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FACT SHEET

Hyperinsulinemic Euglycemic Insulin Sensitivity Clamp

Insulin resistance, which may be defined as an impaired ability of insulin to modulate metabolism in target tissues, is a major therapeutic target in type 2 diabetes. In particular, accurate measurement of insulin action is necessary for the development of novel insulin-sensitizing drugs. The hyperinsulinemic euglycemic clamp, used primarily to assess insulin-mediated glucose disposal, is widely regarded as the reference method. ProSciento offers expertise in the measurement of insulin sensitivity using automated two-step hyperinsulinemic euglycemic clamp technology. This approach offers greater accuracy and less variability than manual clamps that are more operator-dependent.

General Uses and Considerations

Hyperinsulinemic euglycemic clamps can be safely performed in diverse patient groups including the elderly and patients with hepatic and renal disease. Inclusion and exclusion criteria should address issues such as commonly prescribed medications that may influence insulin sensitivity. Intercurrent acute or chronic illnesses and obesity or diabetes-associated co-morbidities may also affect whole-body insulin sensitivity. ProSciento's automated clamp methodology can be combined with complementary techniques such as isotopic determination of glucose turnover, indirect calorimetry to measure substrate utilization and fat, or muscle biopsy for assessment of tissue enzyme activity.

Subjects and Preparation

The subject is fasted >8 hours overnight. Limitations are placed on exercise, alcohol, caffeine and tobacco use, all of which may influence insulin sensitivity. Overnight admission to the clinical research facility prior to the clamp procedure helps ensure compliance with nutrition and exercise prescriptions and helps acclimate the subject to the clinical research environment. For patients with diabetes, a variable rate overnight intravenous infusion may be used to standardize blood glucose levels on the morning of the clamp.

Procedure

The two-step hyperinsulinemic euglycemic clamp typically involves:

- A low-dose insulin infusion period to suppress endogenous (principally hepatic) glucose production
- A high-rate insulin infusion period that provides a robust stimulus to glucose disposal (primarily in skeletal muscle)

The total study duration is six hours. An arm vein is cannulated for the infusion of insulin and glucose. Another venous cannula is placed in the contralateral forearm for sampling. The sampling limb is warmed to open arterio-venous channels providing blood that approximates the arterial supply; this avoids extraction by insulin-sensitive tissues and potential overestimation of apparent insulin action. Soluble human insulin or a rapid-acting insulin analogue is infused using a precision pump at a rate calculated to acutely elevate serum insulin concentration from basal (fasting) levels to predefined plateaus.

Example data

Subjects with type 2 diabetes (n=15) during second step of clamp at steady state; target blood glucose = 110 mg/dL (6.1 mmol/L)

Mean glucose infusion rate (M value) = 9.3 mg/kg/min

Standard deviation of M value = 0.4mg/kg/min

Key Variability Measures

Coefficient of variation of blood glucose = 4.1%

Mean deviation from target = 4.1%

ProSciento's automated clamp technology maintains blood glucose concentrations at target level with greater accuracy and lower variability than the manual glucose clamp method. The glucose infusion rate is adjusted minute-to-minute basis according to a feedback algorithm using glucose measurements obtained from continuously sampled arterialized blood. The algorithm calculates the amount of intravenous glucose (20% v/v) required to maintain the arterialized blood glucose constant at either euglycemia or isoglycemia during hyperinsulinemia.

During the final 30 minutes of each step, when near steady-state has been attained for insulin and glucose levels, the mean glucose infusion rate (M-value) provides a measure of whole-body insulin sensitivity. Greater insulin sensitivity is reflected by higher rates of exogenous glucose required to maintain the target glucose concentration, and vice versa.

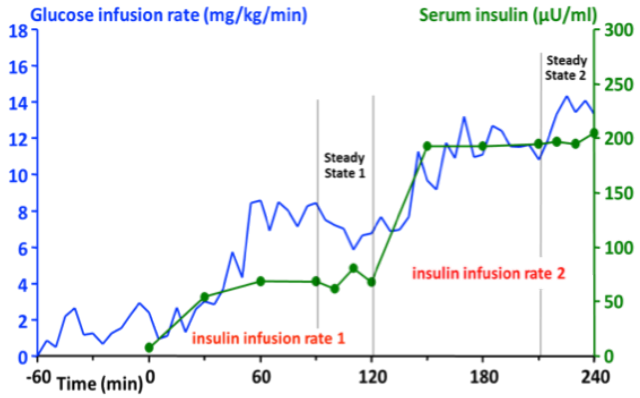

Figure 1: Insulin action is measured as the glucose infusion rate (GIR in mg/kg/min) required to maintain the target blood glucose concentration during the plateaus of hyperinsulinemia. Mean GIR is measured during the final 30 minutes of each step when a near steady state has been attained.

Interpretation

The following commonly used indexes of insulin action may be calculated:

M	(Whole body glucose metabolism at steady-state)	(mg/kg/min)/pmol/L
M/I	(Glucose metabolism divided by mean steady-state insulin concentration)	(mg/kg/min)/pmol/L
SI_{clamp}	(Insulin sensitivity index calculated from two-step clamp)	ml/(min x m^2) per pmol

The insulin sensitivity index (SI_{clamp}) calculated using ProSciento's automated two-step clamp methodology has the advantage of measuring insulin-mediated glucose disposal while accounting for insulin-independent glucose disposal.

Advantages of the Hyperinsulinemic Euglycemic Clamp

- Closed loop system with algorithm-driven glucose infusion reduces operator bias
- Accurate measure of insulin-mediated glucose disposal
- Sensitive and reproducible; co-efficient of variation <5% (see *Example Data: Key Variability Measures*)
- Complementary to other techniques, e.g. isotopic determination of hepatic vs. muscle insulin action

References

Krentz AJ, Heinemann L, Hompesch M. Methods for Quantifying Insulin Sensitivity. In: Krentz AJ, Heinemann L, Hompesch M (Eds). *Translational Research Methods for Diabetes, Obesity, and Cardiometabolic Drug Development: Focus on Early Phase Studies.* Springer 2015.

ProSciento Methodology Fact Sheets

Introduction to Glucose Clamps – Automated Versus Manual Techniques | Euglycemic Time-Action Profile Clamps | Hyperinsulinemic Euglycemic Insulin Sensitivity Clamp | Hypoglycemic Clamp Studies | Oral Glucose Tolerance and Mixed Meal Tolerance Tests | Graded Glucose Infusion for Assessment of β-Cell Function | MRI for Assessment of NAFLD/NASH

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Each fact sheet describes one select technique from our wide scope of complex methodologies for metabolic clinical research. Contact us for fact sheets highlighting additional techniques.

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