One- and Two-Compartment Minimal Models Detect Similar Alterations of Glucose Metabolism Indexes in Hypertension

Silvia Natalucci, Massimo Boemi, Paolo Fumelli, Ivano Testa, Daniele Fumelli, and Roberto Burattini

A standard intravenous glucose tolerance test (IVGTT) was performed in 10 nondiabetic patients with essential hypertension (H group) and 9 normotensive control subjects (N group). A 2-compartment minimal model (2CMM) of glucose kinetics was applied to estimate indexes of glucose effectiveness, S_G^2, and insulin sensitivity, S_I^2, by means of a maximum a posteriori (MAP) bayesian estimation technique. These estimates were contrasted to the S_G^1 and S_I^1 indexes provided by the classic minimal model (1CMM). In both the N group and the H group, the 2CMM underestimated the glucose effectiveness and overestimated the insulin sensitivity. In the H group, S_G^2 was, on average, 63% of S_G^1 ($P > .05$) and S_I^2 was 137% of S_I^1 ($P > .05$). In the N group S_G^2 was 67% of S_G^1 ($P > .05$) and S_I^2 was 134% of S_I^1 ($P > .05$). The 2CMM detected a reduction of approximately 40% ($P > .05$) and approximately 48% ($P > .05$) in S_G^2 and S_I^2 estimates, respectively, from the N group to the H group. Despite its reduced complexity, the 1CMM also detected a reduction of approximately 35% ($P < .05$) and approximately 49% ($P < .05$) in the S_G^1 and in S_I^1 indexes, respectively. Thus, the 1CMM and 2CMM showed a substantial equivalence in detecting a severe reduction in insulin sensitivity and impaired glucose effectiveness in hypertensive patients compared with normal.

ABNORMALITIES IN GLUCOSE, insulin, and lipid metabolism are common in patients with essential hypertension.[1-8] The nature of the relationship between high blood pressure and metabolic abnormalities, however, is still unclear. In a growing number of studies, insulin resistance, defined as a reduced sensitivity to the effects of insulin action, is suggested to be the link between hyperinsulinemia, impaired glucose tolerance, and hypertension.[9-12] To improve the understanding of this link, there is a need to quantify insulin-mediated glucose disposal (insulin sensitivity) and glucose-mediated glucose disposal (glucose effectiveness) under normal and hypertensive conditions. In clinical studies, an evaluation of these indexes and their variation from normal to pathophysiological state can be accomplished by applying the classic minimal model to insulin and glucose data obtained from intravenous glucose tolerance tests (IVGTT). The IVGTT and minimal model technique is a well-recognized and powerful methodology as judged from the hundreds of publications in which it was used.[13]

In a recent study, we applied this methodology to evaluate indexes of glucose effectiveness and insulin sensitivity and their variation between a group of normal subjects and a group of nondiabetic hypertensive patients. The presence of severe insulin resistance and impaired glucose effectiveness in the group of hypertensives was inferred from significant reductions of these indexes.[14] Reliability of this inference depends, of course, on the reliability of the minimal model and IVGTT methodology. This has been a matter of controversy because recent reports have indicated that the single-compartment description of glucose kinetics by the classic minimal model (hereafter denoted as 1CMM) yields an overestimation of glucose effectiveness and an underestimation of insulin sensitivity.[15-25] To resolve this limitation, a new 2-compartment minimal model (2CMM), derived from the 1CMM by introducing a second nonaccessible glucose pool, was applied by Cobelli et al[21] to IVGTT data taken from normal humans. These investigators concluded that the 2CMM yields an improvement over the 1CMM in estimating glucose effectiveness and insulin sensitivity.[21]

Based on these previous reports, the present study was designed to compare the behavior of the 1CMM- and 2CMM-based estimation techniques in detecting alterations of insulin sensitivity and glucose effectiveness from normal to hypertensive state.

MATERIALS AND METHODS

Subjects

Nine normotensive subjects (N group, 6 women and 3 men, 40 ± 4 years) and 10 hypertensive patients (H group, 1 woman and 9 men, 59 ± 2 years) were studied. All of them were volunteers and gave informed consent to the procedures, which were approved by the Ethics Committee of the Istituto Nazionale Riposo e Cura Anziani (INRCA), Ancona, Italy. Normotensive subjects had a seated diastolic blood pressure (DBP) ≤85 mm Hg and a seated systolic blood pressure (SBP) ≤130 mm Hg. The hypertensive patients were recruited among the outpatients of the Metabolic Disease and Diabetes Unit of INRCA, who were under antihypertensive drug therapy with calcium channel blockers or angiotensin-converting enzyme (ACE) inhibitors for more than 2 years. Before the treatment, their pressure levels were DBP ≥ 85 mm Hg and SBP ≥ 130 mm Hg. These populations were screened before participation with a history and physical examination, a complete blood count, fasting serum glucose, and routine chemistries. Subjects were excluded from participation if they had a past history of diabetes mellitus, a fasting serum glucose >120 mg dL^{-1}, and/or evidence from the screening tests of underlying illness or significant laboratory abnormalities. Clinical data of interest for the characterization of the metabolic picture in the 2 groups are presented in Table 1.

IVGTT

In both N and H groups, a standard IVGTT, which is an IVGTT without insulin (or tolbutamide) injection, was performed. An addi-

From the Department of Electronics and Automatics, University of Ancona, Ancona; Metabolic Disease and Diabetes Unit, Istituto Nazionale Riposo e Cura Anziani (INRCA), Ancona; and the Institute of Internal Medicine, University of Ancona, Ancona, Italy.

Submitted November 27, 1999; accepted May 22, 2000.

Supported in part by the Italian Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST, COFIN 98) and by the Istituto Nazionale Riposo e Cura Anziani (INRCA) of Ancona, Italy.

Address reprint requests to Silvia Natalucci, PhD, Department of Electronics and Automatics, University of Ancona, Via Brecce Bianche, 60131 Ancona, Italy.

0026-0495/00/4912-0003$10.00/0

doi:10.1053/meta.2000.18516

tional insulin (or tolbutamide) injection was not considered necessary because it is especially recommended when the endogenous insulin secretion is absent or relatively depressed as in insulin-dependent diabetes mellitus (IDDM) and non–insulin-dependent diabetes mellitus (NIDDM), respectively.[26,27] In such a situation, the insulin profile is low so that insulin sensitivity and glucose effectiveness are likely to be estimated with no accuracy. Among our patients, however, no one exhibited low insulin profiles. Moreover, it has been shown that standard and tolbutamide or insulin modified IVGTT (with different insulin level) give the same insulin sensitivity index.[28]

The IVGTT was performed at the Metabolic Disease and Diabetes Unit of the INRCA Institute of Ancona. Starting time was 8:30 AM after an 8-hour overnight fast. A needle was inserted into an antecubital vein of the patient. The patency of the needle was maintained with a controlled saline infusion throughout the study. At time 0, glucose (300 mg/kg^{-1}) was injected over 1 minute into a contralateral antecubital vein. Three basal blood samples (2 mL) were obtained at −15 and −5 minutes and immediately before the injection. Twenty-four additional blood samples were collected at 2, 3, 4, 5, 6, 8, 10, 12, 15, 20, 25, 30, 35, 40, 60, 80, 100, 120, 140, 160, 180, 210, 240, and 300 minutes. Blood was promptly centrifuged and glucose immediately measured by the glucose oxidase method with an automated glucose analyzer. The remaining plasma was stored at −20°C for later insulin determination. Insulin was measured by commercially available radioimmunoassays (Biodata S.p.A, Guidonia Montecelio, Rome, Italy). The sensitivity and intra- and interprecision of the insulin assays were 1 μU mL^{-1}, (5.4% ± 1.0%) and (5.5% ± 1.2%), respectively. The cross-reactivity for human proinsulin was 14%.

Data Analysis

The temporal dynamics of plasma glucose and insulin concentrations observed during the IVGTTs were used to estimate the characteristic parameters of 2 previously described 1CMM[29] and 2CMM[21,30] of glucose kinetics. A schematic representation of the 1CMM and 2CMM are reported in Figs 1 and 2, respectively. The equations of the models and the concepts incorporated in the schemes of Figs 1 and 2 are presented in detail in Appendix 1. The individual parameters of these models were used to calculate characteristic indexes of glucose metabolism: the glucose effectiveness index and the insulin sensitivity index (see Appendix 1). The glucose effectiveness index quantifies the ability of glucose per se to enhance its own disappearance and to inhibit hepatic glucose production independent of any dynamic change on insulin. The insulin sensitivity index measures the ability of insulin to

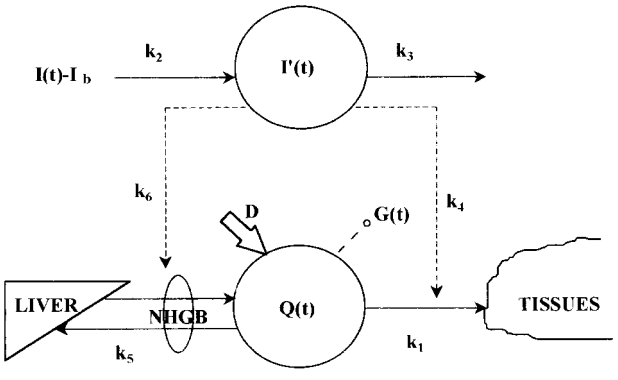

Fig 1. The 1CMM of glucose disappearance. NHGB is the net hepatic glucose balance; D, represents the glucose dose (300 mg/kg); k_is are rate constants characterizing material fluxes (solid lines) or control actions (dashed lines). G(t) and I(t) are glucose and plasma insulin concentrations at time t. I′(t) is insulin concentration at time t in a compartment remote from plasma.

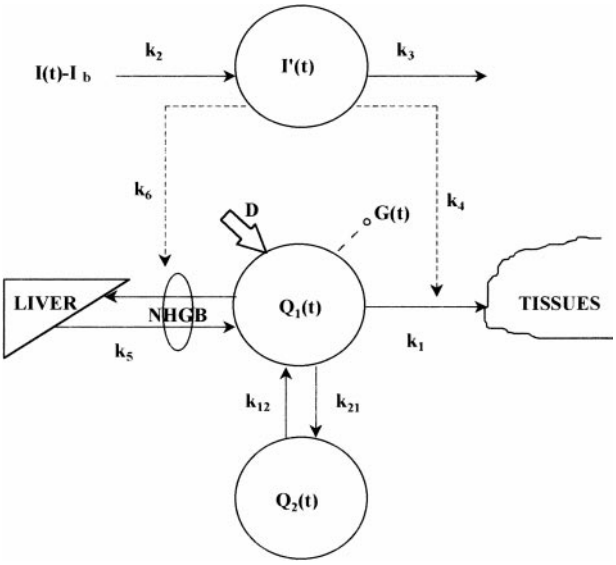

Fig 2. The 2CMM of glucose disappearance. NHGB is the net hepatic glucose balance; D, represents the glucose dose (300 mg/kg); k_is are rate constants characterizing material fluxes (solid lines) or control actions (dashed lines). G(t) and I(t) are glucose and plasma insulin concentrations at time t. I′(t) is insulin concentration at time t in a compartment remote from plasma.

enhance plasma glucose disappearance and to inhibit hepatic glucose production.

Parameter Estimation Procedures

The 1CMM parameters were estimated using a weighted nonlinear least-squares estimation technique implemented by the SAAM II software (SAAM Institute, University of Washington, Seattle, WA[31]). Weights were optimally chosen, ie, equal to the inverse of the variance of the glucose measurement errors.[32] The errors associated with total glucose measurement were assumed to be normally distributed random variables with 0 mean and a constant percent coefficient of variation equal to 1.5%:

$$CV(z_i)\% = \frac{SD_{z_i}}{z_i} \times 100 = 1.5\% \qquad \forall\, i = 1, \ldots\ldots\ldots, N \qquad (1)$$

where z_i is the i-th component of the glucose concentration measurements vector $\bar{z} = [z_1 \ldots z_N]$ and SD_{z_i} is the standard deviation of z_i.

Precision of parameter estimates was expressed as percent coefficient of variation:

$$CV(p_i)\% = \frac{SD_{p_i}}{p_i} \times 100 \qquad i = 1, \ldots\ldots\ldots p \qquad (2)$$

where p_i is the i-th component of the model parameters vector $\bar{p} = [p_1 \ldots . p_p]$ and SD_{p_i} is the standard deviation of p_i, which is calculated as the square root of the diagonal terms of the inverse of the Fisher information matrix.[32]

Glucose samples between 2 and 5 minutes were not considered to improve the approximation of glucose kinetics by single-compartment description.

Theory shows that resolution of the 2CMM from an IVGTT can only be reached by resorting to additional independent knowledge of glucose exchange kinetic parameters (k_{12} and k_{21} in Fig 2).[21] In the present study, such knowledge was incorporated into the 2CMM in a probabilistic context by using the Maximum a Posteriori (MAP) Bayesian

estimator (Appendix 2) implemented by the software ADAPT II.[33] Briefly, the free model parameters are partitioned into 2 uncorrelated components: the first is formed by p1, p_2, p_3, V_1 (Appendix 1), in which we assume to have no a priori knowledge, and the second formed by k_{12} and k_{21}, which are assumed to be normally distributed, with mean ± SD of 0.070 ± 0.018 and 0.050 ± 0.013 min^{-1} respectively, and with a correlation coefficient of 0.90 as suggested by Cobelli et al.[21] As for the 1CMM, weights were chosen optimally and precision of parameter estimates were obtained from the inverse of the Fisher matrix.[32] Glucose samples were used in model identification starting from 3 minutes.

Statistical Analysis

Statistical comparison of hypertensive patients and normotensive control subjects was tested for significance by paired Student's *t* test. Not significant (NS) means a value of $P \geq .05$. All data and results are given as mean ± SE.

RESULTS

In the N group, SBP averaged (± SE) 116 ± 4 mm Hg and DBP averaged 77.0 ± 3.0 mm Hg. In the H group, SBP and DBP measured before the antihypertensive drug therapy with calcium channel blockers or ACE inhibitors were, on average, 160 ± 5 and 100 ± 3 mm Hg, respectively.

Clinical data of interest for the characterization of the metabolic picture in the 2 groups are presented in Table 1. The differences in body mass index (BMI) and fasting plasma cholesterol and triglycerides concentrations between the 2 groups were not statistically significant. Rather, the H group showed a 10% increase in average fasting plasma glucose and a 63% increase in average fasting insulin concentrations that were statistically significant ($P < .05$). Figure 3 shows average insulin and glucose levels in the N group and the H group throughout the entire IVGTT test.

Identification of 1CMM

Individual estimates of 1CMM parameters, p_1, p_2, p_3, and V, determined in the N and H groups are presented in Tables 2 and 3, respectively. On average, the plasma glucose distribution volume, V, calculated in the N group, was not significantly different ($P > .05$) from that determined in the H group (1.92 ± 0.08 *v* 2.21 ± 0.16 dL · kg^{-1}). Precision of parameter estimates was expressed as percent coefficient of variation (CV%, see equation 2) and reported in parentheses in Tables 2 and 3. Individual estimates of glucose effectiveness, S_G^1, and insulin sensitivity, S_I^1, indexes, derived from the 1CMM, are given in Table 4 for the N group and in Table 5 for the H group. These indexes were estimated with an acceptable accuracy in all circumstances. In the N group, the mean values (± SE) were 3.7 ± 0.5 × 10^{-2} dL · min^{-1} · kg^{-1} for S_G^1 and 9.71 ± 1.18 × 10^{-4} dL · min^{-1} · kg^{-1}/[μU · mL^{-1}] for S_I^1. In the H group, S_G^1 averaged 2.4 ± 0.3 × 10^{-2} dL · min^{-1} · kg^{-1}, whereas S_I^1 averaged 4.95 ± 1.16 × 10^{-4} dL · min^{-1} · kg^{-1}/[μU · mL^{-1}].

To assess the goodness of glucose data fit, we analyzed weighted residuals, which are the differences between the data

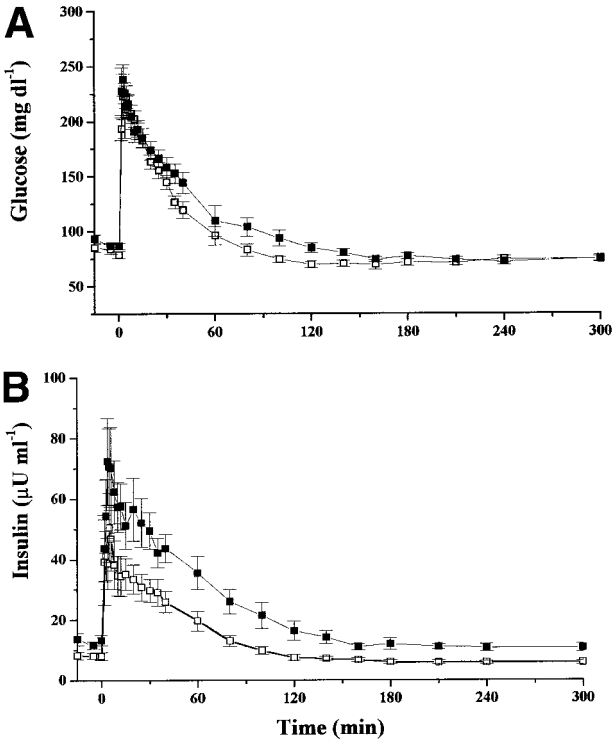

Fig 3. (A) Plasma glucose concentrations during an IVGTT in the H group (■) and the N group (□). (B) Plasma insulin concentrations during intravenous glucose tolerance test in the H group (■) and the N group (□). Values are expressed as mean ± SE.

Table 1. Metabolic Picture of Hypertensive Patients and Normotensive Control Subjects

Variable	Hypertensive (n = 10)	Normotensive (n = 9)	*P*
BMI (kg/m^2)	27.4 ± 1.7	25.4 ± 0.8	NS
Triglycerides (mg/dL)	121 ± 20	85.3 ± 31.1	NS
Cholesterol (mg/dL)	179 ± 8	185 ± 14	NS
Glycemia (mg/dL)	88.9 ± 2.8	80.4 ± 2.7	$P < .05$
Insulinemia (μU/mL)	12.7 ± 1.4	7.78 ± 1.05	$P < .05$

NOTE. Values are mean ± SE over n cases. BMI defined as the ratio between body weight and the square of height. NS, not significantly different ($P > .05$).

Table 2. Estimates of 1CMM Parameters From Normotensive Control Subjects

Subject No.	$p_1 \times 10^2$ (min^{-1})	$p_2 \times 10^2$ (min^{-1})	$p_3 \times 10^5$ (dL · min^{-2} · kg^{-1}/[μU · mL^{-1}])	V (dL · kg^{-1})
1	1.2 (25)	2.5 (30)	1.7 (28)	1.89 (2.8)
2	2.2 (14)	3.4 (23)	1.8 (22)	2.02 (3.6)
3	3.7 (8.6)	2.6 (25)	0.9 (23)	1.39 (2.6)
4	2.5 (14)	7.8 (42)	6.5 (57)	2.04 (2.2)
5	1.3 (26)	9.8 (10)	3.8 (19)	2.16 (2.5)
6	2.6 (10)	2.9 (34)	0.8 (42)	2.11 (2.7)
7	1.5 (13)	1.6 (23)	0.7 (18)	1.78 (2.2)
8	1.3 (6.3)	2.2 (14)	1.0 (16)	2.08 (1.6)
9	1.1 (14)	23 (39)	11 (36)	1.84 (2.5)
Mean ± SE	1.9 ± 0.3	6.2 ± 2.3	3.2 ± 1.2	1.92 ± 0.08

NOTE. The percent coefficient of variation (CV%, see equation 2) in parentheses gives a measure of the precision of the parameter estimate. The parameters p_1, p_2, p_3, and V are defined in the text.

Table 3. Estimates of 1CMM Parameters From Hypertensive Subjects

Subject No.	$p_1 \times 10^2$ (min^{-1})	$p_2 \times 10^2$ (min^{-1})	$p_3 \times 10^5$ ($dL \cdot min^{-2} \cdot kg^{-1}/\mu U \cdot mL^{-1}$])	V ($dL \cdot kg^{-1}$)
1	0.8 (8.5)	1.7 (15)	0.3 (17)	1.90 (1.4)
2	1.1 (7.0)	1.0 (31)	0.2 (32)	1.47 (1.4)
3	1.1 (61)	6.8 (65)	1.2 (117)	2.23 (5.1)
4	1.4 (27)	2.8 (41)	1.0 (44)	3.24 (3.7)
5	1.2 (11)	2.4 (32)	0.2 (45)	2.09 (1.9)
6	0.6 (27)	17 (25)	6.6 (25)	2.74 (2.8)
7	0.5 (32)	6.4 (5.4)	1.9 (6.6)	2.31 (1.8)
8	0.8 (32)	2.6 (19)	0.3 (32)	2.41 (2.6)
9	1.9 (7.4)	22 (159)	0.5 (133)	1.57 (1.9)
10	1.9 (14)	2.1 (28)	0.5 (32)	2.20 (2.8)
Mean ± SE	1.1 ± 0.1	6.5 ± 2.3	1.3 ± 0.6	2.21 ± 0.16

NOTE. The percent coefficient of variation (CV%, see equation 2) in parentheses gives a measure of the precision of the parameter estimate. The parameters p_1, p_2, p_3, and V are defined in the text.

and model-predicted values, divided by the SD of the data. The average weighted residuals for the 1CMM glucose kinetics are presented in the top panel of Fig 4. They have a satisfactory behavior because they show no systematic deviation and are consistent with the hypothesis that the measurement error was a random variable normally distributed, around 0 with a measured percent coefficient of variation (CV%, equation 1) equal to 1.5%.

Identification of 2CMM

Individual estimates and related precision of 2CMM parameters, p_1, p_2, p_3, k_{12}, k_{21}, and V_1, determined in the N and H groups, are presented in Tables 6 and 7, respectively. On average, the volume of the accessible compartment, V_1, calculated in the N group, was not significantly different ($P > .05$) from that determined in the H group (1.84 ± 0.14 *v* 1.53 ± 0.11 $dL \cdot kg^{-1}$). Individual estimates of glucose effectiveness, S_G^2,

Table 4. Estimates of Glucose Effectiveness and Insulin Sensitivity in Normotensive Subjects

Subject No.	Glucose Effectiveness ($dL \cdot min^{-1} \cdot kg^{-1}$)		Insulin Sensitivity ($dL \cdot min^{-1} \cdot kg^{-1}/[\mu U \cdot mL^{-1}]$)	
	$S_G^1 \times 10^2$	$S_G^2 \times 10^2$	$S_I^1 \times 10^4$	$S_I^2 \times 10^4$
1	2.3 (23)	1.8 (53)	13.0 (2.2)	13.9 (4.8)
2	4.5 (11)	1.8 (75)	10.7 (3.9)	13.4 (22)
3	5.2 (6.3)	3.5 (39)	5.20 (4.3)	6.55 (27)
4	5.2 (13)	1.6 (86)	17.0 (19)	35.4 (20)
5	2.9 (24)	3.8 (23)	8.39 (13)	6.99 (34)
6	5.5 (7.9)	4.1 (39)	6.24 (13)	9.63 (53)
7	2.8 (11)	2.4 (29)	8.32 (3.3)	7.95 (2.6)
8	2.7 (5)	1.3 (38)	9.34 (5.3)	13.1 (8.9)
9	0.21 (13)	2.0 (43)	9.26 (13)	9.73 (37)
Mean ± SE	3.7 ± 0.5	2.5 ± 0.3	9.71 ± 1.18	13.0 ± 2.9

NOTE. S_G^1 and S_I^1 indices are derived from the 1CMM (see equations 8 and 9 in Appendix 1). S_G^2 and S_I^2 indices are derived from the 2CMM (see equations 14 and 15 in Appendix 1). The percent coefficient of variation (CV%, see equation 2) in parentheses gives a measure of the precision of the parameter estimate.

Table 5. Estimates of Glucose Effectiveness and Insulin Sensitivity in Hypertensive Patients

Subject No.	Glucose Effectiveness ($dL \cdot min^{-1} \cdot kg^{-1}$)		Insulin Sensitivity ($dL \cdot min^{-1} \cdot kg^{-1}/[\mu U \cdot mL^{-1}]$)	
	$S_G^1 \times 10^2$	$S_G^2 \times 10^2$	$S_I^1 \times 10^4$	$S_I^2 \times 10^4$
1	1.5 (7.3)	0.8 (43)	3.07 (6.1)	4.89 (16)
2	1.6 (5.8)	0.7 (43)	2.94 (10)	7.37 (20)
3	2.4 (56)	0.4 (194)	3.95 (58)	8.18 (18)
4	4.5 (23)	3.1 (28)	11.4 (7.6)	11.7 (10)
5	2.5 (10)	1.6 (27)	2.08 (18)	3.82 (20)
6	1.7 (26)	1.4 (31)	10.9 (9.3)	12.2 (9.5)
7	1.1 (31)	2.3 (18)	6.69 (7.2)	5.07 (13)
8	1.9 (29)	1.7 (37)	2.99 (15)	3.18 (18)
9	3.0 (6.3)	0.7 (212)	3.76 (59)	4.56 (49)
10	4.3 (12)	2.7 (25)	5.18 (8.4)	6.95 (10)
Mean ± SE	2.4 ± 0.3	1.5 ± 0.3	4.95 ± 1.16	6.79 ± 0.99

NOTE. S_G^1 and S_I^1 indices are derived from the 1CMM (see equations 8 and 9 in Appendix 1). S_G^2 and S_I^2 indices are derived from the 2CMM (see equations 14 and 15 in Appendix 1). The percent coefficient of variation (CV%, see equation 2) in parentheses gives a measure of the precision of the parameter estimate.

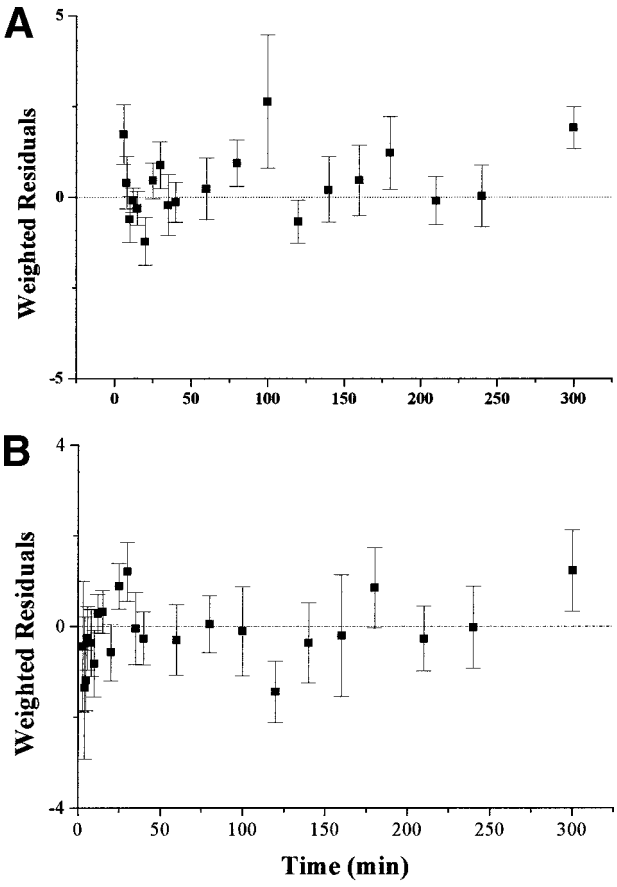

Fig 4. (A) Mean weighted residuals for the 1CMM of glucose kinetics (mean ± SE). Data between 0 and 5 minutes were excluded in model identification to mitigate the approximation of the single-compartment description of glucose kinetics. (B) Mean weighted residuals for the 2CMM of glucose kinetics (mean ± SE).

Table 6. Estimates of 2CMM Parameters From Normotensive Control Subjects

Subject No.	$p_1 \times 10^2$ (min^{-1})	$p_2 \times 10^2$ (min^{-1})	$p_3 \times 10^5$ ($dL \cdot min^{-2} \cdot kg^{-1}/[\mu U \cdot mL^{-1}]$)	$k_{12} \times 10^2$ (min^{-1})	$k_{21} \times 10^2$ (min^{-1})	V_1 ($dL \cdot kg^{-1}$)
1	1.1 (53)	2.7 (43)	2.4 (48)	8.3 (15)	2.6 (32)	1.56 (2.6)
2	0.9 (76)	2.9 (23)	2.0 (14)	0.4 (84)	1.3 (52)	1.98 (2.3)
3	2.4 (40)	2.5 (22)	1.1 (35)	0.5 (103)	1.0 (72)	1.44 (2.3)
4	0.7 (88)	7.3 (33)	12 (39)	0.9 (39)	0.8 (33)	2.21 (2.6)
5	1.9 (23)	5.2 (60)	1.9 (40)	1.5 (89)	0.6 (113)	1.95 (3.1)
6	1.9 (40)	2.1 (27)	1.0 (51)	0.7 (109)	0.7 (102)	2.10 (1.8)
7	2.3 (34)	1.9 (45)	1.4 (41)	13 (11)	9.1 (11)	1.03 (5.6)
8	0.6 (39)	3.5 (21)	1.9 (17)	0.4 (205)	0.2 (96)	2.37 (1.4)
9	1.0 (47)	13 (69)	6.8 (100)	1.9 (46)	0.1 (433)	1.92 (3.5)
Mean ± SE	1.4 ± 0.2	4.6 ± 1.2	3.4 ± 1.2	3.0 ± 1.5	1.8 ± 0.9	1.84 ± 0.14

NOTE. The percent coefficient of variation (CV%, see equation 2) in parentheses gives a measure of the precision of the parameter estimate. The parameters p_1, p_2, p_3, k_{12}, k_{21}, and V_1 are defined in the text.

and insulin sensitivity, S_I^2, indexes derived from the 2CMM in the N and H groups are reported in Tables 4 and 5, respectively. In the N group, the mean values (± SE) were $2.5 \pm 0.3 \times 10^{-2}$ $dL \cdot min^{-1} \cdot kg^{-1}$ for S_G^2 and $13.0 \pm 2.9 \times 10^{-4}$ $dL \cdot min^{-1} \cdot kg^{-1}/[\mu U \cdot mL^{-1}]$ for S_I^2. In the H group, S_G^2 averaged $1.5 \pm 0.3 \times 10^{-2}$ $dL \cdot min^{-1} \cdot kg^{-1}$, whereas S_I^2 averaged $6.79 \pm 0.99 \times 10^{-4}$ $dL \cdot min^{-1} \cdot kg^{-1}/[\mu UmL^{-1}]$. S_I^2 was estimated with an acceptable precision in all cases, whereas S_G^2 accuracy was unsatisfactory in 2 of 19 subjects (subjects 3 and 9, Table 5).

Weighted residuals for the 2CMM showed no systematic deviation (bottom panel of Fig 4). This model shows the initial portion of the IVGTT (2 to 5 minutes), which is not possible with the 1CMM (compare top and bottom panels of Fig 4).

Comparison between 1CMM and 2CMM

The 2CMM glucose effectiveness index, S_G^2, was on average 67% (N group, Table 4) and 63% (H group, Table 5) of the corresponding 1CMM index, S_G^1. The 2CMM insulin sensitivity index, S_I^2, was on average 134% (N group, Table 4) and 137% (H group, Table 5) of the corresponding 1CMM index, S_I^1. Differences between S_G^2 and S_G^1 and between S_I^2 and S_I^1 were not statistically significant ($P > .05$). The 1CMM and 2CMM yielded similar reductions in the insulin sensitivity ($\Delta S_I^1 = -49\%$, $P < .05$; and $\Delta S_I^2 = -48\%$, $P > .05$) and the glucose effectiveness ($\Delta S_G^1 = -35\%$, $P < .05$; and $\Delta S_G^2 = -40\%$, $P > .05$) from the N group to the H group.

DISCUSSION

The estimates of glucose effectiveness and insulin sensitivity provided by the 1CMM and 2CMM applied to the IVGTT data from our N group (Tables 4 and 5) are in good agreement with results previously reported by Cobelli et al[21] for normal humans ($S_G^2 = 2.81 \pm 0.29 \times 10^{-2}$ $dL \cdot min^{-1} \cdot kg^{-1}$, $S_I^2 = 11.67 \pm 1.71 \times 10^{-4}$ $dL\,min^{-1} \cdot kg^{-1}/[\mu U \cdot mL^{-1}]$, $S_G^1 = 4.27 \pm 0.33 \times 10^{-2}$ $dL \cdot min^{-1} \cdot kg^{-1}$ and $S_I^1 = 8.68 \pm 1.62 \times 10^{-4}$ $dL \cdot min^{-1} \cdot kg^{-1}/[\mu U \cdot mL^{-1}]$). Average age in our N group (40 ± 4 years) was significantly higher than the age (28 ± 1 years) of the population considered by Cobelli et al.[21] The similarity in the estimates of glucose effectiveness and insulin sensitivity in these 2 studies, despite age discrepancy, is in agreement with the finding reported by Chen et al[34] that the clustering features of insulin resistance are independent of age and sex in both black and white populations.

Both the Cobelli et al[21] study and the present study show a tendency of the 2CMM model to underestimate the glucose effectiveness and overestimate the insulin sensitivity by approximately 34% with respect to the 1CMM. In our study, however, these variations were not statistically significant (*t* test, $P > .05$).

An original aspect of the present study is the involvement of a group of nondiabetic hypertensive patients (H group) in testing the behavior of the 2CMM versus the 1CMM. In accordance with previous reports,[5,14,35,36] the fact that these patients were on

Table 7. Estimates of 2CMM Parameters From Hypertensive Subjects

Subject No.	$p_1 \times 10^2$ (min^{-1})	$p_2 \times 10^2$ (min^{-1})	$p_3 \times 10^5$ ($dL \cdot min^{-2} \cdot kg^{-1}/[\mu U \cdot mL^{-1}]$)	$k_{12} \times 10^2$ (min^{-1})	$k_{21} \times 10^2$ (min^{-1})	V_1 ($dL \cdot kg^{-1}$)
1	0.5 (42)	1.7 (14)	0.5 (26)	3.8 (20)	1.4 (28)	1.69 (1.8)
2	0.7 (45)	1.4 (14)	1.1 (30)	11 (13)	8.3 (11)	0.95 (3.5)
3	0.3 (197)	5.6 (15)	3.0 (28)	13 (11)	9.2 (12)	1.51 (4.0)
4	1.4 (30)	3.3 (26)	1.7 (33)	15 (10)	9.0 (13)	2.21 (3.6)
5	1.1 (30)	2.7 (20)	0.7 (35)	11 (13)	6.5 (16)	1.46 (4.4)
6	0.8 (33)	6.8 (13)	4.6 (14)	14 (11)	9.6 (12)	1.81 (3.3)
7	2.1 (20)	5.2 (11)	2.4 (11)	15 (8.9)	13 (7.7)	1.12 (2.8)
8	1.2 (40)	2.3 (18)	0.5 (32)	15 (10)	11 (10)	1.36 (3.9)
9	0.4 (212)	1.5 (36)	0.4 (83)	3.1 (53)	1.4 (78)	1.70 (1.6)
10	1.8 (27)	3.0 (20)	1.4 (27)	15 (9.0)	9.5 (11)	1.47 (3.6)
Mean ± SE	1.0 ± 0.2	3.3 ± 0.6	1.6 ± 0.4	11 ± 1.4	7.9 ± 1.2	1.53 ± 0.11

NOTE. The percent coefficient of variation (CV%, see equation 2) in parentheses gives a measure of the precision of the parameter estimate. The parameters p_1, p_2, p_3, k_{12}, k_{21}, and V_1 are defined in the text.

antihypertensive drug therapy with calcium channel blockers or ACE inhibitors is not expected to affect the metabolic syndromes of insulin resistance. In this H group, the 2CMM underestimated the glucose effectiveness by approximately 37% ($P > .05$) and overestimated the insulin sensitivity by approximately 37% ($P > .05$) with respect to the 1CMM. These variations are similar to those found in normal humans as discussed above.

It has been reported previously that the 1CMM produces an overestimation of glucose effectiveness and an underestimation of insulin sensitivity when compared with the glucose clamp technique, which is unanimously considered the gold standard.[15-25] Based on this consideration, the increase in the estimates of glucose effectiveness and the decrease in insulin sensitivity provided by the 2CMM with respect to the 1CMM goes the right direction in approximating the estimates obtained from the glucose clamp.[21] However, the improvement obtained from the 2CMM is weakened in our study by the observations that both the S_G^2 and the S_I^2 were not significantly different ($P > .05$) with respect to the S_G^1 and S_I^1 estimates and that these estimates were associated with higher CV% (Tables 4 and 5).

The goal of assessing the validity of the 2CMM versus the 1CMM in absolute terms is peripheral to the scope of the present work. Here, our issue was to address the question as to whether and how much the use of the 2CMM, rather than 1CMM, would affect the metabolic picture of hypertensive patients when compared with normal subjects. This metabolic picture is, indeed, characterized in terms of variations of insulin sensitivity and glucose effectiveness indexes from normal.

Our results (Tables 4 and 5) show a reduction of approximately 40% ($P > .05$) and approximately 48% ($P > .05$) in S_G^2 and S_I^2 estimates, respectively, detected by the 2CMM from the N group to the H group. Despite its reduced complexity, the 1CMM also detected a reduction of approximately 35% ($P < .05$) and approximately 49% ($P < .05$) in the S_G^1 and in S_I^1 indexes, respectively. Moreover, the variation detected by the 1CMM in both metabolic indexes is statistically significant, the variation detected by the 2CMM is not. Higher parameter estimation errors (CV%, Tables 4 and 5) affecting the 2CMM may explain this discrepancy.

In conclusion, the 1CMM and 2CMM show a substantial equivalence in detecting a severe reduction in insulin sensitivity and impaired glucose effectiveness in hypertensive patients compared with normal. This finding is consistent with previous reports.[4-7] Severe decrease in insulin sensitivity denotes the presence of an insulin-resistant state in hypertension.[9-12] The impaired glucose effectiveness indicates abnormalities in the process of glucose production and utilization.[37,38]

APPENDIX 1

1CMM of Glucose Kinetics

The 1CMM represented in Fig 1 is based on 4 main hypotheses[29]: (1) glucose, Q(t), distributes itself in a single compartment; (2) glucose accelerates its own rate of disappearance and inhibits its own production in a linear fashion independently of any dynamic change of plasma insulin, I(t); (3) glucose uptake and glucose production are directly dependent on the concentration of insulin, not in plasma, but in a second compartment remote from plasma, I′(t); (4) glucose production and hepatic glucose uptake are lumped together as net hepatic glucose balance (NHGB), which may take on positive (production) or negative (uptake) values, while the disappearance of glucose into peripheral tissues, R_{dp}, is represented explicitly. The third proposition is based on the study of Insel et al[39] and is consistent with the existence of a remote receptor poll that is intimately involved in the action of insulin. Equations of the 1CMM are as follows:

$$\dot{Q}(t) = -[p_1 + X(t)] \cdot Q(t) + p_1 \cdot Q_b \qquad Q(0) = Q_b + D \tag{1}$$

$$\dot{X}(t) = -p_2 \cdot X(t) + p_3 \cdot [I(t) - I_b] \qquad X(0) = 0 \tag{2}$$

$$G(t) = Q(t)/V \tag{3}$$

where:

$$X(t) = (k_4 + k_6) \cdot I'(t) \tag{4}$$

$$p_1 = k_1 + k_5 \tag{5}$$

$$p_2 = k_3 \tag{6}$$

$$p_3 = k_2 \cdot (k_4 + k_6) \tag{7}$$

D ($mg \cdot kg^{-1}$) is the glucose dose; k_i's coefficients ($i = 1, \ldots, 6$) are rate constants characterizing either material fluxes (solid lines in Fig 1) or control actions (dashed lines in Fig 1); Q(t) is glucose mass ($mg \cdot kg^{-1}$) and Q_b is its basal (endtest) steady-state value; G(t) and I(t) are plasma glucose ($mg \cdot dL^{-1}$) and insulin ($\mu U \cdot mL^{-1}$) concentrations at time t; I′(t) is insulin concentration, at time t, in a compartment remote from plasma; G_b and I_b are baseline (end-test) glucose and insulin concentrations, respectively, computed as the average of the last 2-3 points; V ($dL \cdot kg^{-1}$) is the distribution volume. From equation 3 results $Q_b = G_b \cdot V$. The free model parameters in equations 1 to 3 are p_1, p_2, p_3, and V, and it has been shown that the 1CMM is *a priori* uniquely identifiable by an IVGTT in this parameterization.[32]

From the 1CMM parameters, one can derive indexes of glucose effectiveness, S_G^1, and insulin sensitivity, S_I^1, as follows:

$$S_G^1 = -\left.\frac{\partial \dot{Q}(t)}{\partial G(t)}\right|_{ss} = p_1 \cdot V \qquad (dL \cdot min^{-1} \cdot kg^{-1}) \tag{8}$$

$$S_I^1 = -\left.\frac{\partial^2 \dot{Q}(t)}{\partial I \partial G(t)}\right|_{ss} = \frac{p_3}{p_2} \cdot V \qquad (dL \cdot min^{-1} \cdot kg^{-1}/\mu U \cdot mL^{-1}) \tag{9}$$

The superscript 1 indicates that these indexes pertain to the 1CMM, the suffix ss denotes that the derivatives are calculated in steady state condition. It is important to note that S_G^1 and S_I^1, at variance with the fractional (ie, per unit volume) indexes commonly expressed elsewhere, have the same units of the analogous glucose clamp indexes, thus allowing a direct comparison. Moreover, the choice of these indexes is the most appropriate to compare the 1CMM and the 2CMM because the 2 models have different accessible pool volumes (see below).[21]

2CMM of Glucose Kinetics

The 2CMM is the natural evolution of the classic 1CMM: a second, nonaccessible glucose compartment that represents tissues in slow exchange with plasma is appended to the accessible glucose compartment that represents plasma and tissues in rapid exchange with plasma (Fig 2). The 2CMM differs from the 1CMM only in allowing an

exchange of glucose between the accessible and the nonaccessible compartment. The equations of the model are as follows:

$$\dot{Q}_1(t) = -[p_1 + k_{21} + X(t)] \cdot Q_1(t) + k_{12} \cdot Q_2(t) + p_1 \cdot Q_{1b} \qquad Q_1(0) = Q_{1b} + D \tag{10}$$

$$\dot{Q}_2(t) = k_{21} \cdot Q_1(t) - k_{12} \cdot Q_2(t) \qquad Q_2(0) = Q_{2b} \tag{11}$$

$$\dot{X}(t) = -p_2 \cdot X(t) + p_3 \cdot [I(t) - I_b] \qquad X(0) = 0 \tag{12}$$

$$G(t) = Q_1(t)/V_1 \tag{13}$$

where $Q_1(t)$ and $Q_2(t)$ are the glucose masses ($mg \cdot kg^{-1}$) in the accessible and nonaccessible pool, respectively, Q_{1b} and Q_{2b} are their basal (endtest) steady-state values; V_1 ($dL \cdot kg^{-1}$) is the volume of the accessible compartment; k_{12} and k_{21} (min^{-1}) are rate parameters describing glucose exchange kinetics; D, G(t), I(t), X(t), p_1, p_2, p_3 are variables and parameters already defined for the 1CMM. From equation 13, one has $Q_{1b} = G_{1b} \cdot V_1$, and from the steady-state constraint ($\dot{Q}_1(t)|_{ss} = 0$), one has

$$Q_{2b} = Q_{1b} \cdot \frac{k_{21}}{k_{12}}.$$

The free model parameters in equations 10 to 13 are p_1, p_2, p_3, V_1, k_{12}, and k_{21}. *A priori* identifiability analysis showed that the 2CMM is not uniquely identifiable in this parameterization by an IVGTT.[21] In particular, p_2, p_3, V_1 are uniquely identifiable; p_1, k_{12}, k_{21} are not. However, it was shown by Cobelli et al[21] that additional independent knowledge on glucose exchange kinetic parameters k_{12} and k_{21} taken from the literature makes the model uniquely identifiable.

Indexes of glucose effectiveness, S_G^2, and insulin sensitivity, S_I^2, from the 2CMM are as follows:

$$S_G^2 = -\left.\frac{\partial \dot{Q}_1(t)}{\partial G(t)}\right|_{ss} = p_1 \cdot V_1 \qquad (dL \cdot min^{-1} \cdot kg^{-1}) \tag{14}$$

$$S_I^2 = -\left.\frac{\partial^2 \dot{Q}_1(t)}{\partial I \partial G(t)}\right|_{ss} = \frac{p_3}{p_2} \cdot V_1 \qquad (dL \cdot min^{-1} \cdot kg^{-1}/[\mu U \cdot mL^{-1}]) \tag{15}$$

The superscript 2 indicates that these indexes pertain to the 2CMM, the suffix ss denotes that the derivatives are calculated in steady state condition.

APPENDIX 2

Given a model structure $M(\bar{p})$, consider the problem of estimating the model parameter vector $\bar{p} = [p_1, \ldots\ldots, p_p]$ from a set of N noisy measurements

$$z_i(t_i) = y(t_i, \bar{p}) + e_i \qquad i = 1, \ldots\ldots, N \tag{1}$$

where $y(t_i, \bar{p})$ is the model prediction at time t_i, and e_i denotes the additive error that affects the i-th measurement z_i. This problem is commonly solved by using Fisherian approach, eg, nonlinear least square or maximum likelihood estimation techniques.[40] A more sophisticated, but less used, approach is Bayesian estimation.[40] The major difference between these 2 approaches is that Fisherian approach considers $\bar{p}$ as unknown, but with a single actual value. Bayesian approach considers a distribution of possible values for $\bar{p}$. Before the observation is made, $\bar{p}$ is assumed to have a known prior probability density $f_p(\bar{p})$. The joint probability density of $\bar{z}$ and $\bar{p}$, $f(\bar{z}, \bar{p})$, satisfies the following relationship:

$$f(\bar{z}, \bar{p}) = f_z(\bar{z}|\bar{p}) \cdot f_p(\bar{p}) = f_p(\bar{p}|\bar{z}) \cdot f_z(\bar{z}) \tag{2}$$

where $f_z(\bar{z}|\bar{p})$ and $f_p(\bar{p}|\bar{z})$ are the posterior probability density for $\bar{p}$ conditional on the data $\bar{z}$ and the posterior probability density for $\bar{z}$ conditional on the parameter vector $\bar{p}$, respectively. $f_z(\bar{z})$ is the prior probability density for $\bar{z}$. From equation 2, one has:

$$f_p(\bar{p}|\bar{z}) = \frac{f_z(\bar{z}|\bar{p}) \cdot f_p(\bar{p})}{f_z(\bar{z})} \tag{3}$$

This is the Bayes' rule, which gives its name to this class of estimators and quantifies what has been learned by collecting data. Because $\bar{z}$ is a vector of known numbers, $f_z(\bar{z})$ is just a normalization constant ensuring that $f_p(\bar{p}|\bar{z})$ is a probability density. To compute $f_p(\bar{p}|\bar{z})$, one therefore only need to know how to express $f_z(\bar{z}|\bar{p})$ by taking advantage of the information or hypotheses on the noise and to have $f_p(\bar{p})$ at one's disposal, which expresses prior knowledge on the parameters. This knowledge may result from previous measurements on the same process or on similar processes.

Taking advantage of the posterior probability density $f_p(\bar{p}|\bar{z})$ is not always easy, and it is often desirable to obtain a point estimate of the parameters, ie, a unique numerical value $\hat{p}$. A Bayesian method that may be used for this purpose is the MAP. The vector $\hat{p}_{map}$ will be a maximum a posteriori estimate if it maximizes the cost function[40]:

$$j_{map}(\bar{p}) = f_p(\bar{p}|\bar{z}) = \frac{f_z(\bar{z}|\bar{p}) \cdot f_p(\bar{p})}{f_z(\bar{z})} \tag{4}$$

As $f_z(\bar{z})$ does not depend on $\bar{p}$, this is equivalent to maximizing $f_z(\bar{z}|\bar{p}) \cdot f_p(\bar{p})$, or

$$j_{map}(\bar{p}) = \ln f_z(\bar{z}|\bar{p}) + \ln f_p(\bar{p}) \tag{5}$$

because logarithm is monotonically increasing function.

Equation 5 gives the general definition of the MAP estimator. In practical applications, the functional in the right side of equation 5 depends on the specific form of both $f_p(\bar{p})$ and $f_z(\bar{z}|\bar{p})$. For example, if vector $\bar{p}$ is normally distributed with mean, $\bar{\mu}$, and known covariance matrix, Ω, and the measurement errors, e_i, are also normally distributed, with 0 mean and variance SD_i^2, it is easy to show that a MAP estimates $\hat{p}_{map}$ of $\bar{p}$ is a minimizer of the quadratic function:

$$j_{ml}(\bar{p}) = \sum_{i=1}^{N} \left(\frac{z(t_i) - y(t_i, \bar{p})}{SD_i}\right)^2 + (\bar{p} - \bar{\mu})^T \Omega^{-1} (\bar{p} - \bar{\mu}) \tag{6}$$

It is worth noting that in the cost function of equation 6 there are 2 contributions. The first term, which coincides with the cost function of LS estimation,[40] measures the adherence to the a posteriori information (the goodness of fit), and the second terms expresses the prior information on the parameters. It is thus easy to incorporate some (objective or subjective) information on the possible values for $\bar{p}$.

REFERENCES

1. Ferrannini E, De Fronzo RA: The association of hypertension, diabetes, and obesity: A review. J Nephrol 1:3-15, 1989

2. MacMahon SW, Macdonald GJ, Blacket RB: Plasma lipoprotein levels in treated and untreated hypertensive men and women. Arteriosclerosis 5:391-396, 1985

3. Modan M, Halkin H, Almong S, et al: Hyperinsulinemia: A link

between hypertension, obesity and glucose intolerance. J Clin Invest 75:809-817, 1985

4. Kautzky-Willer A, Capek M, Weissel M, et al: Insulin sensitivity, secretion and hepatic extraction in untreated hypertensive patients. Curr Top Diab Res 12:250-253, 1993

5. Kautzky-Willer A, Pacini G, Weissel M, et al: Elevated hepatic insulin extraction in essential hypertension. Hypertension 21:646-653, 1993

6. Kautzky-Willer A, Thomaseth K, Pacini G, et al: Role of islet amyloid polypeptide secretion in insulin resistant humans. Diabetologia 37:188-194, 1994

7. Supiano MA, Hogikyan RV, Morrow LA, et al: Hypertension and insulin resistance: Role of sympathetic nervous system activity. Am J Physiol 263:E935-E942, 1992

8. Zavaroni I, Bonora E, Pagliara M, et al: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. N Engl J Med 320:702-705, 1989

9. Ferrannini E, Buzzigoli G, Bonadonna R, et al: Insulin resistance in essential hypertension. N Engl J Med 7:317-350, 1987

10. Reaven GM: Role of insulin resistance in human disease. Diabetes Care 14:195-202, 1991

11. Shen D-C, Shieh S-M, Fuh MM-T, et al: Resistance to insulin-stimulated-glucose uptake in patients with hypertension. J Clin Endocrinol Metab 66:580-583, 1988

12. Swislocki AL, Hoffman BB, Reaven GM: Insulin resistance, glucose intolerance and hyperinsulinemia in patients with hypertension. Am J Hypertens 2:419-423, 1989

13. Bergman RN: The minimal model: Yesterday, today and tomorrow, in Bergman RN, Lovejoy J (eds): The Minimal Model Approach and Determinants of Glucose Tolerance, vol 7. Baton Rouge, LA, Louisiana State University Press, 1997, pp 3-50

14. Natalucci S, Burattini R, Boemi M, et al: Insulin sensitivity in normal and hypertensive subjects. Intern Med 7:41-49, 1999

15. Caumo A, Cobelli C: Hepatic glucose production during the labelled IVGTT: Estimation by deconvolution with a new minimal model. Am J Physiol 264:E829-E841, 1993

16. Caumo A, Cobelli C: Minimal model overestimation of S_G and underestimation of S_I corrected by bayesian identification of a new two-compartment minimal model. Diabetes 47:A285, 1998 (abstr)

17. Caumo A, Cobelli C, Finegood DT: Minimal model estimate of glucose effectiveness: Role of the minimal model volume and of the second hidden compartment. Am J Physiol 274:E573-E576, 1998

18. Caumo A, Vicini P, Cobelli C: Is the minimal model too minimal? Diabetologia 39:997-1000, 1996

19. Caumo A, Vicini P, Zachwieja JJ, et al: Undermodeling affects minimal model indixes: insights from a two-compartment model. Am J Physiol 276:E1171-E1193, 1999

20. Cobelli C, Bettini F, Caumo A, et al: Overestimation of minimal model glucose effectiveness in presence of insulin response is due to undermodeling. Am J Physiol 275:E1031-E1036, 1998

21. Cobelli C, Caumo A, Omenetto M: Minimal model S_G overestimation and S_I underestimation: improved accuracy by a bayesian two compartment model. Am J Physiol 277:E481-E488, 1999

22. Finegood DT, Tzur D: Reduced glucose effectiveness associated with reduced insulin release: An artifact of the minimal model method. Am J Physiol 271:E485-E495, 1996

23. Quon MJ, Cochran C, Taylor SI, et al: Non–insulin-mediated glucose disappearance in subjects with IDDM. Discordance between experimental results and minimal model analysis. Diabetes 43:890-896, 1994

24. Saad MF, Anderson RL, Laws A, et al: A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. Diabetes 43:1114-1121, 1994

25. Vicini P, Caumo A, Cobelli C: The hot IVGTT two-compartment minimal model: Indexes of glucose effectiveness and insulin sensitivity. Am J Physiol 273:E1024-1032, 1997

26. Finegood DT, Hramiak IM, Dupre J: A modified protocol for estimation of insulin sensitivity with the minimal model of glucose kinetics in patients with insulin dependent diabetes. J Clin Endocrinol Metab 70:1538-1548, 1990

27. Welch S, Gebhart SSP, Bergman RN, et al: Minimal model analysis of intravenous glucose tolerance test-derived insulin sensitivity in diabetic subjects. J Clin Endocrinol Metab 71:1508-1518, 1990

28. Pacini G, Tonolo G, Sambataro M, et al: Insulin sensitivity and glucose effectiveness: Minimal model analysis of regular and insulin-modified FSIGT. Am J Physiol 274:E592-E599, 1998

29. Bergman RN, Ider YZ, Bowden CR, et al: Quantitative estimation of insulin sensitivity. Am J Physiol 236:E667-E677, 1979

30. Radziuk J, Norwich KH, Vranic M: Experimental validation of measurements of glucose turnover in nonsteady state. Am J Physiol 234:E84-E93, 1978

31. Barrett PHR, Bell BM, Cobelli C, et al: SAAM II: Simulation, analysis, and modelling software for tracer and pharmacokinetics studies. Metabolism 47:484-492, 1998

32. Carson ER, Cobelli C, Finkelstein L: The Mathematical Modeling of Metabolic and Endocrine Systems. New York, NY, Wiley, 1983

33. D'Argenio DZ, Schumitzky A: Adapt II User's Guide, Pharmacokinetic/Pharmacodynamic Systems Analysis Software. Los Angeles, CA, Biomedical Simulations Resource, University of Southern California, 1997

34. Chen W, Srinivasan SR, Elkasabany A, et al: Cardiovascular risk factors features of insulin resistance syndrome (Syndrome X) in a biracial (Black-White) population of children, adolescents, and young adults: the Bogalusa Heart Study. Am J Epidemiol 150:667-674, 1999

35. Klauser R, Prager R, Gaube S, et al: Metabolic effects of isradipine versus hydrochlorothiazide in diabetes mellitus. Hypertension 17:15-21, 1991

36. Santoro D, Natali A, Palombo C, et al: Effects of chronic angiotensin converting enzyme inhibition on glucose tolerance and insulin sensitivity in essential hypertension. Hypertension 20:181-191, 1992

37. Best JD, Kahn SE, Ader M, et al: Role of glucose effectiveness in the determination of glucose tolerance. Diabetes Care 9:1018-1030, 1996

38. Verdonk CA, Rizza RA, Gerich JE: Effects of plasma glucose concentrations on glucose utilization and glucose clearance in normal man. Diabetes 30:535-537, 1981

39. Insel PA, Liljenquist JE, Tobin JD, et al: Insulin control of glucose metabolism in man. J Clin Invest 55:1057-1066, 1975

40. Walter E, Pronzato L: Identification of Parametric Models from Experimental Data. New York, NY, Springer, 1997