Deterioration of Insulin Sensitivity and Glucose Effectiveness With Age and Hypertension

Roberto Burattini, Francesco Di Nardo, Massimo Boemi, and Paolo Fumelli

**Background:** This study examined the relative role of age and hypertension in deterioration of insulin-dependent (insulin sensitivity, $S_I$) and insulin-independent (glucose effectiveness, $S_G$) actions on glucose tolerance.

**Methods:** We applied the minimal model of glucose kinetics to estimate $S_I$ and $S_G$ indexes from insulinemia and glycemia data detected during a frequently sampled intravenous glucose tolerance test performed in 21 normoglycemic subjects who were not affected by the metabolic syndrome (MS): seven young normotensive subjects (YN; mean age 29.3 ± 1.5 years), six elderly normotensive subjects (EN; mean age 57.0 ± 3.4 years) and eight elderly hypertensive patients (EH; mean age 62.1 ± 2.1 years).

**Results:** Both normotensive subject groups (YN and EN) showed no significant difference in $S_I$ estimates despite significantly different age, whereas a significant reduction was evident in the EH patients compared with these groups. Mean estimates of $S_G$ showed no significant difference in elderly subject groups (EN and EH), irrespective of hypertension, whereas a significant increase was evident in the YN (analysis of variance followed by Scheffé test, $P < .05$).

**Conclusions:** Our study demonstrates that, in the absence of MS: 1) insulin sensitivity in normotensive subjects is independent of age; b) hypertension is associated with insulin resistance in elderly subjects; and c) age is a primary predictor of deterioration in glucose effectiveness, independent of hypertension. Am J Hypertens 2006;19:98–102 © 2006 American Journal of Hypertension, Ltd.

**Key Words:** Glucose effectiveness, glucose resistance, insulin resistance, intravenous glucose tolerance test, minimal model of glucose kinetics.

An association between insulin resistance and essential hypertension has been identified in several studies including our own. A reduced sensitivity of insulin-mediated cellular glucose uptake is the process on which the definition of insulin resistance has classically been based. In most studies, alteration of insulin sensitivity in hypertension has been measured with the euglycemic–hyperinsulinemic clamp technique and by the minimal model analysis of insulinemia and glycemia data obtained from frequently sampled intravenous glucose tolerance test (FSIGTT). An advantage of the minimal model analysis of FSIGTT data is that it provides estimates of insulin sensitivity ($S_I$), and glucose effectiveness ($S_G$) indexes at the same time. Because glucose itself can enhance glucose disposal and suppress endogenous glucose production independent of a change in insulin, it is important to consider the glucose effectiveness factor when determining glucose tolerance in hypertension.

Obesity and age are potential confounding factors that may affect the $S_I$ and $S_G$ indexes beyond hypertension. In respect to the role of obesity it is generally accepted that the presence of elevated blood pressure (BP) in obese subjects points to exaggerated insulin resistance. Rather, contradictory results are found in the literature as to the relative role of age and hypertension in deterioration of insulin sensitivity and glucose effectiveness. In respect to tissue insulin sensitivity, either a reduction or no significant change has been observed in healthy subjects with increasing age, whereas a reduction has been observed in hypertensive patients compared with normotensive subjects who were either matched or not matched for age. In respect to glucose effectiveness, either age-related reduction or no reduction has been observed in hypertensive patients.
reported in healthy subjects. When hypertensive patients were studied, either no change or a significant decrease was observed in comparison to normotensive subjects matched for age and body mass index (BMI).

Based on these considerations, the present study was designed to elucidate the relative role of age and essential hypertension in deterioration of \( S_I \) and \( S_C \) indexes in a group of elderly hypertensive patients compared with two groups of normotensive subjects, one matched for age and the other significantly younger.

### Methods

#### Patients and Protocol

This clinical study included 21 volunteer subjects of white ethnicity who were recruited at the Metabolic Disease and Diabetes Unit of the IRNCA–IRCCS, Ancona, Italy. All subjects gave informed consent to the procedures approved by the Ethics Committee. The subjects were divided into groups as follows: seven young normotensive (YN), six elderly normotensive (EN), and eight elderly hypertensive (EH) subjects. The mean age and male/female ratio for each group are given in Table 1.

To control for confounding effects of metabolic syndrome (MS), defined according to criteria of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III (ATP III), we selected only those normotensive and hypertensive subjects who had no history of diabetes mellitus and who had a fasting glycemia <110 mg/dL. Subjects included in the YN and EN groups had seated diastolic and systolic BP levels \( \leq 85 \) mm Hg and \( \leq 130 \) mm Hg, respectively, and showed no more than two of the remaining three ATP III criteria, as follows: 1) waist circumference >102 cm in men and >88 cm in women; 2) triglycerides \( \geq 150 \) mg/dL; and 3) HDL cholesterol <40 mg/dL in men and <50 mg/dL in women. No more than one of these three criteria was allowed, besides hypertension, in normoglycemic EH patients.

All hypertensive patients were receiving antihypertensive drug therapy with calcium channel blockers or angiotensin-converting enzyme inhibitors for >1 year. Based on previous studies, this antihypertensive drug therapy appears to be metabolically neutral or to induce a small improvement in insulin sensitivity only in the absence of familial predisposition to hypertension. A previous application of minimal model and FSIGTT in hypertensive patients, before and after antihypertensive treatment, showed no significant change in glucose effectiveness. Based on these previous reports, risks of suspension of therapy were avoided in this study.

All subjects underwent FSIGTT. Starting time was 8:30 AM, after overnight fast. Three basal blood samples (2 mL) were taken at \(-15\) and \(-5\) min and immediately before injection of a glucose bolus of 300 mg/kg, over 1 min, into a contralateral antecubital vein. In addition, 24 more blood samples were taken 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 min after glucose injection (time 0). Blood was promptly centrifuged and glucose immediately measured by the glucose oxidase method with an automated glucose analyzer. The remaining plasma was stored at \(-20^\circ\text{C}\) for later insulin dosage. Insulinenia was determined by commercially available radioimmunoassays (Biodata S.p.A, Guidonia Montecelio, Roma, Italy). The sensitivity and intra- and interassay precision of the insulin were 1 \( \mu \)/mL, 5.4% \( \pm \) 1.0%, and 5.5% \( \pm \) 1.2%, respectively. The cross-reactivity for human pro-insulin was 14%.

#### Data analysis

Glycemia and insulinenia data were analyzed with the minimal model of glucose kinetics to estimate \( S_I \), \( S_C \), and glucose distribution volume (V). According to Kahn et al., the \( S_C \) index can be factored out into two components: 1) a basal insulin effect (BIE), which accounts for

<table>
<thead>
<tr>
<th>Table 1. Clinical data for study subjects</th>
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<tr>
<td><strong>Characteristic</strong></td>
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<tr>
<td>Male/female</td>
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<tr>
<td>Age (y)</td>
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<tr>
<td>SBP (mm Hg)</td>
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<tr>
<td>DBP (mm Hg)</td>
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<tr>
<td>Waist circumference (cm)</td>
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<tr>
<td>Triglycerides (mg/dL)</td>
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<td>Cholesterol (mg/dL)</td>
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<tr>
<td>HDL cholesterol (mg/dL)</td>
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<tr>
<td>Glycemia (mg/dL)</td>
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<td>Insulinenia (( \mu )/mL)</td>
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</table>

* Significant difference in marked mean with respect to the other two (ANOVA followed by Scheffé test, \( P < .05 \)). All variables showed normal distribution except triglyceridemia, which underwent Kruskal-Wallis nonparametric version of classical one-way ANOVA.
The SAAM II software\textsuperscript{26} (SAAM Institute, University of Washington, Seattle, WA) was used to estimate $S_G$, $S_P$, and $V$. Further details on model equations and data fit are given in our previous report.\textsuperscript{12} Precision of parameter estimates was expressed as percent coefficient of variation: $CV(p_i)\% = (SD_{p_i}/p_i) \times 100$, where $p_i$ is the $i$th component of the model parameters vector and $SD_{pi}$ 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.

### Statistical Analysis

Data are given as means $\pm$ SE. The Lilliefors test\textsuperscript{27} (suitable for small samples) was used to evaluate the hypothesis that each data vector or parameter vector had a normal distribution with unspecified mean and variance (significance was set at 5\% level). Comparisons among normally distributed samples were performed with one-way analysis of variance followed by the Scheffé test; a statistically significant difference was assumed at $P < .05$. Kruskal-Wallis nonparametric version of the classical one-way analysis of variance was used to compare samples that were not normally distributed.

### Results

Clinical data for the study subjects are presented in Table 1. Compared with both the EN and EH subjects, the YN subjects were characterized by having significantly lower age. The EH group showed significantly higher systolic BP with respect to both of the other two groups. No significant differences among the three groups were observed in all other variables. Fasting insulinemia was within the normal range even in hypertensive patients, with values never exceeding 20 $\mu$U/mL.

Mean glycemia, $G(t)$, and insulinemia, $I(t)$ levels as a function of time are shown in Fig. 1. Mean estimates of $S_P$, $S_G$, and $V$ are presented in Table 2. Mean percent coefficient of variation (CV\%) for all 21 subjects was 12.7\% for $S_P$, 18.8\% for $S_G$, and 3.1\% for $V$.

Both normotensive subject groups (YN and EN) showed no significant difference in $S_P$ estimates despite significantly different age, whereas in comparison with these groups, a significant reduction was evident in the EH

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### Table 2. Estimates of indexes of glucose metabolism

<table>
<thead>
<tr>
<th>Variable</th>
<th>YN group ($n = 7$)</th>
<th>EN group ($n = 6$)</th>
<th>EH group ($n = 8$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_P$ $10^{-4}$ min$^{-1}$/($\mu$U/mL)</td>
<td>4.63 ± 0.79</td>
<td>4.80 ± 0.41</td>
<td>2.20 ± 0.34*</td>
</tr>
<tr>
<td>$S_G$ $10^{-2}$ min$^{-1}$</td>
<td>2.51 ± 0.24*</td>
<td>1.51 ± 0.26</td>
<td>1.50 ± 0.17</td>
</tr>
<tr>
<td>$V$, dL/kg</td>
<td>1.83 ± 0.13</td>
<td>1.90 ± 0.05</td>
<td>2.08 ± 0.09</td>
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</table>

$S_P$ = fractional (ie, per unit distribution volume) insulin sensitivity; $S_G$ = fractional glucose effectiveness; $V$ = glucose distribution volume; other abbreviations as in Table 1.

Values are means $\pm$ SE. $S_P$, $S_G$, and $V$ showed normal distribution.

* Significant difference in the marked mean with respect to the other two (ANOVA followed by Scheffé test, $P < .05$). No significant differences among the three groups were found for $V$. 

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FIG. 1. Time course of glycemia (panel A) and insulinemia (panel B) during frequently sampled intravenous glucose tolerance test in the young normotensive (YN) group (open triangles), the elderly normotensive (EN) group (open circles), and the elderly hypertensive (EH) group (closed circles). Values are expressed as means $\pm$ SE for seven YN, six EN, and eight EH subjects.
group (Table 2). Mean estimates of $S_G$ were not significantly different in elderly subjects (EN and EH groups) irrespective of hypertension, whereas a significant increase was evident in the YN. No significant differences were found in the mean estimates of volume ($V$).

The YN group was characterized by having a significantly higher GEZI (Kruskal-Wallis nonparametric analysis of variance, $P < .05$) with respect to both the EN and EH groups. Mean GEZI to $S_G$ ratio was $0.84 \pm 0.03$ in the YN, $0.66 \pm 0.05$ in the EN, and $0.81 \pm 0.04$ in the EH (Fig. 2).

Discussion

In this study all participants were normoglycemic and did not show the presence of more than two of the remaining four ATP III criteria$^{22}$ for MS. Systolic BP was significantly higher in the EH group (Table 1), despite antihypertensive treatment. The finding of no significant differences in waist circumference, cholesterol, HDL cholesterol, trygliceridemia, glycemia, and insulinemia among the YN, EN, and EH groups is consistent with expectations based on our selection criteria. The BMI (kg/m$^2$) also showed no significant difference among the three groups; the means were $25.4 \pm 1.0$, $26.3 \pm 1.0$, and $26.5 \pm 1.3$ in the YN, EN, and EH groups, respectively. Thus the effects of this potential confounding factor were minimized.

Our comparative analysis of insulin sensitivity and glucose effectiveness (Table 2) was performed in terms of fractional (per unit distribution volume) indexes $S_f$ and $S_G$. Because the products $S_f \cdot V$ and $S_G \cdot V$ yield whole-body insulin sensitivity and glucose effectiveness analogous to those obtained from glucose clamps,$^{10,14,28}$ one may wonder whether these whole-body indexes show significant differences as those observed for the fractional indexes. Mean values of $S_f \cdot V$, expressed as $10^{-2} \cdot \text{min}^{-1} \cdot \text{dL/kg}$, were $4.56 \pm 0.44$, $2.85 \pm 0.45$, and $3.07 \pm 0.29$. Mean $S_f \cdot V$ showed a significant reduction ($P < .05$) in the EH group, whereas mean $S_G \cdot V$ showed a significantly higher ($P < .05$) value in the YN group. These results confirm that $V$ does not affect the trends of whole-body indexes compared with trends of fractional indexes.

Our finding of no significant difference in $S_f$ and $S_f \cdot V$ between elderly (EN) and young (YN) normotensive subjects is consistent with previous reports that insulin action measured with either a FSIGTT or a euglycemic–hyperinsulinemic clamp does not differ in elderly and young healthy subjects when adjusted for BMI or waist-to-hip ratio.$^{17-20}$

The significant reduction of $S_f$ and $S_f \cdot V$ found here in EH patients compared with EN subjects demonstrates the association of insulin resistance and hypertension in elderly subjects in the absence of MS. A significant reduction of insulin sensitivity in hypertension was previously observed by others in elderly$^7$ (61 ± 12 years), middle-aged$^8$ (46 ± 4 years), and young$^9$ (35 ± 2 years) nonobese and nondiabetic hypertensive patients compared with age-matched groups of control subjects. From these previous reports and according to our results we can infer that the association of insulin resistance and hypertension is independent of age.

Comparative analysis of our $S_G$ estimates from YN, EN and EH groups (Table 2) indicates that the elderly normotensive subjects (EN) have a glucose effectiveness deterioration induced by age, without influence of hypertension on the observed mean (EN versus EH). An association of older age with a significant reduction in $S_G$ was observed by others$^{18,19}$ in healthy subjects. Mean $S_G$ values reported in these previous studies for elderly and young subjects are not significantly different from the mean values found here for EN and YN groups, respectively (Table 2).

Glucose effectiveness was factored out into two components: $S_G$ at basal insulin (BIE) and $S_G$ at zero insulin (GEZI).$^{25}$ The $BIE$ and $GEZI$ indexes, although never extensively validated, have been reported in several investigations to provide further information on glucose effectiveness and suggest possible hypotheses without presuming to draw irrefutable conclusions.$^{18,19,25}$ In accordance with previous reports$^{18,19,25}$ the $BIE$ resulted a minor component of $S_G$. The $GEZI$ comprised 84% of $S_G$ in the YN, 66% in the EN and 81% in the EH group (Fig. 2), indicating that tissue glucose uptake independent of insulin (GEZI index) gives a major contribution to $S_G$. In absolute terms, the YN group was characterized by having a significantly higher GEZI compared with both the EN and EH groups. Thus the clinical importance of the reduced $S_G$ in EN and EH subjects in our study is supported by the finding that $S_G$ correlated with the glucose disappearance rate per se (GEZI). The deterioration of GEZI with age (that is, the reduction in the efficiency of glucose uptake by the whole
body) that is occurring independent of insulin is representative of tissue glucose resistance. A novel message derived from our analysis is that a deterioration of the efficiency of glucose uptake is induced by age irrespective of hypertension.

The relatively small size of our population samples might appear as a limitation of this study, and one may argue that some variables could have not shown any statistical differences between groups possibly because of a type II error. On the other hand, this study exercised special care in recruiting subjects to avoid MS as a confounder. Our restrictive selection reduced the number of patients eligible for the study but strengthened the reliability of results in terms of the link between alterations of $S_T$ and $S_G$ indexes with age and hypertension, irrespective of MS.

In conclusion, our study demonstrates that in the absence of MS, insulin sensitivity in normotensive subjects is independent of age; hypertension is associated with insulin resistance in elderly subjects, and age is a primary predictor of deterioration in glucose effectiveness, independent of hypertension.

References