1}$ per μU/ml) for all simulations.

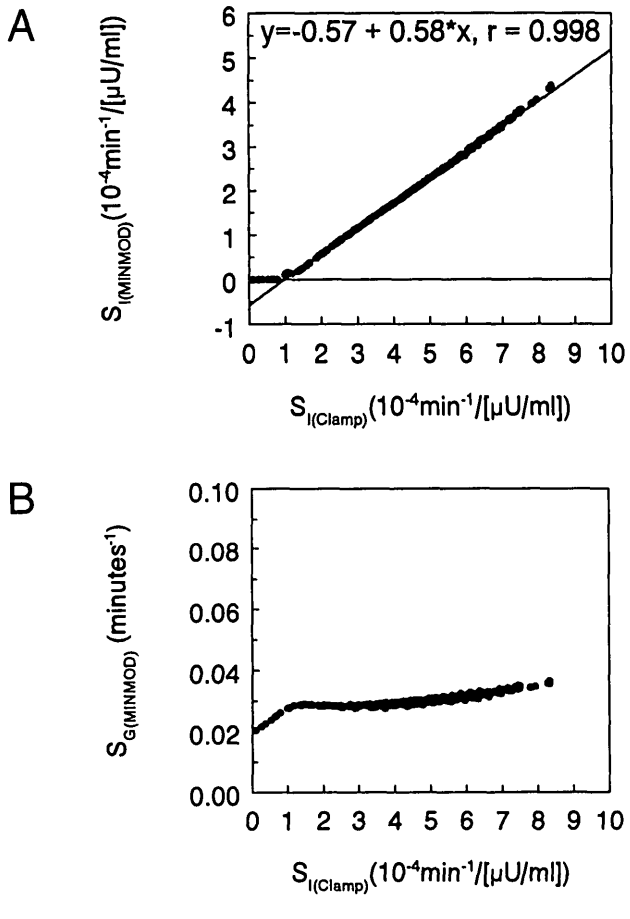

FIG. 5. Correlation of S_I values from two independent measurements (minimal model versus clamp-based measure) in a simulated group with constant S_G and varying S_I. *A*: correlation between $S_{I(MINMOD)}$ and $S_{I(Clamp)}$. *B*: corresponding $S_{G(MINMOD)}$ for all simulations in which S_I was varied. $S_{G(Clamp)}$ remained 0.0298 min^{-1} for all simulations.

ues of S_I (12,17). Although there is evidence for very low insulin sensitivity in NIDDM (20), apparent zeros have emerged even in nondiabetic individuals. For example, in the Insulin Resistance and Atherosclerosis Study of subjects with impaired glucose tolerance, 12% had S_I indistinguishable from zero (16). Given the widespread application of the minimal model technique, it is important to reexamine the model to attempt to understand these apparent anomalies.

$S_{G(MINMOD)}$ correlates well with, but is not equal to, $S_{G(Clamp)}$. In this study, we systematically explored the effect of the single-compartment assumption on glucose effectiveness. Whereas Caumo et al. (10) qualitatively discussed the possible effects of the single-compartment assumption on a two-compartment system, we executed a series of simulations with physiologically relevant parameter values (14,15) to study the quantitative effects of this assumption. In case study 1, we focused on the correlation between $S_{G(MINMOD)}$ and $S_{G(Clamp)}$ in a group within which glucose effectiveness was normally distributed and insulin sensitivity was identical for all subjects. The correlation results are shown in Fig. 4. There are several issues worth discussing regarding this figure.

First, our simulations predicted a strong correlation between $S_{G(MINMOD)}$ and $S_{G(Clamp)}$ ($r = 0.996$); indeed, mean values were not statistically different ($P = 0.187$). However, the slope between the two parameters was not unity (0.54), and the y-intercept differed from the origin (0.014 min^{-1}). This result suggests that, although $S_{G(MINMOD)}$ is a reliable indicator of glucose effectiveness, in some range of values it will differ significantly from the "real" glucose effectiveness. For example, low $S_{G(Clamp)}$ values (less than ~0.03 min^{-1} [region above the 1:1 dashed line Fig. 4*A*]), $S_{G(MINMOD)}$ would quantitatively overestimate $S_{G(Clamp)}$, whereas for $S_{G(Clamp)}$ values greater than ~0.03 min^{-1}, minimal model–derived S_G would be predicted to underestimate $S_{G(Clamp)}$. In the typical range of model-measured S_G of 0.01–0.04 min^{-1}, simulations predict a maximal overestimation of 83% and maximal underestimation of 12%.

One explanation for the quantitative differences resulting from single-compartment modeling is the following. In minimal model analysis, the first 8 min of glucose dynamics are zero weighted, as they are assumed to describe only the "mixing" of glucose between the central and slow compartments (G_1 and G_2) (Fig. 1). If the mixing process has not yet totally completed 8 min after glucose injection (that is, the mass action ratio for glucose between compartments G_1 and G_2 has not

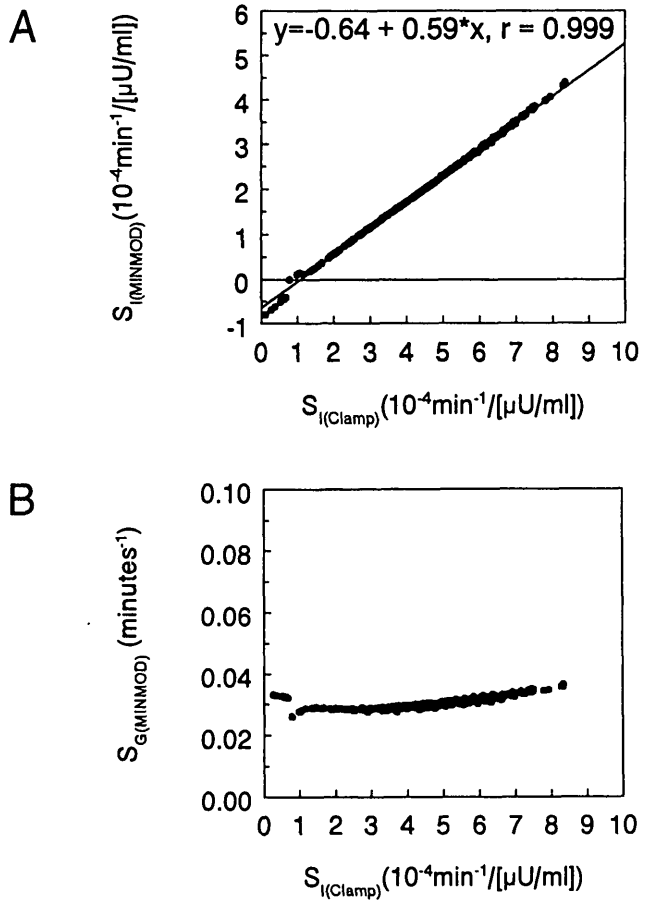

FIG. 6. Repeat of case study 2 except that $S_{I(MINMOD)}$ was allowed to become negative. *A*: correlation between $S_{I(MINMOD)}$ and $S_{I(Clamp)}$. *B*: corresponding $S_{G(MINMOD)}$ for all simulations in which S_I was varied. $S_{G(Clamp)}$ remained 0.0298 min^{-1} for all simulations.

yet attained equilibrium) this mixing process would be considered as part of glucose effectiveness during minimal model analysis. In fact, in our simulations, the ratio of values is 13.5% away from equilibrium at that time (data not shown). If k_{01} is small (and the corresponding $S_{G[Clamp]}$ is small), the continuing transfer of glucose from compartment G_1 (including plasma) to G_2 is greater than the glucose uptake process at t = 8 min. This transfer is seen as insulin-independent glucose disappearance by the minimal model, and therefore $S_{G(MINMOD)}$ will be overestimated. Conversely, for large k_{01}, the continuing transfer of glucose from compartment G_1 to G_2 is less than the glucose uptake process at t = 8 min. This slower transfer is again considered part of the glucose uptake by the minimal model, and therefore $S_{G(MINMOD)}$ will be underestimated. Zero weighting more than 8 min of glucose dynamics might partly correct this deviation, but would also reduce the precision of S_I estimation, since insulin action is likely in effect by 8 min. Finding a more optimal protocol to improve the precision of S_I and S_G estimation within the context of an unlabeled FSIGT and minimal model analysis remains a challenge for further investigation. One possibility is using a nonmetabolizable glucose analog (e.g., L-glucose) as a separate probe for intracompartmental distribution to allow for better estimation of S_I and S_G.

Quon et al. (6) published data suggesting that $S_{G(MINMOD)}$ is overestimated in IDDM subjects. These authors reported that, compared with S_G of nondiabetic individuals (0.025 min^{-1} [5]), minimal model–derived S_G of diabetic individuals was reduced 32% (0.017 min^{-1}). However, they claimed that the true S_G of diabetic subjects was actually much lower, at 0.008 min^{-1}. As shown in Fig. 4*A*, the explanation for this disparity is the one-compartment assumption. This suggests that in the diabetic patients of Quon et al. (6), glucose uptake during the FSIGT was slower than the mixing process, thus resulting in an overestimation of S_G by the minimal model because the mixing process was included in S_G. Of course, there are factors other than the single-compartment assumption that could contribute to discrepancies in S_G estimation (6–8). Finegood and Tzur (8) asserted that accurate estimation of S_G from the minimal model is possible only if insulin secretion is suppressed. In this study, we used standard insulin response profiles, and did not investigate this possibility. How these confounding factors orchestrate and interact to influence S_G estimation remains to be studied.

The second observation from case study 1 (variable glucose effectiveness) was that, although clamp-based insulin sensitivity was the same for all subjects, the resulting $S_{I(MINMOD)}$ also remained relatively constant throughout the whole range of variant glucose effectiveness (Fig. 4*B*). A similar pattern could be found in case study 2 (Fig. 5*B*; see below).

Third, if minimal model–derived S_G is not equal to the real glucose effectiveness, one might question the validity of previously reported results based on minimal model analysis. The answer relies on the focus of the research. If one is studying whether S_G (or S_I) is different among groups (e.g., before and after treatment) or comparing groups with varying tolerance, the deviation between S_G from the minimal model and a two-compartment model would have little effect on minimal model–based conclusions because of the strong linear correlation between parameters derived from the two methods. To demonstrate this point, assume two sample groups (n = 10 each), in which group 1 is the control group (mean $S_{G[Clamp]}$ = 0.027 ± 0.0037 min^{-1}) and group 2 is the treatment group (mean $S_{G[Clamp]}$ = 0.013 ± 0.0022 min^{-1}). Student's t tests indicate that the means are statistically different (P < 0.01). The predicted $S_{G(MINMOD)}$ for these two groups (Fig. 4) would be 0.029 ± 0.002 and 0.021 ± 0.0012 min^{-1}, respectively, which are also statistically different (P < 0.01). This example indicates that results from well-correlated measurements are related in studies of changes in characteristics. However, it must be noted that using correlation to gauge the equivalence of two different methods is often misleading, and high correlation does not guarantee high agreement (18,21). Ultimately, we would like to identify the "absolute" S_G that is a measurement of the ability of glucose per se to enhance whole body glucose uptake and suppress hepatic glucose output simultaneously, independent of an insulin response, model structures, and experimental protocols. However, the current reality is that our understanding of glucose metabolism in vivo remains insufficient to achieve this goal. At this time, minimal model analysis is still one of the better protocols for comparative studies of S_G and S_I in the non–steady-state because of its simplicity, minimal invasiveness, and cost-effectiveness. In contrast to Caumo et al.'s (10) suggestion that $S_{G(MINMOD)}$ is valid only for the first 10–20 min of an FSIGT, we consider $S_{G(MINMOD)}$ a reliable index that is valid for the entire 180-min test, with structural bias that has little effect on the comparative studies.

Introducing "negative S_I" could rectify zero S_I from the minimal model analysis. In case study 2, we focused on the correlation between insulin sensitivity determined from two independent procedures—FSIGT and glucose clamps. The subjects in this particular group had identical glucose effectiveness, but different (normally distributed) insulin sensitivity. The results from the traditional minimal model analysis (non-negative S_I) are shown in Fig. 5, and the results from minimal model analysis modified to allow negative S_I to occur are shown in Fig. 6. There are several issues worth discussing with respect to these results.

First, similar to the results in glucose effectiveness, there is a strong correlation between $S_{I(MINMOD)}$ and $S_{I(Clamp)}$ ($r = 0.998$; Fig. 5*A*). The slope is less than unity (0.58), and the intercept has a negative value (–0.57). We noted that, on average, $S_{I(MINMOD)}$ was only about 45% of $S_{I(Clamp)}$ in magnitude. However, this underestimation may be due in part to the volume term (accessible glucose volume, V_1) used to convert $S_{I(Clamp)}$ to similar units of the minimal model–based parameter. Because insulin and glucose concentrations are both involved in the calculation of $S_{I(Clamp)}$, the accessible glucose volume is not the only option available. Other feasible volumes include total glucose distribution volume, total insulin distribution volume, and plasma insulin distribution volume. However, although using different normalization volumes will result in different absolute values of $S_{I(Clamp)}$, the overall correlation observed here would not change. Another possibility is that, although $S_{I(MINMOD)}$ is proportional to the parameters that define remote compartment insulin (X) kinetics (p_3/p_2 in Fig. 2), $S_{I(Clamp)}$ is not proportional to the corresponding parameters (k_b/k_a in Fig. 1). The values of $S_{I(Clamp)}$ depend not only on k_b/k_a but also on the steady-state plasma insulin levels I_1 and I_2 resulting from the two insulin infusion rates (see APPENDIX). For a single subject, different insulin infusion doses may result in different insulin sensitivity obtained from the glucose clamp because of the limited linear range of insulin action. These two confounding factors—the nonlinearity between $S_{I(Clamp)}$ and k_b/k_a and between $S_{I(Clamp)}$ and plasma insulinemia—might also contribute to the discrepancy between $S_{I(Clamp)}$ and $S_{I(MINMOD)}$.

The second observation from case study 2 (variable insulin sensitivity) is that, although clamp-based glucose effectiveness was identical for all subjects, the corresponding $S_{G(MINMOD)}$ also remained relatively constant throughout all ranges of insulin sensitivity except for the zero-S_I subjects (Fig. 5*B*). This suggests that for non-zero-S_I subjects, S_I estimated by the minimal model can faithfully detect the actual changes of in vivo insulin action in the system of interest. Combined with the similar pattern found in case study 1 (Fig. 4*B*), these results are important in interpreting S_I and S_G from minimal model analysis. These results suggest that, if a shift in $S_{I(MINMOD)}$ or $S_{G(MINMOD)}$ is detected during pathological progress or clinical treatment, this shift reflects the actual change in the corresponding metabolic state in vivo. For example, if in one clinical study mean $S_{I(MINMOD)}$ differs by twofold between subjects of normal versus impaired glucose tolerance, and the mean $S_{G(MINMOD)}$ does not differ significantly between groups, this indicates that impaired glucose tolerance is characterized by defects in insulin sensitivity, but not glucose-dependent metabolism (glucose effectiveness). The results in this study therefore provide another validation for comparative studies using minimal model analysis.

Third, severely insulin-resistant subjects were determined by the minimal model to have zero S_I. The difficulty of differentiating insulin sensitivity among insulin-resistant individuals is not unique to the FSIGT/minimal model approach. Recently it has been proposed that the insulin suppression test has a similar limitation in humans (22). Alzaid et al. (20) showed that, in some NIDDM patients, elevated plasma insulin had no measurable effect on glucose utilization rate, which suggests that zero S_I does exist in NIDDM patients. We might expect that zero S_I reported by the minimal model could indeed indicate a pathological phenomenon (i.e., no insulin sensitivity) in NIDDM patients. However, in this theoretical study, we also raised the possibility that zero S_I from the minimal model might be an artifactual result of the simplified single-compartment assumption embedded in the model. Furthermore, the minimal model normally constrains S_I to a non-negative value, which, although a physiologically plausible assumption, also prevents the minimal model from differentiating insulin sensitivity among insulin-resistant people. Removing this restriction not only restored the differentiating power of the minimal model at this low insulin sensitivity range, but also improved the accuracy of the corresponding glucose effectiveness simultaneously measured by the minimal model (Fig. 6). Additional studies to further understand the negative S_I concept are required.

Model considerations. Two-compartment models of glucose distribution kinetics are not new (13,23–25). The model we used here (Fig. 1) is an extension of a previously validated model that used both labeled and unlabeled glucose injections during somatostatin infusion (14). In the present study, insulin action on both HGO and glucose uptake was implemented, with their relative contributions estimated from Rebrin et al. (26). Whether this implementation of insulin action on HGO and glucose uptake would affect the results presented here has yet to be explored. Parameter sensitivity analysis might give us some insight as to how changes in kinetic parameters affect overall systematic behavior (27). There are many aspects to explore in this area, including the impact of fixed parameters on variables such as the magnitudes of S_G and S_I, the slopes and intercepts in regression analysis, the overall correlation, and the precision of S_G and S_I estimations. More studies are necessary to explore these important issues.

The HGO profile was assumed to be a linear function of plasma glucose in both glucose clamps and FSIGT simulation. Although this relationship has been validated for clamps by Ader et al. (14), it has not yet been validated for the FSIGT. Using a linear function described in equation [5] to represent HGO might be questionable for the early phase of the FSIGT, as this would result in an abrupt decrease of HGO at the beginning of FSIGT that might not reflect the actual HGO profile in vivo. However, other approaches to estimating HGO, such as the deconvolution technique, also have limitations (e.g., numerical uncertainty, sensitivity to noise) (28). Once better estimation of HGO during the FSIGT is available, it would be desirable to incorporate it into our two-compartment model to investigate the effect of HGO representation on the overall correlation results. We are also aware of the fact that renal glucose production might contribute about 25% of total glucose output (29). The relationship between renal glucose output and plasma glucose concentration during the FSIGT is also unknown. Parameter sensitivity and signal propagation analyses might reveal the quantitative influence of questionable parts of the model on the total systematic behavior (27,30).

Whether two-compartment glucose kinetics is appropriate to represent whole body glucose dynamics during the FSIGT is another important issue. Our previous study showed that a two-compartment model is the most appropriate representation for an FSIGT at basal insulin (14). We anticipate that similar conclusions might hold for an FSIGT with an intact insulin response. Some studies have shown that three-compartment models are the best representation for glucose kinetics with intact insulin secretion, but without incorporating insulin action on glucose metabolism (11). The extra compartment presumably includes the central nervous system and other tissues that equilibrate quickly with plasma and the central compartment (11); glucose uptake from this compartment is thought to be independent of insulin, but may not be independent of glucose. From the kinetic parameters shown in Jacquez (11), the third compartment almost reaches equilibrium with the central compartment 2 min after bolus injection. Because the first sample of an FSIGT is drawn 2 min after the bolus injection, it is likely that using a three-compartment model for FSIGT simulation would generate results similar to those of the present study.

Because of requirements for model identifiability, a two-compartment glucose distribution model cannot be completely identified by an unlabeled FSIGT. Tracer injection and additional assumptions are necessary (13,14). These additional requirements will not only increase the cost for the tests but also limit the applicability for large clinical trials. As our results suggest, a well-correlated relationship between $S_{G(MINMOD)}$ (or $S_{I[MINMOD]}$) and comparable clamp-derived parameters exists. Therefore $S_{G(MINMOD)}$ and $S_{I(MINMOD)}$ are still dependable metabolic indexes to gauge in vivo glucose and insulin action. Furthermore, it is possible that better sampling and weighting protocols can improve the estimation of minimal model–based parameters without introducing tracer and any additional assumptions. The two-compartment model constructed here could be used to explore this possibility by testing various sampling schemes and weighting profiles in search of an optimal protocol that could result in a better estimate of S_G.

In conclusion, this study provided a theoretical investigation of the effect of the one-compartment glucose distribution assumption embedded in the minimal model on the determination of insulin sensitivity and glucose effectiveness. Our results suggest that this assumption contributes to the deviation, but not overestimation on average, of $S_{G(MINMOD)}$ in comparison with $S_{G(Clamp)}$. Furthermore, the strong linear correlation between $S_{G(MINMOD)}$ (or $S_{I[MINMOD]}$) and $S_{G(Clamp)}$ (or $S_{I[Clamp]}$) suggests that $S_{G(MINMOD)}$ and $S_{I(MINMOD)}$ are dependable metabolic indexes for clinical and epidemiological studies. The single-compartment assumption may also contribute to the zero S_I phenomenon for insulin-resistant subjects. Allowing $S_{I(MINMOD)}$ to become negative could partly correct this deviation and maintain a better correlation with $S_{I(Clamp)}$. The advantage of the simplicity, minimal invasiveness, reflection of non–steady-state glucose kinetics, and cost-effectiveness of minimal model analysis could in many cases outweigh the structural bias introduced by model simplification.

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APPENDIX

Determination of $S_{G(Clamp)}$ and $S_{I(Clamp)}$ from the two-compartment model. $S_{G(Clamp)}$ and $S_{I(Clamp)}$ are defined under steady-state conditions using equations [1]–[5], which represent the two-compartment glucose kinetics.

$S_{G(Clamp)}$. When stepwise hyperglycemic clamps are performed, glucose effectiveness is defined as the slope of GINF versus glycemia at basal insulin level (14). At steady state, all time derivatives are equal to zero, and the insulin effect (X) is zero, since insulin is fixed at basal by somatostatin. Equations [1]–[5] can be reduced to the following linear algebraic equations for every step i:

$$\frac{dq_{1i}(t)}{dt} = \mathrm{GINF_i} + [\mathrm{HGO_0} - k_L q_{1i}(t)] + k_{12} q_{2i}(t) - [k_{01} + k_{21}] q_{1i}(t) = 0,\ i = 1,2,3 \quad [A1]$$

$$\frac{dq_{2i}(t)}{dt} = k_{21} q_{1i}(t) - [k_{02} + k_{12}] q_{2i}(t) = 0,\ i = 1,2,3 \quad [A2]$$

$$g_{1i}(t) = \frac{q_{1i}(t)}{V_1},\ i = 1,2,3 \quad [A3]$$

Glucose effectiveness, defined as the slope $\frac{\delta \mathrm{GINF}}{\delta g_1}$, can be derived from the above equations:

$$\mathrm{GINF_i} = [k_{01} + \frac{k_{02}k_{21}}{k_{02} + k_{12}} + k_L] q_{1i}(t) - [\mathrm{HGO_0}] \quad [A4]$$

and

$$S_{G(Clamp)} = \frac{\delta \mathrm{GINF_i}}{\delta g_{1i}} = \frac{\delta\{[k_{01} + \frac{k_{02}k_{21}}{k_{02} + k_{12}} + k_L] q_{1i}(t) - [\mathrm{HGO_0}]\}}{\delta[q_{1i}(t)/V_1]} = V_1 \times [k_{01} + \frac{k_{02}k_{21}}{k_{02} + k_{12}} + k_L] \quad [A5]$$

The units of $S_{G(Clamp)}$ are $dl\ min^{-1}$. To directly compare $S_{G(Clamp)}$ to $S_{G(MINMOD)}$, $S_{G(Clamp)}$ is normalized by V_1 to yield comparable units of min^{-1}.

$S_{I(Clamp)}$. Similarly, insulin sensitivity from stepwise hyperinsulinemic clamps can be defined as $\Delta\mathrm{GINF} / (\mathrm{G} \times \Delta\mathrm{I})$, at the same basal glycemic level (3). Thus, if two glucose clamps are performed at the same glucose level (G_b) but two different insulin levels, I_1 and I_2, equation [1]–[5] would become:

$$-\mathrm{GINF_i} = [\mathrm{HGO_0} - (k_L + f_{HGO} \cdot X_i) q_{1b}] + k_{12} q_{2bi} - [k_{01} + k_{21}] q_{1b};\ i = 1,2 \quad [A6]$$

$$k_{21} q_{1b} - [k_{02} + k_{12} + (1 - f_{HGO}) X_i] q_{2bi} = 0;\ i = 1,2 \quad [A7]$$

$$-k_a X_i(t) + k_b [I_i(t) - I_b] = 0;\ i = 1,2 \quad [A8]$$

$$g_{1b} = \frac{q_{1b}}{V_1} \quad [A9]$$

By solving the steady-state equations [A6]–[A9] simultaneously, we could obtain a complicated explicit solution of $S_{I(Clamp)} = (GINF_2–GINF_1)/(g_{1b} \times [I_2–I_1])$. One issue worth mentioning is that equations [A6]–[A9] constitute a nonlinear algebraic system, of which the slope $\partial(GINF/g_{1b})/\partial I$ is not constant over the spectrum of I. Thus, a difference equation $(GINF_2–GINF_1)/(g_{1b} \times [I_2–I_1])$ is used instead of a partial derivative $\partial(GINF/g_{1b})/\partial I$. Furthermore, the units of $S_{I(Clamp)}$ are *dl* $min^{-1}/[\mu U/ml]$. To directly compare $S_{I(Clamp)}$ with $S_{I(MINMOD)}$, $S_{I(Clamp)}$ is normalized by V_1 (31) to yield comparable units of $min^{-1}/[\mu U/ml]$.

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