Insulin kinetics during HyperInsulinemia Euglycemia Therapy (HIET)

S. Penning¹, P. Massion², A.J. Le Compte³, T. Desaive¹ and J.G. Chase³

¹ Cardiovascular Research Centre, University of Liege, Liege, Belgium
² Department of Intensive Care, Liege University Hospital, Liege, Belgium
³ Department of Mechanical Engineering, Centre for Bio-Engineering, University of Canterbury, Christchurch, New Zealand

8th IFAC of Symposium on Biological and Medical Systems 2012
Introduction

Cardiogenic shock
Insulin action
HIET
Research purpose
Introduction > HIET

Hyper-Insulinemia Euglycemia Therapy (HIET)

Cardiogenic shock

- Cardiac pump failure
- Insufficient tissue perfusion
- Anaerobic metabolism
- Cardiac ATP from glucose
- Glucose supply

Calcium metabolism
- Vasodilator effects
- Anti-apoptosis

Energy metabolism
- Anti-oxidative effects
- Anti-inflammatory effects

Insulin

Glucose → ATP

Hyper-Insulinemia Euglycemia Therapy (HIET)
**Introduction > HIET**

**Insulin** 1 U/kg/h

**Dextrose** 400 g/day

- Patient with low insulin sensitivity
- Hypoglycemic risk
- Low insulin action
- Limited glycemia reduction
- Low exogenous glucose input
- Increased insulin sensitivity
- Important insulin action
Introduction > Research purpose

HIET nowadays

- Empirical therapy
- Difficult dosing
- High risk (hypoglycemia)

→ «Last chance» therapy

HIET in the future

- Model-based protocol
- Optimal interventions
- Tightly controlled glycemia

→ Safe and effective therapy

1) Should the insulin-glucose system model be adapted?
2) Should the insulin kinetics be modified at high insulin doses?
3) Is insulin sensitivity decisive for HIET optimisation?
Methods

Model of the glucose-insulin system
Methods > Model

Blood Glucose $G(t)$

- Endogenous glucose production $E_{GP}$
- Central Nervous System Uptake $CNS$ (receptor-bound insulin)
- Other insulin-independent glucose uptake $p_G \times G$
- Insulin-dependent glucose removal through receptor-bound insulin $SI(t) \times G \times \frac{Q}{1 + \alpha_G Q}$

Glucose absorption through stomach and gut $d_1$

Insulin injections $u_{ex}$

Insulin clearance
- Hepatic clearance $n_L \times \frac{I}{1 + \alpha_I I}$
- Kidney clearance $n_K \times I$

Endogenous insulin after 1st pass hepatic filtration $(1 - x_L) u_{en} = f(e^{-I(t)})$

$u_{en} = f(e^{-I(t)})$

Interstitial insulin $Q(t)$

$Q \times n_C \times \frac{1}{1 + \alpha_G Q}$

Interstitial insulin degradation through receptor binding
Results and Discussion

Comparison between measured and simulated $I$

Model adaptation
Results

- Comparison between measured and simulated $I$

Patient 1

- Measured $>$ Simulated
- Lower clearance in the model
Results

- Comparison between measured and simulated $I$

Patient 2

- Saturation at high insulin levels
- Higher clearance in the model

Hypothesis: erroneous measurements
Results

- **Comparison between measured and simulated $I$**

Patient 3

Measured > Simulated
Lower clearance in the model
Results

- **Comparison between measured and simulated $I$**

  Measured $>\sim$ Simulated $I$

  - Lower clearance in the model
  - Saturation at high insulin levels

  - Measured $>$ Simulated
  - Higher clearance in the model
Results

Reduced clearance (0h-10h)

→ Saturated renal clearance
  • Renal tubule receptors

Increased clearance (20 > t > 10h)

→ Unsaturated renal clearance
  • Alternative insulin receptors?

→ Additional clearance process
  • Elimination via urine?
  • Interstitial space storage?

Mechanisms:
  • Time-dependent?
  • Insulin plasma concentration dependent?
  • Insulin exposure dependent?
  • Patient-specific?
Results

- Adapted model

Patient 3
Results

- Adapted model

Patient 3

Graph showing measured and simulated I (mU/L) over time (hours) for Patient 3.
Results

☐ Adapted model

Patient 4

- Measured I
- Simulated I
- Simulated I
Results

- Adapted model

Patient 4

Additional renal process after 15 hours: $-0.7 * I$
Conclusion
Conclusion

1) Should the insulin-glucose system model be adapted? YES
2) Should the insulin kinetics be modified at high insulin doses? YES

Reduced clearance (0h-10h)
→ Saturated renal clearance

Increased clearance (t >10h)
→ Unsaturated renal clearance
→ Additional clearance process

Initial saturation
→ Inotropic insulin action
→ Effective HIET

Body adaptation (t >10h)
→ Large insulin elimination
→ Uneffective therapy
Thank you for your attention

Questions?