Reduced Sample Number for Calculation of Insulin Sensitivity and Glucose Effectiveness From the Minimal Model

Suitability for Use in Population Studies

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The FSIGT has been extensively applied to the minimal model of glucose kinetics to obtain noninvasive measures of S_I. The protocol has been modified by the addition of a bolus tolbutamide or insulin injection 20 min after glucose. Although the modified protocol has improved the S_I estimate, the method still requires a relatively large number of samples (n = 30). To reduce the total number of samples, we choose a sample schedule that minimizes the variance of the parameter estimates and the error in reconstructing the plasma insulin profile. With data from 10 subjects (BMI 30 ± 7 kg/m^2; S_I 0.9–10.2 × 10^{-4} $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$), a schedule consisting of 12 samples (0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 90, and 180 min) was obtained. Estimates of S_I obtained from the reduced sampling schedule were then compared with those obtained with the full sampling schedule. In all 10 individuals, the S_I estimates were almost identical. A second, much larger data base consisting of 118 modified FSIGTs performed in 87 subjects (67 men, 20 women; BMI from 19.6 to 40 kg/m^2 for men and 26.7 to 52.5 for women; S_I from 0.35 to 14.1 × 10^{-4} $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$) was then used to independently assess the efficacy of the reduced sampling protocol. For this data base, the correlation between S_I, which was calculated from the full versus the reduced sampling schedule, was 0.95. The mean relative deviation was −1.5% (not significantly different from zero), and the SD of the relative deviation was 20.2%. Relative deviation was defined as the percentage of difference between S_I calculated from the full sample protocol and S_I calculated from the reduced sample protocol. Thus, the reduced sampling schedule provides an unbiased estimate of a population's S_I, and an individual estimate is generally within 20% of that obtained with the full sampling schedule. A similar analysis of S_G showed that this parameter was equally well determined from the reduced compared with the full sample schedule. *Diabetes* 42:250–56, 1993

Insulin resistance is a major risk factor for the development of NIDDM (1). Insulin resistance has been demonstrated in several populations at substantially higher risk for NIDDM than Caucasians (2,3) and has been closely associated with diseases of the cardiovascular system, including atherosclerosis (4,5) and hypertension (6). Thus, insulin resistance is emerging as a major risk factor in a spectrum of diseases.

Despite its importance, practical methods for assessment of S_I in populations are not yet available. The widely accepted euglycemic glucose clamp has contributed greatly to the understanding of the mechanisms of insulin resistance in vivo; however, it is both labor intensive and costly. Thus, the use of clamps in large-scale clinical or epidemiological studies has been limited. The minimal-model approach for the estimation of S_I has overcome some of these difficulties and has been used for several recent epidemiologically based studies (7,8). However, this method still requires many blood samples to be collected (~30).

Originally, the minimal model was used in conjunction with the FSIGT, in which insulin and glucose dynamics were simultaneously obtained in response to a bolus of glucose. A modified FSIGT was later introduced (9) in which an additional tolbutamide or insulin injection was administered 20 min after the glucose bolus. The modified test was then reported to be more accurate than the original protocol and provided equivalent values of S_I to

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FSIGT, frequently sampled intravenous glucose tolerance test; S_I, insulin sensitivity; BMI, body mass index; S_G, glucose effectiveness; NIDDM, non-insulin-dependent diabetes mellitus; RIA, radioimmunoassay; IVGTT, intravenous glucose tolerance test; CV, coefficient of variation.

those obtained from the euglycemic clamp (10). All reference to the FSIGT in this paper refers to the tolbutamide-modified version, unless otherwise stated.

Several reports have examined the possibility of optimizing the FSIGT protocol (11,12); however, these methods have required a model of insulin secretion. In general, no such model exists for the modified FSIGT. Thus, no reduced sampling schedule for this modified protocol has been proposed.

In this study, we reduced the sampling schedule to 12 blood samples collected over 180 min. We compared S_I and S_G from the reduced protocol with the same parameters calculated from the full 30-sample protocol. Results indicate that the 12-sample approach is overall equivalent to the 30-sample protocol and is of sufficient precision, accuracy, and simplicity to be used in population studies.

RESEARCH DESIGN AND METHODS

Data base. Two previously published data bases were used in this study. One data base, consisting of 10 subjects in whom FSIGTs were performed, was used to define a reduced sample protocol, whereas a second data base, consisting of 87 subjects in whom a total of 118 FSIGT studies had been performed, was used to evaluate the reduced sample protocol. All FSIGTs were performed with tolbutamide.

The first data set (10) was published in a study relating S_I from the minimal model with an analogous parameter calculated from the glucose clamp. The study group consisted of 9 men and 1 woman, with a mean ± SD age of 38.1 ± 10.0 yr; variable body weight (92.9 ± 26.0 kg, range 65–140 kg); and variable BMI (30.0 ± 7.18 kg/m^2, range 21–41 kg/m^2). The FSIGT was performed after an overnight fast as follows: a glucose injection (0.3 g/kg) was administered at t = 0 min followed by a tolbutamide injection (300 mg for BMI <30 kg/m^2, 500 mg for BMI >30 kg/m^2, Orinase, Upjohn, Kalamazoo, MI) at t = 20 min. Thirty blood samples were obtained corresponding to the following sample times: −20, −15, −5, −1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 25, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160, and 180 min.

The second data base consisted of 118 FSIGTs performed in 67 male and 20 female subjects. These studies were performed at the University of Washington for various purposes (13–16). Ages ranged from 19 to 82 yr in men and 25 to 43 yr in women; BMI ranged from 19.6 to 40 kg/m^2 (men) and 26.7 to 52.5 kg/m^2 (women). Thus, this population ranged widely in age and adiposity. Subjects were studied at least once, and a few subjects were studied as many as three times. Dosages used for all tests were 11.4 g/m^2 glucose and 125 mg/m^2 tolbutamide. Thirty-three samples were taken in these tests: −20, −15, −5, −1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min. This second data set was used to evaluate the efficacy of the reduced sampling protocol. That is, minimal-model parameters obtained from the reduced sample protocol were compared with those that had originally been determined with the full sample approach.

Sample handling. As described previously (10), blood samples were collected in chilled tubes and centrifuged soon afterwards so that the plasma could be decanted and frozen for later assay of glucose and insulin. Glucose was assayed with the glucose oxidase method, and insulin was measured with RIA.

Data analysis. The minimal-model method was used to provide quantitative estimates of S_I and S_G, the latter being the effect of glucose itself, independent of an increase in insulin, to increase net glucose utilization. The minimal-model equations are as follows:

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_1G_b$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3(I(t) - I_b)$$

where t is time, G(t) and I(t) are plasma glucose and insulin concentrations, X(t) is insulin effect, and G_b and I_b are basal (180 min) glucose and insulin concentrations. These equations are based on three key physiological assumptions (17): *1*) glucose inhibits its own production and increases its own utilization in proportion to its concentration in plasma; *2*) insulin synergizes these effects of glucose; and *3*) insulin effect is proportional to its concentration in a remote compartment. The remote compartment has previously been hypothesized to be interstitial insulin (18).

S_I is defined as the effect of an incremental change in insulin to increase the fractional glucose disappearance after a glucose injection, independent of the plasma glucose level. By this definition (also see ref. 10 for relation to the glucose clamp), $S_I = P_3/P_2$. The effect of glucose per se on glucose disappearance at basal insulin, independent of an increase in insulin, is $S_G = p_1$.

The application of the minimal model for estimating these parameters has previously been documented in detail (19). Briefly, nonlinear least-squares estimation based on the Marquardt algorithm (20,21) is used to estimate the parameters of the model (p_1, p_2, p_3, and the initial condition for glucose G(0)). The insulin time course I(t) is treated as an independent variable (the input to the model). Choice of sampling times is critical to the accuracy and reliability of this procedure. Poorly chosen sample times would result in poorly reconstructed insulin profiles and/or measurements of glucose that subject the parameter estimates to a high degree of variability.

Reduction of the sampling schedule. Although the detailed approach to defining a reduced sampling schedule will not be described herein, the process may be summarized. The overall goal in choosing a sampling schedule was to obtain equivalent accurate parameter estimates with a reduced number of samples. It can be shown on theoretical grounds that if the insulin profile is known a priori, only four samples (equal to the number of parameters to be identified) would be required to estimate p_1, p_2, p_3, and G(0). Further, the times at which these samples are obtained can be chosen such that the parameter estimates are least sensitive to errors in the measured glucose profile (i.e., those samples in which

glucose has the greatest influence in determining the parameters). Optimally determining these four sampling times involves maximizing the determinant of Fisher's information matrix (12) and results in four different sample times for each individual. Clearly, four sample times are not sufficient to adequately describe an insulin profile consisting of multiple peaks (one after the glucose injection and one after the tolbutamide injection). Thus, additional samples were added to the chosen four to insure adequate reconstruction of the insulin profile. The approach used was largely empirical. Because of the importance of first-phase insulin secretion, not only as a component of total insulin secreted during the IVGTT, but also as a possible early indicator of β-cell dysfunction (22,23), it was necessary to resolve it. For this purpose, samples at 0, 2, 4, and 8 min were included. Samples immediately before and after the tolbutamide/insulin injection (19 and 22 min) were also included, and these samples were added to those samples found most frequently to minimize parameter variance (30, 50, 90, and 180 min). Two further samples (40 and 70 min) were empirically found to reduce the error in reconstructing the insulin profile after the tolbutamide injection. Thus, the reduced 12-sample schedule to be evaluated was 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 90, and 180 min.

Minimal-model parameters for both the full and reduced sampling schedules, were estimated with the computer program MLAB (Civilized Software, Bethesda, MD) on an IBM-compatible 80386-chip computer. Statistics were also performed with MLAB.

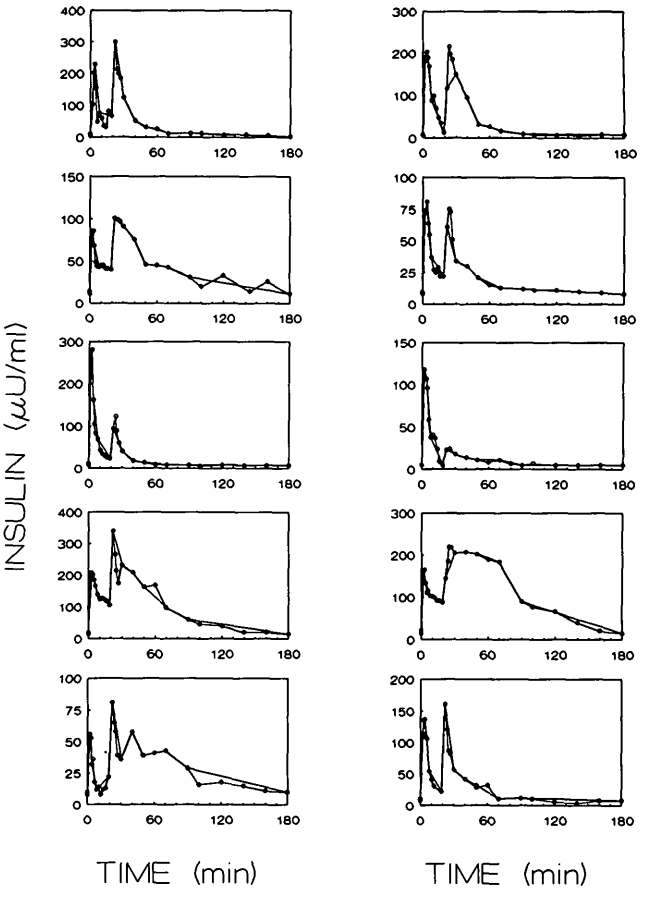

FIG. 1. Insulin reconstruction with 12 samples obtained from minimizing both insulin reconstruction errors and variance of the parameter estimates.

RESULTS

Figure 1 shows that the 12-sample schedule reproduced the plasma insulin pattern for 10 individual cases with reasonable accuracy. To evaluate whether this schedule would accurately predict S_I, we calculated S_I with the reduced sampling schedule and compared it with values emanating from the complete FSIGT schedule (Table 1). In all 10 cases, the values were almost identical (mean S_I determined from the reduced schedule not different from mean S_I determined from the full schedule, $P = 0.46$). Although the tendency was for the CV in individual estimates to increase, the values obtained were still reasonable (CV <20%).

It is not surprising that S_I changes little when the data base used to design the sampling schedule is the same as that used to evaluate it. Therefore, we examined the ability to calculate S_I, with the reduced 12-sample schedule, in a completely independent data set. This data base (see METHODS) consisted of 118 tolbutamide-modified FSIGTs performed on 87 individuals in whom a full (30-sample) modified FSIGT had been performed. S_I for this group, as obtained from the 30-sample protocol, varied from 0.35 to 14.1 × 10^{-4} $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$ (Fig. 2); although the distribution was not normal, the average value was 3.5 ± 0.76 (mean ± SE).

Reduction in sample number from 30 to 12 did not have a significant impact on the calculated value of S_I (Fig. 3). The difference between the full-schedule and reduced-schedule S_I for individual tests was typically <20% (Fig. 3*A*, SD 20.5%). The approximate symmetry of Fig. 3*A* indicates that the reduced sample schedule did not bias the calculated values of S_I (average error of −1.5% not different from 0; $P = 0.55$). The correlation between S_I calculated with the full FSIGT (30 samples) and the reduced (12 samples) version is shown in Fig. 3*B*, where a correlation coefficient of $r = 0.95$ was obtained (24). The slope and intercept of this correlation are near 1 and 0, respectively (slope = 1.1 and intercept = −0.22), although significance testing was not done because both the full sample determination of S_I and reduced sample determination are random variables (both have errors).

S_G was also well estimated by this procedure. Figure 4*A* demonstrates that the reduced sample determination of S_G was generally within 19% of that obtained from the full sample protocol (SD of the relative deviation = 18.7%). The mean relative deviation was −2.1% (not significantly different from 0, $P = 0.27$), indicating that the estimate is unbiased. Figure 4*B* indicates a minor loss in the ability to estimate this parameter for a given individual ($r = 0.85$, slope = 0.82, intercept = 0.34). However, it should be noted that although the correlation coefficient is somewhat less for S_G than for S_I ($r = 0.95$ for S_I vs. 0.85 for S_G), S_G varies within the population less than S_I, leading one to expect a lower correlation for this

TABLE 1
S_I estimates obtained from full (30-sample) and reduced (12-sample) protocols

Subject	Full sample (n = 30)		Reduced sample (n = 12)		Relative difference
	S_I*	CV (%)	S_I*	CV (%)	
1	7.7	3.6	7.2	6.6	0.064
2	6.7	1.7	6.8	2.5	−0.014
3	5.7	10.6	6.0	15.0	−0.052
4	4.4	1.9	4.2	3.5	0.045
5	2.5	2.4	2.7	3.0	−0.080
6	2.4	2.6	2.2	4.5	0.083
7	2.0	3.3	2.1	5.3	−0.050
8	2.0	4.4	1.7	7.7	0.150
9	0.9	1.7	0.8	2.8	0.111
10	0.7	3.2	0.7	4.8	0.0
Mean ± SD	3.50 ± 2.50	3.54 ± 2.63	3.44 ± 2.45	5.57 ± 3.72	0.025 ± 0.076

CV is expressed as 100 × (fractional SD of S_I)/S_1. Relative difference is calculated as $(S_{I(30)} - S_{I(12)})/S_{I(30)}$. Mean relative difference was not different from 0 (P = 0.32).

parameter (i.e., in the extreme, if S_G did not vary within the population at all, the expected correlation in Fig. 4*B* would be 0). Finally, the distributions of S_I and S_G within the population are shown for both the full and reduced sample protocols (Fig. 5). Distributions obtained with the reduced sample protocol are virtually identical to those obtained with the full sample protocol (although distributions obtained in this way are not independent, χ^2 tests between the full and the reduced sample distributions indicated that they were not statistically different: distribution of S_I [full versus reduced] not different, P = 0.47; distribution of S_G [full versus reduced] not different, P = 0.74).

DISCUSSION

It has become clear that epidemiological studies of S_I require large numbers of subjects. Several groups reported a wide variation of S_I in subjects with normal glucose tolerance (23,25,26), leading to the requirement of more subjects to obtain a precise estimate of the population mean. Several groups have data suggesting that S_I may have meaning regarding the genetic propensity for developing NIDDM. That is, Lillioja et al. (27) have reported that the degree of insulin resistance in Pima Indians is family determined, Martin et al. (28) have found familial clustering of S_I, and Kemnitz et al. (29), in collaboration with our group, have data indicating that S_I may be inherited in rhesus monkeys. The last finding is particularly meaningful when one considers recent data that in normal subjects at high risk for NIDDM (two NIDDM parents), low S_I is highly predictive for the even-

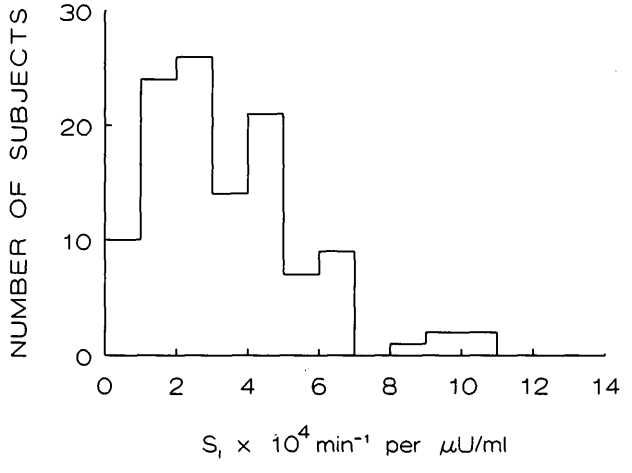

FIG. 2. Distribution of S_I values (histogram) from data set 2 (see text).

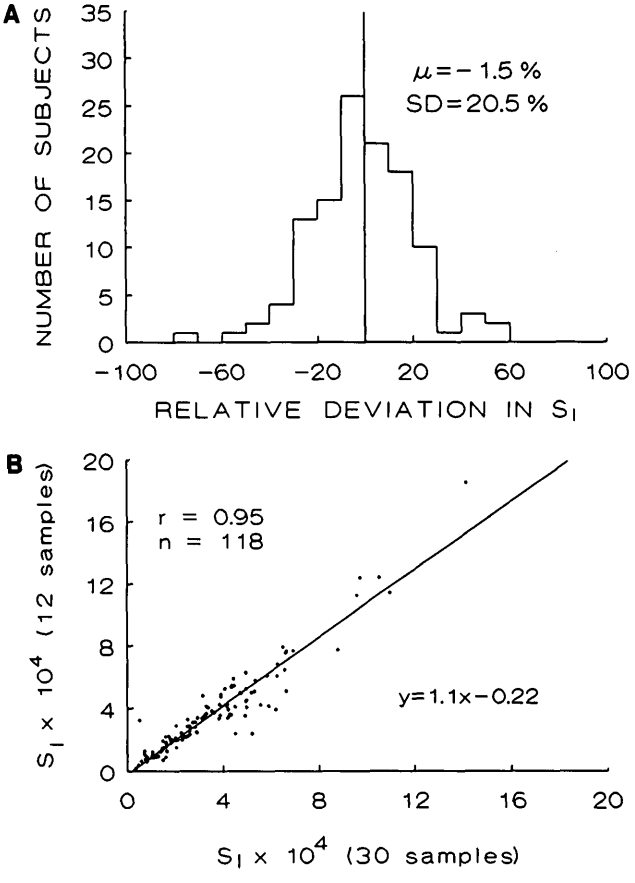

FIG. 3. *A*: Histogram of relative deviations in S_I determined from the full and reduced schedules (percentage of difference). *B*: Correlation of S_I obtained from the full and reduced sample schedules (24).

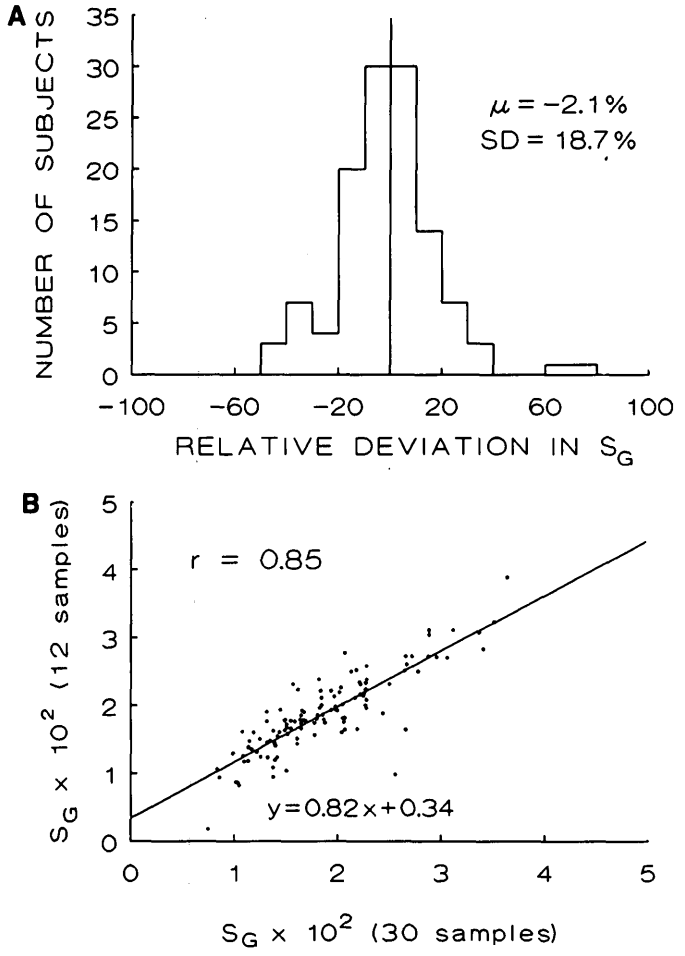

FIG. 4. *A*: Histogram of relative deviations in S_G determined from full and reduced schedules (percent difference). *B*: Correlation of S_G obtained from full and reduced sample schedules.

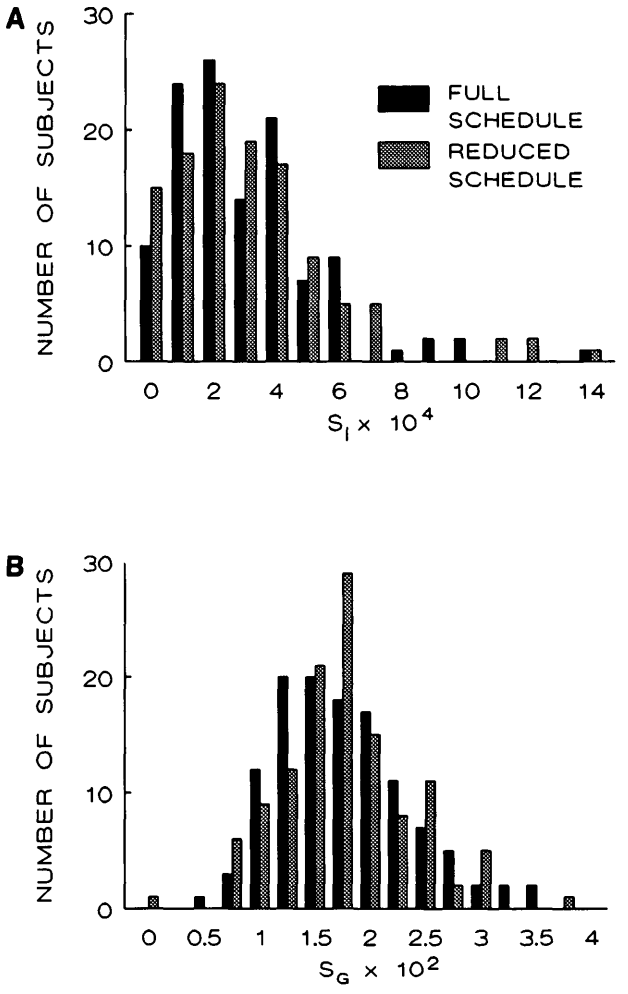

FIG. 5. Estimated distributions for S_I (*A*) and S_G (*B*) obtained with full (■) and reduced (▩) sample schedules with data set 2 (see text).

tual development of NIDDM (7). Thus, the degree of insulin resistance in individual subjects may be a predictor of development of NIDDM, and it will be important to have straightforward methods for assessment of insulin resistance even in normal subjects.

An additional need for the convenient assessment of S_I in vivo arises from recent epidemiological data relating insulin resistance to various chronic conditions other than NIDDM, including atherosclerosis, cardiovascular disease, and hypertension (6). Such an association has resulted in several calls for studies of the importance of insulin resistance as a risk factor in populations of >1000 volunteers. Clearly, the glucose clamp is not a feasible procedure for sensitivity measurements in such large groups, and more practical methods are required.

The minimal-model approach has been used to assess S_I in patient groups as large as 180 (8). This test, as currently practiced (30), requires injections of glucose and tolbutamide (or insulin) and the collection of 30 blood samples over a 3-h interval. The method is advantageous in that it provides independent assessment of S_I and S_G and allows for simultaneous assessment of β-cell function in terms of the first-phase plasma insulin response and intravenous glucose tolerance in terms of the 10- to 19-min K_G value. Although the minimal-model approach is simpler than the glucose clamp, the cost can be steep, and rapid sampling of blood over a 3-h period can be challenging. Thus, in this study, we attempted to reduce the number of samples, with the goal of reducing the cost in money and labor of S_I measurement.

Optimal sampling theory is well established and has been widely applied in biology and pharmacokinetics (11,12). By this theory, optimal sample times are selected as times when the pattern of the predicted variable (glucose) is most affected by changes in the model parameters. In fact, Cobelli et al. (12) applied such theory to the standard (unmodified) FSIGT. In their studies, they assumed that the plasma insulin pattern after glucose injection could be accurately described by the so-called minimal model of insulin secretion. This approach cannot be applied to the modified FSIGT because no accepted model exists for the insulin response to glucose and a second secretagogue (i.e., tolbutamide). Thus, we were unable to assume any mathematical construct for the insulin response per se. Without a model, it is not possible to assume that the stimulus or input to the model (plasma insulin in this case) is known at all times. We were therefore limited by the constraint that the input to

the model would only be known at the times that samples were collected, because the plasma insulin pattern is only revealed a posteriori when measurements are made after the test is complete. Thus, our procedure was altered to allow accurate estimation of the minimal-model values and yield an interpolated plasma insulin pattern (Fig. 1) that closely approximated the actual pattern in plasma. This latter criterion included reconstruction of the first phase of plasma insulin, which may be an early indicator of eventual β-cell failure (22,23).

The 12-sample protocol combines samples that allow for an accurate calculation of S_I from the glucose pattern with samples that yield an accurate interpolated plasma insulin pattern. This protocol uses samples at 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 90, and 180 min. When the protocol was applied to a large population of subjects with variable S_I, little change was observed in S_I measurements compared with the full 30-sample protocol. In fact, individual S_I values calculated from 118 FSIGTs with the 12-sample protocol were within 20% of the values obtained from the full sample protocol 67% of the time, and the distribution within the population was identical for the full and reduced sampling schedules (Fig. 5).

The reduced sampling schedule introduced in this study was primarily concerned with attaining an accurate assessment of S_I. However, other model parameters are also estimated from this protocol. In particular, the S_G parameter is emerging as an important metabolic parameter (31). As seen in Fig. 4, the reduced sample protocol also yields a reasonable estimate for this parameter (percentage of deviation between full and reduced sampling schedules generally <19% with mean error not different from 0, $P = 0.27$). Figure 4*B* indicates a minor loss in the ability to estimate this parameter for a given individual ($r = 0.85$, slope = 0.82, intercept = 0.34), although the loss in fidelity is apparently greater than for S_I itself. However, it should be noted that S_G tends to vary within a population less than S_I does (variance in S_I is approximately fourfold higher than the variance in S_G; Figs. 3*B* and 4*B*). Thus, in studies in which S_G is the primary focus and a limited number of subjects are to be studied, the full sample protocol may be preferable. Further, studies focusing on first-phase insulin secretion or FSIGT-derived glucose tolerance may wish to include a sample at 10 min to remain consistent with accepted definitions (first-phase insulin secretion is often taken as the incremental response of the insulin profile for the first 10 min, and K_G is taken as the slope of the natural log of glucose versus time between 10 and 19 min). Also, in this study, the insulin response to the tolbutamide injection peaked at 22 min; if the tolbutamide is administered more slowly, the 22-min sample may be changed to 24 min, or samples at both 22 and 24 min may be taken.

Welch et al. (32) have introduced a separate protocol for use in diabetic patients that uses insulin injection in place of tolbutamide. This protocol has yet to be fully validated in diabetic people, in part because of a divergence in opinion over how the glucose clamp should be performed (33–35); however for nondiabetic subjects, the reduced sample schedule presented herein works well. With data obtained from Lovejoy et al. (36), some of which has been published previously, 21 nondiabetic subjects in whom full sample insulin FSIGTs had been performed were reidentified with the reduced sample schedule. In these subjects, S_I ranged from 2.1 to 18.2×10^{-4} $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$ whereas S_G ranged from 0.26 to 3.9×10^{-2} $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$. The correlation of S_I determined with a full sample protocol with that obtained from the 12-sample protocol yielded $r = 0.99$, whereas that obtained for S_G was 0.94 (data not shown). Thus, in nondiabetic subjects, we conclude that the reduced sampling schedule works equally well for the insulin-injection protocol.

In summary, the tolbutamide-modified FSIGT protocol, used to measure S_I in humans, was reduced in sample number from 30 to 12 samples to be collected over 3 h. The reduced protocol yields an accurate, unbiased assessment of S_I, with the value calculated usually deviating no more than 20% from the value calculated with the full protocol. The reduced protocol also provides an unbiased assessment of S_G. We suggest that this reduced protocol is of sufficient precision, accuracy, and simplicity to be used in population studies of insulin resistance.

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