Reduced Sampling Protocols in Estimation of Insulin Sensitivity and Glucose Effectiveness Using the Minimal Model in NIDDM

PHILIP A. COATES, RICHARD L. OLLERTON, STEPHEN D. LUZIO, IKRAM S. ISMAIL, AND DAVID R. OWENS

Recent work in healthy subjects, the aged, and subjects with gestational diabetes or drug-induced insulin resistance using minimal model analysis of the tolbutamide-modified frequently sampled intravenous glucose tolerance test suggested that a reduced sampling regimen of 12 time points produced unbiased and generally acceptable estimates of insulin sensitivity (S_I) and glucose effectiveness (S_G) compared with a full sampling schedule of 30 time points. We have used data from 26 insulin-modified frequently sampled intravenous glucose tolerance tests in 21 subjects with NIDDM to derive and compare estimates of S_I and S_G from the full sampling schedule ($S_{I(30)}$, $S_{G(30)}$) with those estimated from the suggested 12 time points ($S_{I(12)}$, $S_{G(12)}$) and those estimated with the addition of a 25-min time point ($S_{I(13)}$, $S_{G(13)}$). Percentage relative errors were calculated relative to the corresponding 30 time-point values. A statistically significant bias of 15% (97% confidence interval from 7.4 to 25.6%, interquartile range 25%) was introduced by the estimation of $S_{I(12)}$ but not $S_{I(13)}$ (1%, 97% confidence interval from −9.4 to 9.3%, interquartile range 21%). Results for $S_{G(12)}$ (−12%, 97% confidence interval from −46.7 to 1.2%, interquartile range 49%) and $S_{G(13)}$ (−5%, 97% confidence interval from −27.8 to 6.8%, interquartile range 37%) were statistically equivocal. The precision of estimation of $S_{I(12)}$, $S_{G(12)}$, and $S_{G(13)}$ measured by the interquartile range of the percentage relative errors was poor. The precision of determination measured by the median minimal model coefficient of variation was 18, 29, and 27% for $S_{I(30)}$, $S_{I(12)}$, and $S_{I(13)}$ and 9, 11, and 11% for $S_{G(30)}$, $S_{G(12)}$, and $S_{G(13)}$, respectively. Thus, the application of minimal model analysis to the 12 time-point protocol of the insulin-modified IVGTT for the estimation of S_I and S_G in NIDDM may necessitate an inordinately large number of subjects. Although the 13 time-point protocol may be more acceptable for the assessment of S_I in population studies, we recommend retention of the full sampling schedule where feasible. *Diabetes* 42:1635–41, 1993

The minimal model analysis of the FSIVGTT devised by Bergman et al. (1) derives estimates of both insulin-mediated glucose disposal (S_I) and the ability of glucose to restore its own concentration independent of a change in insulin regardless of the prevailing glycemia (S_G). This approach has been used to examine alterations in S_I in subjects with a variety of physiological and pathophysiological states such as in the elderly (2), normotensive subjects with a family history of hypertension (3), obese subjects (4), and those receiving anabolic steroids (5) or oral contraceptive agents (6). The euglycemic-hyperinsulinemic clamp is, however, widely regarded as a reference method for this type of investigation (7). Theoretical considerations aside, the clamp technique is labor intensive for both subject and investigator and as such is unsuitable for widespread use in the investigation of defects of insulin sensitivity. In comparison, minimal model analysis of the FSIVGTT is a relatively simple procedure to carry out (8). For NIDDM, where reduced S_I is of major pathophysiological significance (9), its use has been restricted by the requirement of the model for an adequate insulin response during the test procedure. Additionally, the number of blood samples required (usually ~30) is high.

From the Diabetes Research Unit, University of Wales College of Medicine, Cardiff, Wales; and Department of Mathematics, Faculty of Science and Technology, University of Western Sydney, Nepean, Sydney, Australia.

Address correspondence and reprint requests to Dr. David R. Owens, University of Wales College of Medicine, Diabetes Research Unit, Department of Medicine, Heath Park, Cardiff CF4 4XN, Wales.

Received for publication 25 March 1993 and accepted in revised form 17 June 1993.

NIDDM, non-insulin-dependent diabetes mellitus; IVGTT, intravenous glucose tolerance test; FSIVGTT, frequently sampled intravenous glucose tolerance test; S_I, insulin sensitivity; S_G, glucose effectiveness; MINMOD, minimal model; CV, coefficient of variation; %RE, percentage relative error; IQR, interquartile range; CI, confidence interval; HOMA, homeostasis model assessment; CIGMA, continuous infusion of glucose with model assessment; SITT, short insulin tolerance test; BSA, body surface area; BMI, body mass index.

TABLE 1
Subject characteristics at initial FSIVGTT

M/F Age (yr)	56.4 ± 8.8 (39–74)
HbA_1 (%)	10.4 ± 2.28 (7.1–14.0)
BMI (kg/m^2)	28.38 ± 3.75 (21.8–34.4)
Fasting plasma glucose (mM)	11.45 ± 3.40 (6.3–19.1)

Data are means ± SD (range).

Modification of the FSIVGTT technique with the use of intravenous tolbutamide 20 min after the glucose bolus produces a substantial peak plasma concentration of insulin in normal subjects aiding both the disposal of glucose and the accuracy of subsequent modeling. Reasonable agreement has been claimed between estimates of S_I derived from the tolbutamide-modified FSIVGTT and the euglycemic-hyperinsulinemic clamp in both normal weight and obese nondiabetic subjects (8,10).

As a result of the unpredictable insulin response to intravenous tolbutamide of many subjects with NIDDM, the use of an intravenous bolus of soluble insulin has been suggested (11). In normal healthy subjects, this insulin-modified FSIVGTT has been shown to result in similar estimates of S_I to those from tolbutamide-modified tests (11,12). Recently, Steil et al. (13) suggested that the number of blood samples required for estimation of S_I and S_G in healthy subjects, the aged, and subjects with gestational diabetes or drug-induced insulin resistance can be reduced from the original 32 to 12 with a minor loss of precision, making the technique useful for population studies. As a result of this suggestion, we have examined data from 26 insulin-modified FSIVGTTs using the full sampling schedule carried out in subjects with established NIDDM. This study aimed to determine whether the above-mentioned reduced sampling regimen could produce estimates of S_I and S_G that approximate those estimates derived from the full sampling schedule or whether, as intimated by Steil and Bergman (14) and Bergman et al. (15), additional modification of the timings of the reduced sampling regimen could reduce bias and improve on this precision.

RESEARCH DESIGN AND METHODS

After local ethical committee approval and informed consent, 21 normotensive Caucasian subjects (16 men and 5 women) were recruited from the Diabetic Clinic at the University Hospital of Wales. All subjects were either newly presenting and previously untreated (9 men and 4 women) or were treated by diet alone (7 men and 1 woman). All were free of specific diabetes-related complications. Five subjects (4 men and 1 woman) had repeat tests 3 or 6 mo later, and their indicators of metabolic control were sufficiently different to regard the repeat tests as independent of the original tests, thus making a total data set of 26 full sampling schedule insulin-modified FSIVGTTs. Table 1 gives a summary of subject characteristics.

The insulin-modified FSIVGTT took place after a 10-h overnight fast. An intravenous cannula was placed in an antecubital fossa vein of each arm and maintained patent

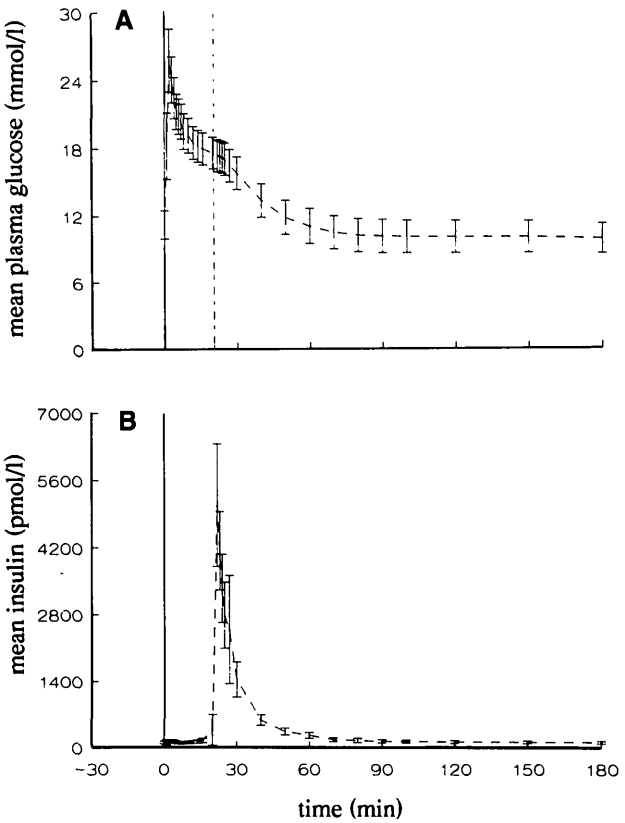

FIG. 1. Mean plasma glucose (*A*) and insulin (*B*) profiles. Glucose (300 mg/kg) was infused intravenously at time 0 min followed by a bolus of 0.05 U/kg soluble insulin at time 20 min. Bars represent 95% CIs of means. Individual profiles were consistent with the mean profile. Dashed lines connecting mean values may not represent actual values (n = 26)

by a slow running infusion of 0.9% saline. After 15 min of rest, basal blood samples were taken at −30, −15, and 0 min. Immediately after the 0-min sample, 300 mg/kg of glucose was infused intravenously at a constant rate over 2 min into the contralateral cannula, followed at time 20 min by a bolus intravenous injection of 0.05 U/kg Human Actrapid (Novo Nordisk, Bagsvaerd, Denmark). Sampling for glucose and insulin took place during the basal period and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, and 180 min. The samples were separated in a refrigerated centrifuge and stored at −20°C until subsequent assay.

Analytical methods. Plasma glucose was assayed by an autoanalyzer (Chemlab, Hornchurch, Essex, UK) with the use of an enzymatic colorimetric method with intra- and interassay CVs of <2%. Immunoreactive insulin was assayed with the use of a modification of the technique of Heding (16) with intra- and interassay CVs of 4.6 and 7.3%, respectively. Glycosylated hemoglobin was assayed by column chromatography with the use of standard reagents (Test-combination HbA_1, BCL, Lewes, Sussex, UK).

MINMOD analysis. S_I and S_G (full and reduced sampling schedules) with corresponding CVs were calculated from the FSIVGTT data with the use of the MINMOD program

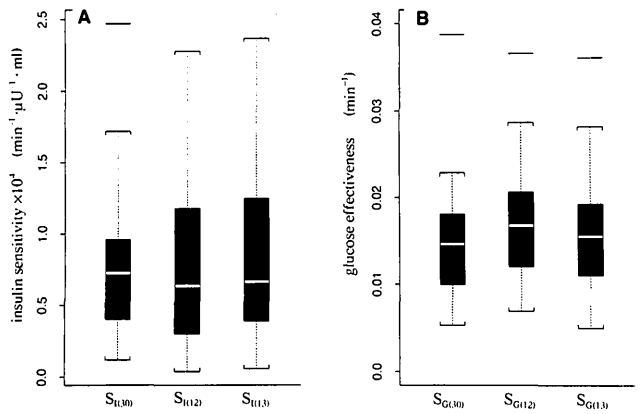

FIG. 2. *A*: Distributions of S_I data. The white line inside each box represents median value; the height of the box gives the IQR; lines outside the "whiskers" denote outliers (n = 26). *B*: Distributions of S_G data (n = 26).

(courtesy of R.N. Bergman) with weighting of data as recommended by Pacini and Bergman (17). Sample times used were 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, and 180 min to give $S_{I(30)}$ and $S_{G(30)}$ and, as suggested by Steil et al. (13), 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 90, and 180 min to give $S_{I(12)}$ and $S_{G(12)}$. $S_{I(13)}$ and $S_{G(13)}$ were determined after the inclusion of the 25-min time point. In all cases, the 0 value was calculated as the mean of the basal samples.

Statistical analysis. A study size calculation was conducted based on the following paired values: $\alpha = 0.01$ (probability of null hypothesis rejection error), $\beta = 0.15$ (probability of null hypothesis acceptance error), and $\sigma = 20$ (estimated SD of %RE) as in Steil et al. (13) and $\Delta = 15$ (minimum %RE required to detect). On this basis, a study size of 26 was used.

%REs of S_I and S_G for the reduced sampling regimens versus the full sampling schedule were calculated according to 100(full − reduced)/(full).

Boxplots, histograms, and quantile-quantile plots were used to assess the normality of the %RE data. Study size, skewed distributions, and the presence of outliers necessitated the use of a nonparametric statistical approach.

The reduced sampling protocols were assessed in terms of bias (the presence of systematic error), precision of estimation (the level of agreement with the full sampling protocol values), and precision of determination (the size of the CVs).

Wilcoxon's signed rank test was used to evaluate the statistical support for bias in the estimation of $S_{I(30)}$ by $S_{I(12)}$ and $S_{I(13)}$ and of $S_{G(30)}$ by $S_{G(12)}$ and $S_{G(13)}$. Nonspecific alternative hypotheses were used (P values are two sided). CIs of the medians were calculated according to the nonparametric method given by Gardner and Altman (18). The IQRs of %RE data were used to gauge the precision of the reduced sampling protocol estimates. CVs calculated by MINMOD were used to assess

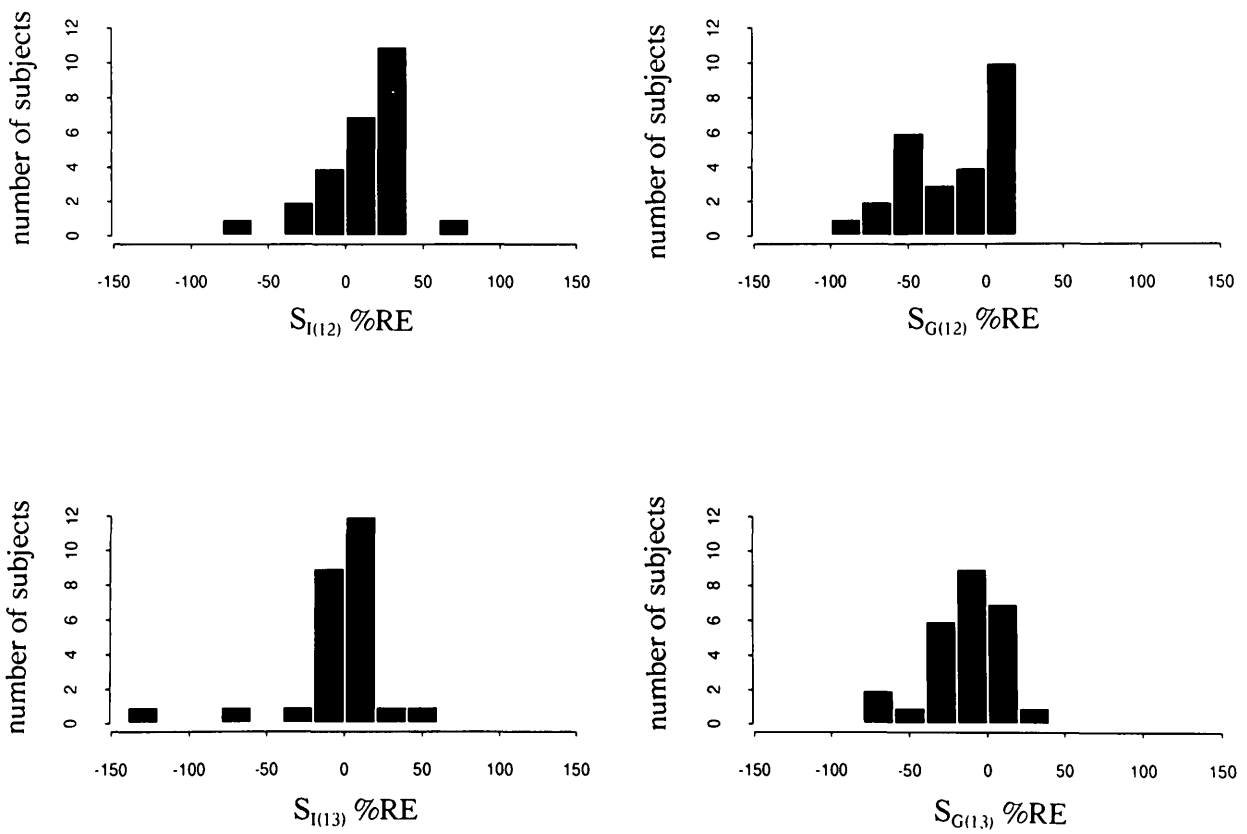

FIG. 3. Histograms of S_I and S_G %REs comparing the bias and accuracy of estimation of the reduced sampling protocols. Unbiased estimates have distributions centered around 0. Accuracy can be gauged from the spread of the distribution (the smaller the better) (n = 26).

TABLE 2
S_I data

	Full		Reduced					
	$S_{I(30)}$	CV (%)	$S_{I(12)}$	CV (%)	%RE	$S_{I(13)}$	CV (%)	%RE
	0.96	17	1.22	28	−27	1.25	27	−30
	0.4	54	0.42	66	−5	0.44	51	−10
	0.17	55	0.13	60	24	0.18	58	−6
	0.64	11	0.51	14	20	0.70	14	−9
	0.94	11	0.87	18	7	1.04	17	−11
	0.77	16	0.69	25	10	0.82	23	−6
	1.65	10	1.29	14	22	1.59	13	4
	1.35	10	1.18	18	13	1.37	17	−1
	0.43	24	0.32	52	26	0.39	47	9
	0.44	28	0.3	72	32	0.39	50	11
	0.67	15	0.46	28	31	0.56	25	16
	0.73	40	0.73	58	0	0.72	52	1
	0.16	117	0.28	117	−75	0.36	97	−125
	0.12	20	0.15	30	−25	0.21	29	−75
	1.72	10	1.21	13	30	1.52	14	12
	0.72	22	0.72	30	0	0.61	28	15
	0.82	18	0.69	28	16	0.7	24	15
	0.91	15	0.78	27	14	0.9	25	1
	0.12	56	0.04	236	67	0.06	243	50
	0.29	23	0.22	33	24	0.3	31	−3
	0.8	28	0.58	37	28	0.63	38	21
	1.32	18	1.40	63	−6	1.46	57	−11
	2.47	10	2.28	16	8	2.37	14	4
	1.58	11	1.46	16	8	1.75	15	−11
	0.49	22	0.32	30	35	0.46	27	6
	0.34	13	0.24	21	29	0.32	20	6
Median	0.725	18.4	0.635	29.0	15.1	0.665	27.0	1.2
IQR	0.548	15.3	0.798	37.5	25.2	0.808	31.2	20.7

S_I data in $min^{-1} \cdot \mu U^{-1} \cdot ml \times 10^4$.

the precision of determination. Data analysis was conducted using S-Plus software (19).

RESULTS

Figure 1 illustrates the mean glucose and insulin concentrations from the full sampling schedule of insulin-modified FSIVGTTs (95% CIs of the means are also shown). Values calculated for S_I and S_G are given in Tables 2 and 3, respectively, together with their corresponding CVs and %REs. Median and IQR data are also given. Boxplots showing the median (white line inside the box), IQR (height of the box), and outliers (lines outside the "whiskers") are presented for $S_{I(30)}$, $S_{I(12)}$, and $S_{I(13)}$ in Fig. 2*A*. Figure 2*B* depicts the corresponding information for the S_G data.

Bias of estimates. Table 4 gives the statistics calculated to assess the bias introduced by the reduced sampling regimens. CIs of the medians are actually 97% intervals because of the nonparametric nature of the method of calculation. Both CIs and the test statistics imply statistical support for the rejection of the null hypothesis (true median is equal to zero) for $S_I(12)$. This is not the case for

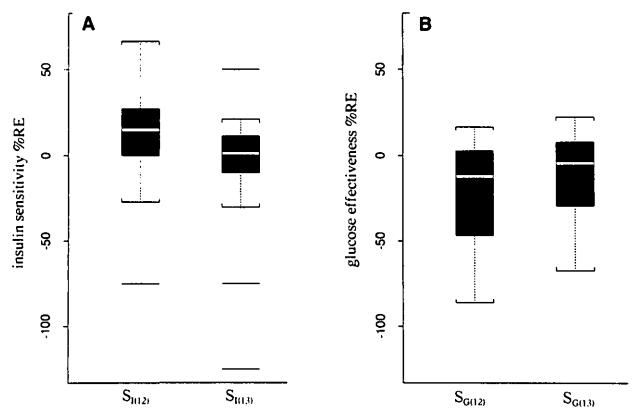

FIG. 4. *A*: Distributions of %REs of S_I estimates (n = 26). *B*: Distributions of %REs of S_G estimates (n = 26).

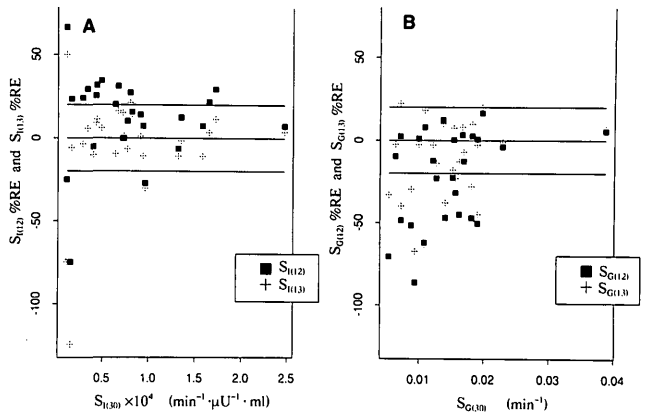

FIG. 5. *A*: %REs of S_I estimates vs. $S_{I(30)}$ showing ± 20% RE ranges (n = 26). *B*: %REs of S_G estimates vs. $S_{G(30)}$ showing ± 20% RE ranges (n = 26).

TABLE 3
S_G data

	Full		Reduced					
	$S_{G(30)}$ (min^{-1})	CV (%)	$S_{G(12)}$ (min^{-1})	CV (%)	%RE	$S_{G(13)}$ (min^{-1})	CV (%)	%RE
	0.01898	6	0.01880	9	1	0.01952	8	−3
	0.01820	6	0.01770	10	3	0.01623	10	10
	0.01668	9	0.01610	14	3	0.01528	14	8
	0.00709	15	0.00690	24	3	0.00499	33	22
	0.00630	17	0.00690	25	−9	0.00627	26	−2
	0.01537	7	0.01530	11	0	0.01416	12	8
	0.00528	22	0.00900	18	−70	0.00695	22	−33
	0.01519	6	0.01860	8	−22	0.01779	8	−18
	0.01564	9	0.02060	11	−32	0.01921	11	−23
	0.01810	8	0.02660	9	−47	0.02311	9	−28
	0.01270	6	0.01560	8	−23	0.01454	8	−14
	0.02285	7	0.02369	10	−4	0.02308	10	−1
	0.03874	3	0.03650	5	6	0.03599	4	7
	0.01369	8	0.01200	15	12	0.01215	14	10
	0.00721	16	0.01070	16	−48	0.00995	16	−40
	0.00992	13	0.00980	21	1	0.01019	19	−2
	0.01088	12	0.01000	23	8	0.00910	24	18
	0.01404	9	0.02060	9	−47	0.01935	9	−38
	0.01903	6	0.02860	7	−50	0.02810	7	−45
	0.00878	14	0.01330	16	−52	0.01098	19	−30
	0.01972	12	0.01600	23	17	0.01533	23	20
	0.01080	18	0.01750	45	−62	0.01759	41	−63
	0.00935	7	0.01740	8	−86	0.01560	8	−67
	0.01690	6	0.01900	8	−12	0.01813	8	−7
	0.01623	11	0.02350	11	−45	0.01818	14	−13
	0.01214	7	0.01360	9	−12	0.01248	9	−3
Median	0.01462	8.6	0.01675	11.1	−12.2	0.01547	11.3	−4.8
IQR	0.00766	6.4	0.00767	9.0	49.2	0.00768	10.9	36.5

$S_{I(13)}$. The bias introduced by the 12-point sampling regimen was of the order of 15% ($P = 0.0068$) (IQR 25%), whereas the corresponding value for $S_{I(13)}$ was 1% ($P = 0.88$) (IQR 21%). Results for S_G were equivocal. Wilcoxon's signed rank test strongly supported the rejection of the null hypothesis for $S_{G(12)}$ ($P = 0.0048$); however, the CI includes 0. This is unusual but not impossible and may be caused by a combination of the effects of a possible bimodality in the $S_{G(12)}$ %RE data (Fig. 3) and the nonparametric method of calculating the CIs. The median %RE was −12% (IQR 49%) for $S_{G(12)}$. Wilcoxon's signed rank test supported the rejection of the null hypothesis for $S_{G(13)}$ at the 5% level but not at the 1% level ($P = 0.035$). The median %RE for $S_{G(13)}$ was −5% (IQR 37%). The histograms of Fig. 3 illustrate the shift away from 0 %RE produced by the 12 time-point regimen compared with the 13 time-point regimen.

Precision of estimation. Figure 3 also highlights the improved precision of the 13 time-point regimen values, increased numbers of %REs near 0 indicating closer agreement. Figures 4*A* and *B* show boxplots of S_I %REs and S_G %REs, respectively ($S_{I(13)}$ IQR 21% vs. $S_{I(12)}$ IQR 25%) ($S_{G(13)}$ IQR 37% vs. $S_{G(12)}$ IQR 49%). These, together with Figs. 5*A* and *B* (%REs vs. full sampling schedule estimates), demonstrate the reduction in both the size and spread of %REs obtained by introducing the 25-min time-point data. In Fig. 5, note that the outlying %RE values occur only for the lowest values of S_I.

Precision of determination. CVs of the minimal model estimates were of the order of 18 (IQR 15%), 29 (IQR 38%), and 27% (IQR 31%) for $S_{I(30)}$, $S_{I(12)}$, and $S_{I(13)}$ and of 9 (IQR 6%), 11 (IQR 9%), and 11% (IQR 11%) for $S_{G(30)}$, $S_{G(12)}$, and $S_{G(13)}$, respectively. Median increases in CV for $S_{I(12)}$ and $S_{I(13)}$ compared with $S_{I(30)}$ were 9 and

TABLE 4
Assessment of bias estimates

	Median %RE	95% CI of median*	*Z* statistic†	*P* value
$S_{I(12)}$	15.1	7.4, 25.6	2.706	0.0068
$S_{I(13)}$	1.2	−9.4, 9.3	0.1524	0.8789
$S_{G(12)}$	−12.2	−46.7, 1.2	−2.819	0.0048
$S_{G(13)}$	−4.8	−27.8, 6.8	−2.108	0.0350

Null hypothesis: true mean %RE is equal to zero.
*Actually 97% CIs as a result of the nonparametric method of calculation.
†Normal statistic with tie correction for Wilcoxon's signed rank test.

7%, respectively. Median increases in CV for $S_{G(12)}$ and $S_{G(13)}$ compared with $S_{G(30)}$ were both 2%.

DISCUSSION

A variety of methods exists for the estimation of S_I from plasma concentrations of glucose and insulin that include the euglycemic-hyperinsulinemic clamp (7), the FSIVGTT (1), HOMA (20), CIGMA (21), and the SITT (22). The choice of method to be used is based on the type of study and practical and logistical considerations. However, the relative ease of carrying out the FSIVGTT, HOMA, CIGMA, and SITT techniques compared with the euglycemic clamp remains attractive to investigators.

The advantages of the full sampling schedule FSIVGTT include the comparative simplicity of the technique and its ability to provide estimates of both S_I and S_G, but in its original form, the full sampling schedule requires a large number of blood samples. Based on the study of a small number of normal subjects ($n = 10$), Steil et al. (13) attempted to demonstrate that a reduced sampling regimen in a tolbutamide-modified IVGTT could adequately estimate S_I and S_G in a wider group ($n = 87$, with a total of 118 tolbutamide-modified FSIVGTTs), including healthy subjects, the aged, and subjects with gestational diabetes or drug-induced insulin resistance, and as such would be suitable for use in certain population studies. Our study addresses the specific questions about the introduction of bias and the precision of estimation and determination of S_I and S_G from two reduced sampling regimens used during an insulin-modified IVGTT in NIDDM subjects treated with diet only. In method-comparison studies, these questions cannot be adequately answered by use of correlation and regression analyses (18,23).

In this study, statistically significant and clinically important bias was introduced by the use of reduced sampling regimens in the case of $S_{I(12)}$ but not $S_{I(13)}$. Results for $S_{G(12)}$ and $S_{G(13)}$ were statistically equivocal, but the introduction of bias cannot be discounted. Introduction of the 25-min time-point data resulted in improvement in the accuracy and precision of estimation of the $S_{I(13)}$ values. The precision of estimation of the $S_{I(12)}$, $S_{G(12)}$, and $S_{G(13)}$ values was substantially decreased. This time point was introduced empirically because of concerns over the reconstruction of the insulin profile in the critical period after the insulin bolus at 20 min. The precision of determination of S_I was markedly reduced for both $S_{I(12)}$ and $S_{I(13)}$, but this was not the case for $S_{G(12)}$ and $S_{G(13)}$. The CVs reported here appear larger than those reported originally by Bergman (1) and recently by Steil et al. (13), but this may be a result of the low S_I values estimated in these NIDDM subjects. When taken in combination, these effects may accumulate to such an extent that the resulting values are of little use even for large population studies. Power calculations to determine the actual size of such studies have yet to be made.

In a wider context, since the introduction of minimal modeling of the FSIVGTT, the methodologies used by investigators have varied considerably. Unmodified FSIVGTTs have been used to investigate subjects in whom the insulin response is adequate for modeling (5,6,24,25). Even within these studies, however, the sampling regimens have varied from 10 (6) to 19 time points (24). Additionally, a recent study in individuals at risk of NIDDM in whom the insulin response cannot be presumed to be unimpaired used an unmodified IVGTT with a sampling regimen of 13 time points (26). A modification of the FSIVGTT has been introduced to augment the insulin response in normal subjects using a single intravenous dose of tolbutamide (300 mg) regardless of subject size (3) or varying the dose according to BSA (8,13). An insulin-modified FSIVGTT protocol in subjects with NIDDM has used insulin either as an intravenous bolus (12) or an infusion over 5 min (27). The MINMOD program also exists in several versions with possible additional modifications having been made by the individual investigators without adequate documentation. Minimal modeling analysis of the unmodified and modified FSIVGTT remains a useful and flexible technique for the investigation of S_I, but it clearly needs standardization with guidelines for the appropriateness of protocol modifications depending on the questions to be answered by the investigation and the subjects to be investigated.

In NIDDM, we conclude that the 12 time-point protocol for the IVGTT in conjunction with MINMOD analysis should be restricted to large population studies. A 13 time-point protocol as described here is clearly more acceptable for the estimation of S_I in large population studies of NIDDM but still cannot be recommended for the assessment of S_G, a fact appreciated and commented on by Steil et al. (13). Therefore, for clinical research in subjects with NIDDM, we regard the retention of the full sampling protocol to be prudent.

ACKNOWLEDGMENTS

We are grateful to Sister Hilary Smith and nurse Miriam Khan for conducting the FSIVGTTs, Peter Ashley for the assays, and Katherine Srodzinski for data preparation.

REFERENCES

1. Bergman RN, Ider YZ, Bowden CR, Cobelli C: Quantitative estimation of insulin sensitivity. *Am J Physiol* 236:E667–77, 1979
2. Chen M, Bergman RN, Pacini G, Porte Jr D: Pathogenesis of age related glucose intolerance in man: insulin resistance and decreased B-cell function. *J Clin Endocrinol Metab* 60:13–20, 1985
3. Allemann Y, Horber FF, Colombo M, Ferrari P, Shaw S, Jaeger P, Weidmann P: Insulin sensitivity and body fat distribution in normotensive offspring of hypertensive parents. *Lancet* 341:327–31, 1993
4. Bergman RN, Phillips LS, Cobelli C: Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and B-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest* 68:1456–67, 1981
5. Godsland IF, Shennan NM, Wynn V: Insulin action and dynamics modeled in patients taking the anabolic steroid methandienone (Dianabol). *Clin Sci* 71:665–73, 1986
6. Godsland IF, Walton C, Felton C, Proudler A, Patel A, Wynn V: Insulin resistance, secretion, and metabolism in users of oral contraceptives. *J Clin Endocrinol Metab* 74:64–70, 1991
7. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237:E214–23, 1979
8. Bergman RN, Prager R, Vølund A, Olefsky JM: Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. *J Clin Invest* 79:790–800, 1987
9. Defronzo RA, Bonadonna RC, Ferrannini E: Pathogenesis of

NIDDM: a balanced overview. *Diabetes Care* 15:318–68, 1992
10. Beard JC, Bergman RN, Ward WK, Porte D Jr: The insulin sensitivity index in nondiabetic man: correlation between clamp-derived and IVGTT-derived values. *Diabetes* 35:362–69, 1986
11. Welch S, Gebhart SSP, Bergman RN, Phillips LS: Minimal model analysis of intravenous glucose tolerance test–derived insulin sensitivity in diabetic subjects. *J Clin Endocrinol Metab* 71:1508–18, 1990
12. 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* 70:1538–49, 1990
13. Steil GM, Vølund A, Kahn SE, Bergman RN: Reduced sample number for calculation of insulin sensitivity and glucose effectiveness from the minimal model: suitability for use in population studies. *Diabetes* 42:250–56, 1993
14. Steil GM, Bergman RN: Reduced sampling for the minimal model estimate of insulin sensitivity from the modified and standard frequently sampled IVGTT (Abstract). *Diabetes* 40 (Suppl. 1):38A, 1991
15. Bergman RN, Steil GM, Bradley DC, Watanabe RM: Modeling of insulin action in vivo. *Annu Rev Physiol* 54:861–83, 1992
16. Heding LG: Determination of total serum insulin (IRI) in insulin-treated diabetic patients. *Diabetologia* 8:260–66, 1972
17. Pacini G, Bergman RN: MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. *Comp Prog Biomed* 23:113–22, 1986
18. Gardner MJ, Altman DG: *Statistics With Confidence: Confidence Intervals and Statistical Guidelines*. Belfast, UK, The Universities Press, 1989
19. Becker RA, Chambers JM, Wilks RA: *The New S Language*. Pacific Grove, CA, Wadsworth/Brooks-Cole, 1988
20. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–19, 1985
21. Hosker JP, Matthews DR, Rudenski AS, Burnett MA, Darling P, Bown EG, Turner RC: Continuous infusion of glucose with model assessment: measurement of insulin resistance and B-cell function in man. *Diabetologia* 28:401–11, 1985
22. Akinmokun A, Selby PL, Ramaiya K, Alberti KGMM: The short insulin tolerance test for determination of insulin sensitivity: a comparison with the euglycaemic clamp. *Diabetic Med* 9:432–37, 1992
23. Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1:307–10, 1986
24. Bruce R, Godsland I, Stevenson J, Devenport M, Borth F, Crook D, Ghatei M, Whitehead M, Wynn V: Danazol induces resistance to both insulin and glucagon in young women. *Clin Sci* 82:211–17, 1992
25. Walton C, Godsland IF, Proudler AJ, Felton CV, Wynn V: Effect of body mass index and fat distribution on insulin sensitivity, secretion, and clearance in nonobese healthy men. *J Clin Endocrinol Metab* 75:170–75, 1992
26. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR: Role of glucose and insulin resistance in development of type II diabetes mellitus: results of a 25-year follow-up study. *Lancet* 340:925–29, 1992
27. Taniguchi A, Nakai Y, Fukushima M, Kawamura H, Imura H, Nagata I, Tokuyama K: Pathogenic factors responsible for glucose intolerance in patients with NIDDM. *Diabetes* 41:1540–46, 1992