A Novel Index to Identify Steady-State Glucose Infusion Rates during a Clamp

S. Pagilialunga1, A. Guerrero1,2 and C.A. Dehn1,3

Celerion, Tempe, AZ USA, 2Clinical Trials of Texas, TX USA; and 3umbrella corporation, TX USA

BACKGROUND

In clinical research, a hyperinsulinemic-euglycemic clamp is considered the gold standard to evaluate insulin sensitivity, however there is no agreement on the duration of a clamp as they can range from 2 to 6 hours. The outcome of this method is the glucose infusion rate (GIR). At a constant insulin infusion, GIR rises in a monoeponential fashion until it reaches a plateau. A flat GIR curve, suggestive of a steady-state condition, is then used for insulin sensitivity determinations. Currently, an arbitrary timeframe; the last 40 min of the protocol designates steady state. However, this strategy may not be ideal as results can greatly differ depending on the length of the elected steady-state phase 1-3.

AIMS

To precisely identify GIR flatness during the steady state by applying the CONGIR (Continuous Overall Nat GIR calculation), a formula originally developed to examine glucose excursions for contrast glucose monitoring “and proven to be useful to an clinician to assess insulin action time profile 4.

To compare GIR flatness and insulin sensitivity after 2 hours (short protocol) and 3 hours (longer protocol) from the start of the insulin infusion.

STUDY DESIGN

Healthy adult males and females were recruited to participate in a 6-hour two-step (10 and 40 mU/m2*min-1) hyperinsulinemic-euglycemic clamp study. The protocol was approved by an ethics research board and informed consent was obtained from each subject.

Screening assessments included a 2-hour oral glucose tolerance test (OGTT) and 2-hour insulin sensitivity test in subjects with diabetes (20-250 mg/dL) or glucose (200 mg/dL). Subjects were asked to remain on a stable diet for 3 days prior to the clamp and instructed to fast the evening before the procedure.

Plasma glucose samples were measured every 5 min, at time 0 min, baseline (B) insulin infusion was started at a constant rate of 10 mU/m2*min-1 for 15 min, after which insulin infusion was increased to 40 mU/m2*min-1 until 300 min. Dextrose 20% (w/v) was infused to maintain target blood glucose of 90 mg/dL (Figure 1).

RESULTS

Table 1. Subject Characteristics and Anthropometric Results. Parameter Male (n=6) Female (n=9) Group (n=15)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male (n=6)</th>
<th>Female (n=9)</th>
<th>Group (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.8±3.9</td>
<td>30.8±3.3*</td>
<td>28.8±4.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177.3±5.8</td>
<td>157.3±6.9</td>
<td>167.3±5.0</td>
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<tr>
<td>Weight (kg)</td>
<td>86.7±12.7</td>
<td>69.9±14.1</td>
<td>79.0±13.3</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>25.8±3.9</td>
<td>23.3±2.7</td>
<td>24.6±2.9</td>
</tr>
</tbody>
</table>

By convention, the M-value is determined over a 20 min period 6. A higher M-value signifies greater peripheral glucose metabolism and insulin sensitivity. Overall, a flatter curve region, 300-360 min, yields a significantly greater M-value. Table 2. CONGIR is more sensitive than %Coefficient of Variation (CV) to Identify Flatness.

CONCLUSIONS

To our knowledge, this is the first application of CONGIR to a hyperinsulinemic-euglycemic clamp. CONGIR was more sensitive than %CV in distinguishing flatness between two segments of the GIR curve.

Our findings highlight the need for longer clamp duration to ensure a true steady state is achieved.

Since hyperinsulinemic-euglycemic clamps are widely used in early phase clinical research to evaluate diabetes drug efficacy, a novel measure of GIR flatness is a valuable pharmacodynamic tool for ensuring the integrity of insulin sensitivity determinations.

REFERENCES


CONTACT INFORMATION

Sabra Pagilialunga, PhD
Metabolic and Pharmacodynamic Specialist, Celerion
sabrar.pagilialunga@celerion.com

www.celerion.com