Maximizing the success rate of minimal model insulin sensitivity measurement in humans: the importance of basal glucose levels

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ABSTRACT

Minimal model analysis of glucose and insulin concentrations in the intravenous glucose tolerance test (IVGTT) has been widely used to obtain a measure of insulin sensitivity in humans. Issues of model validity and IVGTT protocol have been explored extensively. Less attention has been paid, however, to the computer programming protocol for estimating the model parameters (programming implementation). Minimal model analysis of data from an IVGTT protocol involving a high glucose dose (0.5 g/kg) and a reduced sample schedule, employed in healthy pre- or post-menopausal women, healthy men or men with coronary heart disease or chronic heart failure (20 in each group), was undertaken according to 12 different programming implementations using a commercially available model-equation-solving program. The ability of the program to arrive at an acceptable solution to the model equations gave a success rate of between 39% and 96%, depending on the implementation. Variation in basal glucose assignment significantly affected the magnitude of estimates of insulin sensitivity. The maximum modelling success rate was achieved by introduction of an imputed glucose measurement at 360 min from the glucose injection, taking the basal glucose level as the fasting glucose concentration, and overweighting the initial glucose measurement after a delay for mixing. Use of this implementation to analyse data from a study comparing insulin sensitivities obtained using the minimal model and a euglycaemic clamp reference gave a correlation of 0.80 (P < 0.001) between the two methods. Straightforward variations in programming implementation, involving appropriate assignment of the basal glucose concentration and use of an imputed glucose measurement signifying re-establishment of basal glucose levels following the IVGTT, can considerably improve modelling success rate.

INTRODUCTION

The minimal model of glucose disappearance was introduced in 1979 by Bergman and colleagues [1] as a means of deriving measurements of insulin sensitivity from glucose and insulin concentrations during an intravenous glucose tolerance test (IVGTT). The model is embodied in two differential equations, and a measure of insulin sensitivity, $S_I$, is provided by the parameters of the equations [2]. The usefulness of the minimal model approach is demonstrated by the growing number of published studies in which the technique has been employed (37 listed in Medline during the 1980s, compared with 319 during the 1990s).

Studies designed to test model assumptions and comparisons with other methods for measuring insulin sensitivity have demonstrated that the minimal model equations provide a good approximation to true whole-
body glucose and insulin kinetics [3–5]. Other methodological studies have focused on the IVGTT procedure itself. Improved precision of insulin sensitivity estimates and increased modelling success rate can be achieved by augmenting IVGTT insulin concentrations, either endogenously, using tolbutamide [3,6] or an increased glucose load [7,8], or exogenously by injection of insulin [9,10]. Reduced sampling schedules have been introduced to make the technique more acceptable for large-scale studies [11,12]. Inclusion of isotopically labelled glucose can improve the accuracy of insulin sensitivity estimates and extend the information that can be derived from the technique [13,14], and a two- rather than a one-compartment description of glucose kinetics has been proposed [15].

Beyond the validity of the equations themselves and optimization of the IVGTT protocol, two further issues have been given less attention. These include the computer program used to estimate the parameters of the minimal model equations, and the parameter estimation protocol, or implementation, according to which the programming conditions for solving the model equations are set up. These issues are important, because the model equations must be solved using computer-based numerical methods. These identify the unique values of the equation parameters that allow the best-fit prediction of the observed IVGTT glucose profile from the accompanying insulin profile and the model equations [1]. In practice, however, different ways of setting up the program may lead to variability in parameter estimates. Moreover, instances of failure of the program to converge on a solution, or the emergence of excessively high parameter coefficients of variation, indicate that it is not always possible to arrive at a definitive solution to the equations. A solution may also involve unphysiological negative parameter estimates.

In the present study, the effects of some simple expedients selected to improve the success rate of modelling analysis are explored. One concern has been to establish whether a single, optimized, modelling protocol can be arrived at, which could be used without modification in batch analysis of large numbers of IVGTTs. A commercially available program package (MLAB) is used according to a set-up which is invariant with the exception of three aspects, namely: (1) assignment of the basal glucose concentration, (2) the use of glucose and insulin concentrations imputed to a hypothetical measurement beyond the end of the IVGTT (which signifies that physiological basal glucose levels are re-established following the IVGTT), and (3) overweighting of the first glucose measurement following an initial mixing phase (which requires the solution to the model equations to fit the predicted IVGTT glucose profile to pass through this measurement). These are issues that have been explored empirically over the past two decades by ourselves and others using the minimal model, but which have, hitherto, not been addressed in a formal published analysis.

**METHODS**

**IVGTT data**

A set of sample data from 100 IVGTT glucose and insulin concentration profiles was selected from previously published studies for analysis. This sample comprised five groups of 20 IVGTTs from studies of apparently healthy pre- and post-menopausal women (groups 1 and 2) [16,17], apparently healthy men (group 3), and men with coronary heart disease (group 4) or chronic heart failure (group 5) [18]. The studies from which these data were taken received local ethics committee approval, and all subjects gave their written, informed consent. The first 20 consecutive IVGTTs by date-of-test in each group were selected for inclusion in the present analysis. The IVGTT procedure from which these data were derived has been described previously [19]. In brief, a high glucose dose (0.5 g/kg) was employed without injection of tolbutamide or insulin, and there was a reduced sampling schedule, with samples taken at −5, 0, 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150 and 180 min relative to commencement of the glucose injection. Insulin concentrations were measured by RIA using a non-specific anti-insulin antibody. Insulin sensitivity estimates derived using this protocol have been shown to correlate well with those from the euglycaemic hyperinsulinaemic clamp, and to behave as expected in situations in which variation in insulin sensitivity has been previously well characterized [8,19].

**Model identification**

The minimal model of glucose disappearance comprises two equations, the first describing the rate of change in glucose concentration following a bolus intravenous glucose injection (dG/dt), and the second describing the accompanying rate of change in insulin in a compartment remote from the plasma (dX/dt). The equations are:

\[
\begin{align*}
\frac{dG}{dt} &= -p_1 \cdot G_t - G_i + p_1 \cdot G_s \\
\frac{dX}{dt} &= -p_2 \cdot X_t + p_3 \cdot (I_t - I_s)
\end{align*}
\]

The equations incorporate: plasma glucose concentration at time t (Gt); plasma insulin concentration at time t (It); insulin in a remote compartment at time t (Xt); basal glucose (Gi) and basal insulin (Ii); and parameters p1, p2, and p3. A further parameter is p5, the glucose concentration that would have been obtained at time 0 had the intravenous glucose bolus been injected and distributed instantaneously throughout the body. Insulin sensitivity, S, is given by p2/p5, and glucose effectiveness, SΔ, by p1. The process of solving the minimal model equations (i.e. determining values for p1, p2, p3 and p5) for...
a given IVGTT glucose and insulin profile is termed ‘model identification’.

In the present analysis, model identification was undertaken using the commercially available MLAB general mathematical modelling package (Civilized Software Inc., Bethesda, MD, U.S.A.). The package is currently provided with specific instructions for the solution of the minimal model equations. In the present analysis, initial parameter values were invariant, with values of: $p_1 = 0.02$, $p_2 = 0.002$, $p_3 = 0.000004$ and $p_4 =$ maximum IVGTT glucose concentration. Curve fitting commenced at the 10 min sample, to allow for a mixing phase, during which an even distribution of the injected glucose throughout the body is achieved. Glucose measurements prior to 10 min were zero-weighted. Glucose measurements were then weighted as the reciprocal of the square of the product of the glucose assay coefficient of variation (CV) and the glucose concentration [i.e. $1/(\text{glucose assay CV} \times \text{glucose concentration})^2$] [20]. The glucose assay CV was set at 1.5%. The sum of squares by $(1–0.00001)$ sum of squares. Parameter values were constrained not to be less than zero. [In the modelling package employed, it was found that if this expedient was not used, the time for a modelling analysis to reach completion was unacceptably lengthened.]

Analysis of the 100 IVGTT’s included in the present study with or without this constraint made no difference to the values of $S_t$ or $S_o$ that were obtained, nor was there any difference in the modelling success rate (results not shown). The only difference was that, in place of negative parameter estimates, parameter estimates of zero or exceptionally high parameter coefficients of variation (pcvs) ($>10^{14}$) were obtained when the constraint was used.] In the event of the model identification returning a parameter value of zero, the identification was rejected. In accordance with previous studies, identifications were also rejected if the pcv of either $S_t$ or $S_o$ was greater than 100%.

**Imputed measurement**

Modelling analyses were undertaken either without or with an imputed measurement. The glucose concentration for the imputed measurement was taken as the mean of the fasting and the 180 min glucose concentrations, and the insulin concentration as the minimum insulin concentration measured during the procedure. The timing of the imputed measure was taken at 240, 300 or 360 min after starting the IVGTT.

**Basal glucose assignment**

The value assigned to the basal glucose concentration, $G_o$, was taken as the fasting glucose concentration ($G_f$), the 180 min glucose concentration at the end of the IVGTT ($G_{180}$) or, when an imputed measure was used, the imputed glucose concentration, i.e. $G_{240}$, $G_{300}$ or $G_{360}$ depending on the timing of the imputed measurement.

**Overweighting**

Modelling analysis was undertaken either without or, in accordance with previous descriptions of the modelling process [20], with overweighting of the first glucose measurement following the mixing phase (i.e. the 10 min IVGTT glucose concentration). An overweight of 1000 was used, which had the effect of forcing the fitted glucose concentration profile through the 10 min glucose measurement.

**Implementations**

Different combinations of (1) basal glucose assignment, (2) use of an imputed measurement, (3) timing of the imputed measure, and (4) weighting of the first glucose measurement following the mixing phase gave rise to 22 different implementations. Twelve of these were investigated in the present study, these being chosen to distinguish optimally any effects of basal glucose assignment, use of an imputed measurement, weighting after the mixing phase and timing of the imputed measurement. The twelve implementations explored are listed in Table 1.

**Statistical analysis**

Statistical analyses were carried out using the SYSTAT statistical package (SYSTAT Inc., Evanston, IL, U.S.A.). Values of $S_t$ and $S_o$ were transformed logarithmically and by taking square roots respectively, to normalize their distributions [19]. Results were examined to determine the proportion of successful model identifications achieved by each implementation, along with the number of identification failures in each of the categories defined by $S_t = 0$, pcv $S_t > 100\%$, $p_2 = 0$ or $p_3 = 0$ and pcv $S_o > 100\%$. Median values for $S_t$, pcv $S_t$, $S_o$ and pcv $S_o$ were derived for the four most successful implementations (these gave modelling success rates of 88% or more; see Results). It was considered that only these implementations were likely to be of practical use. Variation in $S_t$, pcv $S_t$, $S_o$ and pcv $S_o$ according to each of the four different implementations was explored by repeated-measures ANOVA. Median values for age, body mass index, mean fasting glucose concentration, imputed-measure glucose concentration and $S_t$ for each of the four most successful implementations were derived in each of the five sets of sample data. Variation in these measures according to grouping was explored by ANOVA.

**Comparison with the euglycaemic clamp**

In a previously published study [8], 15 volunteers (10 apparently healthy men and women and five patients with chronic heart failure) each underwent a euglycaemic
hyperlinsinaemic clamp and an IVGTT according to the protocol described above. In the present study, the IVGTT data were re-analysed according to the four most successful implementation procedures, and the values for $S_f$ obtained were correlated with a clamp-derived measure of insulin sensitivity. The measure used was the one that is most similar to $S_f$, namely the steady-state glucose infusion rate ($M$) divided by the mean increment in insulin following commencement of a 40 m-unit·min⁻¹·m² insulin infusion multiplied by the mean clamped glucose level $[M/(M-G)]$ [21].

RESULTS

The percentage of successful model identifications ranged from 39% to 96%, depending on the programming implementation used (Table 1). The principal findings are illustrated in Figure 1, where it can be seen that the highest success rates were achieved with use of an imputed measurement at 360 min, with either the fasting or imputed glucose concentration as the basal level. Some further improvement was achieved by overweighting the first glucose measurement after the mixing phase.

The specific effect of variation in the assignment of basal glucose concentration on identification success rate was apparent when comparing implementations in which use of an imputed measurement or weighting of the first glucose measurement following the mixing phase (wt1) was the same, but assignment of basal glucose concentration ($G_b$) differed. These were implementations 1 and 2 ($G_b = G_f$, versus $G_b = G_{180}$, no imputed measure, wt1 = 1), 6 and 7 ($G_b = G_f$, versus $G_b = G_{360}$, no imputed measure, wt1 = 1000), 3, 4 and 5 ($G_b = G_f$, versus $G_b = G_{180}$ versus $G_b = G_{360}$, 360 min imputed measure, wt1 = 1), and 10, 11 and 12 ($G_b = G_f$, versus $G_b = G_{180}$ versus $G_b = G_{360}$, 360 min imputed measure, wt1 = 1000). In

### Table 1: Number (i.e. percentage) of identification failures using the minimal model of glucose disappearance, according to reason for rejection

Analyses were undertaken using differing basal glucose ($G_b$), imputed measure and initial glucose measurement overweighting (wt1) assignments in 100 IVGTTs from non-diabetic individuals. In those cases where the percentages according to reasons for rejection and the percentage of successful identifications add up to more than 100%, the excess is accounted for by the pcv of $S_f$ and $S_b$ both being > 100%. Additionally, for implementation 4, one $p_2$ value of zero was associated with a pcv $S_f$ of > 100%. This was also the case for two sets of results from implementation 7 and one set from implementation 12.

<table>
<thead>
<tr>
<th>Implementation …</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<th>11</th>
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<td>$G_{360}$</td>
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<td>360</td>
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<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
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<td>0</td>
<td>1</td>
<td>0</td>
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<td>pcv $S_f &gt; 100%$</td>
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<td>25</td>
<td>9</td>
<td>29</td>
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<td>11</td>
<td>20</td>
<td>33</td>
<td>17</td>
<td>4</td>
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<td>0</td>
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<td>28</td>
<td>30</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>16</td>
<td>2</td>
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<tr>
<td>Successful identification (%)</td>
<td>46</td>
<td>39</td>
<td>91</td>
<td>53</td>
<td>88</td>
<td>43</td>
<td>40</td>
<td>66</td>
<td>82</td>
<td>96</td>
<td>71</td>
<td>92</td>
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</table>
Figure 1 Percentage of successful analyses using various implementations of the minimal model

Percentage success varied according to basal glucose assignment ($G_f$, fasting glucose concentration, $G_{180}$, 180 min glucose concentration and $G_{360}$, imputed-measure glucose concentration), whether imputed glucose and insulin concentrations at 360 min after the start of the IVGTT were used, and whether overweighting of the first glucose measurement after the mixing phase (weight 1) was used. See Table 1 for further details.

The effect of overweighting the initial glucose measurement following the mixing phase was apparent when comparing implementations in which assignment of basal glucose concentration and use of an imputed measure were the same, but implementations differed according to whether overweighting was used. These implementations were: 1 and 6 ($G_b = G_f$, no imputed measure: 46% success rate without overweighting; 43% success rate with overweighting), 2 and 7 ($G_b = G_{180}$, no imputed measure: 39% and 40% respectively), 3 and 10 ($G_b = G_f$, 360 min imputed measure: 91% and 96% respectively), 4 and 11 ($G_b = G_{180}$, 360 min imputed measure: 53% and 71% respectively), and 5 and 12 (imputed glucose as basal, 360 min imputed measure: 88% and 92% respectively). Therefore, with no imputed measure, overweighting made little difference to the success rate. However, with an imputed measure, overweighting led, on average, to a 9% improvement in success rate.

Beyond the effect of implementation itself, reasons for model identification failure were explored in relation to the basal glucose concentration and IVGTT insulin concentrations. The effect of degree of insulin resistance on identification failure was also explored, according to whether the individual concerned belonged to one of the more or less insulin-resistant groups studied. No consistent influence of any of these factors on model failure could be distinguished (results not shown).

Of the 12 implementations, the four most successful (implementations 3, 5, 10 and 12) gave success rates of 88% or better (the other eight ranged between 39% and 82%). Use of an imputed measure was necessary for an acceptable success rate, but these four most successful implementations varied according to whether the fasting or imputed measure was taken as the basal glucose concentration, and/or whether the initial measure after the mixing phase was overweighted. There was significant variation in $S_I$, pcv $S_I$, $S_G$ and pcv $S_G$ across these four implementations (Table 2). Median values for $S_I$ were unaffected by overweighting, but were about 40% higher when the fasting glucose concentration was taken as basal compared with the imputed glucose concentration. Median values for $S_G$ were unaffected by assignment of basal glucose.
Table 3  $S_3$ values obtained by minimal model implementation for 20 control premenopausal women, 20 control postmenopausal women, 20 control men, 20 men with coronary heart disease and 20 men with chronic heart failure

Only results from the four most successful implementations (implementations 3, 5, 10 and 12; failure rate < 12%) were analysed. All implementations included a 360 min imputed measure. Numbers of successful modelling analyses are given below each median (range). CHD, coronary heart disease; CHF, chronic heart failure; BMI, body mass index; NS, not significant.

<table>
<thead>
<tr>
<th></th>
<th>Pre-menopausal women</th>
<th>Post-menopausal women</th>
<th>Control men</th>
<th>Men with CHD</th>
<th>Men with CHF</th>
<th>ANOVA significance</th>
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<tr>
<td><strong>Age (years)</strong></td>
<td>31.3</td>
<td>54.5</td>
<td>53.7</td>
<td>56.2</td>
<td>54.1</td>
<td>$P &lt; 0.001$</td>
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<tr>
<td></td>
<td>(24.0–45.1)</td>
<td>(48.6–58.6)</td>
<td>(30.3–67.8)</td>
<td>(42.3–60.3)</td>
<td>(45.9–75.7)</td>
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</tr>
<tr>
<td><strong>BMI (kg·m$^{-2}$)</strong></td>
<td>29.0</td>
<td>24.0</td>
<td>24.4</td>
<td>26.5</td>
<td>27.0</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td></td>
<td>(17.6–25.2)</td>
<td>(20.0–27.9)</td>
<td>(20.4–34.9)</td>
<td>(23.1–29.7)</td>
<td>(23.6–37.0)</td>
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</tr>
<tr>
<td><strong>Fasting glucose (mg·dl$^{-1}$)</strong></td>
<td>86.5</td>
<td>91.0</td>
<td>90.8</td>
<td>96.3</td>
<td>95.2</td>
<td>$P &lt; 0.001$</td>
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<tr>
<td><strong>Imputed glucose (mg·dl$^{-1}$)</strong></td>
<td>81.8</td>
<td>81.8</td>
<td>83.9</td>
<td>83.1</td>
<td>84.8</td>
<td>NS</td>
</tr>
<tr>
<td>$G_3$ (min$^{-1}$·μ-unit·ml$^{-1}$·10$^9$)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Implementation 3:</td>
<td>5.50</td>
<td>5.87</td>
<td>4.07</td>
<td>3.36</td>
<td>2.73</td>
<td>$P &lt; 0.001$</td>
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<tr>
<td></td>
<td>(2.24–10.4)</td>
<td>(2.87–11.6)</td>
<td>(1.93–26.1)</td>
<td>(1.13–7.51)</td>
<td>(1.80–8.70)</td>
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<tr>
<td>$G_3 = G_{w1}·wt1 = 1$</td>
<td>16</td>
<td>19</td>
<td>19</td>
<td>18</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Implementation 5:</td>
<td>3.78</td>
<td>3.62</td>
<td>3.57</td>
<td>2.31</td>
<td>1.82</td>
<td>$P &lt; 0.001$</td>
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<tr>
<td></td>
<td>(2.25–5.51)</td>
<td>(2.12–6.72)</td>
<td>(1.62–9.11)</td>
<td>(0.79–3.62)</td>
<td>(0.84–5.01)</td>
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<tr>
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<td>18</td>
<td>17</td>
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<td>$P &lt; 0.01$</td>
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<td>Implementation 10:</td>
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<td>4.43</td>
<td>3.75</td>
<td>3.16</td>
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<tr>
<td></td>
<td>(1.84–10.9)</td>
<td>(2.92–12.9)</td>
<td>(2.13–28.6)</td>
<td>(1.29–8.43)</td>
<td>(1.87–9.26)</td>
<td></td>
</tr>
<tr>
<td>$G_3 = G_{1000}·wt1 = 1000$</td>
<td>17</td>
<td>20</td>
<td>19</td>
<td>20</td>
<td>20</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Implementation 12:</td>
<td>3.85</td>
<td>3.84</td>
<td>2.93</td>
<td>2.28</td>
<td>1.73</td>
<td></td>
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<tr>
<td></td>
<td>(1.84–5.43)</td>
<td>(1.97–6.69)</td>
<td>(1.59–9.02)</td>
<td>(0.75–3.60)</td>
<td>(0.84–4.69)</td>
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<tr>
<td>$G_3 = G_{1000}·wt1 = 1000$</td>
<td>18</td>
<td>19</td>
<td>18</td>
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</tr>
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</table>

Glucose concentration, but were about 14 % higher when overweighting was used. Median values of pcv $S_3$ were relatively unaffected by differing assignments of the basal glucose concentration or by overweighting. The median pcv $S_3$ was somewhat reduced by overweighting, but increased markedly when the imputed-measure glucose concentration was taken as basal.

$S_3$ values obtained from each of the four most successful implementations varied significantly across the five different patient groups studied (Table 3). The lowest median values for $S_3$ were encountered among men with chronic heart failure, followed by men with coronary heart disease, followed by healthy men. Median values of $S_3$ among healthy men tended to be lower than those among pre- or post-menopausal women, although this was not the case for implementation 5 ($G_3 = G_{1000}$, 360 min imputed measure, wt1 = 1). Median values of $S_3$ among premenopausal women tended to be the same as those among postmenopausal women, although they were somewhat higher among postmenopausal women for implementation 10 ($G_3 = G_{a}$, 360 min imputed measure, wt1 = 1000). There was, however, no significant variation in $S_3$ between the male and female control groups for implementations 3, 5, 10 or 12 when these groups were analysed separately (results not shown).

When measures of $S_3$ obtained from the 15 IVGTTs from the comparison with the euglycaemic clamp were compared with the clamp-derived measure of insulin sensitivity, highly significant ($P < 0.001$) correlations were found for each of the most successful implementations (3, 5, 10 and 12), with correlation coefficients ranging between 0.79 and 0.81. In this subanalysis, modelling analysis using each of these four implementations was successful for all 15 IVGTTs.

The marked differences in model identification success rate between implementations in the present study allowed a further important issue to be explored, namely the validity of pcv $S_3$ or pcv $S_4$ = 100 % as the upper limit for successful model identification. Values for $S_3$ and $S_4$ from implementations with a substantial proportion of values for pcv $S_3$ or pcv $S_4$ of > 100 % could be compared with those from more successful implementations, in which the corresponding values for $S_3$ or $S_4$ were no longer associated with pcvs of > 100 %. Overall, implementation 1 ($G_3 = G_{a}$, no imputed measure, wt1 = 1) gave 46 successful identifications, whereas implementation 3 ($G_3 = G_{a}$, imputed measure at 360 min, wt1 = 1)
which pcv identifications for which pcv S13 identifications returned values for pcv S1 station 1 (regression slope 2.75, values with the corresponding values from implementation 1 or 3, or both, returned a pcv S values of 68 and 85, compared with S1 values of 4.2 and 4.3 using implementation 3. The others were associated with S1 values in excess of 1015. These findings indicate that, as pcv S1 increases beyond 100%, S1 values become unrealistically high.

With regard to S0, implementation 1 returned 18 identifications for which pcv S0 was > 100%, and implementation 3 returned nine. No zero values were obtained for S0. There were 21 IVGTTs for which implementation 1 or 3, or both, returned a pcv S0 of 100% or more. The maximum value for pcv S0 was 460%. For the 79 identifications that were successful using both implementations, there was reasonable agreement in the S0 values returned (regression line slope 0.85, r = 0.95), but for the 21 IVGTTs with pcv S0 100%, agreement was very good (regression line slope 1.00, r = 0.97). This suggests that, in contrast with S1 values of S0 are relatively unaffected at pcvs above 100%. This analysis was repeated with implementations 6 and 10 (differing from 1 and 3 in the use of an overweight for the first glucose measurement following the mixing phase). The findings were virtually identical with those for implementations 1 and 3. These observations indicate that a limit of 100% is likely to be appropriate with regard to pcv S0, but that this limit may be extended, at least to 500%, with regard to pcv S0. Consequently, success rates of between 98 and 100% may be considered for the four most successful implementations, i.e. 3, 5, 10 and 12.

DISCUSSION

Without imputing a hypothetical glucose and insulin measurement to a time beyond completion of the IVGTT, successful modelling analysis could only be achieved in about 40% of the IVGTTs analysed in this study. Use of an imputed measure increased this proportion to between 88% and 96%, depending on whether the fasting or imputed-measure glucose concentration was taken as basal and/or whether there was overweighting of the first glucose measurement following the mixing phase. Sub-analysis of the validity of parameter estimates associated with pcvs of > 100% indicated that identifications returning values for pcv S1 of up to 500% could be acceptable, in which case the success rate for the four most successful implementations would increase to 98–100%. These implementations were each able to distinguish expected differences in insulin sensitivity in five sets of test data, derived from groups with a range of insulin sensitivities that would encompass most insulin-resistant states, including obesity and impaired glucose tolerance.

The reasons for these differences in identification success rate, their implications for minimal model analysis and their consequences for modelling procedure need to be carefully considered if the findings reported here are to be interpreted and applied constructively. First, it must be emphasized that these findings were derived from an IVGTT procedure which was selected to be applicable in studies of large numbers of subjects, and this necessitates the use of a reduced sample schedule. Furthermore, the studies were of non-diabetic subjects, which obviated the need for exogenous administration of insulin during the IVGTT. The deciding factor in our choice of IVGTT protocol was the need to measure both insulin sensitivity and insulin secretion, in both the first and second phases, during the IVGTT. Artificial augmentation of IVGTT insulin concentrations was, therefore, unacceptable. An adequate endogenous insulin response was instead ensured by use of a higher dose of glucose than is currently generally employed (0.5 rather than 0.3 g/kg). This, incidentally, provided continuity with IVGTT data acquired previously by the protocol in use in the 1960s and 1970s, which has proved of value in other studies [22,23].

Model identification failure has been explored previously in the context of the adequacy of the insulin response during the IVGTT [24], or the number of sampling points during the IVGTT [11]. Re-establishment of basal glucose levels following intravenous glucose injection provides another such area of investigation. For example, following the glucose injection, if a steady state has not been re-established by the final glucose measurement, accurate modelling of basal glucose levels could be compromised. The substantial improvement in modelling analysis success rate resulting from the use of an imputed measure in the present study suggests that inadequate modelling of basal glucose levels may, in fact, have been of considerable importance in modelling failure. In the absence of injected tolbutamide or insulin, the typical IVGTT glucose profile comprises a decay phase, during which glucose levels fall to a minimum, followed by a slight rise, after which glucose levels remain constant. However, particularly in insulin-resistant states, glucose levels may still be falling after 180 min, and the best fit to the observed IVGTT glucose profile may then require glucose levels to fall indefinitely. In such cases, negative values for the model parameters p2
or \( p_s \), may be encountered (or zero parameter values or exceptionally high \( p_s \) if parameter values are constrained to be non-negative; see above). Use of an imputed measure restricts the solution of the equations of the minimal model to one whereby the predicted glucose concentrations beyond the end of the IVGTT reflect the re-establishment of a steady-state basal level.

A further consideration in the effective modelling of basal glucose levels is the actual value to be assigned to the basal glucose concentration. Accepted practice has generally been to take this as the 180 min glucose value, but this assumes that a basal steady state has been re-established by 180 min. It is noteworthy that use of the 180 min glucose value as basal with an imputed measure led to a relatively high rate of identification failure compared with the rate achieved when either the fasting or imputed glucose concentration was taken as basal. The present analysis suggests that the fasting glucose concentration should be taken as the basal level, although the imputed glucose concentration was almost equally effective in the most successful implementations. The analysis also indicates, however, that absolute values of \( S_i \) are highly dependent on the choice of basal glucose assignment. Median fasting glucose levels were higher than the imputed glucose levels, which were, in turn, higher than the 180 min glucose levels, and median \( S_i \) values showed a similar pattern according to whether the fasting, imputed or 180 min glucose levels were taken as basal (results not shown). This variation is a mathematical consequence of the role played by the basal glucose level in the minimal model equation term \( +p_1 \cdot G_i \). This acts, in effect, to quantify glucose production during the IVGTT. If a higher basal glucose is used when modelling a given IVGTT (e.g. as when the fasting rather than the 180 min IVGTT glucose is taken as basal), glucose production will be greater during that IVGTT. In order to sustain the same fitted glucose profile, the solution to the model equations then requires higher insulin sensitivity to counterbalance the increased glucose production. This raises the possibility that minimal-model-derived measures of insulin sensitivity might be influenced excessively by variation in a measurement (i.e. the basal glucose level) that is unrelated to variations in glucose elimination and insulin levels during the IVGTT. However, if this were the case, taking the fasting glucose level as basal would result in a positive association between fasting glucose levels and \( S_i \). In the 100 IVGTTs analysed here, a negative association was found (results not shown); low fasting glucose levels were associated with high insulin sensitivity, which is the expected physiological relationship; this indicates that, within a given modelling analysis procedure, any modelling-associated influence of the basal glucose level is not excessive.

Overweighting the initial glucose value following mixing was a strategy that was introduced at the inception of the minimal model, having been found empirically to reduce the number of modelling failures due to poor identification of the parameter of glucose effectiveness, \( p_i \). In the present analysis, use of such overweighting significantly increased the success rate of modelling analysis, had no effect on \( S_i \) and increased the median \( S_{iv} \). While it is clear that assignment of the basal glucose concentration should be invariant for a given set of modelling analyses, the question arises as to whether such overweighting, or even an imputed measure, should be used in every model identification, or only in those identifications in which there is modelling failure in the absence of such interventions. When results from analyses with and without an imputed measure were compared, it was found that introduction of an imputed measure per se had no effect on values of \( S_i \) or \( S_{iv} \), but reduced the median \( p_s \) for these parameters by 30–50% (results not shown). Pragmatically, it would therefore seem appropriate to use an imputed measure in every case. Use of overweighting significantly increased values of \( S_{iv} \), indicating that, if such overweighting is to be used at all, it should be used in every case, so as to avoid the possible introduction of bias into analyses of glucose-dependent glucose disposal.

Optimization of an investigative procedure requires a balanced appraisal of, among other things, the numbers of cases to be studied, the costs involved, the precision required and the acceptability of the procedure. It should be clear that there is no ‘right’ way of using the minimal model; rather, there are a range of alternatives which, by analogy with the equivalent steady-state procedure, the euglycaemic hyperinsulinaemic clamp, can be modified and extended in a number of ways, which are equally valid when used appropriately. The present analysis has focused on the use of a few simple expedients to improve the success rate of modelling analysis in the context of a commercially available software package and an IVGTT protocol involving a high glucose dose and a reduced sample schedule, and has raised questions regarding the modelling of basal glucose concentrations by the minimal model procedure. An underlying concern in this has been whether a single, pre-set, operator-independent series of modelling operations could be arrived at, suitable for the semi-automated analysis of large numbers of IVGTTs. The results described above suggest that this is feasible without undue imprecision or loss of data. There is no a priori reason why these strategies to improve modelling success rate could not apply equally to data from other IVGTT protocols. It would be of value to have these issues addressed further in published studies, particularly with regard to the widely used insulin-modified IVGTT.

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