Insulin kinetics during HyperInsulinemia Euglycemia Therapy (HIET)

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Introduction

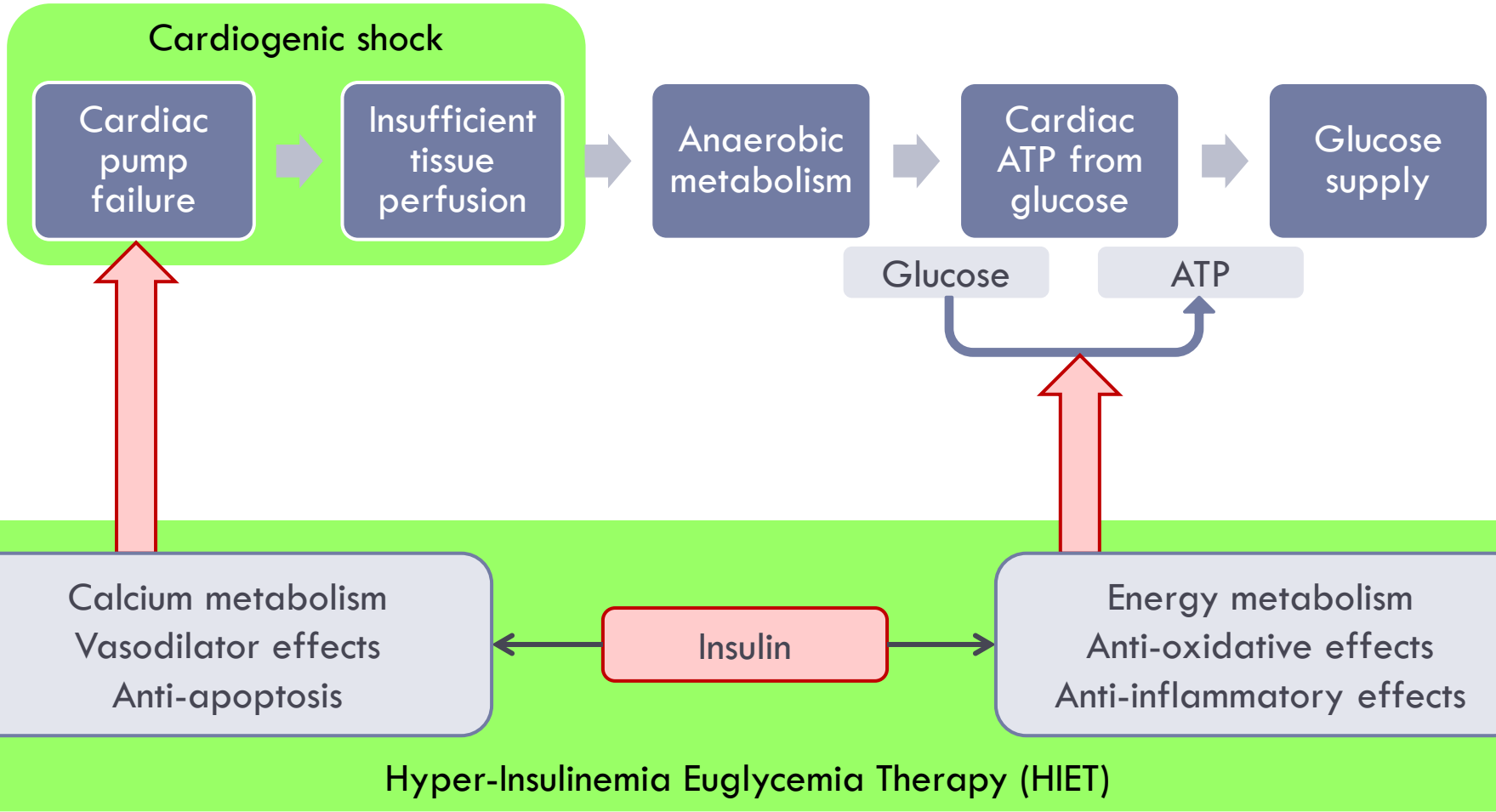
Cardiogenic shock

Insulin action

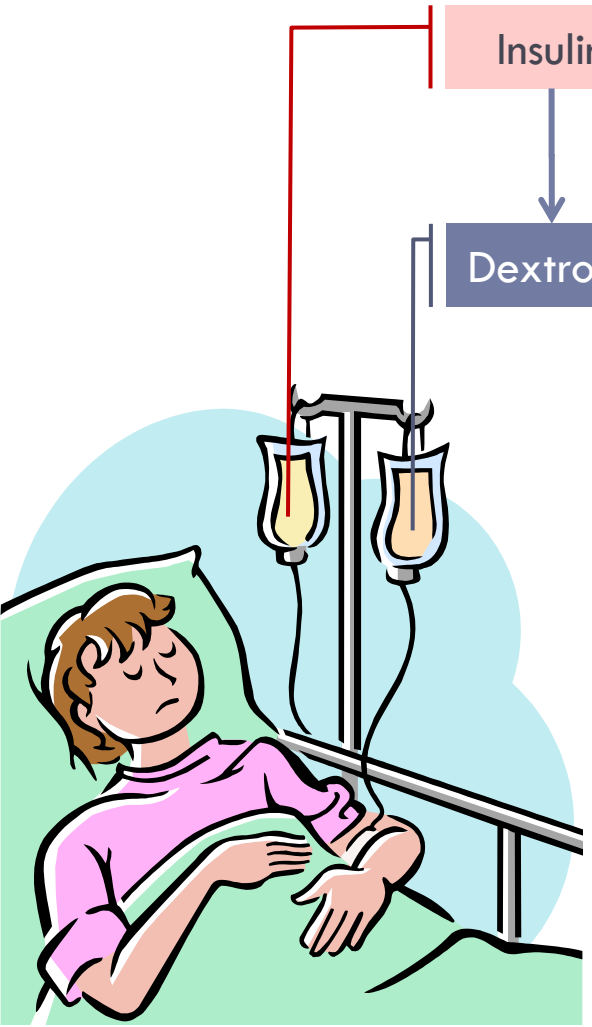
HIET

Research purpose

Introduction > HIET



Introduction > HIET



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

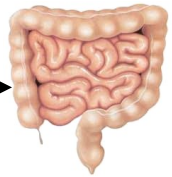
→ Safe and effective therapy

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



Central Nervous System Uptake CNS

Endogenous glucose production EGP

Other insulin-independent glucose uptake $p_G \times G$

d_1

d_2

Blood Glucose G(t)

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

PN

receptor binding

Insulin injections

u_{ex}

Plasma Insulin I(t)

n_I

Interstitial Insulin Q(t)

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

Interstitial insulin degradation through receptor binding

$(1-x_L)u_{en}$

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

Endogenous insulin after 1st pass hepatic filtration

Hepatic clearance

$$n_L \times \frac{I}{1+\alpha_I I}$$

Kidney clearance

$n_K \times I$

Results and Discussion

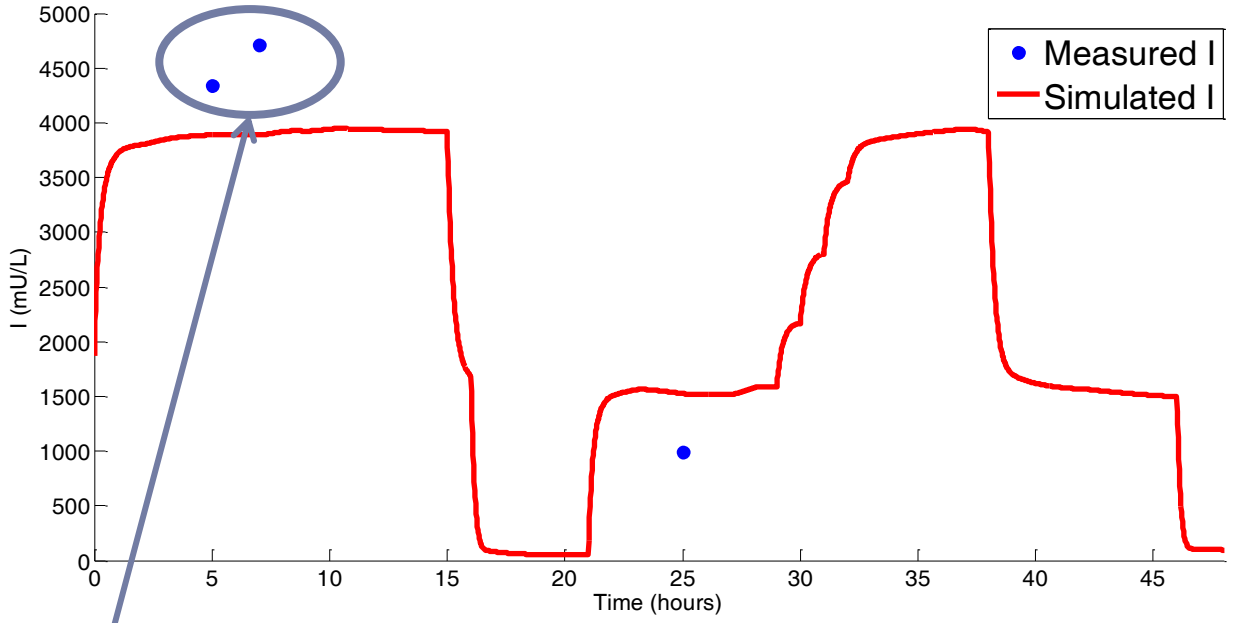
Comparison between measured and simulated I

Model adaptation

Results

- Comparison between measured and simulated I

Patient 1

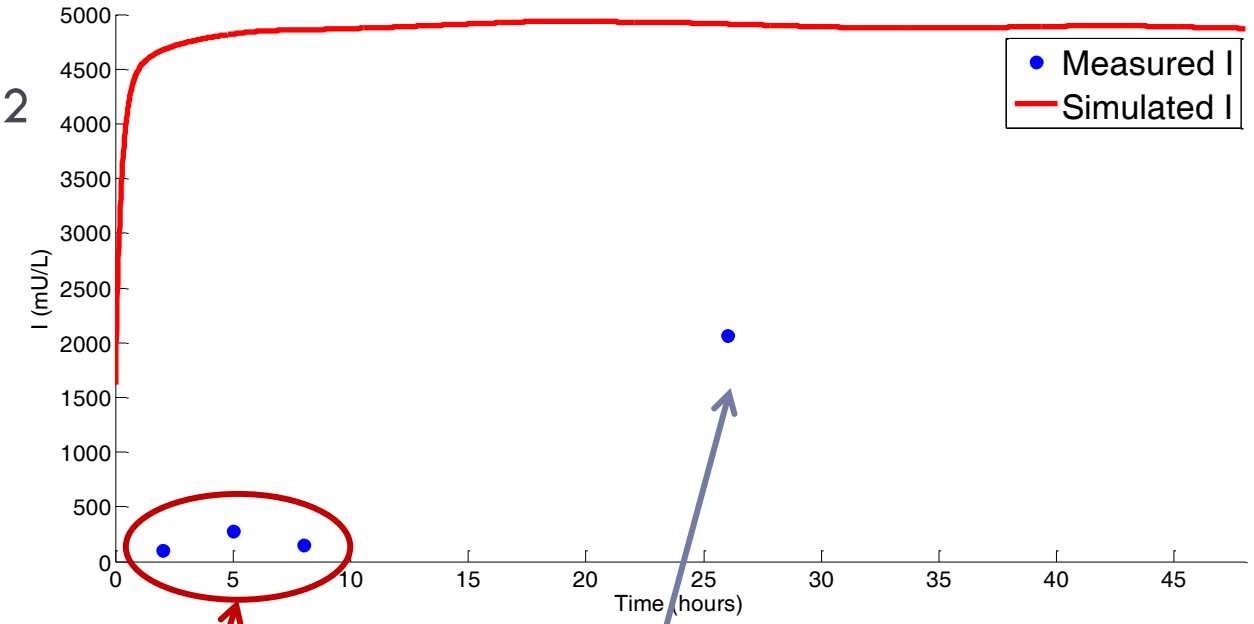


Measured > Simulated → Lower clearance in the model

Results

- Comparison between measured and simulated I

Patient 2



Saturation at high insulin levels

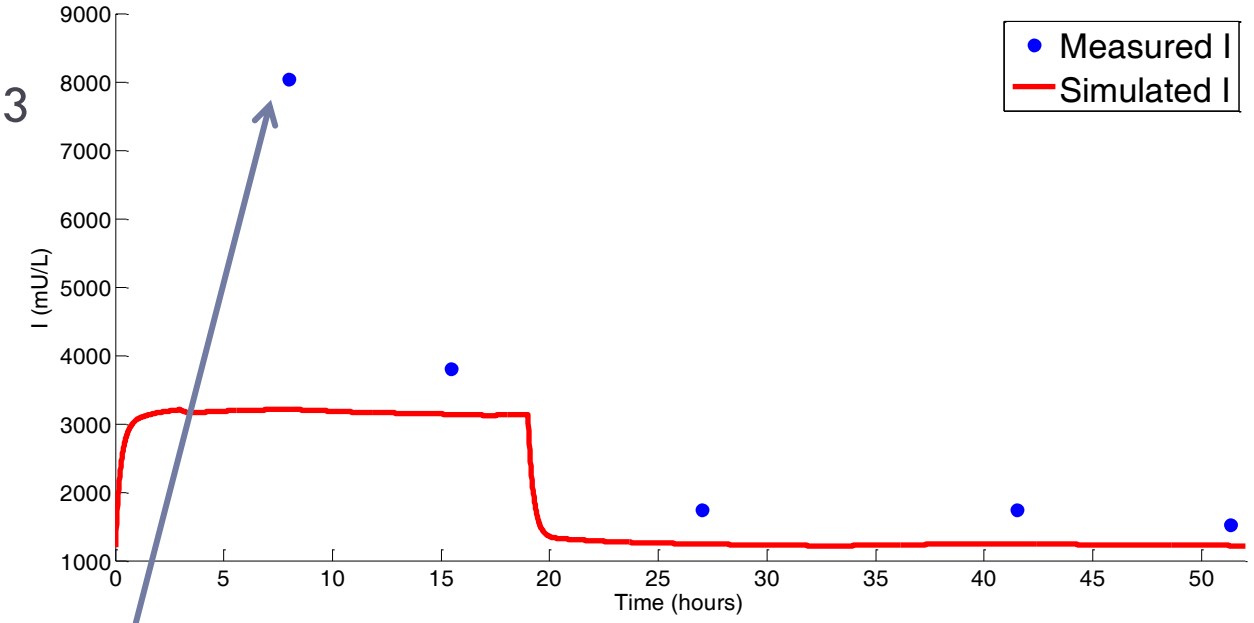
Higher clearance in the model

Hypothesis: erroneous measurements

Results

- Comparison between measured and simulated I

Patient 3

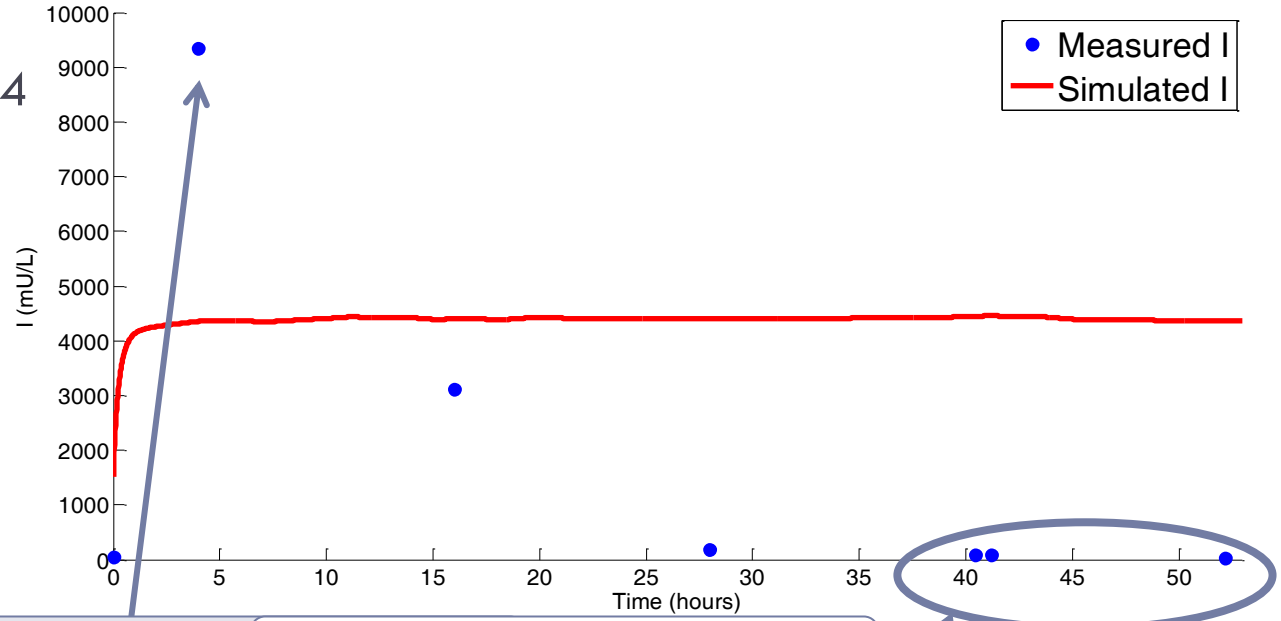


Measured > Simulated → Lower clearance in the model

Results

- Comparison between measured and simulated I

Patient 4



Measured > Simulated → Lower clearance in the model

Saturation at high insulin levels → 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?

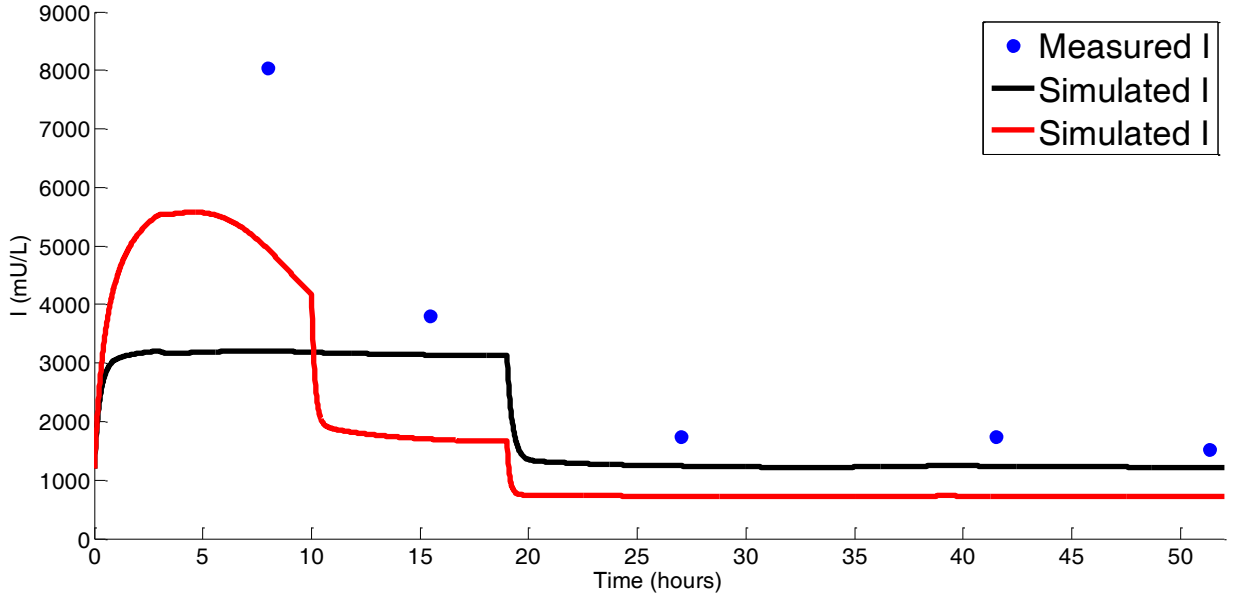
Mechanisms:

- Time-dependent?
- Insulin plasma concentration dependent?
- Insulin exposure dependent?
- Patient-specific?

Results

- Adapted model

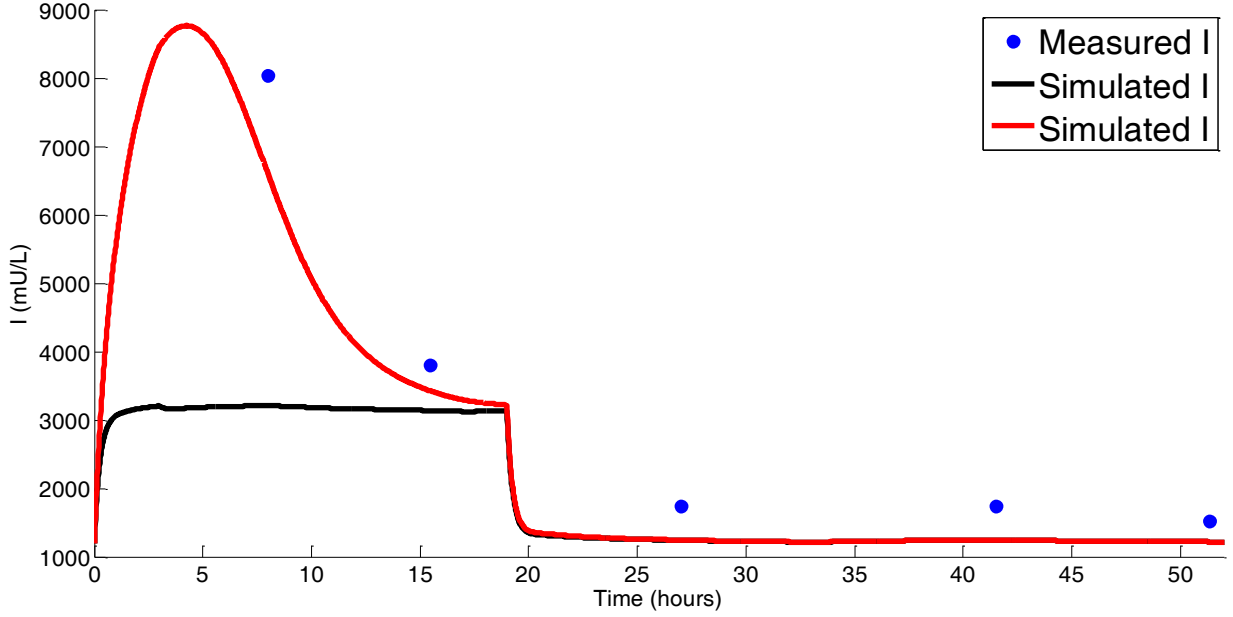
Patient 3



Results

- Adapted model

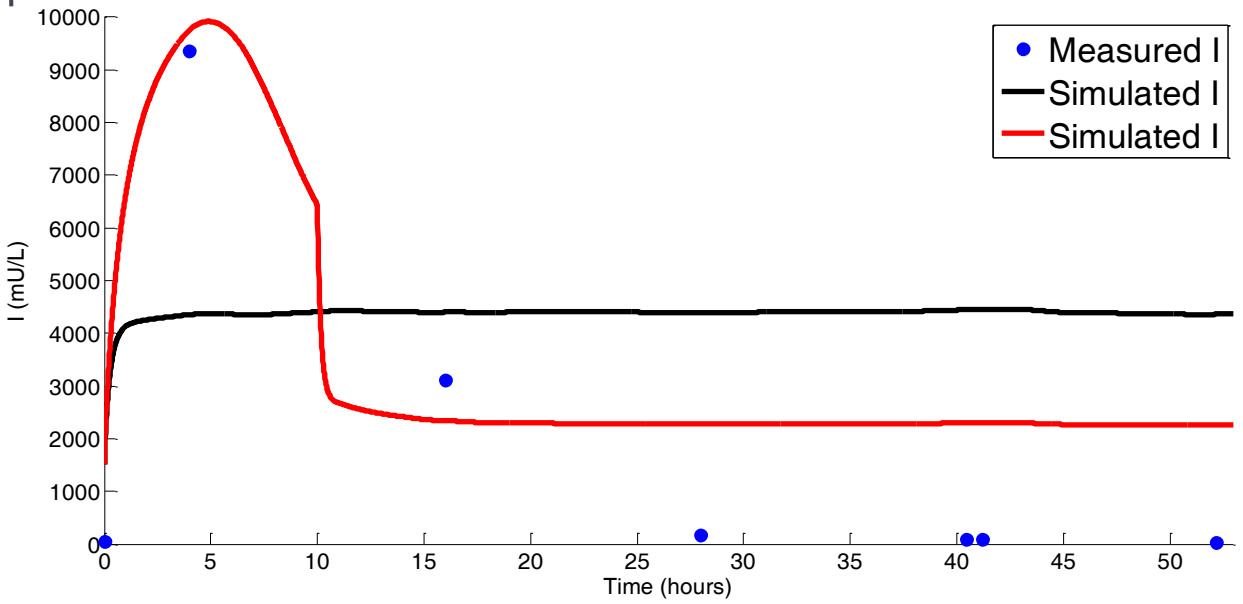
Patient 3



Results

- Adapted model

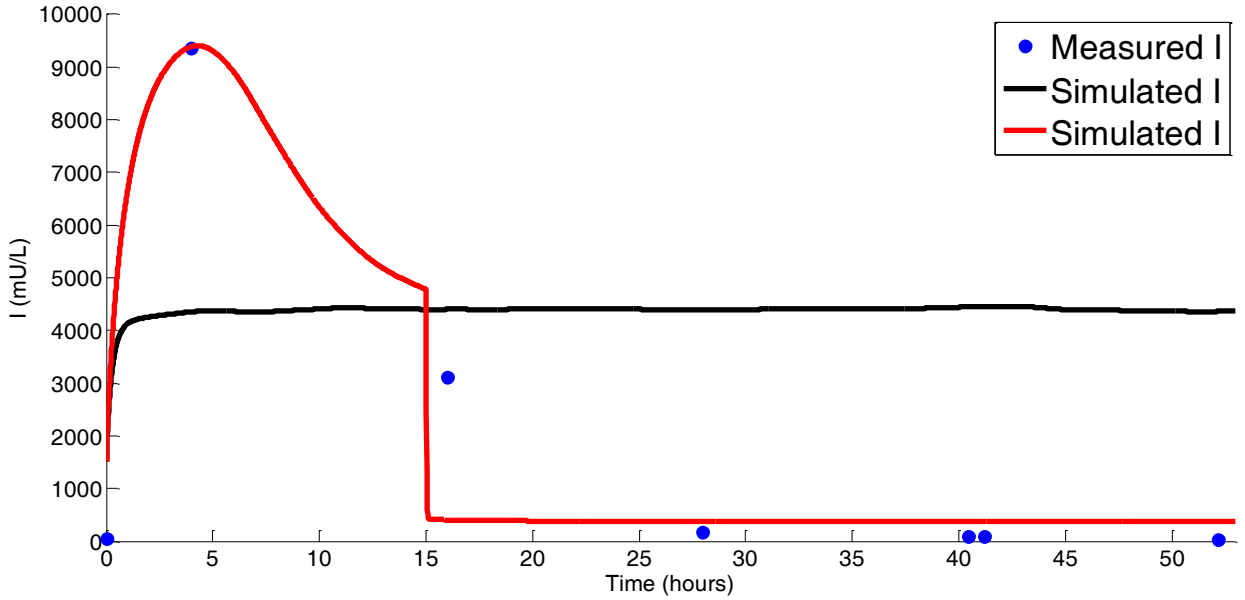
Patient 4



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?