The glucose clamp is a highly reproducible and reliable method of assessing pancreatic ß-cell sensitivity to glucose and tissue sensitivity to insulin. The clamp also benefits from limiting the incidence of hypoglycaemic episodes due to the high frequency of blood glucose samples taken during the procedure. Since its introduction, the use of the glucose clamp technique has been widespread and is considered the gold standard technique for assessing ß-cell function and in vivo insulin sensitivity.

Benefits of Glucose Clamping

Blood glucose concentration is maintained at the desired level by use of an intravenous infusion of glucose (usually a 20% solution). By keeping the glucose concentration constant the normal glucose-insulin feedback mechanism is overridden and the plasma glucose concentration is placed under the control of the investigator. The glucose infusion rate (GIR) at any given time is equal to the net disappearance of glucose from the blood, in effect the ‘drug action’. The clamp technique provides the direct pharmacodynamic (PD) effect of the ‘drug’ to be assessed using the GIR-time profile. The blood glucose concentration is maintained at the desired level by frequently taken blood samples. During clamps, which can run up to 48 hours in duration, samples are usually taken every 5-15 minutes.

Clamping Services

ICON has extensive experience in glucose clamping at our San Antonio TX facility, with services that include:

- Clamp Protocol Design and Consultation
- Clamping Procedures
- Clamp Data Analysis

Types of Clamps Offered

- Euglycemic Clamp, where the glucose concentrations are maintained at their basal value
- Hyperinsulinemic Euglycemic Clamp, where hyperinsulinemia is achieved by intravenous infusion of insulin in order to stimulate peripheral glucose uptake and suppress hepatic glucose production while maintaining target euglycemia with a variable infusion of dextrose
- Hyperglycemic Clamp, where glucose concentrations are raised and maintained at an elevated concentration
- Hypoglycemic Clamp, where glucose concentrations are reduced in a controlled environment

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**Dedicated Clamping Ward**

- Battery and generator backup for uninterrupted service of critical equipment
- ACLS crash cart
- Securable, ability to limit access
- 6 dedicated intensive monitoring beds for clamping procedures
- Capabilities to perform six short duration clamps and four long duration clamps per day (twelve 30-hour clamps per week)
- Harvard high precision syringe pumps used for glucose/insulin infusions
- Isotope use for Hepatic glucose production

**Manual and Computer Algorithm Controlled Clamping**

ICON has employed both manual and computer algorithm controlled clamping strategies to maintain blood glucose concentrations and have developed their own “in-house” algorithm for such purpose. In manual clamping a trained operative decides upon the rate at which glucose is to be infused. The operative takes into account the difference from target concentration of the most recent blood glucose measurement and also takes into account the behavior of the glucose over the last few samples i.e. any overlying increasing/ decreasing trends.

The computer algorithm was developed based upon the principles of manual clamping and the algorithm uses current and previous blood glucose concentrations along with the current and previous infusion rates to predict the GIR needed to be infused to maintain the glucose concentration at the desired concentration.

**Clamping Expertise at ICON**

Dariush Elahi PhD

Dr. Elahi Leads ICON’s early phase glucose clamping programs globally, and provides expert, scientific consultation to sponsors who are developing therapeutic agents to treat endocrine/ metabolic disease.

Clinical physiologist with over 30 years of research experience, predominantly focused on translational investigations in humans in the area of regulation of glucose homeostasis in states of glucose tolerance and intolerance; including the study of volunteers with “normal” glucose tolerance, obesity, type II diabetes mellitus, and aged volunteers with academic appointments as a professor at The Johns Hopkins University School of Medicine.

Expert with respect to the methodologies used to conduct these types of investigations, including the clamp technique (Hyperinsulinemic / Euglycemic, Time-Action Profile, Hyperglycemic, Hypoglycemic, Pancreatic), the MinMod technique, as well as measurements of hormones (IRA and ELISA); and kinetics analyses of fuel substrates using both stable and radioactive tracers and the employment of these techniques during clamp studies.

Authored 147 scientific publications and is nationally and internationally recognised for his work on the role of insulin. Served as Research Physiologist and Senior Staff Fellow at the National Institutes of Health (NIH) and National Institutes on Aging.

Cyril Clarke, BSc,MB,BS MFPM VP, Translational Medicine

Dr. Cyril Clarke is a Clinical Pharmacologist with over 21 years’ experience in clinical research; 17 of these are within pharmaceutical industry clinical pharmacology.

Dr. Clarke trained in medicine and immunology at University College London and has had a long standing interest in the utilization of biomarker strategies in early clinical development. He teaches clinical pharmacology on the UK-based Diploma in Pharmaceutical Medicine course. Dr. Clarke has particular interest in the rational early development of biopharmaceuticals.

Dr. Clarke received his BSc in Immunology and Immunopharmacology and in 1989 his MBBS from University College, London. After training in internal medicine, he joined ICON in 1994 as Clinical Research Physician. He then moved into the roles of Associate Medical Director, Medical Director, and then Medical and Scientific Vice President prior to taking up his current role as Vice President of Translational Medicine.
Dr. Clarke has acted as Principal Investigator for over 300 Phase I studies, is Chair of the ABPI Experimental Medicine Expert network, and is an Honorary Senior Lecturer in Translational Medicine at the University of Manchester. He has extensive experience in the development of glucose lowering agents.

He has extensive experience in the development of glucose lowering agents and the development of glucose clamp methodology.

**Complete Metabolic Development Solution**

With industry-leading, globally harmonised early phase clinical operations, validated PD techniques, PK/PD modeling & simulation and a full range of supporting services; ICON delivers best-in-class metabolic development services on a stand-alone basis or as part of an integrated full-service solution. Our expertise, experience and established techniques, paired with proven patient access, allows us to effectively design, execute and analyse the clinical studies needed to expedite your early-phase metabolic programs.

**Clamping Study 2014**

IV Hyperinsulinemic-Euglycemic Clamps (N=6)
Glucose Goal 90mg/dL

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean GI</th>
<th>SE</th>
<th>CV%</th>
<th>SE</th>
<th>%goal</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-120 mins</td>
<td>91.0</td>
<td>2.8</td>
<td>4.24</td>
<td>0.52</td>
<td>97.1</td>
<td>0.9</td>
</tr>
<tr>
<td>90-120 mins</td>
<td>92.0</td>
<td>3.0</td>
<td>3.68</td>
<td>0.41</td>
<td>98.2</td>
<td>1.0</td>
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</tbody>
</table>

SC Hyperinsulinemic-Euglycemic Clamps (N=9) Glucose Goal 80 mg/dL

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean GI</th>
<th>SE</th>
<th>CV%</th>
<th>SE</th>
<th>%goal</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-150 mins</td>
<td>77.6</td>
<td>1.1</td>
<td>4.6</td>
<td>0.4</td>
<td>97.0</td>
<td>1.4</td>
</tr>
<tr>
<td>120-150 mins</td>
<td>77.5</td>
<td>1.0</td>
<td>4.1</td>
<td>0.5</td>
<td>96.8</td>
<td>1.3</td>
</tr>
</tbody>
</table>

**For more information contact:**

210-283-4553
or
210-283-4500

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