# Differences Between the Tolbutamide-Boosted and the Insulin-Modified Minimal Model Protocols

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**The insulin-modified frequently sampled intravenous glucose tolerance test (FSIGTT) with minimal model analysis (MINMOD) was compared with the tolbutamide protocol and the glucose clamp in 35 nondiabetic subjects (age 38 ± 2 years [mean ± SE], BMI 27.2 ± 0.9 kg/m$^2$). Each subject underwent two FSIGTTs, one with tolbutamide (300 mg) and the other with insulin (0.03 U/kg) and a euglycemic hyperinsulinemic clamp (40 mU · m$^{-2}$ · min$^{-1}$). Insulin sensitivity was determined from each FSIGTT with MINMOD and from the clamp. Insulin sensitivity indexes ($S_I$) from the two FSIGTTs were significantly correlated ($r$ = 0.77, $P$ < 0.001), but $S_{I(insulin)}$ was 29 ± 4% lower than $S_{I(tolbutamide)}$. Both $S_{I(insulin)}$ and $S_{I(tolbutamide)}$ correlated significantly with $S_{I(clamp)}$ ($r$ = 0.70 and 0.71, $P$ < 0.001 for each). Expressed in the same units (dl/min per μU/ml), $S_{I(tolbutamide)}$ was on average 13 ± 6% lower than $S_{I(clamp)}$ (4.51 ± 0.40 vs. 5.36 ± 0.36 × 10$^{-2}$, $P$ = 0.009), whereas $S_{I(insulin)}$ was 44 ± 4% lower. $S_{G(tolbutamide)}$ and $S_{G(insulin)}$ were not different (1.88 ± 0.10 vs. 2.01 ± 0.09 × 10$^{-2}$ min$^{-1}$, $P$ = 0.167) and were significantly correlated ($r$ = 0.50, $P$ = 0.002). Thus, insulin sensitivity estimates from both protocols correlate significantly with each other and with the clamp. They are quantitatively discrepant, however, possibly due to differences in the route of insulin delivery, saturation of insulin action, and/or tolbutamide-induced proinsulin release. Data obtained from these two MINMOD protocols are not directly comparable, and the same protocol must be used in any single cross-sectional or longitudinal study.**
***Diabetes* 46:1167–1171, 1997**

Minimal model analysis (MINMOD) was introduced in 1979 by Bergman et al. (1) for determination of insulin sensitivity through computer modeling of glucose and insulin dynamics from the frequently sampled intravenous glucose tolerance test (FSIGTT). Due to a weak correlation between insulin sensitivity determined with this approach and that with the glucose clamp (2,3), a modification that entailed sequential injection of glucose and tolbutamide was adopted (4,5). This modification increased the accuracy of parameter estimates and gave measures of insulin sensitivity that correlated strongly with and were equivalent to those obtained with the glucose clamp (4,5). Several investigators (6–9) have used a protocol in which tolbutamide was replaced by insulin to be able to use MINMOD for determination of insulin sensitivity across the spectrum of glucose tolerance. We have recently shown that the insulin-modified FSIGTT gave insulin sensitivity estimates that correlated significantly with those from the glucose clamp but were on average 50% lower (10). This finding suggested differences in MINMOD insulin sensitivity estimates from the tolbutamide-boosted and the insulin-modified FSIGTTs. The present work was, therefore, undertaken to compare the two MINMOD protocols directly.

## RESEARCH DESIGN AND METHODS

**Subjects.** This study included 35 healthy nondiabetic men aged 38 ± 2 years (mean ± SE) with an average BMI of 27.2 ± 0.9 kg/m$^2$ (range 20.8–43.1). Women were not included because of possible changes in insulin sensitivity during the menstrual cycle (11). Subjects were admitted to the General Clinical Research Center of the University of Southern California and kept on a weight-maintaining diet throughout the period of the study. Each subject underwent two FSIGTTs, one with tolbutamide and another with insulin. The insulin sensitivity of each subject was calculated from each FSIGTT with the computer program MINMOD. In addition, every subject underwent a hyperinsulinemic euglycemic clamp. The different tests were performed 2–7 days apart in random sequence. The experimental protocol was approved by the Institutional Review Board of the University of Southern California, and all subjects gave informed consent.

**The FSIGTT.** After subjects fasted overnight for 10–12 h, intravenous cannulas were placed in both antecubital veins. A bolus of 50% glucose solution (0.3 g/kg) was injected over 1 min at time zero. Tolbutamide (300 mg; Upjohn, Kalamazoo, MI) or regular human insulin (0.03 U/kg; Novo Nordisk, Princeton, NJ) was given as an intravenous bolus at 20 min. Blood samples were collected at –15, –10, –5, –1, 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 50, 70, 100, 140, and 180 min for the determination of plasma glucose and insulin concentrations.

**The hyperinsulinemic glucose clamp.** The clamp was performed with a modification of the method of DeFronzo et al. (12). After patients fasted overnight for 10–12 h, an intravenous catheter was placed in an antecubital vein for infusion of insulin, glucose, and [3-$^3$H]glucose. Another catheter was placed retrograde in a dorsal vein of the contralateral hand for blood withdrawal. The hand was placed in a heating pad to arterialize the blood. A primed-continuous infusion of [3-$^3$H]glucose (25 μCi prime, 0.25 μCi/min continuous) was started at 0600. After 150 min, a primed-continuous infusion of regular human insulin (400 mU/m$^2$ prime, 40 mU · m$^{-2}$ · min$^{-1}$ continuous) was given for 3 h. Arterialized plasma glucose concentration was measured every 5 min. A variable infusion of 20% glucose was given to maintain plasma glucose concentration at the fasting level. A tracer quantity of [3-$^3$H]glucose (0.25 μCi/ml) was added to the 20% glucose solution to avoid the underestimation of hepatic glucose output (13). Blood samples were collected for determination of plasma glucose and insulin concentrations and [3-$^3$H]glucose-specific activity every 10 min during the 30 min preceding the insulin infusion (the basal period). Subsequently, samples were collected for these measurements at 20-min intervals until the last hour, when they were collected every 10 min. During the steady-state period (the last 40 min of insulin infusion), mean plasma glucose and insulin concentrations were 5.26 ± 0.05 mmol/l and 480 ± 18 pmol/l with average coefficients of variation of 1.2 ± 0.2 and 5.9 ± 0.8%, respectively.

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Received for publication 17 September 1996 and accepted in revised form 28 February 1997.

AUC, area under the curve; FSIGTT, frequently sampled intravenous glucose tolerance test; MINMOD, minimal model analysis; $R_a$, rate of endogenous appearance; $R_d$, rate of disappearance; $S_G$, glucose effectiveness; $S_I$, insulin sensitivity index.

**Biochemical analysis.** Plasma glucose concentration was measured by the glucose oxidase method with a Beckman glucose analyzer (Beckman Instruments, Fullerton, CA). Plasma insulin concentration was determined by radioimmunoassay (14) with an interassay coefficient of variation of 6–8%. Plasma C-peptide and proinsulin concentrations were measured by radioimmunoassay with reagents from Linco Research (St. Louis, MO) with interassay coefficients of variation of 5–9% and 7–10%, respectively. [3-$^3$H]glucose-specific activity was determined after deproteinization with barium hydroxide and zinc sulfate, as previously described (13). All samples from a single participant were measured in the same assay.

**Calculations**

***The minimal model.*** The insulin sensitivity index ($S_I$) was calculated from each FSIGTT with version 3.0 of the program MINMOD (copyright R.N. Bergman, 1986) (15). This program accepts as input the temporal pattern of plasma insulin and glucose and fits a simple model of insulin-dependent glucose utilization to the measured glucose pattern. The equations of the minimal model are as follows.

$$dG(t)/dt = -[p_1 + X(t)]G(t) + p_1G_b$$

$$dX(t)/dt = -p_2X(t) + p_3[I(t) - I_b]$$

where $G(t)$ and $I(t)$ are plasma glucose and insulin concentrations as a function of time, respectively, $X(t)$ is the time course of the insulin effect to increase the rate of glucose utilization, and $G_b$ and $I_b$ are basal plasma glucose and insulin levels. $p_1$, $p_2$, and $p_3$ are the model parameters estimated from nonlinear least-square fitting of the glucose data. Parameter $p_2$ is the disappearance rate constant of insulin from the remote (interstitium) compartment. Parameter $p_3$ characterizes the ability of insulin to cross the capillary endothelium and its subsequent effects to both increase peripheral glucose disposal and inhibit net hepatic glucose production. The ratio $p_3/p_2$ is an index of insulin sensitivity ($S_I$) and is the steady-state effect of an incremental change in plasma insulin to increase fractional glucose disappearance independent of glycemia and is expressed in $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$. The half-life of this effect is determined by $p_2$ ($T_{1/2} = LN\ (2)/p_2$); i.e., insulin action [$X$(t)] is proportional to insulin in the remote compartment, the time course of which is determined by $p_2$. Parameter $p_1$ is the fractional glucose disappearance rate at basal insulinemia independent of the increment in insulin and is a measure of glucose effectiveness ($S_G$).

***The glucose clamp.*** The rates of disappearance ($R_d$) and endogenous appearance ($R_a$) of glucose were calculated from [3-$^3$H]glucose-specific activity with a modification of Steele's equation (13,16) during the basal and steady-state periods. Insulin sensitivity from the clamp was expressed as $S_{I(clamp)}$ and $S_{IP(clamp)}$, as previously described (4,17). In brief, $S_{I(clamp)} = GINF/(\Delta I \cdot G)$ where $GINF$ is the steady-state total body glucose infusion rate in mg/min, $G$ is the steady-state plasma glucose concentration in mg/dl, and $\Delta I$ is the increment in plasma insulin (steady state insulin – basal insulin) in μU/ml. Because exogenous glucose infusion compensates for both the decrease in hepatic glucose output and the increase in glucose disposal caused by insulin, $S_{I(clamp)}$ is an index of the effect of insulin on total glucose metabolism corrected for steady-state plasma glucose level. In contrast, $S_{IP(clamp)} = \Delta R_d/(\Delta I \cdot G)$ where $\Delta R_d$ is the increment in total body glucose disposal (steady-state $R_d$ – basal $R_d$) in mg/min. Since $R_d$ at any insulin concentration represents the sum of insulin-mediated and non-insulin-mediated glucose disposal rates, $\Delta R_d$ is used in calculating $S_{IP(clamp)}$ to eliminate the latter component. The use of $\Delta R_d$ also excludes the effect of insulin on hepatic glucose production. $S_{IP(clamp)}$ is, therefore, an index of peripheral insulin sensitivity. $S_{I(clamp)}$ and $S_{IP(clamp)}$ are thus expressed as change in glucose clearance per unit change in plasma insulin level (dl/min per μU/ml).

***The minimal model versus the glucose clamp.*** To test whether MINMOD and the clamp estimates of insulin sensitivity were equivalent, $S_I$ was expressed in the same units as $S_{I(clamp)}$ and $S_{IP(clamp)}$. $S_I$ was, therefore, multiplied by the glucose volume of distribution ($V_D$). MINMOD assumes a single extracellular compartment for glucose distribution, the volume of which is equal to the injected glucose dose divided by the estimated increment in plasma glucose immediately following glucose injection, i.e., $V_D$ = glucose dose/($G_0 - G_b$) where $G_0$ is the postinjection glucose concentration and is calculated when glucose data are fitted to MINMOD (4).

***Portal insulin concentration.*** The insulin secretion rate was mathematically estimated from plasma C-peptide levels by deconvolution with a two-compartment model for C-peptide disappearance kinetics (18). The standard kinetic parameters for C-peptide clearance described by Van Cauter et al. (19) were used in the analysis. Plasma C-peptide levels between 2 and 10 min were pre-smoothed with a nonparametric smoothing algorithm (5-point moving average). Calculations were made with MLAB (Civilized Software, Bethesda, MD). Portal plasma insulin concentration was calculated as (insulin secretion rate/portal plasma flow) + systemic insulin level. Portal plasma flow was assumed to average 700 ml/min in a normal man (20); studies in dogs showed that portal plasma flow did not change during the FSIGTT (M. Hamilton-Wessler, R.N.B., unpublished observations).

**Statistical analysis.** Data are expressed as means ± SE. Statistical analyses were performed with programs of GraphPad Software (San Diego, CA; 21). Within-group comparisons were performed with the paired $t$ test or repeated measures ANOVA. Tukey's test was used for multiple comparisons. Linear regression and/or Pearson's product moment correlations were used to evaluate the agreement among measures of insulin sensitivity from MINMOD of the two FSIGTTs as well as those from the glucose clamp.

## RESULTS

Figure 1 shows plasma glucose and insulin concentrations during the tolbutamide-boosted and the insulin-modified FSIGTTs. Peak plasma insulin level was, on average, 2.2 times higher and occurred earlier after insulin than after tolbutamide injection (Table 1). Similarly, the insulin area under the curve in the period 20–180 min ($AUC_{20-180}$) was 21 ± 8% higher after insulin than after tolbutamide. The incremental glucose AUC was 12 ± 15% lower, however, during the tolbutamide protocol. Nadir plasma glucose concentration occurred at a median of 100 min during both tests but was significantly lower after tolbutamide administration. Calculated portal insulin concentration was higher during the tolbutamide protocol in the period 20–180 ($AUC_{20-180}$ : 79,350 vs. 57,560 pmol $\cdot$ l$^{-1}$ $\cdot$ 160 min; $P$ = 0.003; Fig. 2). Tolbutamide also caused the release of proinsulin, whose levels were approximately twofold higher than after insulin administration (AUC: 3,399 ± 404 vs. 2,140 ± 289 pmol $\cdot$ l$^{-1}$ $\cdot$ 180 min; Fig. 3).

$S_{I(insulin)}$ was 29 ± 4% lower than $S_{I(tolbutamide)}$, and the two indexes were significantly correlated ($r$ = 0.77, $P$ < 0.001; Fig. 4). When the two components of $S_I$ were examined separately, a higher value for parameter $p_2$ accounted for the difference between $S_{I(insulin)}$ and $S_{I(tolbutamide)}$, but there was no difference in $p_3$ (Table 1). Thus, the time course of insulin action [$X(t)$] was more prolonged after tolbutamide than after insulin administration (Fig. 5). $S_{G(tolbutamide)}$ and $S_{G(insulin)}$ were

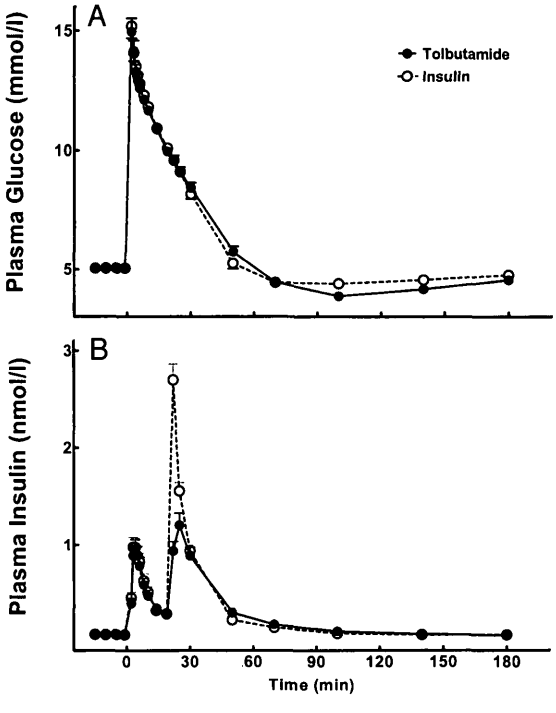


**FIG. 1. Changes in glucose (*A*) and insulin (*B*) concentrations during the tolbutamide-boosted and the insulin-modified FSIGTTs.**

TABLE 1
Insulin and glucose concentrations and minimal model parameters from the tolbutamide and insulin protocols

| | Tolbutamide | Insulin | *P* |
|---|---|---|---|
| Peak insulin concentration (pmol/l) | 1,260 ± 126 | 2,754 ± 150 | <0.001 |
| Insulin $AUC_{20-180}$ (pmol · $l^{-1}$ · 160 min) | 34,614 ± 3,810 | 41,502 ± 3,588 | 0.018 |
| Glucose AUC (mmol · $l^{-1}$ · 180 min) | 112.5 ± 12.8 | 141.4 ± 11.6 | 0.035 |
| Nadir glucose concentration (mmol/l) | 3.48 ± 0.11 | 3.91 ± 0.09 | <0.001 |
| $S_I \times 10^{-4}$ ($min^{-1}$ · $\mu U^{-1}$ · $ml^{-1}$) | 3.21 ± 0.29 | 2.09 ± 0.18 | <0.001 |
| $S_G \times 10^{-2}$ ($min^{-1}$) | 1.88 ± 0.10 | 2.01 ± 0.09 | 0.167 |
| $p_2 \times 10^{-2}$ ($min^{-1}$) | 3.05 ± 0.19 | 4.43 ± 0.44 | 0.002 |
| $p_3 \times 10^{-4}$ ($min^{-2}$ · $\mu U^{-1}$ · $ml^{-1}$) | 0.97 ± 0.10 | 1.01 ± 0.14 | 0.682 |

Data are means ± SE.

not different (1.88 ± 0.10 vs. 2.01 ± 0.09 × $10^{-2}$ $min^{-1}$, $P = 0.167$) and were significantly correlated ($r = 0.50$, $P = 0.002$).

Both $S_{I(insulin)}$ and $S_{I(tolbutamide)}$ correlated significantly with $S_{I(clamp)}$ ($r = 0.70$ and 0.71, $P < 0.001$ for each; Fig. 6). When MINMOD and clamp-based measures of insulin sensitivity were expressed in the same units (dl/min per μU/ml), $S_{I(tolbutamide)}$ was, on average, 13 ± 6% lower than $S_{I(clamp)}$ (4.51 ± 0.40 vs. 5.36 ± 0.36 × $10^{-2}$, $P = 0.009$), whereas $S_{I(insulin)}$ was 44 ± 4% lower (Fig. 7). Both $S_{I(tolbutamide)}$ and $S_{I(insulin)}$ correlated significantly with $S_{IP(clamp)}$ ($r = 0.74$ and 0.75, $P < 0.001$ for each). $S_{I(tolbutamide)}$ was 27 ± 10% higher than $S_{IP(clamp)}$ (4.51 ± 0.40 vs. 4.05 ± 0.34 × $10^{-2}$, $P = 0.028$), whereas $S_{I(insulin)}$ was 17 ± 7% lower.

## DISCUSSION

Our data show that both the tolbutamide and insulin MINMOD protocols give insulin sensitivity measures that correlate strongly with each other and with those from the glucose clamp in nondiabetic individuals. Nevertheless, substantial differences between the two protocols exist. When expressed in the same units, insulin sensitivity estimates from the tolbutamide protocol were only 13% lower than those calculated from the clamp. In contrast, insulin sensitivity measures from the insulin protocol were much lower than those from both the tolbutamide protocol and the clamp (Fig. 7). Thus, while the tolbutamide protocol gives a quantitative measure of insulin action nearly equivalent to that from the glucose clamp, which is "the gold standard," the insulin protocol provides only an index for insulin sensitivity. Consequently, data obtained from these two MINMOD protocols are not directly comparable, and the same protocol must be used in any single cross-sectional or longitudinal study.

The higher $S_I$ values from the tolbutamide protocol were associated with a more prolonged insulin action (Fig. 5). This prolongation is possibly due to higher portal insulin concentrations after tolbutamide than after insulin injection (Fig. 2) resulting in a more sustained effect on hepatic glucose output and/or uptake. Several studies (22–24) have questioned, however, the role of portal insulin release in regulating hepatic glucose production. That is, in clamp studies in which peripheral insulin levels were matched, intraportal and systemic insulin infusions were equipotent in suppressing hepatic glucose output (22–24). Nevertheless, these clamp experiments were done under steady-state conditions, and their results may not apply to the dynamic conditions of the FSIGTT. This possibility is supported by our finding that $S_{I(tolbutamide)}$ was only slightly lower than $S_{I(clamp)}$ and 27 ± 10% higher than $S_{IP(clamp)}$. While both $S_{I(tolbutamide)}$ and $S_{I(clamp)}$ reflect insulin's effect on total glucose metabolism, $S_{IP(clamp)}$ excludes the non-insulin-mediated glucose disposal as well as insulin's effect on hepatic glucose output (17). Thus, the higher portal insulin concentrations after tolbutamide injection could produce more sustained hepatic effects that result in higher insulin sensitivity estimates, especially as MINMOD lumps together and assumes the same time course for hepatic and peripheral insulin actions.

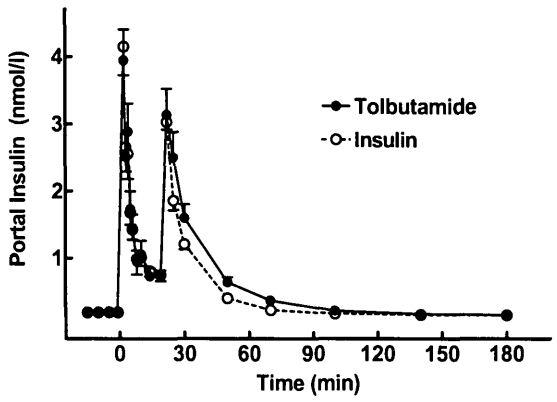


**FIG. 2. Calculated portal plasma insulin concentration during the tolbutamide and insulin protocols.**

Alternatively, saturation of insulin action or its transendothelial transport might explain the lower $S_I$ values from the insulin protocol. Prigeon et al. (25) suggested that saturation could occur during the insulin-modified FSIGTT with an insulin dose of 0.025 U/kg given as a bolus. Our findings do not support, however, the notion of saturation for several reasons. Plasma insulin concentrations during the tolbutamide and insulin protocols were almost superimposable except in the period of 19–30 min, when they were signifi-

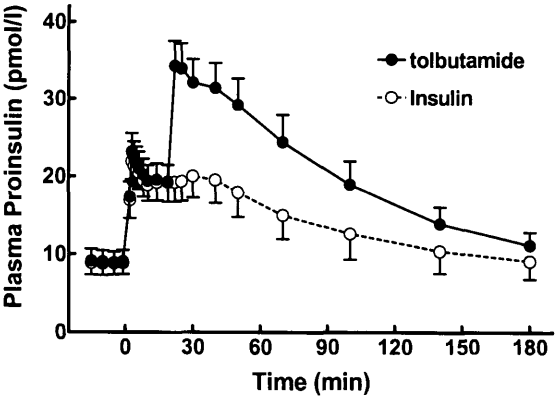


**FIG. 3. Plasma proinsulin concentration during the tolbutamide and insulin protocols.**

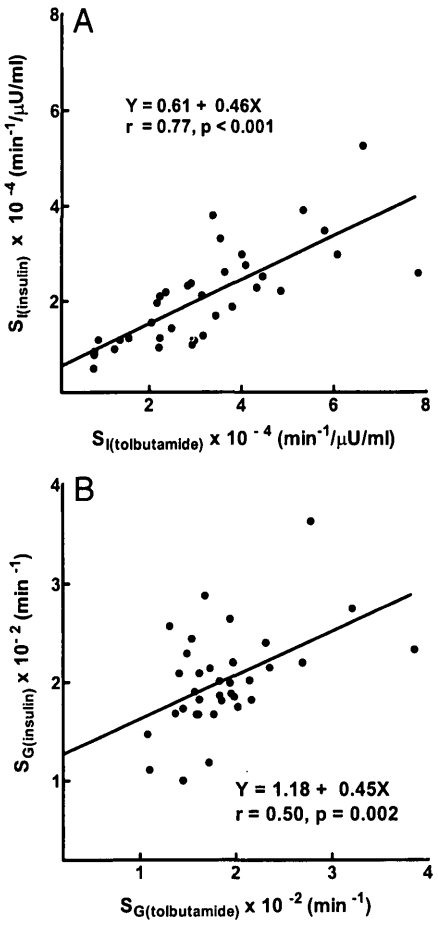


**FIG. 4. The relation between insulin sensitivity (*A*) and glucose effectiveness (*B*) indexes calculated from the tolbutamide and the insulin protocols.**

cantly higher after the insulin injection (Fig. 1). Further, the insulin level at which the half-maximal effect on glucose disposal occurs (600 pmol/l according to Freidenberg et al. [26]) was exceeded for similar periods during the two protocols. Finally, the lower $S_I$ values from the insulin protocol were

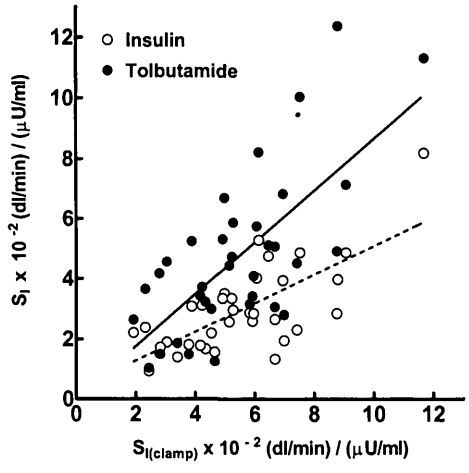


**FIG. 6. The relation between insulin sensitivity from the tolbutamide and the insulin protocols and $S_{I(clamp)}$. For $S_{I(tolbutamide)}$, $y$ = 0.036 + 0.86$x$; $r$ = 0.70, $P$ < 0.001. For $S_{I(insulin)}$, $y$ = 0.34 + 0.47$x$; $r$ = 0.71, $P$ < 0.001. The slopes of the two regression lines are significantly different ($P$ = 0.028).**

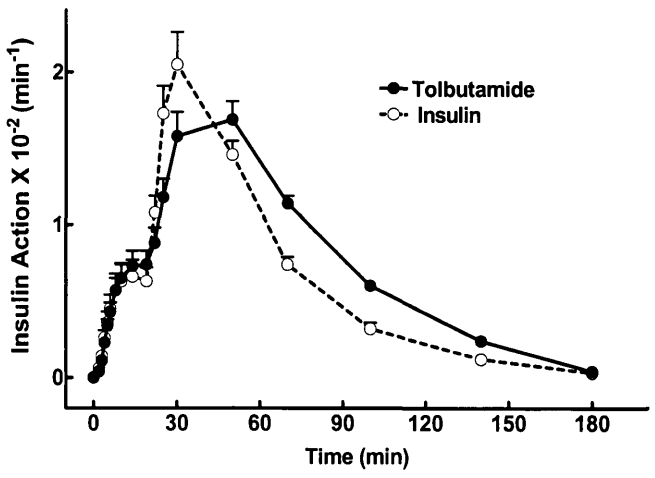


**FIG. 5. The time course of insulin action during the tolbutamide-boosted and the insulin-modified FSIGTTs.**

associated with a more rapid decay of insulin action (Fig. 5). If saturation were to occur after the insulin bolus, the time course of insulin action should have been at least similar to that observed after tolbutamide injection, i.e., with saturation, the higher insulin levels should not increase insulin action or result in a lower absolute effect. Further work is needed, however, to define the contribution of saturation to the difference between the two MINMOD protocols.

It is unlikely that tolbutamide itself contributed to the observed prolongation of insulin action. Although in vitro studies have suggested a direct tolbutamide action on glucose metabolism (27–29), a recent in vivo human study did not show such an effect (30). Nevertheless, tolbutamide-induced proinsulin release could play a role (Fig. 3). On a molar basis, proinsulin has only 5–10% of the biological potency of insulin (31,32). Proinsulin has, however, a lower metabolic clearance rate, a longer half-life, and a more prolonged effect on glucose metabolism than does insulin (33). Proinsulin may contribute, therefore, to the more sustained effects of insulin observed after tolbutamide administration.

There was no difference in $S_G$ estimates from the tolbutamide and insulin protocols. This result was not surprising,

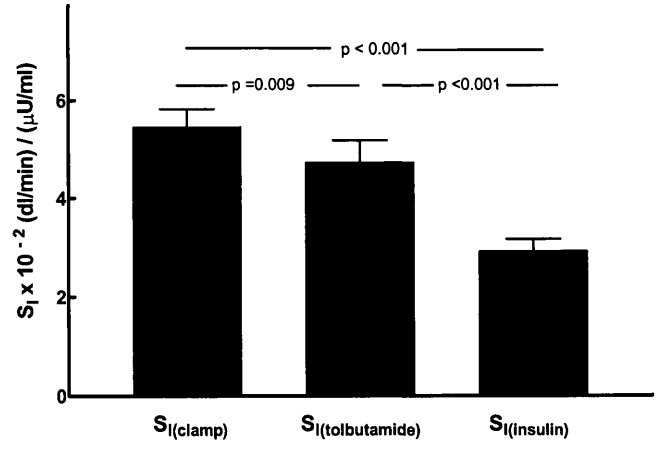


**FIG. 7. Insulin sensitivity indexes from the clamp and the two FSIGTTs expressed in the same units.**

since $S_G$ is estimated mainly from the glucose data in the period of 8–20 min (34), i.e., before tolbutamide or insulin administration. The correlation between $S_{G(tolbutamide)}$ and $S_{G(insulin)}$ was, however, relatively weak.

In conclusion, substantial differences between the insulin and tolbutamide protocols exist. The tolbutamide protocol gives insulin sensitivity measures nearly equivalent to those from the clamp, while the insulin protocol yields considerably lower $S_I$ values. This quantitative discrepancy is possibly due to differences in the route of insulin delivery, saturation of insulin action, and/or tolbutamide-induced proinsulin release. Data obtained from these two MINMOD protocols are not directly comparable, and the same protocol must be used in any single cross-sectional or longitudinal study.

## ACKNOWLEDGMENTS

Supported in part by National Institutes of Health Grants HL-47902 (The Insulin Resistance Atherosclerosis Study), DK-27619, and DK-29867 and the General Clinical Research Centers Program (NCRR GCRC MO1 RR-43) and by a grant from the American Diabetes Association.

We thank the staff and the nurses of the General Clinical Research Center at the University of Southern California for their excellent help in performing the study.

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