The hot IVGTT two-compartment minimal model: an improved version

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Toffolo, Gianna, and Claudio Cobelli. The hot IVGTT two-compartment minimal model: an improved version. Am J Physiol Endocrinol Metab 284: E317–E321, 2003. First published October 1, 2002; 10.1152/ajpendo.00499.2001.—The two-compartment minimal model (2CMM) interpretation of a labeled intravenous glucose tolerance test (IVGTT) is a powerful tool to assess glucose metabolism in a single individual. It has been reported that a derived 2CMM parameter describing the proportional effect of glucose on insulin-independent glucose disposal can take physiologically unfeasible negative values. In addition, precision of 2CMM parameter estimates is sometimes not satisfactory. Here we resolve the above issues by presenting an improved version of 2CMM that relies on a new assumption on the constant component \( R_0 \) of insulin-independent glucose disposal. Here \( R_0 \) is not fixed to \( 1 \text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) but instead is expressed as a fraction of steady-state glucose disposal. The new 2CMM is identified on the same stable labeled IVGTT data base on which the original 2CMM was formulated. A more reliable insulin-independent glucose disposal portrait is obtained while that of insulin action remains unchanged. The new 2CMM also improves the precision with which model parameters and metabolic indexes are estimated.

Another reported finding is that sometimes the precision of the parameter estimates of 2CMM is not satisfactory.

This brief contribution aims at resolving the above issues by an improved version of 2CMM. In particular, we first outline the conditions under which parameter \( k_p \) can take on positive values by reconsidering the assumptions underlying the model. Next, we formulate an improved version of the model that guarantees positive values of all parameters. Results on the same 14 subjects studied previously (10) are presented and compared with those obtained with the previous version of the model.

THE TWO-COMPARTMENT MINIMAL MODEL

The 2CMM (Fig. 1) is described by the following equations:

\[ q_1(t) = -\left[ k_p + \frac{R_0}{Q_1(t)} + k_{21} \right] q_1(t) + k_{12} q_2(t) \]

\[ q_2(t) = k_{21} q_1(t) - [k_{21} + x(t) + k_{12}] q_2(t) \quad q_2(0) = 0 \]

\[ x(t) = -p_2[x(t) - s_0[I(t) - I_0]] \quad x(0) = 0 \]

\[ g(t) = \frac{q_1(t)}{V_1} \]

where \( q_1(t) \) and \( q_2(t) \) denote tracer glucose masses at time \( t \) in the first (accessible) and second (slowly equilibrating) compartments, respectively (mg/kg for a stable-label IVGTT); \( x(t) = k_p \Gamma(t) \) is insulin action (min\(^{-1}\)), where \( \Gamma(t) \) is the concentration of insulin remote from plasma (\( \mu \text{U/mL} \)); \( I(t) \) and \( I_0 \) are plasma insulin and basal (end-test) insulin, respectively (\( \mu \text{U/mL} \)); \( Q_1(t) \) is total glucose mass in the accessible pool (mg/kg); \( g(t) \) is plasma tracer glucose concentration (mg/dl); \( p_2 \) is the tracer glucose dose (mg/kg); \( V_1 \) is the volume of the accessible pool (ml/kg); \( R_0 \) (mg·kg\(^{-1}·\text{min}^{-1} \)) is the constant component of glucose disposal, whereas \( k_p \) (min\(^{-1}\)) is the proportionality constant between glucose disposal from the accessible compartment and insulin sensitivity; glucose effectiveness; glucose production; mathematical model; parameter estimation; intravenous glucose tolerance test.
GLUCOSE MASS IN THE SAME COMPARTMENT; $k_{21}$ (min$^{-1}$), $k_{12}$ (min$^{-1}$), and $k_{02}$ (min$^{-1}$) are parameters describing glucose kinetics; and $p_2 = k_b$ (min$^{-1}$) and $s_k = k_b/k_b$ (ml$^{-1}$·μU$^{-1}$·min$^{-1}$) are parameters describing insulin action. Capital and lowercase letters are used to denote variables related to cold and tracer glucose, respectively, and overdot notation refers to time rates of change for respective variables.

The model assumes that pools 1 and 2 represent, respectively, plasma plus insulin-independent tissues, rapidly equilibrating with plasma, and insulin-dependent tissues (utilization depends on insulin in addition to glucose), slowly exchanging with plasma. Glucose disposal from the accessible pool, $R_{d1}$, is the sum of two components, one constant ($R_{d0}$) and the other $(k_{p}Q_{1})$ proportional to glucose mass $Q_{1}$, thus accounting for the inhibition of glucose clearance by glucose itself. Thus the rate constant describing the irreversible loss of both tracer and tracee from the accessible pool is

$$\frac{R_{d1}(t)}{Q_{1}(t)} = r_{d1}(t) = k_{p} + \frac{R_{d0}}{V_{1}G_{b}} = k_{p} + \frac{R_{d0}}{V_{1}G(t)}$$

where $r_{d1}$ is insulin-independent tracer glucose disposal and $G_{b}$ is the glucose concentration in the accessible pool of volume $V_{1}$.

Glucose disposal from the slowly exchanging pool is assumed to be parametrically controlled by insulin in a remote compartment represented by variable $x$. The rate constant describing irreversible loss of tracee and tracer from compartment 2, $R_{d2}$ and $r_{d2}$, respectively, is then

$$\frac{R_{d2}(t)}{Q_{2}(t)} = r_{d2}(t) = k_{02} + x(t)$$

Arriving at a priori unique identifiability requires two assumptions (3). First, in normal subjects in the basal steady state (ss), insulin-independent glucose disposal is three times glucose disposal from insulin-dependent tissues ($R_{d1}^{SS} = 3R_{d2}^{SS}$, see Refs. 4 and 6). This materializes in an additional relationship among the model parameters

$$k_{p} + \frac{R_{d0}}{V_{1}G_{b}} = \frac{3k_{21}k_{02}}{k_{02} + k_{12}}$$

where $G_{b}$ is basal (evaluated from end test values) glucose concentration (mg/dl). Moreover, $R_{d0}$ is fixed to the experimentally determined value of 1 mg·kg$^{-1}$·min$^{-1}$.

The 2CMM allows the estimation of glucose effectiveness, insulin sensitivity, and plasma clearance rate.

**Glucose Effectiveness**

Glucose effectiveness ($S_{G}^{SS}$; ml·kg$^{-1}$·min$^{-1}$) quantifies the ability of glucose to promote its own disposal at steady state

$$S_{G}^{SS} = \frac{\partial R_{d}(t)}{\partial G(t)} = \left( k_{p} + \frac{k_{21}k_{02}}{k_{02} + k_{12}} \right) V_{1}$$

where $R_{d} = R_{d1} + R_{d2}$.

**Plasma Clearance Rate**

Plasma clearance rate (PCR; ml·kg$^{-1}$·min$^{-1}$) measures glucose disposal at basal steady state, per unit glucose concentration

$$PCR = \frac{R_{d}^{SS}}{G_{b}} = \left( k_{p} + \frac{R_{d0}}{V_{1}G_{b}} + \frac{k_{21}k_{02}}{k_{02} + k_{12}} \right) V_{1} = \left( \frac{k_{21}k_{02}}{k_{02} + k_{12}} \right) V_{1}$$

where the last equality follows from Eq. 4.
Insulin Sensitivity

Insulin sensitivity (S_{I}^{ss}, ml·kg^{-1}·min^{-1} per μU/ml) quantifies the ability of insulin to enhance glucose effectiveness

\[ S_{I}^{ss} = \frac{\delta^2 R_d(t)}{\delta G(t)\delta I(t)} \bigg|_{ss} = s_k \frac{k_{21}k_{12}}{(k_{02} + k_{12})^2} V_1 \]  
(7)

MODEL ASSUMPTIONS AND PARAMETER \( k_p \)

Model assumptions do not guarantee positive values for parameter \( k_p \), in all circumstances. In fact, from Eq. 4, \( k_p \) is the difference between the following two terms

\[ k_p = 3 \frac{k_{21}k_{02}}{k_{02} + k_{12}} - \frac{R_{d0}}{V_1G_b} \]  
(8)

and assumes positive values only when

\[ R_{d0} = 1 \text{ mg·kg}^{-1}·\text{min}^{-1} < 3 \frac{k_{21}k_{02}}{k_{02} + k_{12}} V_1G_b \]  
(9)

that is, from Eq. 6, when

\[ R_{d0} = 1 \text{ mg·kg}^{-1}·\text{min}^{-1} < 0.75 \text{ PCR} G_b = 0.75 R_{a}^{ss} \]  
(10)

Thus \( k_p \) is positive if the constant component \( R_{d0} \), which is fixed equal to 1 mg·min^{-1}·kg^{-1} in all subjects, is less than the steady-state value of glucose disposal from the accessible compartment, which accounts for three-fourths of total glucose disposal. This condition can also be read as a lower bound for total glucose disposal at steady state

\[ R_{d0}^{ss} > 1.33 \text{ mg·kg}^{-1}·\text{min}^{-1} \]  
(11)

The assumption of a constant component of glucose disposal equal to 1 mg·min^{-1}·kg^{-1} is thus critical because it leads to a negative value of the \( k_p \) parameter in those subjects having a total glucose disposal in the basal state <1.33 mg·min^{-1}·kg^{-1}.

AN IMPROVED 2CMM

To ensure positive values of \( k_p \), we formulate the needed (for a priori identifiability reasons) constraint on \( R_{d0} \) in an alternative way. The idea is to relate it to total glucose disposal in steady state, by assuming that \( R_{d0} \) accounts for a fixed fraction of it

\[ R_{d0} = \alpha R_{d}^{ss} \]  
(12)

where \( \alpha \) is constant among individuals. Values of \( R_{d0} \) and \( R_{d}^{ss} \) measured in a group of nondiabetic subjects (2), namely \( R_{d}^{ss} = 21.71 \) and \( R_{d0} = 10.1 \text{ μmol}·\text{min}^{-1}·\text{kg} \) lean body mass^{-1} (\( R_{d0} \) is not far from 1 when expressed as mg·min^{-1}·kg^{-1}), suggest to fix \( \alpha = 0.465 \). With this value for \( \alpha \), Eq. 10, which ensures positive \( k_p \), becomes

\[ R_{d0} = 0.465 R_{d}^{ss} < 0.75 R_{a}^{ss} \]  
(13)

Thus the new assumption on \( R_{d0} \), Eq. 12, while still ensuring a priori identifiability of the model structure, is also able to guarantee positive values of \( k_p \). In fact, by using Eq. 12 in Eq. 8, \( k_p \) becomes

\[ k_p = \frac{k_{21}k_{02}}{k_{02} + k_{12}} (3 - 4\alpha) = \frac{k_{21}k_{02}}{k_{02} + k_{12}} 1.14 \]  
(14)

and always assumes positive values.

Metabolic indexes \( S_{G}^{ss} \), PCR, and \( S_{I}^{ss} \) are still defined as before and can be evaluated from model parameters by using the same expressions (Eqs. 5–7).

MODEL IDENTIFICATION

The new 2CMM equations to be used in normal subjects are Eqs. 1a–1d, coupled with Eq. 14 for parameter \( k_p \) appearing in Eq. 1a and with the following equation, derived from Eqs. 6 and 12, for \( R_{d0}/Q_1(t) \), also appearing in Eq. 1a

\[ \frac{R_{d0}}{Q_1(t)} = \frac{k_{21}k_{02}}{k_{02} + k_{12}} \frac{G_b}{G(t)} 4\alpha \]  
(15)

Unknown model parameters \( k_{21}, k_{12}, k_{02}, s_k, p_2 \), and \( V_1 \) were estimated in each individual by using SAAMII software (1). Weights were chosen as described previously (10).

RESULTS

In a previous study (10), the 2CMM was identified on stable labeled IVGTT data performed in 14 young
In most subjects. Conversely, average values of SG are higher with the new model version, as shown in Table 2, because their sum, which gives insulin-independent glucose disposal, is similar in the two model versions. All of the remaining model indexes are also similar. It is not possible to prove that the new model provides more accurate estimates of SG, since we do not have a model-independent reference for it. However, we can argue that, because the new 2CMM avoids some inconsistencies of the original 2CMM (negative k_p), it provides a more reliable description of the system and thus a more reliable value for SG. Similarly, we can also argue that the new model should provide more reliable estimates of endogenous glucose production. Finally, with the new assumption, precision of parameter estimates considerably improves.

The 2CMM, developed here for application in normal subjects, can be extended to impaired glucose-tolerant or diabetic subjects. This, however, requires reconsideration of some model assumptions, as discussed in the APPENDIX.

**DISCUSSION**

We have presented a new version of 2CMM that guarantees positive values of the derived parameter k_p in all individuals. This goal is accomplished by introducing a different, but still physiologically sound, assumption on R_d0. R_d0 is a nonphysiological parameter that represents the nonzero intercept of the linear approximation, in the experimental glucose range, of the relationship between insulin-independent glucose disposal and glucose concentration.

In all likelihood, this relationship is a sigmoidal-shaped curve that, starting at zero (glucose utilization is 0 at 0 glucose concentration), saturates at a plateau. It is also often described by a Michaelis-Menten relationship, but the range of glucose concentrations spanned during an IVGTT does not allow for reliable estimation of the two parameters of this model. The relationship is then approximated by a straight line, having k_p as a slope and R_d0 as an intercept. In the new version, R_d0 is adjusted in every subject on the basis of his/her value of total glucose disposal in the basal state, R_d0 = 0.78 ± 0.6 mg·min⁻¹·kg⁻¹, which is less than the value R_d0 = 1 mg·min⁻¹·kg⁻¹ assumed in the original version. The decrease in R_d0 is balanced by an increase in the glucose-dependent component of glucose disposal, and thus by an increase of k_p and SG, because their sum, which gives insulin-independent glucose disposal, is similar in the two model versions. All of the remaining model indexes are also similar. It is not possible to prove that the new model provides more accurate estimates of SG, since we do not have a model-independent reference for it. However, we can argue that, because the new 2CMM avoids some inconsistencies of the original 2CMM (negative k_p), it provides a more reliable description of the system and thus a more reliable value for SG. Similarly, we can also argue that the new model should provide more reliable estimates of endogenous glucose production. Finally, with the new assumption, precision of parameter estimates considerably improves.
In conclusion, this improved version of 2CMM, by avoiding some inconsistencies of the original 2CMM (negative $k_p$), provides a more reliable and precise parametric portrait of glucose metabolism during an IVGTT.

**APPENDIX**

The use of 2CMM in glucose-tolerant or diabetic subjects requires reconsideration of some model assumptions. For instance, values of $R_{d0} = 14.6 \, \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg} \, \text{lean body mass}^{-1}$ and $R_{a0} = 19.2 \, \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg} \, \text{lean body mass}^{-1}$ measured in diabetic subjects (2) result in a different $\alpha$ ($\alpha = 0.759$). Also, the proportion between glucose disposal from insulin-independent and insulin-dependent tissues in the basal state is in all likelihood different from the 3:1 ratio assumed in normal subjects and moves to a higher value. For instance, if in diabetics a 5:1 ratio is assumed, i.e., a glucose disposal from insulin-independent tissues accounts for 83.5% of total glucose disposal in the basal state, then Eq. 14 becomes

$$k_p = \frac{k_{21}k_{02}}{k_{02} + k_{12}} \left(5 - 6\alpha\right) = \frac{k_{21}k_{02}}{k_{02} + k_{12}} \times 0.446 \quad \text{(A1)}$$

which still guarantees positive values for $k_p$.

In the general case, if a ratio $\beta/1$ is assumed between glucose disposal from insulin-independent and insulin-dependent tissues under basal conditions, model equations are Eqs. 1a-1d, coupled with the following equations for $k_p$ and $R_{d0}/Q_1(t)$

$$k_p = \frac{k_{21}k_{02}}{k_{02} + k_{12}} \left[\beta - (\beta + 1)\alpha\right] \quad \text{(A2)}$$

$$\frac{R_{d0}}{Q_1(t)} = \frac{k_{21}k_{02}}{k_{02} + k_{12}} \frac{G_1}{G(t)} \left(\beta + 1\alpha\right) \quad \text{(A3)}$$

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**REFERENCES**


