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Use of Animal Testing for Evaluations of Physiologic Closed Loop Controllers – Fluid Resuscitation

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COI

– No commercial conflicts – MK

– Stock Ownership Arcos, Patents UTMB -- GK

FDA meeting 10-14-2015

Advantages of Animal Research

- **Focused – Test Hypothesis**
- **Rapid Results - potentially**
- **Lower Costs - usually**
- **Reproducible – ideally**
- **More Definitive – possibly**

e.g. when using specific focused animal model,

i.e. 40 %TBSA + moderate inhalation injury

Clinical Research
Advantages/Disadvantages

- **Definitive – potentially - usually**

- **Relevant**

  Most burn patients have co-morbidities
  except for DOD

- **Cost - high usually**

- **Long Development Times - usually**

!! Randomized Controlled Trials
Often Fail on Primary Endpoint
–often only generate new questions!

Pathways to Closed Loop

via road stops of Decision Support

Fluids to treat

Burn Shock

Hemorrhagic hypotension

Pressors

Hemodynamic Instability - Vasoplegia

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Start of the CL Pathway

Mathematical Models

Animal Data (pressors, fluids)

Patient Data (burn fluids)

Expert Opinion

Expert Panel – Physiologic Perspectives

Animal Testing (hemorrhage-vasoplegia)

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First Stop on the CL Pathway

- - Burn Resuscitation

Replace vascular losses

Least amount of fluid

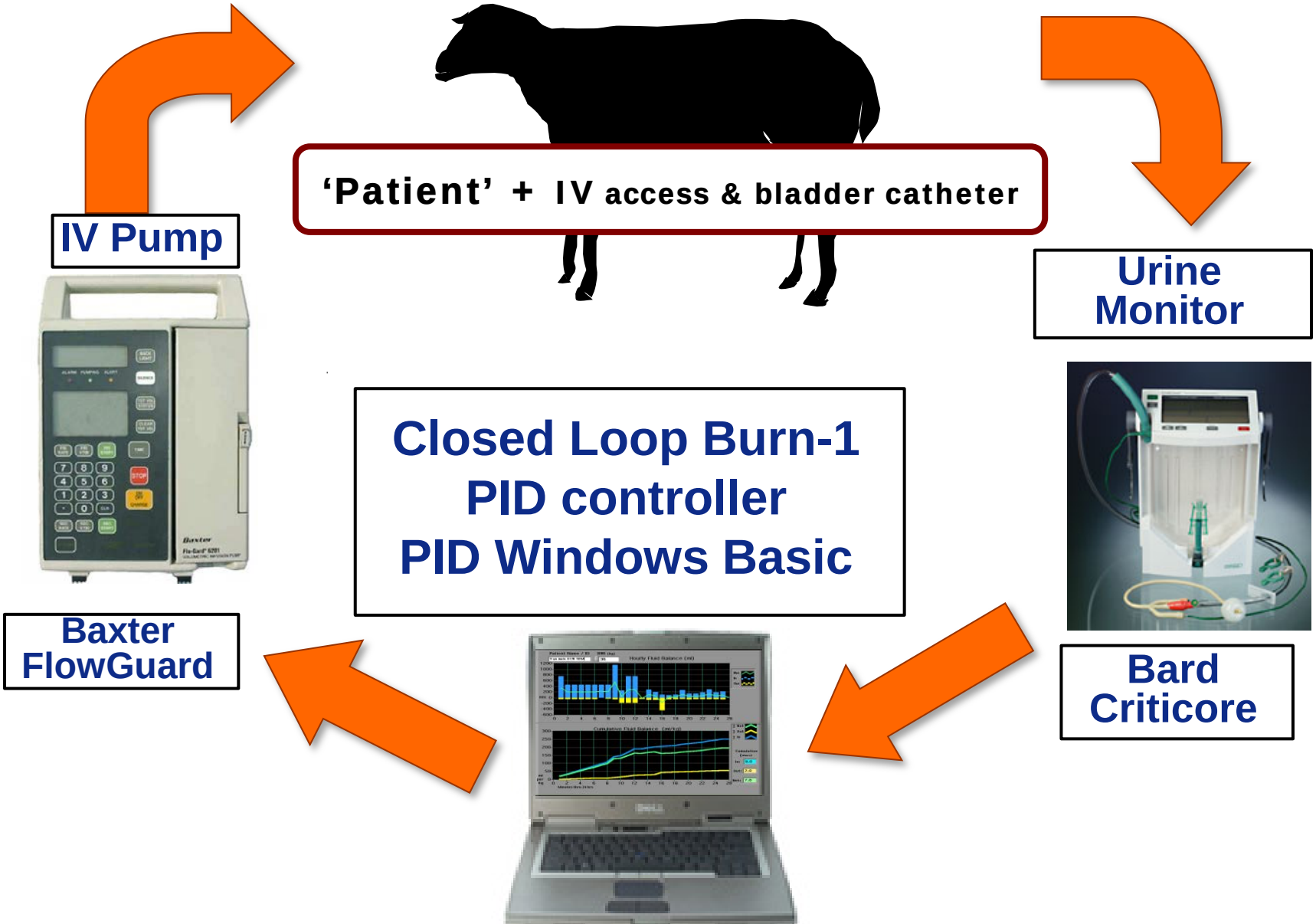
- that meet physiologic needs
  - endorgan perfusion
  - global perfusion

Use Urinary Output as surrogate for

- endorgan perfusion & cardiac output

Closed Loop Burn Resuscitation

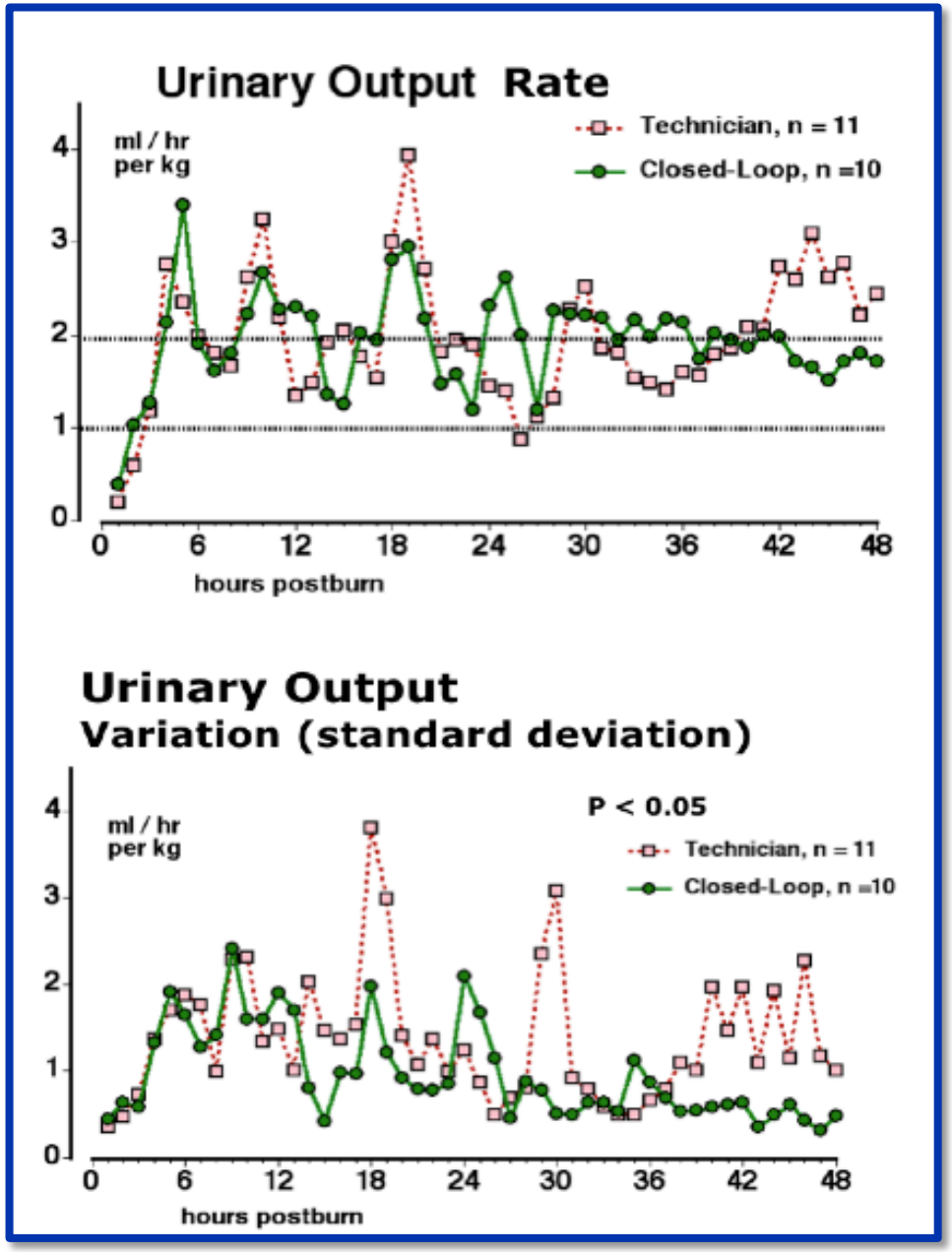
- - Hoskins, 2006



Closed-Loop Resuscitation of Burn Shock

Stephen L. Hoskins, PhD, Geir Ivar Elgjo, MD, PhD,*
Jialung Lu, PhD,* Hao Ying, PhD,† James J. Grady, Dr PH,*
David N. Herndon, MD‡, George C. Kramer, PhD*

(J Burn Care Res 2006;27:377–385)



Closed Loop UO

More time in target range

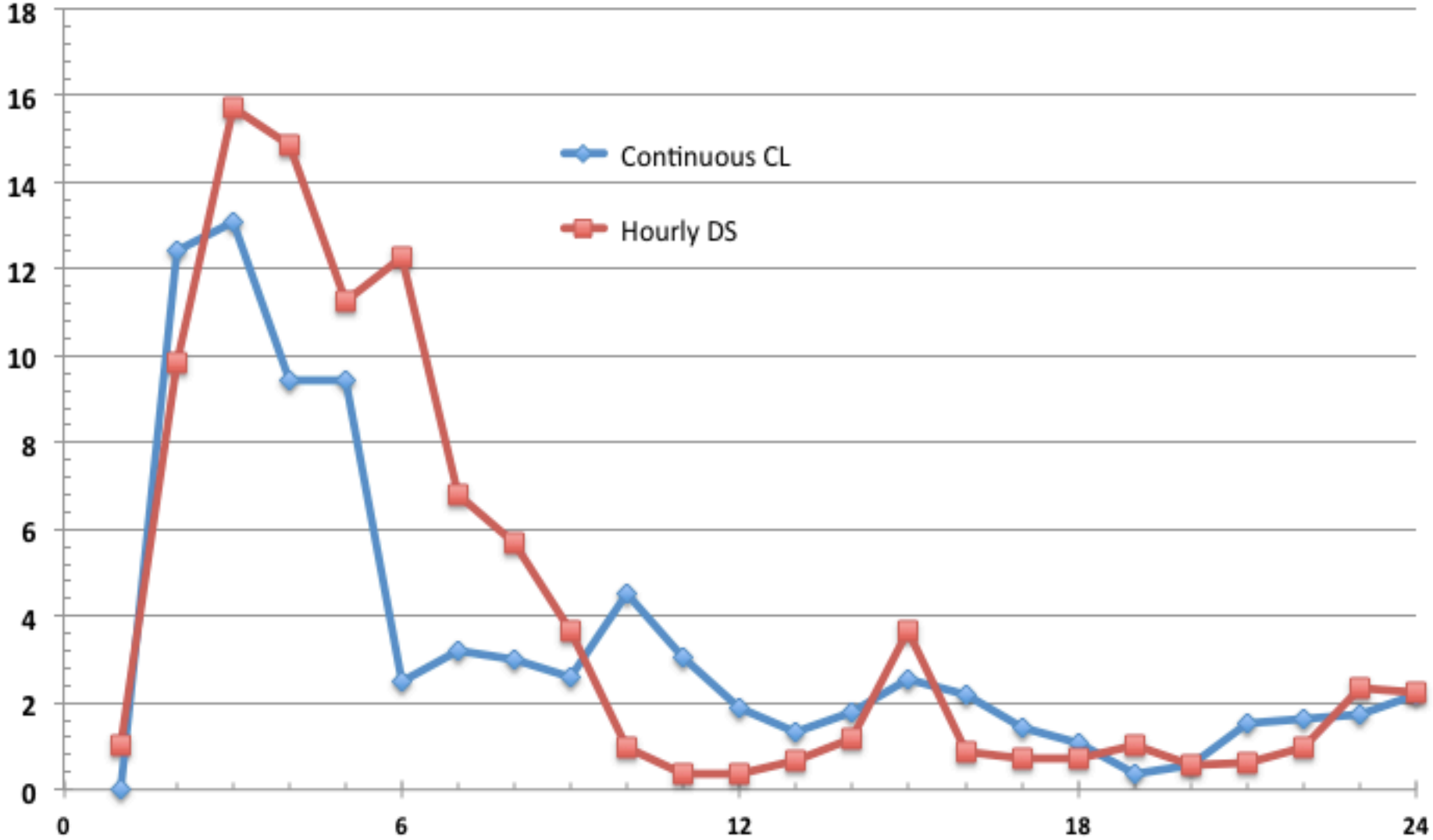
Less variability

Lower Fluid Volumes

LR Infused
ml/kg per hour

Sheep weight = 35 -55 Kg

40% TBSA burn alone



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In 2007 we concluded that ….

Closed Loop Burn Resuscitation is feasible and may be efficacious.

more UO on target, less fluid requirements

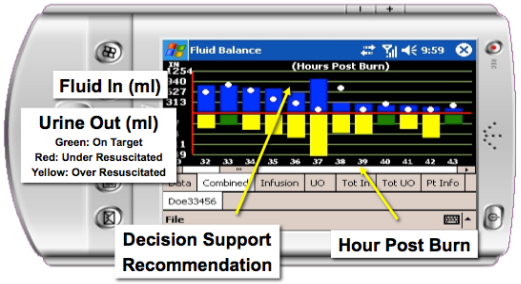
There was

no regulatory appetite for Closed Loop Fluid Therapy.

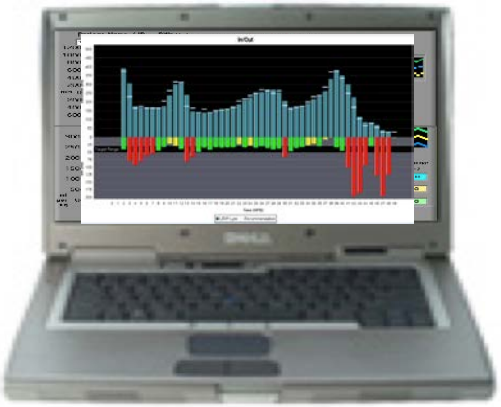
We would tackle Decision Support Burn Resuscitation.

Computerized Burn Resuscitation Decision Support via Salinas algo

PDA



Laptop



Server Based

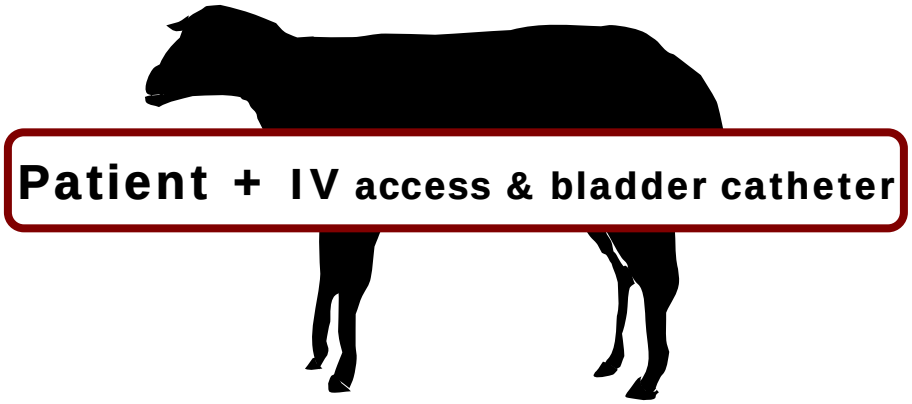
Product

Closed Loop Burn

2014 - 2015

Burn Resuscitation Closed Loop

Kramer, Salinas, Fenrich, 2014



IV Pump

Urine Monitor

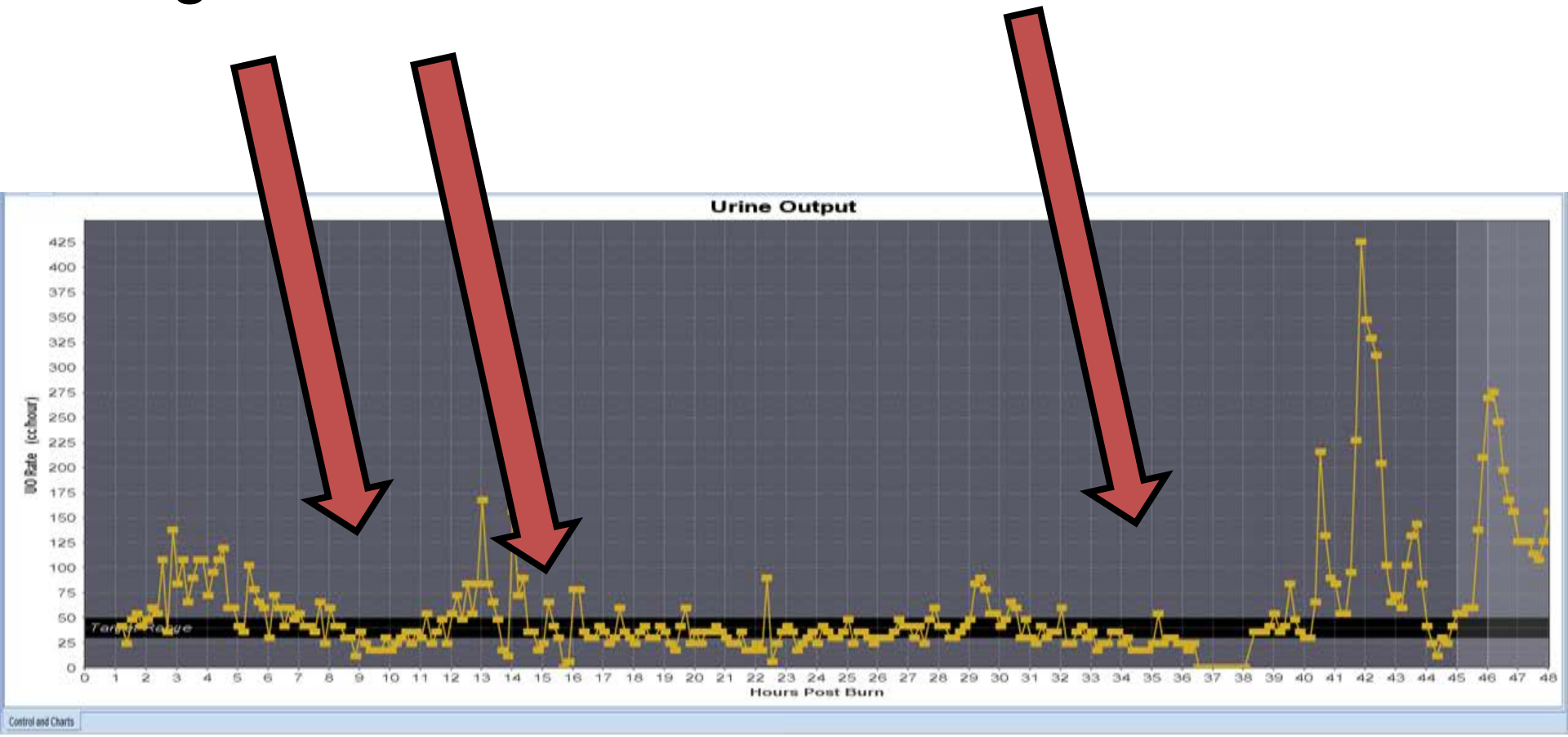
Closed Loop Controller
Salinas algo

Options

Sheep 38 48 hrs of Closed Loop Control
Salinas Closed Loop Algorithm

Infusion rate adjusted very 10 minutes

Target UO achieved

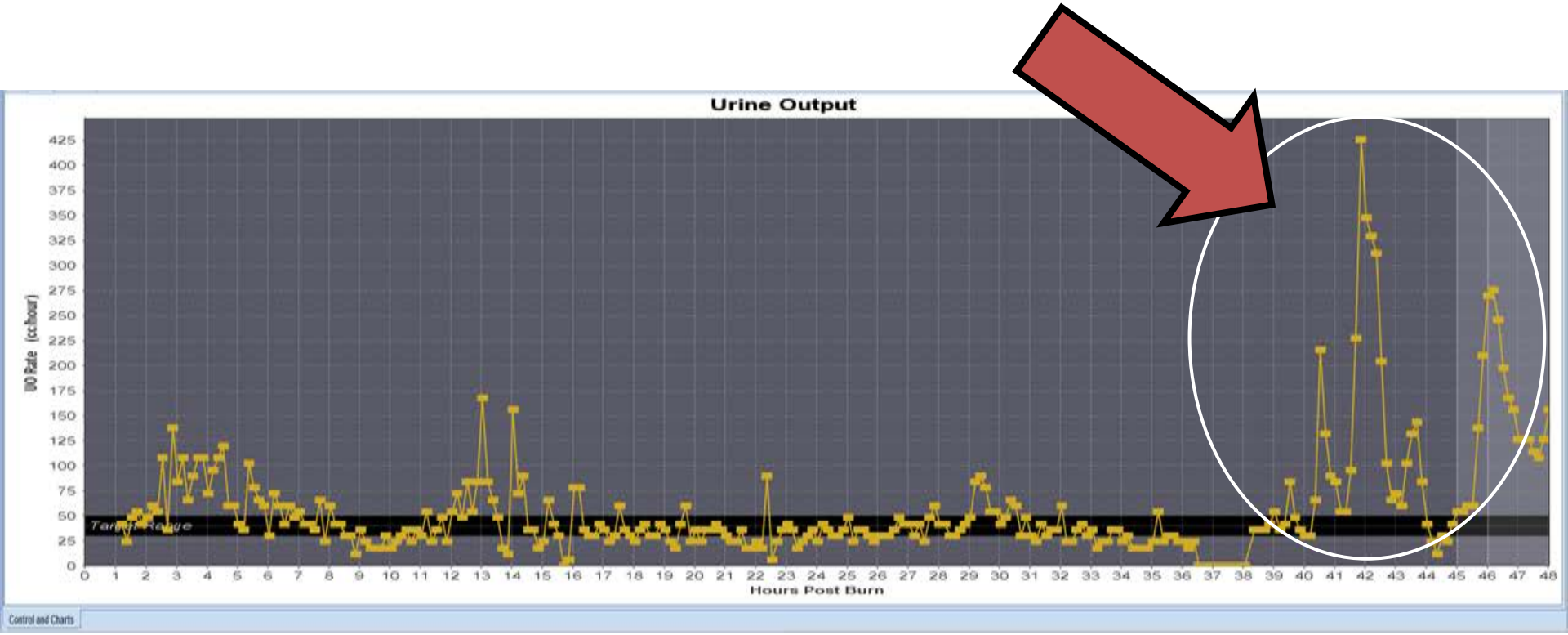


Sheep 38 48 hrs of Closed Loop Control
Salinas Closed Loop Algorithm

Target UO achieved.

Animal was mobilizing fluid at 39 hours post burn.

Resuscitation complete.



Planned Studies

Closed Loop Burn 2016- 17

- More Severe Burn Injuries
- Combined Injuries
- Burn + Lung Injury
- Burns + Abdominal Compartment Syndrome
- Burns + Hemorrhage

- -

Closed Loop Burn 2017- 18

- Patient Studies

Closed Loop Fluids for Hemorrhagic Hypotension

- PI controller
- Non-linear Decision Tables
- Fuzzy Logic Controller
- Titrated Bolus Therapy

Other Stop on the Pathway

- - Pressor Control of Vasoplegia

Titrate Phenylephrine

- **Collect Dose Response Data – swine**
- **Construct Model**
- **Develop algorithm – test and tune**
- **Compare Intensivist vs. Computerized Algorithm**

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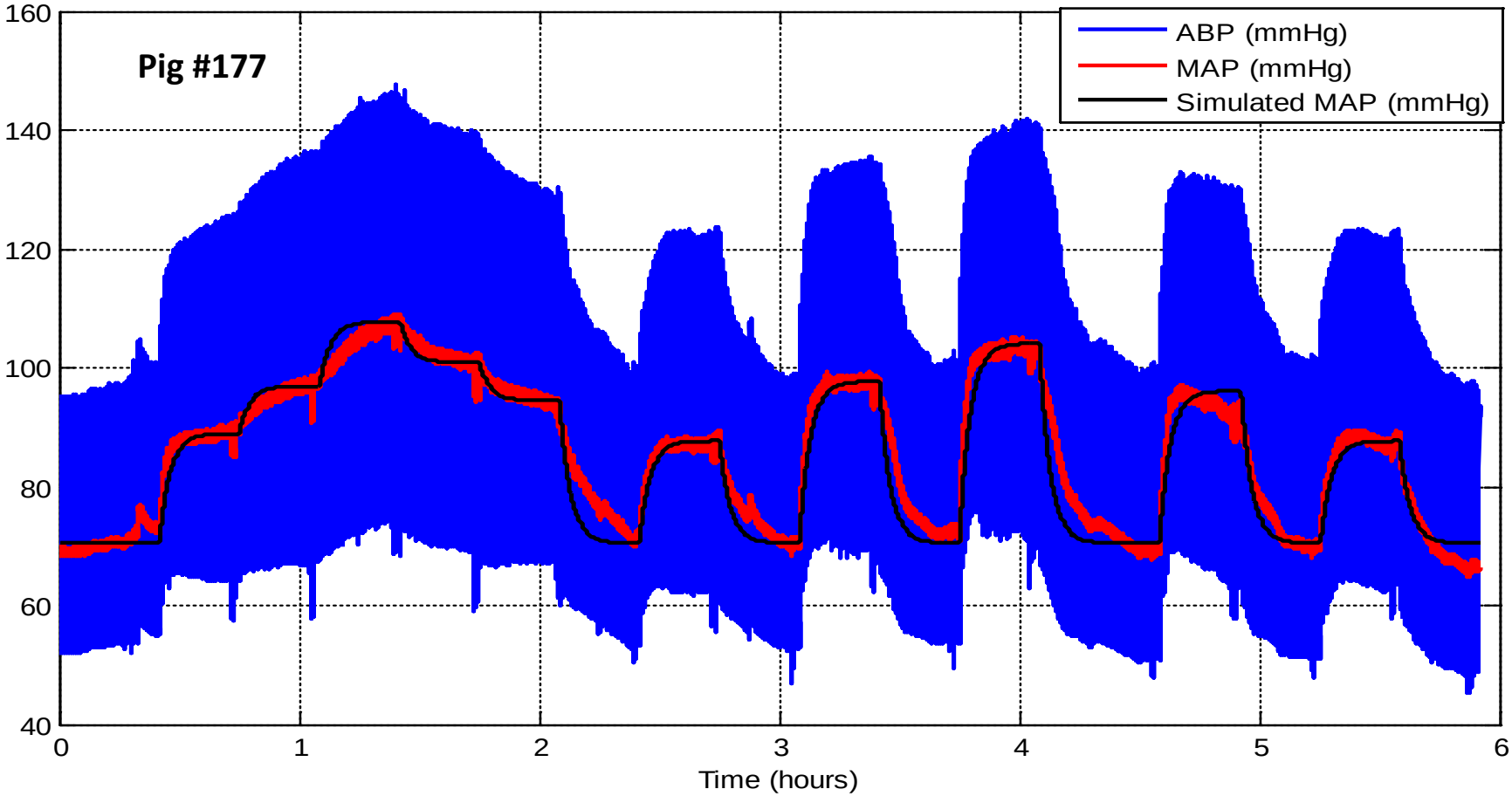
Dose Response and Model

Measured vs. Simulated PHP Response

Step Changes in Phenylephrine



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Modeling PHP Response

- First order plus time delay model

$$G(s) = \frac{\Delta P(s)}{I(s)} = K\frac{e^{-Ts}}{\tau s + 1}$$

K (in mmHg/ml/hr) variable sensitivity to PHP.
τ First order lag constant resulting from the uptake, distribution and bio-transformation of PHP.
T (in seconds) initial activation time delay.

- Model parameters (from 15 anesthetized swine)

$$\Delta\dot{P}(t) = -\frac{1}{\tau}\Delta P(t) + \frac{K}{\tau}I(t-T)$$

$$MAP(t) = \Delta P(t) + MAP_{base}$$

$0.1 \le K \le 1.2$ (mmHg/ml/hr)
$140 \le \tau \le 280$ (sec)
$20 \le T \le 50$ (sec)

PHP Algorithm

- An anti windup PI controller was designed

$$I(t) = K_P e(t) + K_I\int_0^t e(\tau)d\tau \quad = \quad K_P\left[e(t) + \frac{1}{T_I}\int_0^t e(\tau)d\tau\right]$$

- Tuning parameters were obtained by applying robust control techniques

Closed Loop System – PACCS
Computer vs. Doctor

Body Guard Twin
IV Drug Pump

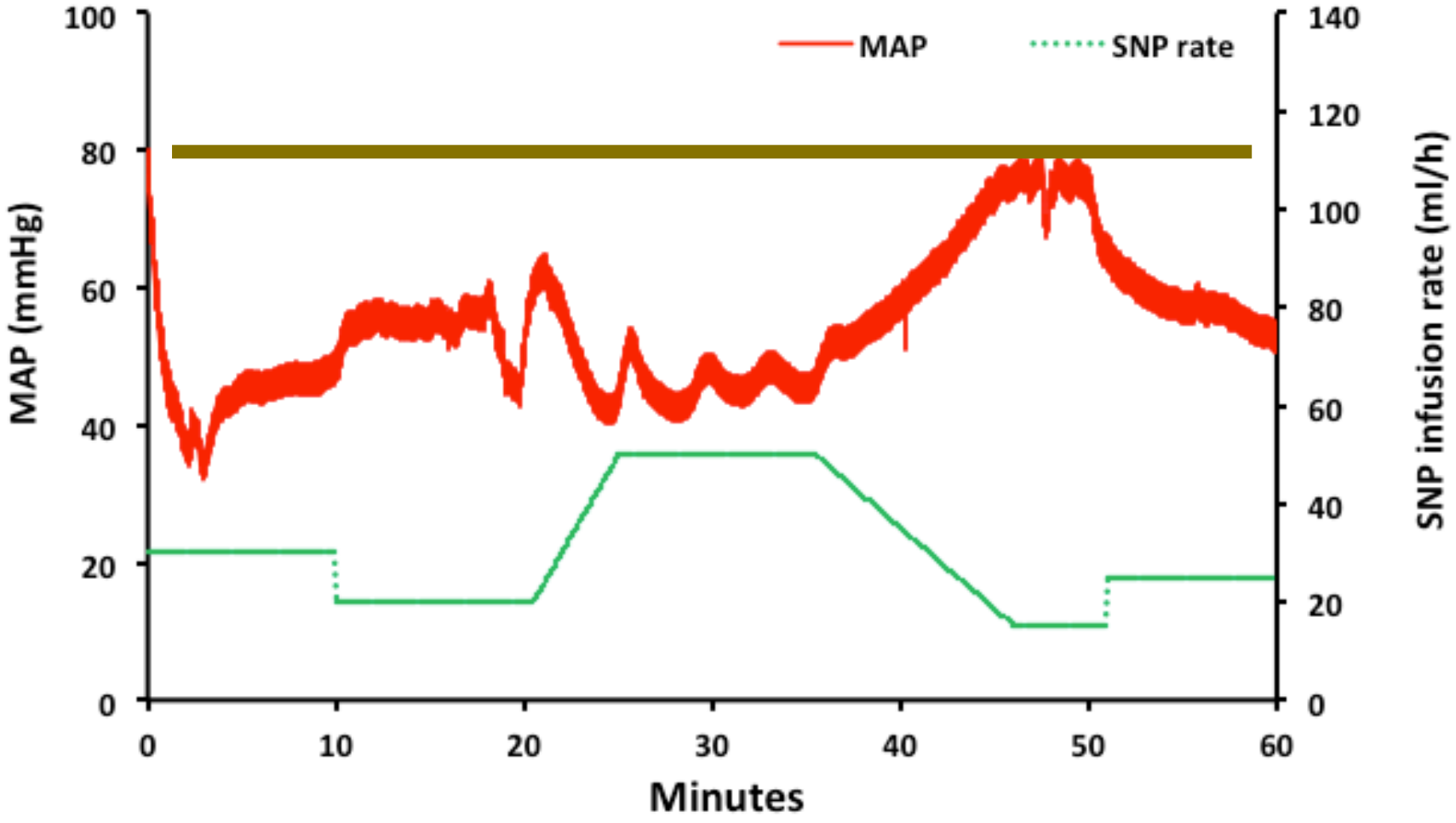
Philips MP2

Computer

vs.

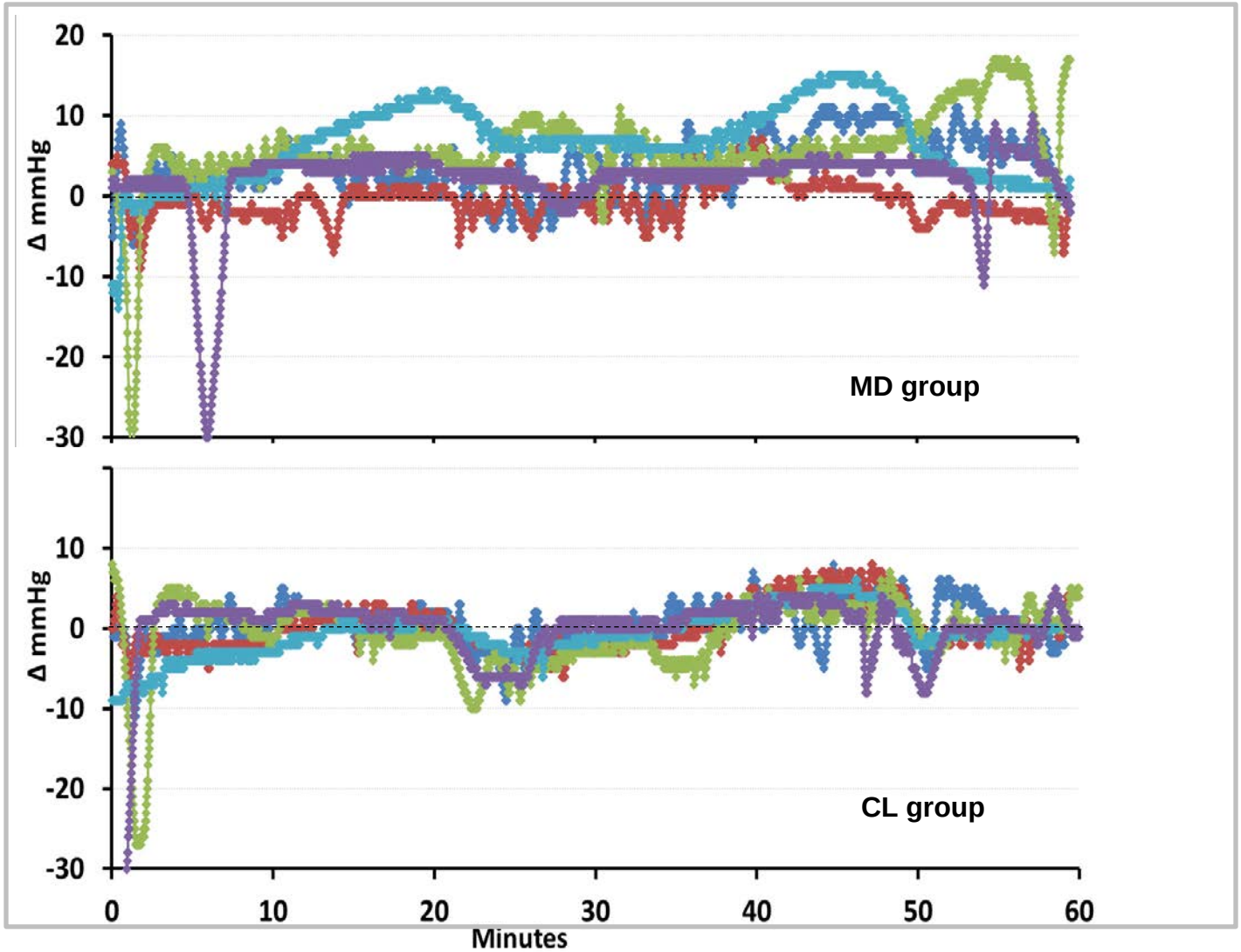
Anesthesiologist

Hypotension – Nitroprusside Challenge



5 pigs with SNP challenge - cross over design
Anesthesiologist vs. Computer

MAP measured - MAP target (Δ mmHg) during a 1-hour study.



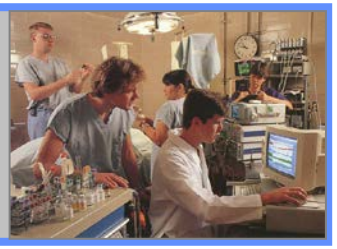
Closed Loop Pressors

- Feasible
- Less variability
- Equivalent to fully focused intensivist!
- Perhaps less physiologic cost
- Next step
  - More challenging animal models
  - Patient studies

Questions

UTMB
The University of Texas Medical Branch

Resuscitation
Research
Laboratory



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