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Claudio Cobelli, Andrea Caumo and Matteo Omenetto

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Overestimation of minimal model glucose effectiveness in presence of insulin response is due to undermodeling

CLAUDIO COBELLI,¹ FRANCESCA BETTINI,¹ ANDREA CAUMO,² AND MICHAEL J. QUON³

¹Department of Electronics and Informatics, University of Padova, 35131 Padova; ²San Raffaele Scientific Institute, 20132 Milan, Italy; and ³Hypertension-Endocrine Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892

Cobelli, Claudio, Francesca Bettini, Andrea Caumo, and Michael J. Quon. Overestimation of minimal model glucose effectiveness in presence of insulin response is due to undermodeling. *Am. J. Physiol.* 275 (*Endocrinol. Metab.* 38): E1031–E1036, 1998.—Glucose effectiveness is an important determinant of glucose tolerance that can be derived from minimal model analysis of an intravenous glucose tolerance test (IVGTT). However, recent evidence suggests that glucose effectiveness is overestimated by minimal model analysis. Here we compare a new model-independent estimate of glucose effectiveness with the minimal model estimate by reanalyzing published data in which insulin-dependent diabetic subjects were each given IVGTTs under two conditions (Quon, M. J., C. Cochran, S. I. Taylor, and R. C. Eastman. *Diabetes* 43: 890–896, 1994). In one case, a basal insulin level was maintained (BI-IVGTT). In the second case, a dynamic insulin response was recreated (DI-IVGTT). Our results show that minimal model glucose effectiveness is very similar to the model-independent measurement during a BI-IVGTT but is three times higher during a DI-IVGTT. To investigate the causes of minimal model overestimation in the presence of a dynamic insulin response, Monte Carlo simulation studies on a two-compartment model of glucose kinetics with various insulin response patterns were performed. Results suggest that minimal model overestimation is due to single-compartment representation of glucose kinetics that results in a critical oversimplification in the presence of increasingly dynamic insulin secretion patterns.

intravenous glucose tolerance test; glucose kinetics

GLUCOSE EFFECTIVENESS, an important component of glucose tolerance (1, 3), is defined as the ability of glucose to promote its own disposal and inhibit its own production in the absence of an incremental insulin effect (i.e., when insulin is at basal levels) (2, 3).

An estimate of glucose effectiveness (S_G) can be obtained from the minimal model analysis of an intravenous glucose tolerance test (IVGTT). However, both indirect (6–8) and direct (10, 12) experimental evidence indicates that S_G is an overestimate of the true glucose effectiveness and that S_G estimation is influenced by the insulin profile during the IVGTT.

The overestimation of S_G has been suggested (7) to be due, in large part, to the single-compartment approximation of glucose kinetics used by the minimal model. Specifically, S_G would incorporate a component reflecting the exchange kinetics between the accessible and

the inaccessible pool of the glucose system. The relationship between S_G and a reference index of glucose effectiveness has recently been investigated with model simulation studies (9, 11, 13), but conflicting results have been produced. Whereas in Refs. 9 and 13 no correlation with the reference index was found, in Ref. 11 an excellent concordance was obtained. Evidence has been provided (13), however, that the simulation conducted in Ref. 11 poorly reflects real life (e.g., only one parameter at a time is allowed to vary in the Monte Carlo runs).

The sensitivity of S_G to the insulin profile during the IVGTT has not been well characterized, and many issues remain open to question (5). Does overestimation of S_G occur only during an IVGTT when a dynamic insulin response is elicited but not during an optimal protocol (i.e., during an IVGTT when insulin is clamped at its basal value)? If so, what is the cause? Another issue that needs to be addressed is the following: if S_G depends on insulin dynamics during the IVGTT, what is the role played by the insulin response during the first 20 min of the test? This issue has practical relevance because the insulin profile in the first 20 min of the IVGTT is due exclusively to endogenous insulin secretion and may differ considerably among groups, whereas from 20 min on, the insulin profile is made much more homogenous by exogenous insulin administration.

In the present study we sought to address these questions. To do so we relied on both experimental and computer simulation studies. The data base consists of a set of published data (12) in which subjects with insulin-dependent diabetes mellitus (IDDM) were given an IVGTT on one occasion with only basal insulin provided (BI-IVGTT) and on a second occasion in the presence of a dynamic insulin response (DI-IVGTT), in which a normal insulin response was recreated through a computer-controlled infusion of insulin. In our reanalysis of this data, we first calculated from BI-IVGTT data the model-independent reference measure of glucose effectiveness, GE, recently proposed in Ref. 1. We next used the minimal model to obtain estimates of S_G from both the BI-IVGTT and DI-IVGTT. Our results show that S_G derived from the BI-IVGTT is similar and very well correlated to GE. In contrast, S_G derived from the DI-IVGTT is overestimated and correlates weakly with GE. Finally, to investigate whether overestimation of S_G in the presence of an incremental insulin response might be due to single-compartment undermodeling, we used a two-compartment model of glucose kinetics with various patterns of dynamic insulin responses to generate computer simulation results. We show that

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the effect of insulin dynamics on S_G is most likely a consequence of undermodeling and that S_G decreases as insulin availability in the first 20 min of the test decreases.

METHODS

The Data

The data we reanalyzed in this study were previously published, and we refer to the original publication for all details concerning subjects, experimental protocol, and assays (12). Briefly, seven subjects with IDDM, who had no detectable endogenous insulin secretion, each underwent a BI-IVGTT and a DI-IVGTT (0.3 g/kg). During the BI-IVGTT, insulin was infused at a basal rate identical to that required to keep the patient euglycemic during an overnight fast. During the DI-IVGTT, a computer-controlled insulin infusion was given in response to the intravenous glucose load to mimic a normal insulin secretory response.

Glucose Effectiveness: Model-Independent Estimation

It has recently been shown (1) that glucose effectiveness can be calculated under very general assumptions, i.e., virtually in a model-independent way, from an experiment in which exogenous glucose is administered to produce a transient excursion of glucose above basal levels while insulin remains at basal levels (e.g., BI-IVGTT). Under these conditions, the assessment of glucose effectiveness does not require any structural modeling of the glucose system and is simply given by the ratio between the amount of exogenous glucose administered and the area under the curve (AUC) of the glycemic excursion above basal levels. It is worth remarking that this AUC-based index of glucose effectiveness is also equivalent, as shown in Ref. 1, to the analogous clamp-based index. During a BI-IVGTT, glucose effectiveness (GE) is

$$GE = \frac{D}{\text{AUC}[\Delta G(t)]} \quad (1)$$

where D is the glucose bolus dose, and $\text{AUC}[\Delta G]$ is the area under the curve of the glucose concentration excursion above basal (ΔG). It is worth noting that GE, which has the dimension of a clearance rate, i.e., $\text{dl} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, measures the effect of glucose not only to stimulate glucose utilization but also to inhibit glucose production.

$\text{AUC}[\Delta G]$ can be evaluated with the trapezoidal rule or by fitting a parametric function to the glucose data, e.g., a sum of polynomials or exponentials, and deriving the AUC from the estimated parameter values. The latter approach is statistically more robust, because it allows one to assess not only the value of GE but also its precision. Because BI-IVGTT glucose data ΔG are glucose decay data after a bolus injection, the natural candidate to describe them is a sum of decaying exponentials. We found that a two-exponential model was necessary and sufficient, according to Akaike's criterion (4), to describe ΔG data

$$\Delta G(t) = Ae^{-\alpha t} + Be^{-\beta t} \quad (2)$$

Parameters A , α , B , and β were estimated by weighted nonlinear least squares (4) with the assumption of a 2% glucose measurement error and with weights chosen optimally, i.e., equal to the inverse of the measurement error variance. Precision of parameter estimates was obtained from the inverse of the Fisher information matrix (4). By express-

ing $\text{AUC}[\Delta G]$ as a function of the two-exponential parameters, one has

$$GE = \frac{D}{\frac{A}{\alpha} + \frac{B}{\beta}} \quad (3)$$

Precision of GE estimates can be obtained from the precision of A , α , B , and β estimates by error propagation (4).

Glucose Effectiveness: Minimal Model Estimation

Glucose effectiveness was estimated with the minimal model of glucose disappearance (2) from both DI- and BI-IVGTT data. As usually done in minimal model identification, the first 10-min glucose samples were ignored to favor the single-compartment approximation of glucose kinetics.

DI-IVGTT. During the DI-IVGTT, glucose disappearance was described by the classical minimal model equations (2)

$$\begin{aligned} \dot{G}(t) &= -G(t)[S_G + X(t)] + S_G G_b & G(0) &= G_b + \frac{D}{V} \\ \dot{X}(t) &= -p_2 + p_3[I(t) - I_b] & X(0) &= 0 \end{aligned} \quad (4)$$

where S_G (min^{-1}) is glucose effectiveness, V is the minimal model volume of glucose distribution (dl/kg), G is plasma glucose concentration, I is plasma insulin concentration, X is insulin action, p_2 and p_3 are rate parameters, and suffix b denotes basal (end-test) values.

Parameters S_G , V , p_2 , and p_3 were estimated by weighted nonlinear least squares (6) by assuming a 2% glucose measurement error with weights chosen optimally. Precision of parameter estimates was obtained from the inverse of the Fisher information matrix (4).

BI-IVGTT. During the BI-IVGTT, the above basal insulin action X is identically null, and the model reduces to

$$\dot{G}(t) = -S_G[G(t) - G_b] \quad G(0) = G_b + \frac{D}{V}$$

As a result, the model predicts that glucose decay is monoexponential

$$G(t) = \frac{D}{V} e^{-S_G t} + G_b$$

Parameters S_G and V were estimated as described above.

Monte Carlo Simulation

To test the hypothesis that single-compartment undermodeling is responsible for the discrepancies between estimates of glucose effectiveness obtained by model-independent and minimal model analysis, we resorted to Monte Carlo simulation such as in Refs. 9 and 13. The details of the Monte Carlo simulation ingredients, e.g., model structure, parameter values, and noise level, are fully described in Ref. 13. Briefly, a two-compartment model of glucose kinetics with endogenous glucose production described by the same glucose-insulin relationship embodied in the minimal model (2) was used as a reference. Normal parameter values were chosen. Six different insulin profiles (see Fig. 3 in RESULTS) were used as input to the two-compartment model and, for each insulin profile, 200 noisy IVGTT glucose data sets were generated. In addition to the standard (see Fig. 3A) and the basal insulin IVGTT (see Fig. 3F), profiles from an insulin-modified IVGTT showing a progressively decreasing first-phase insulin response (from normal in Fig. 3C to no response in Fig. 3E) were

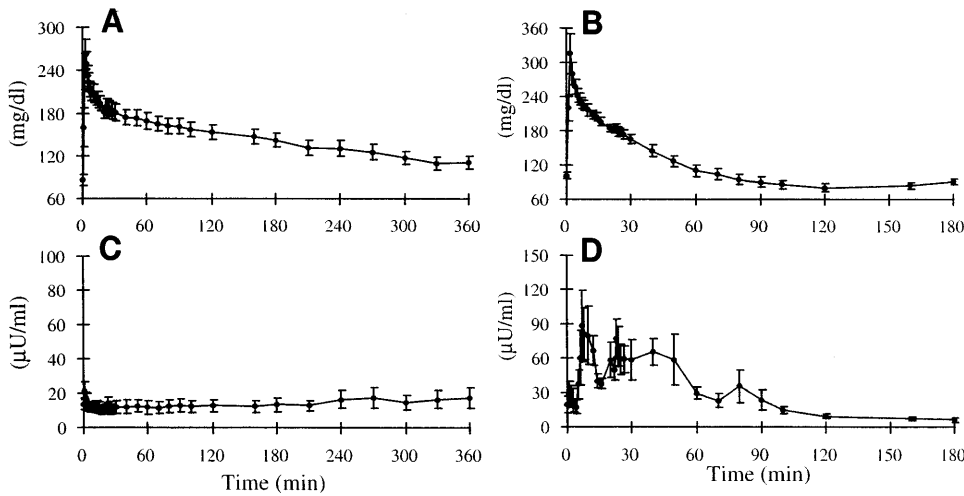


Fig. 1. Plasma glucose (A and B) and insulin (C and D) concentration time courses in insulin-dependent diabetes mellitus (IDDM) subjects (means \pm SE, $n = 7$) during intravenous glucose tolerance test (IVGTT) studies in which basal insulin levels are maintained (BI-IVGTT, left) or in which a dynamic, incremental insulin response was recreated through a computer-controlled insulin infusion (DI-IVGTT, right).

also used. This allowed us to evaluate the sensitivity of the minimal model glucose effectiveness to insulin dynamics in the initial 20 min of the test. The generated plasma glucose and insulin time courses were then used to estimate glucose effectiveness with the minimal model (assuming known the basal glucose and insulin concentrations and ignoring, as usual, the first 10-min glucose samples).

Statistical Analysis

Data in the text and Figs. 1–3 are given as means \pm SE. Linear regression analysis was used to evaluate the relationship between GE and the minimal model assessment of glucose effectiveness. The paired Student’s *t*-test was used to compare different measures of glucose effectiveness made in the same subject. *P* values <0.05 were considered statistically significant.

RESULTS

Experimental Data

The time courses of plasma glucose (*top*) and insulin (*bottom*) concentrations during the BI-IVGTT and DI-IVGTT are shown in Fig. 1 (*left* and *right*, respectively). During the BI-IVGTT, the insulin level was relatively constant, and the glucose profile approached the baseline ~ 6 h after the glucose injection. During the

DI-IVGTT, the glucose profile was similar to the one that is commonly observed in subjects with normal glucose tolerance.

Model-Independent GE

The two-exponential model fit was very good and is shown in Fig. 2. The model-independent GE was calculated from precisely estimated parameters. For example, $\alpha = 0.205 \pm 0.022 \text{ min}^{-1}$, with a mean precision of 17% (range 11–30%), and $\beta = 0.0040 \pm 0.0009 \text{ min}^{-1}$, with a mean precision of 21% (range 3–24%). GE was $0.0099 \pm 0.0017 \text{ dl} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, with a mean precision of 3% (Table 1).

Minimal Model Analysis of BI-IVGTT and DI-IVGTT Data

The minimal model fit of BI-IVGTT data was as good as that provided by the two-exponential model from 10 min on (Fig. 2). Parameters S_C and V were estimated with good precision. The mean values of S_C and V were, respectively, $0.0044 \pm 0.0007 \text{ (min}^{-1}\text{)}$ and 2.76 ± 0.25

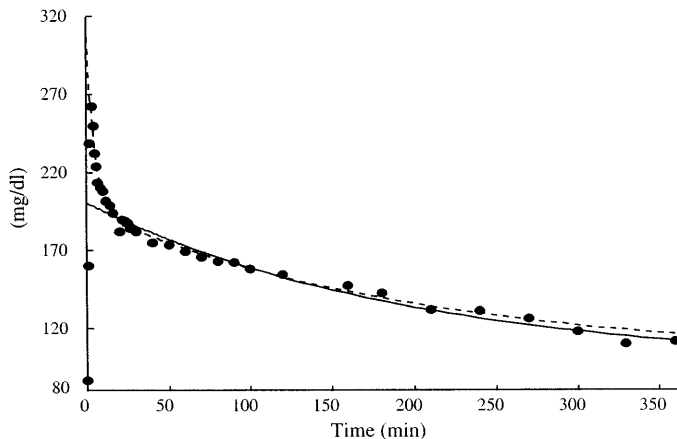


Fig. 2. Two- (dashed line) and one-exponential (continuous line) model fit to BI-IVGTT glucose data of Fig. 1. Values are means of models fitted in each individual.

Table 1. Model-independent and minimal model estimates of glucose effectiveness

Subject No.	Model Independent GE, dl·min ⁻¹ ·kg ⁻¹	Minimal Model S _C V, dl·min ⁻¹ ·kg ⁻¹	
		DI-IVGTT	BI-IVGTT
1	0.0135 (2)*	0.0333 (7)	0.0142 (2)
2	0.0052 (3)	0.0507 (9)	0.0073 (9)
3	0.0021 (2)	0.0381 (27)	0.0069 (10)
4	0.0097 (4)	0.0151 (23)	0.0099 (3)
5	0.0137 (3)	0.0215 (71)	0.0141 (2)
6	0.0119 (3)	0.0222 (63)	0.0121 (7)
7	0.0132 (2)	0.0248 (20)	0.0138 (3)
Mean			
	\pm SE 0.0099 \pm 0.0017 (3)†	0.0294 \pm 0.0050 (31)	0.0112 \pm 0.0012 (5)

GE and S_CV, model-independent and minimal model measures, respectively, of glucose effectiveness. BI-IVGTT and DI-IVGTT, intravenous glucose tolerance tests, respectively, in which a basal insulin level was maintained or a dynamic insulin response was recreated. Nos. in parentheses represent *individual or †mean precision of parameter estimates expressed as percentages of the fractional SD.

(dl/kg) with a mean precision of 5% (range 2–12%) and 2% (range 1–4%). Of note is that S_G ($0.0044 \pm 0.0007 \text{ min}^{-1}$) virtually coincided with the slowest component β ($0.0044 \pm 0.0009 \text{ min}^{-1}$) of the two-exponential model and that there was an excellent correlation between them ($r = 0.99$, $P < 0.001$).

In the case of DI-IVGTT, the minimal model fit assessed in terms of residuals was good, and all the parameters S_G , V , p_2 , and p_3 were estimated with satisfactory precision. In particular, the mean value of S_G was $0.0152 \pm 0.0029 \text{ min}^{-1}$, with a precision of 34% (range 9–74%), and that of V was $2.01 \pm 0.17 \text{ dl/kg}$, with a precision of 3% (range 2–5%).

Comparison Among Different Estimates of Glucose Effectiveness

Estimates of glucose effectiveness derived from both model-independent and minimal model analysis of this data are shown in Table 1. Because S_G measures fractional glucose effectiveness (i.e., per unit of glucose distribution volume), it was multiplied by V to obtain a minimal-model measure of glucose effectiveness, $S_G V$, comparable with GE (1, 5). Precision of $S_G V$ was obtained by error propagation. $S_G V$ estimated from BI-IVGTT data ($0.0112 \pm 0.0012 \text{ dl} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, mean precision 5%) was virtually identical to GE. In addition, $S_G V$ was highly correlated with GE ($r = 0.97$, $P < 0.001$), with the regression line not statistically different from the identity line. In contrast, $S_G V$ from DI-IVGTT data ($0.0294 \pm 0.0050 \text{ dl} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) was three times higher than GE, and the two measures were poorly correlated ($r = -0.4$).

The agreement between $S_G V$ derived from the BI-IVGTT and GE was remarkable in each individual except for *subject no. 3*, where $S_G V$ was three times higher than GE. To ascertain if this discrepancy could be due to the presence in this subject of a fast component still playing an important role after 10 min, we repeated the identification in all subjects by ignoring the first 20-min glucose samples. $S_G V$ in *subject no. 3* decreased from 0.0069 to 0.0033 min^{-1} , thus approaching $GE = 0.0021 \text{ min}^{-1}$, whereas no appreciable modifications were noted in the other six subjects. As a result, the mean value of $S_G V$ became $0.0105 \pm 0.0016 \text{ min}^{-1}$, and the correlation with GE improved ($r = 0.999$, $P < 0.000001$).

Monte Carlo Simulation

The six insulin profiles used for the Monte Carlo simulations to assess the effect of insulin dynamics on S_G estimation are shown in Fig. 3. The results are reported in Table 2. They show that, when the minimal model is used to interpret glucose data generated by a more complex two-compartment model, S_G estimation is markedly influenced by insulin dynamics. Glucose effectiveness was virtually the same with the standard and the insulin-modified IVGTT, i.e., the DI-IVGTT (*profiles A and B*) but markedly decreased with the early insulin response (*profiles C, D, and E*). When

insulin remained at the basal level throughout the test (*profile F*), as during the BI-IVGTT, the lowest value of glucose effectiveness was obtained.

DISCUSSION

The IVGTT minimal model method provides, in addition to an index of insulin sensitivity, an index of glucose effectiveness that measures the ability of glucose to favor its own disappearance from plasma by promoting its own utilization and inhibiting its own endogenous production when insulin is at basal levels. This index has been shown to characterize several pathophysiological states as well as to have predictive power (see recent review in Ref. 3). However, recent experimental evidence (10, 12) has shown that glucose effectiveness estimated from a standard or an insulin-modified IVGTT (when a dynamic incremental insulin response is present) is overestimated when compared with values derived from an IVGTT in which the potentially confounding effect of hyperinsulinemia is eliminated by maintaining insulin at its basal level throughout the test. However, until recently it was not possible to easily investigate the mechanism underlying this discrepancy, because a minimal model-independent measure of glucose effectiveness was needed to relate minimal model estimates to a reference measure.

In this study we have used the recently proposed model-independent measure of glucose effectiveness (1) to assess the domain of validity of the minimal model measurement. Our results indicate that when the minimal model index of glucose effectiveness (expressed as the product $S_G V$) is estimated from an IVGTT in which insulin is kept constant at the basal level (BI-IVGTT), its results are virtually identical to the glucose effectiveness index GE obtained in a model-independent way from AUC calculations. In contrast, when insulin changes dynamically (DI-IVGTT), the minimal model overestimates the model-independent measure of glucose effectiveness by a factor of three.

The excellent concordance between the minimal model estimate of glucose effectiveness obtained from the BI-IVGTT and GE is in contrast with the findings of Finegood and Tzur (10), who reported no correlation between the S_G derived from the BI-IVGTT and $S_{G(\text{clamp})}$, i.e., the clamp-based index of glucose effectiveness. A likely explanation of this discrepancy is related to the fact that glucose effectiveness spans a relatively narrow range in many different metabolic states. This makes the correlation analysis between different estimates of glucose effectiveness extremely sensitive to measurement errors and day-to-day variability. Note that in this study $S_G V$ and GE have been calculated from the same BI-IVGTT data, whereas in Ref. 10 the S_G and $S_{G(\text{clamp})}$ were estimated with different experimental approaches on different days.

The concordance between $S_G V$ obtained from the BI-IVGTT and GE indicates that the single-compartment minimal model is adequate to measure glucose effectiveness when insulin remains basal during the

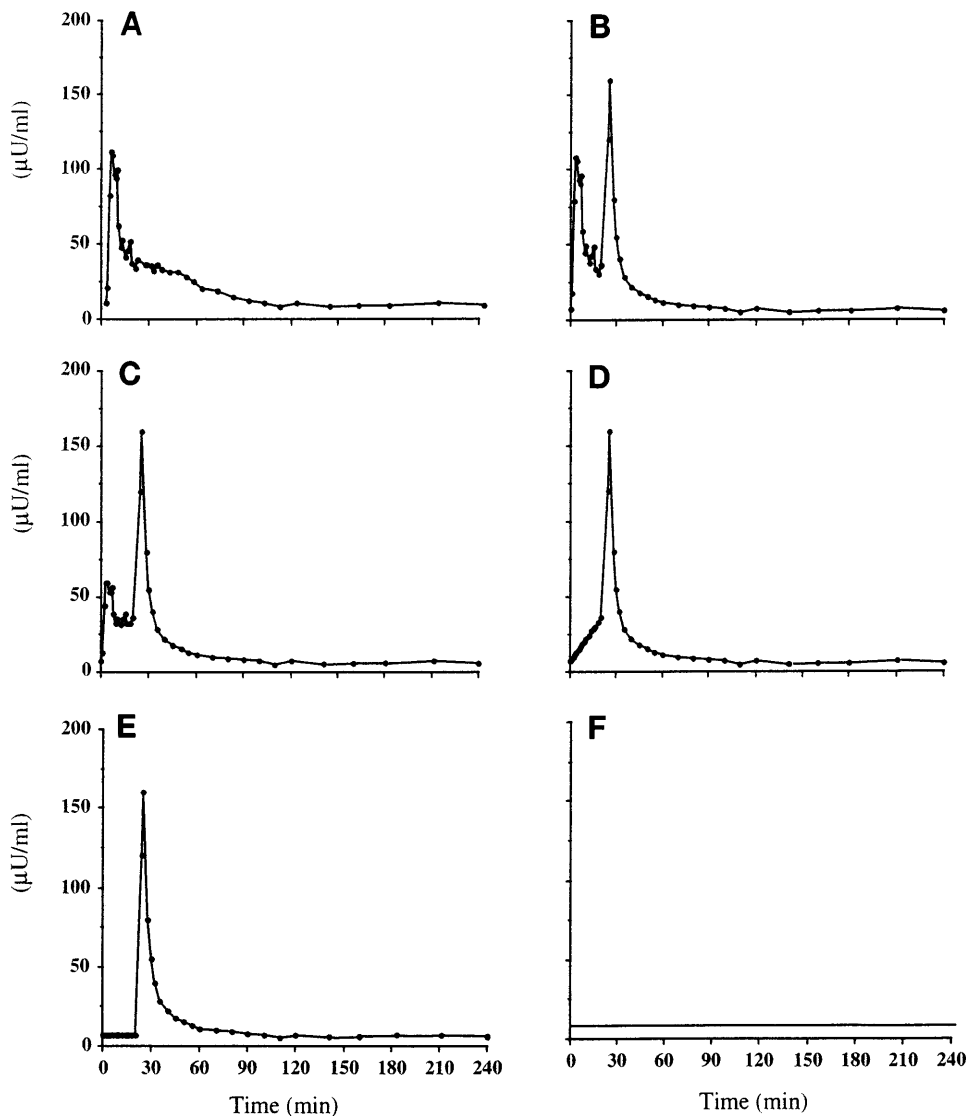


Fig. 3. Insulin profiles used in Monte Carlo simulation. Insulin profiles *A* and *B* are typical of a standard and an insulin-modified IVGTT, respectively. Profiles *C*, *D*, and *E* are from an insulin-modified IVGTT showing progressively decreasing first-phase insulin response. Profile *F* comes from an IVGTT in which insulin is maintained at the basal level throughout the study.

IVGTT. This occurs despite the fact that the minimal model S_GV hinges on a single-pool description of the glucose system and is calculated by ignoring the first 10-min glucose samples, whereas GE is based on much broader assumptions about the glucose system and is calculated by relying on the whole glucose data set from 0 to 180 min. The reason why this happens is that, during a BI-IVGTT, the fast component of glucose

disappearance, which is not accounted for by the minimal model, quickly fades away (within the initial 20 min of the test). From that time on, glucose decay is well described by the slow component only. This can easily be seen by referring to the parameters of the two-exponential function used to calculate $\text{AUC}[\Delta G]$, as in Eq. 3. Because $A/\alpha \ll B/\beta$ (see RESULTS), for the calculation of $\text{AUC}[\Delta G]$, and thus of GE, the (slowest) exponential function is enough, or, in other terms, the contribution to $\text{AUC}[\Delta G]$ of the fast exponential is negligible. Now, if one sees the minimal model in its exponential version (Eq. 6), it is clear why the model-independent GE and the minimal model S_GV give the same results. Note that this reasoning would have been much less transparent if the trapezoidal method had been used to calculate $\text{AUC}[\Delta G]$, and thus GE. One additional observation is that the equivalence between S_GV and GE, which holds for a BI-IVGTT, cannot be taken for granted in other experimental conditions, even when insulin is maintained at the basal level. In fact, there may be cases in which, due to a format of glucose administration with relatively rapid and fre-

Table 2. Minimal model glucose effectiveness with different insulin profiles

Insulin Profile	S_G min^{-1}	V dl/kg	S_GV $\text{dl} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$
A	0.023	2.0	0.046
B	0.024	1.9	0.045
C	0.020	2.0	0.040
D	0.017	2.1	0.035
E	0.014	2.2	0.031
F	0.009	2.5	0.023

S_G , minimal model fractional glucose effectiveness in DI-IVGTT; V, minimal model volume of glucose distribution; S_GV , minimal model glucose effectiveness.

quent changes, the behavior of the glucose system cannot be well approximated by a single-compartment model.

Our result, that the minimal model glucose effectiveness obtained from a DI-IVGTT is three times higher than that estimated from a BI-IVGTT, is clearly a symptom of model error. The sensitivity of S_G to the IVGTT insulin profile has also recently been observed in dog studies by Finegood and Tzur (10), but no mechanistic explanation of why this happens was offered in that study. In the present study, we resorted to Monte Carlo simulation to clarify whether single-compartment undermodeling can explain S_G sensitivity to insulin dynamics. A physiologically based two-compartment model was used to simulate IVGTT glucose data in the presence of different insulin profiles. We reasoned that, if undermodeling plays a role in making S_G sensitive to insulin dynamics during the IVGTT, the minimal model S_G estimated from simulated BI-IVGTT and DI-IVGTT data should exhibit the same trend observed with real data. As a matter of fact, similarly to Finegood and Tzur (10) and to the experimental results obtained in the present study, S_G estimated from a simulated DI-IVGTT (Fig. 3, profiles A and B) was higher than that estimated from a simulated BI-IVGTT (profile F). Moreover, S_G progressively decreased with the early insulin response (Fig. 3, profiles C, D, and E), thus corroborating the suggestion of Finegood and Tzur that caution must be exercised in the interpretation of differences in the estimates of S_G between subject groups with significant differences in β -cell function. Of note is that the value of S_{GV} estimated from simulated BI-IVGTT (profile F) was close to the glucose effectiveness of the reference two-compartment model (0.0023 vs. 0.0021 dl·min⁻¹·kg⁻¹). This result obtained from simulated data confirms that the minimal model yields an accurate estimate of glucose effectiveness only when insulin remains at the basal level during the IVGTT.

All in all, the experimental results of this study, those of Finegood and Tzur (10), and our Monte Carlo simulations suggest that the single-pool description is reasonably adequate when the glucose system is studied at basal insulin but becomes critical when insulin is elevated in the initial portion of the IVGTT. A possible explanation is related to the fact that, at variance with the BI-IVGTT when glucose decay is dictated by glucose effectiveness only, during a DI-IVGTT the minimal model has to distinguish between the individual contributions of glucose and insulin action to glucose disappearance. During a DI-IVGTT, S_G is mainly estimated in the initial portion of the test, when glucose concentration is high and insulin action, albeit increasing, is still low. As a result, S_G assumes a value that reflects both the fast and slow components of glucose disappearance per se. The value taken on by S_G progressively decreases with the early insulin response, because the portion of the IVGTT crucial for its estimation (i.e., when glucose is high and insulin action is low) becomes wider and wider. As a consequence, S_G reflects a combination of the two components in which the role played by the fast component becomes less and less

important. In particular, during a BI-IVGTT, S_G gets close to the slow component because S_G is estimated from the entire 180-min glucose data set.

In conclusion, the results of the present study show that the minimal model estimate of glucose effectiveness is very similar to a model-independent measurement when insulin is kept at basal level, but not when it exhibits the dynamic pattern traditionally observed during an IVGTT. Monte Carlo simulation results suggest that single-compartment undermodeling can explain S_G sensitivity to insulin dynamics and that the early insulin response during the IVGTT markedly influences the value assumed by S_G .

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Address for reprint requests: C. Cobelli, Dept. of Electronics and Informatics, Via Gradenigo 6/A, Univ. of Padova, 35131 Padova, Italy. Received 7 May 1998; accepted in final form 17 August 1998.

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