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Insulin secretion rate and β-cell sensitivity from oral glucose tolerance test in normotensive and normoglycemic humans

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Abstract—**Aim of the study was to test the reproducibility of estimates of static, Φ_s, and dynamic, Φ_d, β-cell sensitivity to glucose, and predictions of the insulin secretion rate, *SR(t)*, provided by the C-peptide oral minimal model (COMM) applied to oral glucose tolerance tests (OGTT) of various complexity. The study involved six volunteer, normotensive and normoglycemic subjects who underwent a 300-minute OGTT. Results from a full 22-sampling schedule ($OGTT_{300/22}$), were compared with those from two reduced schedules consisting of 11 samples in 300 min ($OGTT_{300/11}$) and 7 samples in 120 min ($OGTT_{120/7}$). Our results showed that both reduced-sample protocols did not affect significantly the estimates of Φ_d. Intraclass correlation coefficients were higher than 0.9. The Φ_s appeared more sensitive to reductions of protocol complexity. Nevertheless, intraclass correlation coefficients kept higher than 0.7. No significant differences were found in model predictions of *SR(t)* profiles among all tested OGTT protocols. These findings confirm the COMM as a potentially useful tool to quantify β-cell sensitivity and insulin secretion rate in pathophysiological studies, from relatively low-cost OGTT.**

I. Introduction

IT has recently been demonstrated that, by extending to the oral glucose tolerance test (OGTT) the C-peptide minimal model developed for intravenous glucose infusion, it is possible to quantify characteristic parameters of β-cell function. These are a static sensitivity index, Φ_s, that quantifies insulin secretion in response to a given glucose concentration, and a dynamic sensitivity index, Φ_d, that quantifies the response to the rate of change in glucose concentration [1]-[3]. Prediction of insulin secretion profile, *SR(t)*, is also allowed. Given that the OGTT is the most commonly used test in clinics, this C-peptide oral minimal model (COMM) has particular interest. Simultaneous use of the COMM with the oral minimal model (OMM) of glucose kinetics is expected to allow accurate assessment of β-cell function in relation to the degree of insulin sensitivity [3],[4]. Because easier and less costly applications of oral glucose tests, interpreted with the COMM, can be accomplished by optimization of the sampling schedule, reported studies have focused on protocols of time length from 300 to 120 min with 22 to 7 blood samples, in nondiabetic individuals with a large spectrum of glucose tolerance [2],[3].

The aim of the present study was to test the reproducibility of Φ_d and Φ_s estimates, and of *SR(t)* profile obtained from applying the COMM to OGTT data measured in normotensive and normoglycemic patients, not affected by the metabolic syndrome, MS [5]. The perspective was to build control values useful to pursue future pathophysiological studies.

II. Methodology

A. Subjects and protocol

This study included six subjects (3 men and 3 women) with mean age of 46.2 (SD=13.2) yr and body mass index, BMI, of 24.2 (SD=3.4) kg/m^2. All they gave informed consent to the procedures approved by the Ethics Committee. All subjects were normotensive and normoglycemic, and met no more than two of the three other ATP III criteria of MS, i.e. abdominal obesity, decreased HDL cholesterol and elevated serum triglycerides [5]. Each subject underwent an OGTT for measurements of glucose, insulin and C-peptide plasma concentration data, starting at 8:30 a.m., after overnight fast. One blood sample was taken immediately before a 75 g glucose load administration (t=0), and 21 more blood samples were taken at minutes 10, 20, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 225, 240, 255, 270, 285 and 300 ($OGTT_{300/22}$) [2]. Competing reduced protocols were an $OGTT_{300/11}$ with samples at minutes 0, 10, 20, 30, 60, 90, 120, 150, 180, 240 and 300; and an $OGTT_{120/7}$ obtained from the $OGTT_{300/11}$ by reducing the time-length to 120 min [3].

B. Model identification

Evaluation of Φ_d and Φ_s indexes, and *SR(t)* profile was accomplished by fitting the COMM to C-peptide data [2], [3]. The method proposed by Van Cauter et al. [6] was used for calculation of parameters of C-peptide kinetics.

COMM-based evaluation of β-cell sensitivity from the $OGTT_{120/7}$ protocol suffers from a lack of information that does not allow a reliable estimation of the glucose threshold above which insulin secretion occurs. To overcome this limitation, the threshold was assumed equal to basal glucose concentration [3].

C. Reproducibility analysis

Intraclass correlation coefficient [7] (irrespective of

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CV%) was used to evaluate the agreement of both Φ_d and Φ_s estimates obtained from the full and the reduced OGTTs.

III. Results

Mean fasting plasma concentrations of glucose, insulin and C-peptide were 79.3 (SD=10.9) mg/dl, 5.03 (SD=1.79) μU/ml and 480 (SD=210) pmol/l, respectively. Waist circumference was 86.2 (SD=12.8) cm. Serum triglycerides and HDL cholesterol were 77.0 (SD=55.5) mg/dl and 55.7 (SD=15.4) mg/dl, respectively.

Means and 95% confidence intervals (CI) of Φ_d (dimensionless) were Φ_d^{22} = 583 (228-937) $\times 10^{-9}$ from $OGTT_{300/22}$, Φ_d^{11} = 559 (274-844) $\times 10^{-9}$ from $OGTT_{300/11}$, and Φ_d^{7} = 589 (322-855) $\times 10^{-9}$ from $OGTT_{120/7}$. Mean (CI) Φ_s estimates ($10^{-9}\cdot min^{-1}$) were Φ_s^{22} = 39.5 (19.9-58.1), Φ_s^{11} = 51.8 (25.0-78.6), and Φ_s^{7} = 63.3 (29.1-97.6). Mean CV% did not exceed 42% for Φ_d and 19% for Φ_s.

Compared to Φ_d^{22}, the intraclass correlation coefficient was 0.96 for Φ_d^{11} and 0.91 for Φ_d^{7}. Compared to Φ_s^{22}, the intraclass correlation coefficient was 0.84 for Φ_s^{11} and reduced to 0.71 for Φ_s^{7}.

The *SR(t)* profiles obtained from the three different OGTT data sets are compared in Fig. 1.

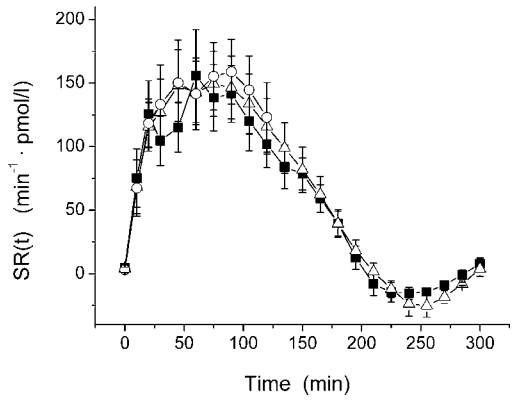

Fig. 1. Mean (± SE) values of insulin secretion rate, *SR(t)*, predicted in our subjects by the COMM, after application to $OGTT_{300/22}$ (full squares), $OGTT_{300/11}$ (open triangles) and $OGTT_{120/7}$ (open circles).

IV. Discussion

Our selection criteria limited the number of participants in this study, but allowed us to control for confounding effects of hypertension [8] and metabolic syndrome, MS, defined according to the ATP III criteria [5].

The application of the COMM to the full $OGTT_{300/22}$ data set yielded mean (±SE) estimates of Φ_d^{22} = 583±181 $\times 10^{-9}$ and Φ_s^{22} = 39.5±10.0 $\times 10^{-9}\cdot$ min^{-1}, that fall between the mean values of 871±46 $\times 10^{-9}$ and 42.4±1.6 $\times 10^{-9}\cdot$ min^{-1}, respectively, reported in [3], and the mean values of 314±231 $\times 10^{-9}$ and 18.3±4.1 $\times 10^{-9}\cdot$ min^{-1}, respectively, reported in [9], for nondiabetic control subjects.

Our analysis of intraclass correlation coefficients [7] indicated that sampling schedule reductions from 300 min and 22 samples to 120 min and 7 samples do not affect significantly the Φ_d estimates. A greater effect was seen on Φ_s estimates, but concordance levels were still acceptable.

Application of the COMM to a 300-minute OGTT protocol allows prediction of the full profile of *SR(t)*. In our subjects, the initial rise (0÷30 min) and the tail (150÷300 min) of the profiles derived from the $OGTT_{300/22}$ and the $OGTT_{300/11}$ were practically superimposed, while visible differences in the time frame between 30 and 120 min were not significant (ANOVA, $p<0.05$). Thus, a 50% reduction in the number of samples did not affect significantly the prediction of *SR(t)* all over the 300 min time frame. The *SR(t)* profile obtained from the minimized $OGTT_{120/7}$ protocol (Fig. 1) was practically superimposed to that obtained from the $OGTT_{300/11}$, within the time frame where the comparison is possible.

In conclusion, the COMM appears a potentially useful tool to quantify β-cell sensitivity and insulin secretion rate in pathophysiological studies, from relatively low-cost OGTT.

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