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## The hot IVGTT two-compartment minimal model: indexes of glucose effectiveness and insulin sensitivity

PAOLO VICINI,<sup>1</sup> ANDREA CAUMO,<sup>2</sup> AND CLAUDIO COBELLI<sup>1</sup>

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**Vicini, Paolo, Andrea Caumo, and Claudio Cobelli.** Hot IVGTT two-compartment minimal model: indexes of glucose effectiveness and insulin sensitivity. *Am. J. Physiol.* 273 (*Endocrinol. Metab.* 36): E1024–E1032, 1997.—A two-compartment minimal model (2CMM) has been proposed [A. Caumo and C. Cobelli. *Am. J. Physiol.* 264 (*Endocrinol. Metab.* 27): E829–E841, 1993] to describe intravenous glucose tolerance test (IVGTT) labeled (hereafter hot) glucose kinetics. This model, at variance with the one-compartment minimal model (1CMM), allows the estimation of a plausible profile of glucose production. The aim of this study is to show that the 2CMM also allows the assessment of insulin sensitivity ( $S_I^{2*}$ ), glucose effectiveness ( $S_G^{2*}$ ), and plasma clearance rate (PCR). The 2CMM was identified on stable-isotope IVGTTs performed in normal subjects ( $n = 14$ ). Results were (means  $\pm$  SE)  $S_G^{2*} = 0.85 \pm 0.14 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ,  $\text{PCR} = 2.02 \pm 0.14 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , and  $S_I^{2*} = 13.83 \pm 2.54 \times 10^{-2} \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$ . The 1CMM was also identified; glucose effectiveness and insulin sensitivity indexes were  $S_G^*V = 1.36 \pm 0.08 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and  $S_I^*V = 12.98 \pm 2.21 \times 10^{-2} \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$ , respectively, where  $V$  is the 1CMM glucose distribution volume.  $S_G^*V$  was lower than PCR and higher than  $S_G^*$  and did not correlate with either [ $r = 0.45$  (NS) and  $r = 0.50$  (NS), respectively], whereas  $S_I^*V$  was not different from and was correlated with  $S_I^{2*}$  ( $r = 0.95$ ;  $P < 0.001$ ).  $S_G^*$  compares well ( $r = 0.78$ ;  $P < 0.001$ ) with PCR normalized by the 2CMM total glucose distribution volume. In conclusion, the 2CMM is a powerful tool to assess glucose metabolism in vivo.

intravenous glucose tolerance test; tracer kinetics; plasma clearance rate

THE LABELED (hereafter hot) intravenous glucose tolerance test (IVGTT) interpreted with the single-compartment minimal model of hot glucose disappearance (1CMM) is a powerful, noninvasive tool to characterize glucose disposal in vivo (1, 7, 10). The model provides metabolic indexes measuring glucose effectiveness ( $S_G^*$ ) and insulin sensitivity ( $S_I^*$ ) in an individual (10). However, when the model is used in conjunction with unlabeled (hereafter cold) glucose data to estimate endogenous glucose production during the IVGTT by deconvolution, an unphysiological time course results due to the well-known limitations of the monocompartmental representation of glucose kinetics in non-steady state (7, 8). A two-compartment minimal model (2CMM) has recently been proposed to solve this problem (8).

The 2CMM provides a physiologically plausible profile of endogenous glucose production during the test, thus overcoming the limitations of the 1CMM.

The aim of this study is to show that the new model, in addition to endogenous glucose release, also provides indexes of glucose effectiveness and insulin sensitivity. In particular, the 2CMM overcomes the drawback of the 1CMM, which is unable to single out estimates of glucose effectiveness and plasma clearance rate (they are, in fact, the same parameter,  $S_G^*$ ) (7). Thus, in addition to a new index of insulin sensitivity ( $S_I^{2*}$ ), the 2CMM provides new indexes separately measuring glucose effectiveness ( $S_G^{2*}$ ) and plasma clearance rate at basal state (PCR). Finally, the relationships between the indexes estimated with the 1CMM and 2CMM are elucidated.

### THE TWO-COMPARTMENT HOT MINIMAL MODEL

The 2CMM, proposed in Ref. 8 and shown in Fig. 1, is described, in its uniquely identifiable parameterization, by the following equations

$$\dot{q}_1(t) = -\left[k_p + \frac{R_{d,0}}{Q_1(t)} + k_{21}\right]q_1(t) + k_{12}q_2(t) \quad (1a)$$

$$q_1(0) = d$$

$$\dot{q}_2(t) = k_{21}q_1(t) - [k_{02} + x(t) + k_{12}]q_2(t) \quad q_2(0) = 0 \quad (1b)$$

$$\dot{x}(t) = -p_2[x(t) - s_k\{I(t) - I_b\}] \quad x(0) = 0 \quad (1c)$$

$$g(t) = \frac{q_1(t)}{V_1} \quad (1d)$$

where  $q_1$  and  $q_2$  denote hot glucose masses in the first (accessible pool) and second (slowly equilibrating) compartments, respectively (mg/kg for a stable-label IVGTT);  $x(t) = k_c I'(t)$  is insulin action ( $\text{min}^{-1}$ ), where  $I'(t)$  is the concentration of insulin remote from plasma ( $\mu\text{U/ml}$ );  $I(t)$  and  $I_b$  are plasma insulin and basal (end test) insulin, respectively ( $\mu\text{U/ml}$ );  $Q_1(t)$  is cold glucose mass in the accessible pool (mg/kg);  $g(t)$  is plasma hot glucose concentration (mg/dl);  $d$  is the hot glucose dose (mg/kg);  $V_1$  is the volume of the accessible pool (ml/kg);  $R_{d,0}$  ( $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) is the constant component of glucose disposal (8, 14), accounting for the inhibition of glucose clearance by glucose itself;  $k_p$  ( $\text{min}^{-1}$ ) is the proportionality constant;  $k_{21}$  ( $\text{min}^{-1}$ ),  $k_{12}$  ( $\text{min}^{-1}$ ), and

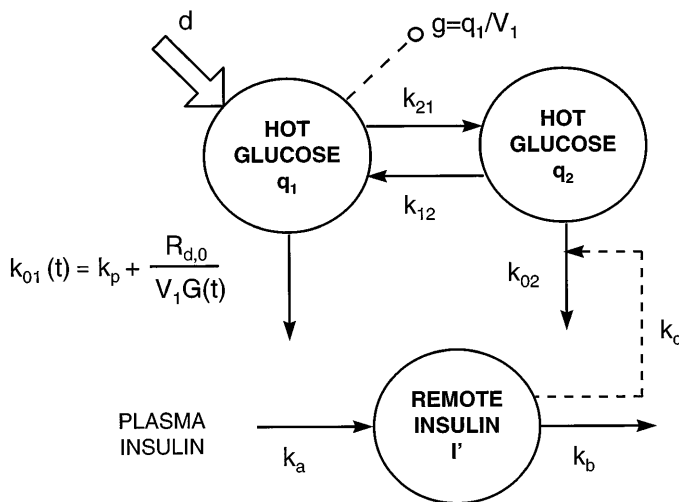


Fig. 1. The two-compartment minimal model (2CMM). Capital and lowercase letters denote variables related to cold and hot glucose, respectively. See Eqs. 1a–1d for model parameterization details.  $q_1$  and  $q_2$ , hot glucose masses in the first (accessible pool) and second (slowly equilibrating) compartments, respectively;  $I'$ , concentration of insulin remote from plasma;  $g$ , plasma hot glucose concentration;  $G$ , cold glucose concentration in the accessible pool;  $d$ , hot glucose dose;  $V_1$ , volume of the accessible pool;  $R_{d,0}$ , constant component of glucose disposal that accounts for inhibition of glucose clearance by glucose itself;  $k_p$ , proportionality constant;  $k_{21}$ ,  $k_{12}$ , and  $k_{02}$ , glucose kinetic parameters; and  $k_a$ ,  $k_b$ , and  $k_c$ , insulin action parameters.

$k_{02}$  ( $\text{min}^{-1}$ ) are parameters describing glucose kinetics; and  $p_2 = k_b$  ( $\text{min}^{-1}$ ) and  $s_k = k_a k_c / k_b$  ( $\text{ml} \cdot \mu\text{U}^{-1} \cdot \text{min}^{-1}$ ) are parameters describing insulin action. Capital and lowercase letters are used to denote variables related to cold and hot glucose, respectively, and overdot notation refers to time rates of change for respective variables [e.g.,  $\dot{q}_1(t)$ ,  $\dot{q}_2(t)$ , and  $\dot{x}(t)$ ].

Briefly, the model structure assumes that insulin-independent glucose disposal takes place in the accessible pool and is the sum of two components, one constant and the other proportional to glucose mass. This brings us to the rate constant describing the irreversible loss from the accessible pool

$$k_p + \frac{R_{d,0}}{Q_1(t)} = k_p + \frac{R_{d,0}}{G(t)V_1} \quad (2)$$

where  $G(t)$  is the glucose concentration in the accessible pool of volume  $V_1$ . It is worth noting that inhibition has been described by a linearized version, with nonzero intercept, of the  $R_d$  vs.  $G$  characteristic, which is actually of Michaelis-Menten type, where  $R_d$  is the rate of glucose disappearance from the accessible pool. The two are virtually coincident in the range of IVGTT glucose concentrations. Therefore, in the 2CMM, any changes in glucose concentration affect glucose clearance instantaneously. Of course, this may be an oversimplification because the dynamics of glucose's effect on its own clearance are likely to be more complex, entailing, for instance, a delay between a change in plasma glucose concentration and the corresponding change in glucose clearance. However, in the model, we preferred to keep the description of glucose's effect on its own clearance as simple as possible because, to the best of

our knowledge, there are no data in the literature providing insight into the dynamics of this effect under non-steady-state conditions.

Insulin-dependent glucose disposal occurs in the slowly exchanging pool and is assumed to be parametrically controlled, not by plasma, but by insulin in a remote compartment (13). The interstitial fluid has been suggested as a possible physiological correlate of this compartment (4). This brings us to the irreversible loss from the second compartment

$$k_{02} + x(t) \quad (3)$$

Arriving at a priori unique identifiability requires two assumptions. First, we assume that, in the basal steady state, insulin-independent glucose disposal is three times insulin-dependent glucose disposal (9). This brings us to an additional relationship among the model parameters

$$k_p + \frac{R_{d,0}}{G_b V_1} = \frac{3k_{21}k_{02}}{k_{02} + k_{12}} \quad (4)$$

where  $G_b$  is basal (end test) glucose concentration ( $\text{mg/dl}$ ). The second assumption is that  $R_{d,0}$  is fixed to the experimentally determined value of  $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (5).

The uniquely identifiable parameterization, as shown in Ref. 8, is  $V_1$ ,  $k_{21}$ ,  $k_{12}$ ,  $k_{02}$ ,  $p_2$ , and  $s_k$ .

#### DERIVATION OF METABOLIC INDEXES

We show below that the 2CMM provides indexes of glucose effectiveness and insulin sensitivity. For the sake of standardization, the two indexes will be derived in the same units as the corresponding indexes derived using the glucose-clamp technique; i.e., we will apply their definitions starting from the  $R_d$  vs.  $G$  steady-state characteristic.

**Glucose effectiveness.** Glucose effectiveness is defined as the ability of glucose to promote its own disposal. If one measures glucose disposal by its rate of disappearance from the accessible pool,  $R_d(t)$ , glucose effectiveness is then given by the derivative of  $R_d(t)$  with respect to glucose concentration  $G(t)$  at basal steady state (SS)

$$\text{glucose effectiveness} \triangleq \left. \frac{\partial R_d(t)}{\partial G(t)} \right|_{ss} \quad (5)$$

The  $R_d(t)$  predicted by the model is, by using the tracer-tracee indistinguishability principle

$$R_d(t) = \left[ k_p + \frac{R_{d,0}}{V_1 G(t)} + k_{21} \right] Q_1(t) - k_{12} Q_2(t) \quad (6)$$

Thus (see APPENDIX) glucose effectiveness (in  $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) from the 2CMM is

$$S_G^{2*} = \left. \frac{\partial R_d(t)}{\partial G(t)} \right|_{ss} = V_1 \left( k_p + \frac{k_{21}k_{02}}{k_{02} + k_{12}} \right) \quad (7)$$

**Plasma clearance rate.** Another parameter of interest that can be derived from the 2CMM is the steady-state

plasma clearance rate, which is defined as

$$\text{plasma clearance rate} \triangleq \left. \frac{R_d(t)}{G(t)} \right|_{ss} \quad (8)$$

Thus, by using Eq. 6, one has

$$\text{PCR} = V_1 \left( k_p + \frac{R_{d,0}}{V_1 G} + \frac{k_{21} k_{02}}{k_{02} + k_{12}} \right) \quad (9)$$

In the following, PCR will be calculated at basal (end test) glucose concentration,  $G_b$ . Note that, in the 2CMM, PCR is different from glucose effectiveness  $S_G^{2*}$  because the 2CMM explicitly describes the decrease of PCR when  $G$  increases, via the nonzero intercept  $R_{d,0}$  of the characteristic  $(R_d, G)$ . This condition is not true for the 1CMM (3, 7), in which  $R_{d,0} = 0$ , so that glucose effectiveness and glucose clearance coincide.

**Insulin sensitivity.** Insulin sensitivity is defined as the ability of insulin to enhance glucose effectiveness. Formally, one has

$$\text{insulin sensitivity} \triangleq - \left. \frac{\partial^2 R_d(t)}{\partial G(t) \partial I(t)} \right|_{ss} \quad (10)$$

where all derivatives are evaluated at the basal (end test) steady state. When this definition is applied to the 2CMM, insulin sensitivity  $S_I^{2*}$  is (see APPENDIX)

$$S_I^{2*} = V_1 s_k \frac{k_{21} k_{12}}{(k_{02} + k_{12})^2} \quad (11)$$

Its units ( $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$ ) are the units of a clearance ( $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) per unit of insulin concentration ( $\mu\text{U}/\text{ml}$ ).

The factor  $s_k = k_a k_c / k_b$  has an interesting interpretation: it is a measure of the insulin sensitivity of the tissues represented by the slowly exchanging glucose compartment, in which utilization is directly controlled by insulin. It has the units of a fractional clearance per unit of insulin concentration ( $\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$ ).

The 2CMM also provides an estimate of total glucose distribution volume ( $V_D$ )

$$V_D = V_1 \left( 1 + \frac{k_{21}}{k_{02} + k_{12}} \right) \quad (12)$$

#### DATABASE AND EXPERIMENTAL PROTOCOL

This study includes 14 stable isotopically labeled IVGTTs performed on young adults. A bolus of glucose enriched with  $[6,6\text{-}^2\text{H}_2]$ glucose was rapidly injected intravenously at *time 0* in all cases except two (*subjects 2 and 13*), in which  $[2\text{-}^2\text{H}]$ glucose was the tracer. Thirty blood samples were taken at 0, 2, 3, 4, 5, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 40, 45, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, 180, 210, and 240 min. Isotope ratios, plasma glucose, and insulin were measured (Fig. 2). The total glucose dose ranged from 0.25 to 0.33 g/kg, with the tracer being on average 10% of the dose. The

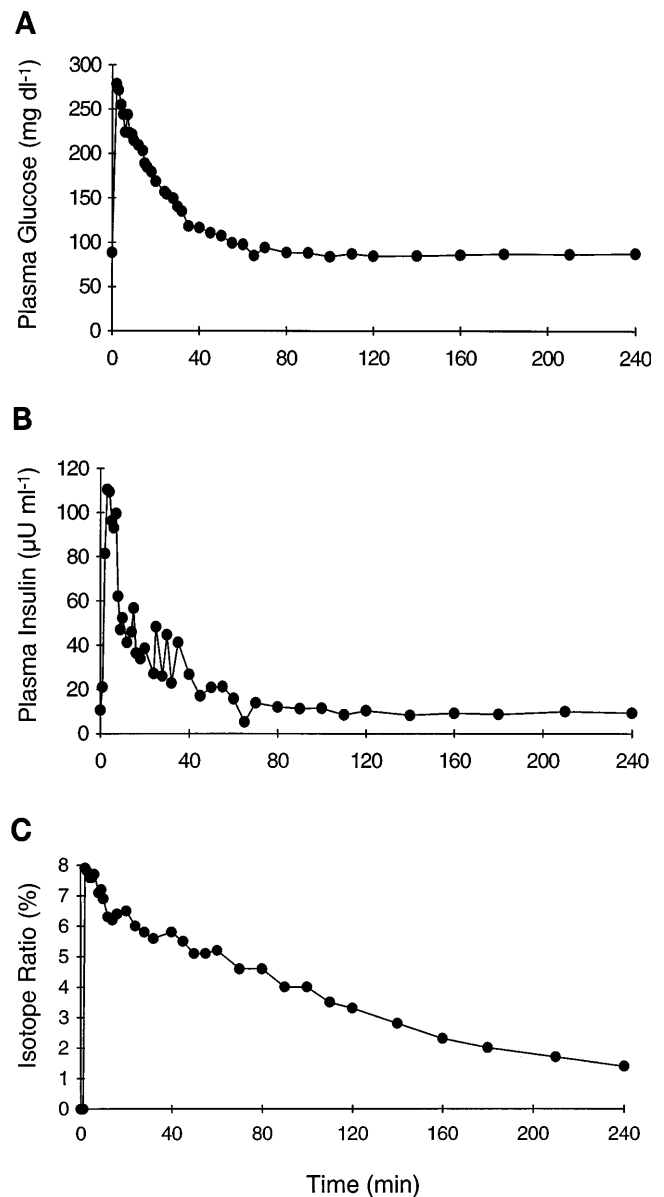


Fig. 2. Mean data for plasma glucose (A), plasma insulin (B), and isotope ratio (C).

baseline end-test glucose and insulin concentrations were (means  $\pm$  SE)  $86 \pm 2$  mg/dl and  $9 \pm 1$   $\mu\text{U}/\text{ml}$ , respectively, which were not different from the pretest values of  $88 \pm 2$  mg/dl and  $11 \pm 1$   $\mu\text{U}/\text{ml}$ , respectively.

Six of these experiments (*subjects 1–6*) have been previously analyzed in Ref. 1 with the 1CMM and in Ref. 8 with the 2CMM for the estimation of endogenous glucose production. Of the remaining eight experiments, five (*subjects 7–11*) were obtained at the Department of Pediatrics and Medicine, Washington University School of Medicine, St. Louis, Missouri (D. M. Bier, K. Yarasheski, and J. J. Zachwieja, unpublished data), and the remaining three (*subjects 12–14*) at the Center for Metabolic Diseases, University of Padova, Padua, Italy (A. Avogaro, unpublished data).

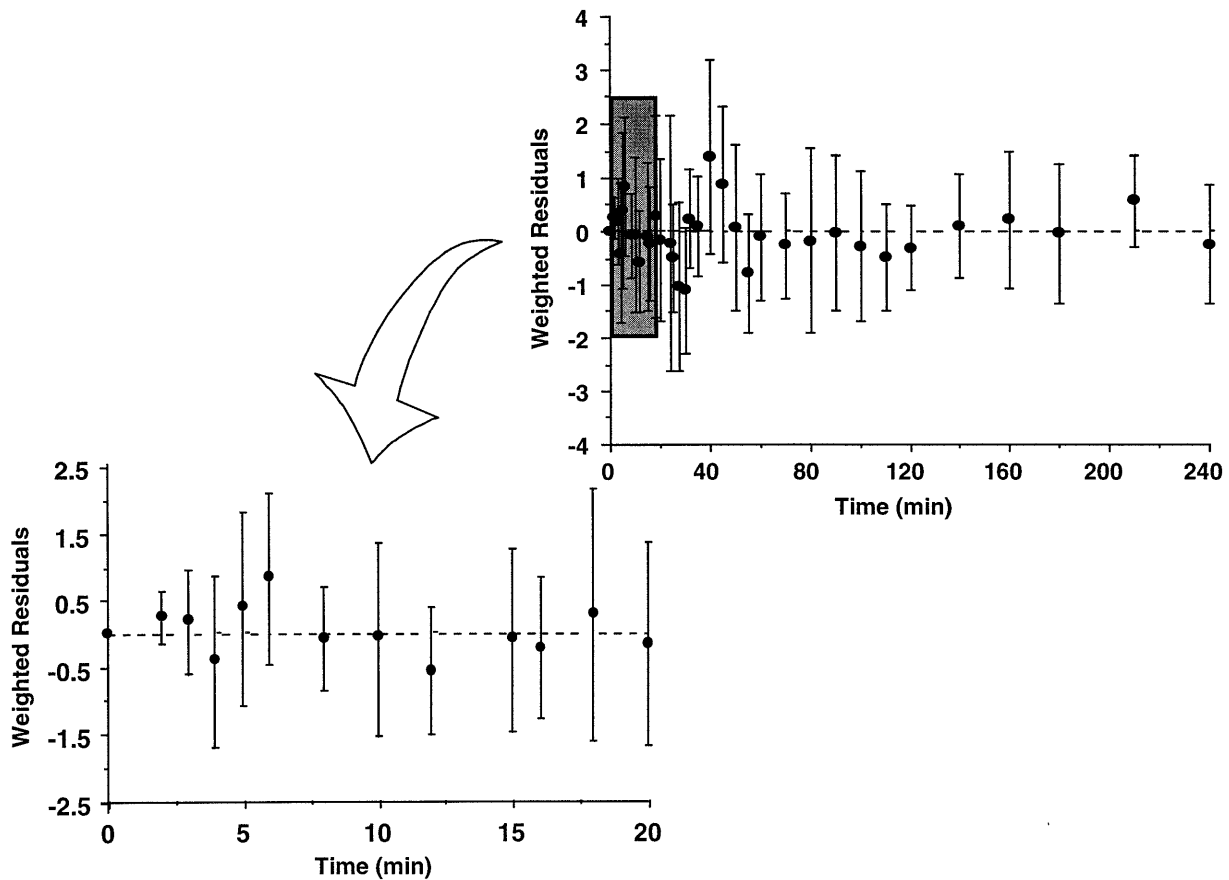


Fig. 3. Mean weighted residuals for the 2CMM. Shaded zone between 0 and 20 min is enlarged to better visualize model fitting of data.

### ESTIMATION OF METABOLIC INDEXES

The model was identified from hot glucose concentration data, calculated as described in Ref. 1 for *subjects 1–6* and in Ref. 2 for *subjects 7–14*. For a discussion of the rationale underlying the two approaches, see Refs. 2, 11, and 12. Weighted nonlinear least squares (6) were used. The measurement error associated with the tracer measurements was assumed to be independent, white, and Gaussian, with zero mean and a variance generated by error propagation from isotope ratio measurement error variance (12). Measurement error coefficient of variation ranged from 2 to 7% on average, with lower precision associated with lower tracer concentrations. Weights were chosen optimally, i.e., equal to the inverse of the measurement error variance (6). Model identification was always performed relying on the whole data set, a method at variance with the 1CMM, in which glucose samples between 0 and 8 min were neglected to mitigate the single-compartment approximation. Precision of parameter estimates (for  $V_1$ ,  $k_{21}$ ,  $k_{12}$ ,  $k_{02}$ ,  $p_2$ , and  $s_k$ ) was obtained from the inverse of the Fisher information matrix, whereas that of the metabolic indexes was obtained by error propagation (6). For example, if one assumes higher order terms can be neglected, then the following expression is valid for

the variance of PCR, defined as in Eq. 9

$$\text{Var}(\text{PCR}) = \frac{\partial(\text{PCR})}{\partial \mathbf{p}} \text{Cov}[\mathbf{p}] \frac{\partial(\text{PCR})}{\partial \mathbf{p}} \quad (13)$$

where  $\mathbf{p} = [V_1, k_{21}, k_{12}, k_{02}, p_2, s_k]$ , partial derivatives are evaluated at the estimated parameter values, and  $\text{Cov}(\mathbf{p})$  is the covariance matrix, i.e., the inverse of the Fisher information matrix.

The average weighted residuals are shown in Fig. 3 (mean  $\pm$  SD) and show no systematic deviations.

In Table 1 parameter estimates of the 2CMM are reported for the 14 subjects, together with their precision. The calculated total glucose distribution  $V_D$  is also shown. The metabolic indexes of the 2CMM are in Table 2. Their mean values are  $S_G^{2*} = 0.85 \pm 0.14 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ,  $\text{PCR} = 2.02 \pm 0.14 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , and  $S_I^{2*} = 13.83 \pm 2.54 \times 10^{-2} \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$ . Their mean precision is 21% for PCR (range 5–65%), 66% for  $S_G^{2*}$  (range 14–231%), and 76% for  $S_I^{2*}$  (range 5–401%).  $S_I^{2*}$  and  $S_G^{2*}$  precision is unsatisfactory in 3 of 14 subjects.

### TWO- VS. SINGLE-COMPARTMENT HOT MINIMAL MODEL INDEXES

Before the 2CMM and 1CMM indexes are compared, it is convenient to briefly review the 1CMM and the indexes it provides.



Table 1. Two-compartment minimal model: parameter estimation results

Subject No.	Estimated Parameters						
	$V_1$ , ml/kg	$k_{21}$ , min <sup>-1</sup>	$k_{12}$ , min <sup>-1</sup>	$k_{02}$ , min <sup>-1</sup>	$p_2$ , min <sup>-1</sup>	$S_k$ , min <sup>-1</sup> ·μU <sup>-1</sup> ·ml	$V_D$ , ml/kg
1	124.3 (4)	0.053 (15)	0.040 (31)	0.00299 (45)	0.0253 (86)	0.00050 (43)	277.5
2	139.7 (3)	0.040 (12)	0.031 (29)	0.00296 (28)	0.0411 (107)	0.00027 (30)	306.0
3	154.0 (2)	0.032 (12)	0.024 (40)	0.00396 (88)	0.0097 (341)	0.00051 (341)	330.0
4	151.9 (3)	0.023 (16)	0.013 (75)	0.00255 (116)	0.0218 (580)	0.00018 (170)	375.0
5	130.2 (7)	0.107 (34)	0.172 (30)	0.00541 (10)	0.0851 (16)	0.00068 (11)	208.4
6	128.4 (5)	0.119 (19)	0.100 (23)	0.00281 (7)	0.0927 (14)	0.00140 (10)	277.4
7	143.5 (11)	0.101 (45)	0.111 (45)	0.03376 (9)	0.0889 (22)	0.00140 (13)	270.3
8	145.0 (9)	0.087 (54)	0.152 (76)	0.00381 (27)	0.2285 (82)	0.00281 (48)	225.7
9	156.6 (15)	0.081 (87)	0.112 (112)	0.00532 (13)	0.0723 (29)	0.00370 (41)	264.4
10	108.8 (12)	0.113 (49)	0.155 (48)	0.00442 (13)	0.1248 (62)	0.00157 (17)	185.6
11	133.9 (4)	0.068 (25)	0.084 (49)	0.00373 (17)	0.2358 (177)	0.00190 (34)	238.1
12	139.7 (5)	0.050 (36)	0.038 (83)	0.00400 (15)	0.1894 (116)	0.00040 (110)	304.7
13	154.6 (3)	0.049 (17)	0.048 (22)	0.00401 (8)	0.2738 (464)	0.00113 (40)	299.7
14	128.1 (12)	0.061 (57)	0.036 (119)	0.00376 (10)	0.1183 (77)	0.00093 (178)	325.8
Mean ± SE	138.5 ± 3.7	0.070 ± 0.008	0.080 ± 0.014	0.00379 ± 0.00023	0.1148 ± 0.0229	0.00124 ± 0.00027	277.8 ± 13.7

Values are parameter estimates, except total glucose distribution volume ( $V_D$ ), which is calculated. Nos. in parentheses are estimate precisions expressed as percent coefficient of variation (%CV).  $V_1$ , volume of the accessible pool;  $k_{21}$ ,  $k_{12}$ , and  $k_{02}$ , glucose kinetic parameters;  $p_2$  and  $S_k$ , insulin action parameters.

**Review of 1CMM.** The 1CMM (10), shown in Fig. 4, is described, in its uniquely identifiable parameterization, by

$$\dot{q}(t) = -[p_1 + x(t)]q(t) \quad q(0) = d \quad (14a)$$

$$\dot{x}(t) = -p_2x(t) + p_3[I(t) - I_b] \quad x(0) = 0 \quad (14b)$$

$$g(t) = \frac{q(t)}{V} \quad (14c)$$

where  $p_1$ ,  $p_2$ ,  $p_3$ , and  $x$  relate to  $k_1$ ,  $k_2$ ,  $k_3$ ,  $k_4$ , and  $I'$  of Fig. 4 as follows:  $x(t) = k_4I'(t)$ ,  $p_1 = k_1$ ,  $p_2 = k_3$ , and  $p_3 = k_2k_4$ . Note that, for the sake of comparison with the 2CMM, we did not use the superscript asterisk for hot glucose-related variables, as was done in the original study (10).

Table 2. Two-compartment minimal model: metabolic indexes

Subject No.	PCR, ml·kg <sup>-1</sup> ·min <sup>-1</sup>	$S_{I_1}^{2*}$ , 10 <sup>2</sup> ml·kg <sup>-1</sup> · min <sup>-1</sup> ·μU <sup>-1</sup> ·ml	$S_G^{2*}$ , ml·kg <sup>-1</sup> ·min <sup>-1</sup>
1	1.83 (22)	7.09 (67)	0.63 (64)
2	1.97 (11)	4.14 (38)	0.87 (25)
3	2.79 (34)	7.67 (401)	1.49 (64)
4	2.27 (34)	3.42 (251)	0.96 (80)
5	1.69 (5)	5.17 (7)	0.61 (14)
6	1.68 (9)	20.33 (5)	0.64 (23)
7	1.71 (11)	17.17 (6)	0.70 (27)
8	1.23 (15)	22.12 (29)	0.08 (231)
9	2.30 (27)	38.13 (10)	1.28 (49)
10	1.36 (8)	11.73 (11)	0.25 (44)
11	1.55 (14)	18.91 (9)	0.20 (109)
12	2.64 (32)	6.02 (71)	1.34 (63)
13	2.33 (9)	15.09 (30)	1.01 (21)
14	2.97 (65)	16.58 (128)	1.84 (105)
Mean ± SE	2.02 ± 0.14	13.83 ± 2.54	0.85 ± 0.14

Values are 2-compartment model metabolic index estimates; nos. in parentheses are estimate precisions (%CV). PCR, plasma clearance rate;  $S_{I_1}^{2*}$ , insulin sensitivity;  $S_G^{2*}$ , glucose effectiveness.

$S_G^* = p_1$  (min<sup>-1</sup>) and  $S_{I_1}^* = p_3/p_2$  (min<sup>-1</sup>·μU<sup>-1</sup>·ml) measure, respectively, fractional (i.e., per unit of glucose distribution volume) glucose effectiveness at basal insulin and fractional insulin sensitivity, i.e., the ability of insulin to enhance fractional glucose effectiveness.

1CMM indexes of glucose effectiveness and insulin sensitivity with the same units as those derived for the 2CMM can be calculated by directly applying their definition. They are

$$\left. \frac{\partial R_d(t)}{\partial G(t)} \right|_{ss} = \left. \frac{\partial [dQ(t)/dt]}{\partial G(t)} \right|_{ss} = S_G^*V \quad (15a)$$

· (ml·kg<sup>-1</sup>·min<sup>-1</sup>)

$$\left. \frac{\partial^2 R_d(t)}{\partial G(t)\partial I(t)} \right|_{ss} = \left. \frac{\partial^2 [dQ(t)/dt]}{\partial G(t)\partial I(t)} \right|_{ss} = S_{I_1}^*V \quad (15b)$$

· (ml·kg<sup>-1</sup>·min<sup>-1</sup>)/(μU/ml)

By definition, both indexes refer to the same volume of distribution, i.e., the volume of the accessible pool,  $V$  (and thus of the system because the 1CMM is single compartment, and therefore the initial and the total distribution volumes coincide).

At this point, an important difference with the 2CMM needs to be pointed out. In the 2CMM, glucose effectiveness  $S_G^{2*}$  and plasma clearance rate PCR are different because of the presence of the inhibitory effect term,  $R_{d,0}/Q_1(t)$ , in  $R_d$  (Eq. 6). On the other hand, the 1CMM does not account for a nonzero  $R_{d,0}$ : it assumes  $R_{d,0} = 0$  (glucose disappearance is proportional to glucose concentration). In fact, the rate of glucose disappearance of the 1CMM is given by

$$R_d(t) = [S_G^* + x(t)]Q(t) = [S_G^* + x(t)]G(t)V \quad (16)$$

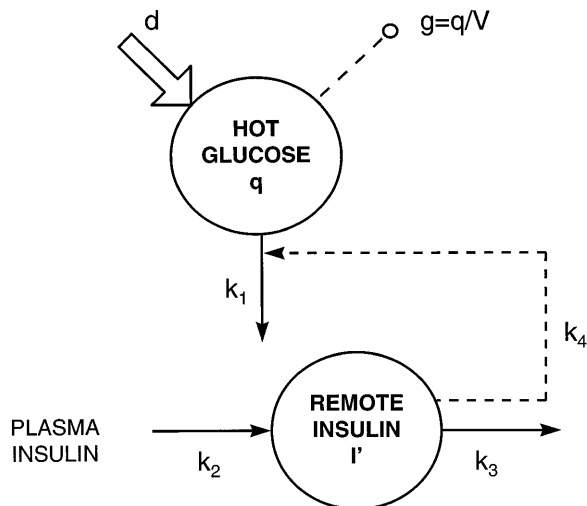


Fig. 4. The one-compartment minimal model (1CMM). See Eqs. 14a–14c for model parameterization details.

When this expression is applied to the definition of glucose effectiveness (Eq. 5) and the definition of plasma clearance rate in Eq. 8, it is easy to see that both come out equal to  $S_G^*V$ . Therefore, for the 1CMM, the estimates of glucose effectiveness and plasma clearance rate coincide, and both are (by definition) equal to  $S_G^*V$ . The ability of the 2CMM to single out glucose effectiveness and insulin sensitivity is therefore unique to the 2CMM.

The 1CMM parameters were estimated from hot glucose concentration data by weighted nonlinear least squares, as described in ESTIMATION OF METABOLIC INDEXES. In model identification, glucose samples between 0 and 8 min were not considered, in order to mitigate the approximation of the single-compartment description of glucose kinetics.

The mean weighted residuals of the 1CMM are shown in Fig. 5. The 1CMM indexes  $S_G^*V$  and  $S_I^*V$  have been calculated for all subjects and are reported in Table 3 together with their precision.  $S_G^*V$  was  $1.37 \pm$

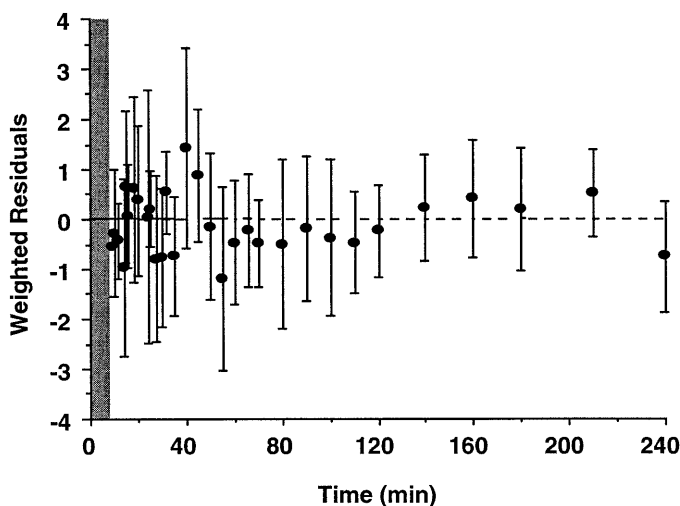


Fig. 5. Mean weighted residuals for the 1CMM. In model identification, data between 0 and 8 min are excluded.

Table 3. Single-compartment model indexes in human subjects

Subject No.	$S_G^*V$ , $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	$S_I^*V$ , $10^2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$
1	1.14 (5)	5.75 (3)
2	1.10 (5)	5.62 (3)
3	1.89 (2)	8.40 (6)
4	0.94 (7)	8.39 (4)
5	1.52 (4)	4.47 (5)
6	1.36 (5)	18.25 (4)
7	1.40 (4)	16.39 (4)
8	1.04 (4)	15.24 (3)
9	1.92 (4)	35.64 (6)
10	1.26 (5)	8.77 (9)
11	1.22 (8)	13.57 (5)
12	1.65 (3)	6.20 (4)
13	1.38 (12)	15.78 (5)
14	1.27 (6)	19.24 (4)
Mean $\pm$ SE	$1.36 \pm 0.08$	$12.98 \pm 2.21$

Values are 1-compartment model (1CMM) index estimates; nos. in parentheses are estimate precisions (%CV).  $S_G^*V$  and  $S_I^*V$  are glucose effectiveness and insulin sensitivity, respectively, where  $V$  is 1CMM glucose distribution volume.

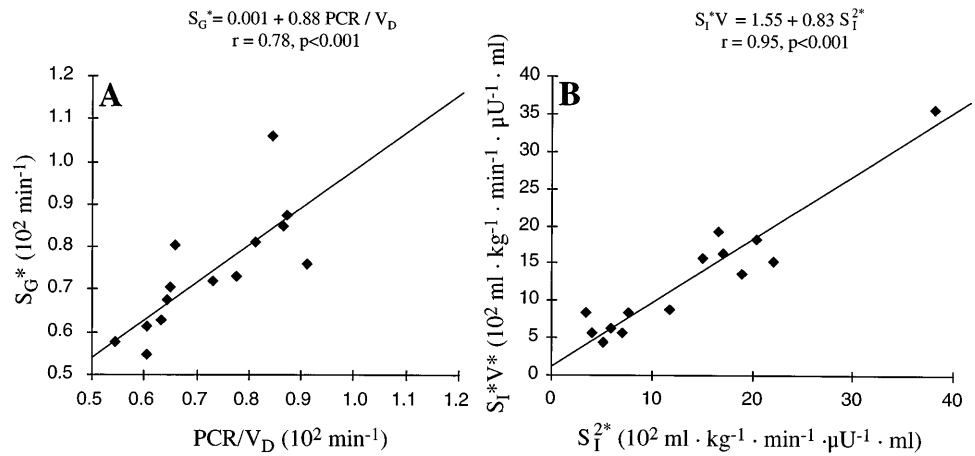
$0.15 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  ( $S_G^* = 0.74 \pm 0.04 \times 10^{-2} \text{ min}^{-1}$ ), and  $S_I^*V$  was  $12.98 \pm 2.21 \times 10^{-2} \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$  ( $S_I^* = 6.82 \pm 0.99 \times 10^{-4} \text{ min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$ ). Mean precision of the metabolic indexes, calculated via error propagation (6), was 5% for  $S_G^*V$  (range 2–12%) and 5% for  $S_I^*V$  (range 3–9%).

At this point, a natural question remains, How do the 1CMM indexes compare with the 2CMM indexes?

**Comparison of hot 1CMM and 2CMM indexes.** To compare the 1CMM and 2CMM indexes, we compared the mean of  $S_G^*V$  vs. either PCR or  $S_G^{2*}$  and  $S_I^*V$  vs.  $S_I^{2*}$ .  $S_G^*V$  is significantly lower ( $P < 0.001$ ) than PCR but greater ( $P < 0.001$ ) than  $S_G^{2*}$ .  $S_I^*V$  is not different from  $S_I^{2*}$  (NS). If we now compare  $S_G^*V$  vs.  $S_G^{2*}$ ,  $S_G^*V$  vs. PCR, and  $S_I^*V$  vs.  $S_I^{2*}$  by linear regression, we find that  $S_G^*V$  correlates weakly with  $S_G^{2*}$  ( $r = 0.50$ , NS) and with PCR ( $r = 0.45$ , NS), whereas  $S_I^*V$  correlates very well with  $S_I^{2*}$  (Fig. 6B) ( $r = 0.95$ ,  $P < 0.001$ ). Notably, the regression line between  $S_I^*V$  and  $S_I^{2*}$  is not different from the identity line (slope  $0.83 \pm 0.08$ ,  $P = 0.05$ , intercept  $1.55 \pm 1.31$ , NS). It is worth noting that, given this near-perfect correlation and the remarkable precision with which the 1CMM index is estimated, in case the two-compartment  $S_I^{2*}$  is estimated with unsatisfactory precision, one can use the single-compartment value,  $S_I^*V$ , instead.

To elucidate the reasons that the comparison of  $S_G^*V$  with  $S_G^{2*}$  and PCR is unsatisfactory, we may usefully analyze the two components of the product  $S_G^*V$  separately. Let us examine  $S_G^*$  first.  $S_G^*$  is estimated in the final portion of the tracer disappearance curve and thus measures the fractional disappearance rate of glucose when insulin and (cold) glucose concentrations have almost reached steady state. Under these circumstances, the contribution of the fast component of glucose kinetics and the inhibitory effect of hyperglycemia on glucose clearance have both become negligible.

Fig. 6. Scatterplot and regression line of  $S_G^*$  vs.  $PCR/V_D$  (A) and of  $S_I^*V$  vs.  $S_I^{2*}$  (B).  $S_G^*$ , 1CMM fractional glucose effectiveness (i.e., per unit of glucose distribution volume); PCR, 2CMM plasma clearance rate;  $V_D$ , 2CMM total glucose distribution volume;  $S_I^*V$ , 1CMM insulin sensitivity;  $S_I^{2*}$ , 2CMM insulin sensitivity.



As a result, the disappearance of hot glucose is governed by only the slow component of glucose kinetics, and the single-pool description of glucose kinetics given by the 1CMM is in all likelihood accurate. In other words, in this portion of the IVGTT, the glucose system behaves like a single-pool system, characterized by a fractional disappearance rate equal to  $S_G^*$  and a volume of glucose distribution close to the entire glucose distribution space. Thus the product of  $S_G^*$  and the total volume of glucose distribution should provide an estimate of basal PCR (not of  $S_G^{2*}$ ). Because the 1CMM uses a single compartment to represent the entire glucose system, the volume  $V$  should coincide with the total volume of glucose distribution and the product  $S_G^*V$  should measure basal PCR. This, however, does not occur ( $S_G^*V < PCR$ , as shown above) because  $V = 185 \pm 6$  ml/kg is markedly lower than the total glucose distribution volume (usually 260 ml/kg). When we multiply  $S_G^*$  by the literature value  $V_D = 260$  ml/kg, the mean value of  $S_G^*V$  ( $1.92$  ml  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ ) becomes quite close to PCR. However, the correlation remains poor as before ( $r = 0.55$ ,  $P = 0.04$ ). A likely explanation for this outcome is the need for individual estimates of  $V_D$ . By normalizing the individual values of PCR using the corresponding estimate of  $V_D$  provided by the 2CMM in each subject ( $278 \pm 14$  ml/kg on average), one has  $PCR/V_D = 0.73 \pm 0.03 \times 10^{-2}$  min $^{-1}$ , which is not different (NS) from  $S_G^* = 0.74 \pm 0.04 \times 10^{-2}$  min $^{-1}$ . The correlation (Fig. 6A) is also good ( $r = 0.78$ ;  $P < 0.001$ ), with the regression line not different from the identity line (slope  $0.88 \pm 0.21$ , NS; intercept  $0.0010 \pm 0.0015$ , NS). These results again indicate that  $S_G^*$  has the unequivocal meaning of a fractional clearance rate.

## CONCLUSIONS

The hot 2CMM of glucose kinetics provides three new metabolic indexes: glucose effectiveness ( $S_G^*$ ), insulin sensitivity ( $S_I^{2*}$ ), and plasma clearance rate PCR. These indexes take into account the fact that glucose kinetics is more accurately described by a two-compartment model. When they are compared with the 1CMM indexes, i.e., glucose effectiveness (or plasma clearance

rate) ( $S_G^*V$ ) and insulin sensitivity ( $S_I^*V$ ), one has that, although  $S_I^*V$  is very well correlated with  $S_I^{2*}$ ,  $S_G^*V$  underestimates PCR and overestimates  $S_G^{2*}$  and is uncorrelated with both. This result is due to the fact that the 1CMM assumes that glucose disappearance is proportional to glucose concentration, whereas the 2CMM properly takes into account the inhibitory effect of glucose on its own clearance. In conclusion, the hot IVGTT 2CMM, by allowing the derivation, in addition to endogenous glucose production, of a rich parametric portrait of glucose disposal, constitutes a powerful tool to assess glucose metabolism in various physiopathological conditions.

## APPENDIX

*Glucose effectiveness.* By applying the definition of glucose effectiveness to the rate of disappearance of glucose measured by the 2CMM, one has

$$S_G^* = \frac{\partial R_d(t)}{\partial G(t)} \Big|_{ss} = - \frac{\partial [\dot{Q}_1(t)]}{\partial G(t)} \Big|_{ss} \quad (A1)$$

$$= V_1 \left[ k_p + k_{21} - k_{12} \frac{\partial Q_2(t)}{\partial Q_1(t)} \right] \Big|_{ss}$$

Because, from Eq. 1b

$$\dot{Q}_2(t) = k_{21} Q_1(t) - [k_{02} + x(t) + k_{12}] Q_2(t) \quad (A2)$$

by taking the first derivative of  $\dot{Q}_2(t)$  with respect to  $Q_1(t)$ , we have [because  $\partial x(t)/\partial Q_1(t) = 0$ ]

$$\frac{\partial \dot{Q}_2(t)}{\partial Q_1(t)} = k_{21} - [k_{02} + x(t) + k_{12}] \frac{\partial Q_2(t)}{\partial Q_1(t)} \quad (A3)$$

At steady state

$$x = 0 \quad (A4)$$

and

$$\frac{\partial \dot{Q}_2(t)}{\partial Q_1(t)} \Big|_{ss} = 0 \quad (A5)$$



Therefore

$$k_{21} - [k_{02} + k_{12}] \frac{\partial Q_2(t)}{\partial Q_1(t)} \Big|_{ss} = 0 \quad (A6)$$

Rearranging

$$\frac{\partial Q_2(t)}{\partial Q_1(t)} \Big|_{ss} = \frac{k_{21}}{k_{02} + k_{12}} \quad (A7)$$

Substituting Eq. A7 into Eq. A1, we have the expression for  $S_G^{2*}$

$$S_G^{2*} = V_1 \left( k_p + \frac{k_{21} k_{02}}{k_{02} + k_{12}} \right) \quad (A8)$$

Note that for the 2CMM, at variance with the 1CMM, the accessible pool does not coincide with the system. Thus, in addition to the glucose disappearance rate from the accessible pool, it is also possible to calculate the rate of glucose disappearing from the system, i.e., glucose utilization, U

$$\begin{aligned} U(t) &= \left[ k_p + \frac{R_{d,0}}{Q_1(t)} \right] Q_1(t) + [k_{02} + x(t)] Q_2(t) \\ &= R_{d,0} + k_p Q_1(t) + [k_{02} + x(t)] Q_2(t) \end{aligned} \quad (A9)$$

It is easy to verify that, if one derived glucose effectiveness from the expression of glucose utilization, thus without having to refer to the accessible pool only

$$S_G^{2*} = \frac{\partial U(t)}{\partial G(t)} \Big|_{ss} \quad (A10)$$

then the resulting expression of  $S_G^{2*}$  would be the same as in Eq. A8.

*Insulin sensitivity.* By applying the definition of insulin sensitivity to the 2CMM, one has

$$S_I^{2*} = \frac{\partial^2 [\dot{Q}_1(t)]}{\partial G(t) \partial I(t)} \Big|_{ss} = -V_1 k_{12} \frac{\partial^2 [Q_2(t)]}{\partial Q_1(t) \partial I(t)} \Big|_{ss} \quad (A11)$$

Because, from Eq. 1b

$$\dot{Q}_2(t) = k_{21} Q_1(t) - [k_{02} + x(t) + k_{12}] Q_2(t) \quad (A12)$$

by taking the first derivative of  $\dot{Q}_2(t)$  with respect to  $Q_1(t)$ , we have [because  $\partial x(t)/\partial Q_1(t) = 0$ ]

$$\frac{\partial \dot{Q}_2(t)}{\partial Q_1(t)} = k_{21} - [k_{02} + x(t) + k_{12}] \frac{\partial Q_2(t)}{\partial Q_1(t)} \quad (A13)$$

Rearranging

$$\frac{\partial Q_2(t)}{\partial Q_1(t)} = - \frac{[\partial \dot{Q}_2(t)/\partial Q_1(t)]}{k_{02} + x(t) + k_{12}} + \frac{k_{21}}{k_{02} + x(t) + k_{12}} \quad (A14)$$

If we take now the derivative of both members of this equation with respect to  $I(t)$ , we have

$$\begin{aligned} \frac{\partial^2 Q_2(t)}{\partial Q_1(t) \partial I(t)} &= - \frac{\partial}{\partial I(t)} \left[ \frac{[\partial \dot{Q}_2(t)/\partial Q_1(t)]}{k_{02} + x(t) + k_{12}} \right] \\ &\quad + \frac{\partial}{\partial I(t)} \left[ \frac{k_{21}}{k_{02} + x(t) + k_{12}} \right] \end{aligned} \quad (A15)$$

and

$$\begin{aligned} \frac{\partial^2 Q_2(t)}{\partial Q_1(t) \partial I(t)} &= - \frac{\partial}{\partial I(t)} \left[ \frac{[\partial \dot{Q}_2(t)/\partial Q_1(t)]}{k_{02} + x(t) + k_{12}} \right] \\ &\quad - k_{21} \frac{\partial [-\dot{x}(t)/p_2 + s_k I(t)]/\partial I(t)}{[k_{02} + x(t) + k_{12}]^2} \end{aligned} \quad (A16)$$

Because, in steady state,  $\dot{Q}_2 = 0$  and  $x = \dot{x} = 0$ , we have

$$\frac{\partial^2 Q_2(t)}{\partial Q_1(t) \partial I(t)} \Big|_{ss} = \frac{\partial^2 Q_2(t)}{\partial I(t) \partial Q_1(t)} \Big|_{ss} = \frac{k_{21} s_k}{(k_{02} + k_{12})^2} \quad (A17)$$

and substituting in Eq. A11, we have the expression for the 2CMM insulin sensitivity

$$S_I^{2*} = V_1 s_k \frac{k_{21} k_{12}}{(k_{02} + k_{12})^2} \quad (A18)$$

This formulation suggests an interesting interpretation of  $S_I^{2*}$ . Provided that  $s_k$  is the (fractional) insulin sensitivity of the tissues represented by the slowly exchanging glucose compartment, in which utilization is directly controlled by insulin, then  $S_I^{2*}$  corresponds to  $s_k$  multiplied by the volume of the second compartment "as seen from" the accessible compartment. This representation is better understood by rearranging Eq. A18 to the form

$$S_I^{2*} = \left( V_1 \frac{k_{21}}{k_{02} + k_{12}} \right) s_k \frac{k_{12}}{k_{02} + k_{12}} \quad (A19)$$

in which the term in parentheses is the volume of the second compartment and the last factor is a partition coefficient.

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## REFERENCES

1. **Avogaro, A., J. D. Bristow, D. M. Bier, C. Cobelli, and G. Toffolo.** Stable-label intravenous glucose tolerance test minimal model. *Diabetes* 38: 1048–1055, 1989.
2. **Avogaro, A., P. Vicini, A. Valerio, A. Caumo, and C. Cobelli.** The hot but not the cold minimal model allows precise assessment of insulin sensitivity in NIDDM subjects. *Am. J. Physiol.* 270 (*Endocrinol. Metab.* 33): E532–E540, 1996.
3. **Bergman, R. N., Y. Z. Ider, C. R. Bowden, and C. Cobelli.** Quantitative estimation of insulin sensitivity. *Am. J. Physiol.* 236 (*Endocrinol. Metab. Gastrointest. Physiol.* 5): E667–E677, 1979.
4. **Bergman, R. N., D. T. Finegood, and M. Ader.** Assessment of insulin sensitivity in vivo. *Endocr. Rev.* 6: 45–86, 1985.
5. **Best, J. D., J. Taborsky, Jr., J. B. Halter, and D. Porte, Jr.** Glucose disposal is not proportional to plasma glucose level in man. *Diabetes* 30: 847–850, 1981.
6. **Carson, E. R., C. Cobelli, and L. Finkelstein.** *The Mathematical Modeling of Metabolic and Endocrine Systems*. New York: Wiley, 1983.

7. **Caumo, A., A. Giacca, M. Morgese, G. Pozza, P. Micossi, and C. Cobelli.** Minimal model of glucose disappearance: lessons from the labelled IVGTT. *Diabet. Med.* 8: 822–832, 1991.
8. **Caumo, A., and C. Cobelli.** Hepatic glucose production during the labeled IVGTT: estimation by deconvolution with a new minimal model. *Am. J. Physiol.* 264 (*Endocrinol. Metab.* 37): E829–E841, 1993.
9. **Cobelli, C., G. Toffolo, and E. Ferrannini.** A model of glucose kinetics and their control by insulin, compartmental and noncompartmental approaches. *Math. Biosci.* 72: 291–315, 1984.
10. **Cobelli, C., G. Pacini, G. Toffolo, and L. Saccà.** Estimation of insulin sensitivity and glucose clearance from minimal model: new insights from labeled IVGTT. *Am. J. Physiol.* 250 (*Endocrinol. Metab.* 13): E591–E598, 1986.
11. **Cobelli, C., G. Toffolo, and D. M. Foster.** Tracer-to-tracee ratio for analysis of stable isotope tracer data: link with radioactive kinetic formalism. *Am. J. Physiol.* 262 (*Endocrinol. Metab.* 25): E968–E975, 1992.
12. **Cobelli, C., P. Vicini, and A. Caumo.** The hot IVGTT minimal model: simultaneous assessment of disposal indexes and endogenous glucose production. In: *The Minimal Model Approach and Determinants of Glucose Tolerance*, edited by R. N. Bergman and J. Lovejoy. Baton Rouge, LA: Louisiana State Univ., 1997, vol. 7. (Pennington Center Nutrition Series)
13. **Sherwin, R. S., K. J. Kramer, J. D. Tobin, P. A. Insel, J. E. Liljenquist, M. Berman, and R. Andres.** A model of the kinetics of insulin in man. *J. Clin. Invest.* 53: 1481–1492, 1974.
14. **Verdonk, C. A., R. A. Rizza, and J. E. Gerich.** Effects of plasma glucose concentration on glucose utilization and glucose clearance in normal man. *Diabetes* 30: 535–537, 1981.

