Cardiorenal Function Estimation Using Near-Infrared Fluorimetry

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Disclosures

• Support:
  – The STA/Fresenius Research Award
    • THANK YOU!
  – K08 DK 090754
• IP (published)
  – Relating to:
    • General anesthesia (20150027439)
    • Critical care patient safety (2015095408)
    • Cycling safety (20140118129)
  – None in the space we will discuss
Perioperative AKI

- 1% major noncardiac surgery (Kheterpal 2007, 2009)
  - 27m operations/y = 270,000 cases of AKI/y
- 5-30% cardiac/vascular (Hou, 1983, others)
- Mild AKI ↑ risk of hospital death 6-8x (KDIGO, 2012)
- Critically ill: 70% (Schreier, 2004, Xue 2006, Waikar 2006)

Perioperative AKI Pathophysiology

- Most common cause of AKI (all comers)
  - Hypoperfusion
- Other insults in periop environment
  - Nephrotoxins (abx, contrast)
  - Obstruction
  - Rare
- Perioperative renal monitoring should focus on physiologic indicator of renal hypoperfusion

Diagnosis Delayed
GFR: The Concept of Clearance

- Glomerular Filtration Rate is plasma clearance by the kidney of a filtered molecule
  \[
  \frac{dx}{dt} = \frac{\text{mass}}{\text{time}} = \frac{\text{volume}}{\text{time}} = \text{flow}
  \]

- “The volume of plasma completely filtered per unit time”

GFR: The Concept of Clearance

- Availability to the nephron is assumed
- Altered by:
  - Extrarenal elimination,
  - secretion
  - resorption
- May measure plasma disappearance of applicable substance
  - Inulin, urea

GFR in AKI

- Greatly reduced within minutes of renal ischemia
  - Mechanism not well understood
- Physiologic indicator of extent of renal insult
- Closely correlates with outcomes including death and dialysis
- Periop renal monitoring of GFR or correlate may yield actionable data
Need for a Perioperative Monitor

Clearance modeling from Concentration
- $C = V_0 \ln(2) / t_{1/2}$
  - Requires $V_0$
- 1 compartment model
  - $GFR = \text{dose} (k_1) / A$

From Brenner & Rector, Ch 25

Renal Clearance & Imaging
- Iodinated Contrast
  - Extensive literature, strong data
  - Paradoxical...
- Fluorophores and Fluorimetry
  - FITC...
AKI Model: CA/CPR

• 8 min KCl-induced cardiac arrest
• CPR with epinephrine
• Robust AKI measured 24h after CA/CPR
  – 10-15% cell death in PT
  – Creatinine 4-8x normal
  – GFR ~zero
  – Resolves by day 3

An Observation...

Imaging Cardiac Function

• Many attempts
  – Diffusion
  – Interference (Hb)
  – Fluorophore toxicity
  – Competing clearance
  – Heterogeneous methods
  – Experimental/equipment limitations
Near-Infrared Fluorimetry

- Long wavelengths penetrate tissue well
- INVOS, others
- Few physiologic fluorophores but active investigation
- Frangioni Lab

**ZW800-1**

- Zwitterionic
- MW 943 D
  - Creatinine ~100
  - Inulin ~5000
- 90% 4h recovery in urine (Choi, 2011)
- Nontoxic
- \( \varepsilon = 2x \) ICG
- NEXT molecule

**Early Data with ZW800-1**
Early Data with ZW800-1

No CA/CPR 24h after CA/CPR

0 min

1 frame/5 min total 125 min

Early Data with ZW800-1

ZW800 Clearance in 5 mice

Normalized AFU

Time

Device Concept

- TCS3200 sensor-on-chip
  - A-D+amplification
  - Intensity:frequency
- Custom filterset
- 5 W LED's
- Power source
- microcontroller
Device Implementation

- 3D printed envelope
- 2 Filtersets for correlation
  - FITC (inulin)
  - ZW800-1
- Satisfactory linear response

Device Implementation

Device Data

- Low frequency at low brightness
- Time dependence
- Reasonable clearance signal
- Interference in FITC channel
- Opacity of 3D printed material
Technology Second Stage

- Biomedical Innovation Program Proposal
  - Not our molecule
  - FDA
  - Drug-device (high risk)
  - Is there any way to get around the need for exogenous fluorophore?

Decay without Clearance

- Noted loss of signal in nephrectomized mice
- Serum decay rate matched nephrectomy decay
- Nonrenal clearance entirely decay.
- Limitation
  - Longer clearance time results in greater decay

ZW800-1/FITC-Inulin Paired Clearance

- LICOR whole-animal near infrared imager
- Simultaneous injection of FITC-Inulin and ZW800-1
  - Sham and 24h after CA/CPR
  - FITC-inulin 10mg 100% lethal in CA/CPR mice
- Collect 800nm images q5m for 180 m
  - Second phase 55min-180 min
    - 1 phase model
- Collect tail blood (microcap)x4
  - 490-530nm excitation/fluorescence for FITC
    - 1 phase model
Imaging ZW800-1 Renal Clearance

**FITC-Inulin: ZW 800 Clearance Correlation**

- \( r = 0.9 \)
- \( p < 0.0001 \)

**Bland-Altman Analysis**

- Bias = 6.5 ± 26 @L/min
Cardiac Function and Fluorescence

- Conceptually:
  - Signal ~ k1*( molecules )
  - Molecules~dose-time(rate delivered)
  - Rate~cardiac output-diffusion restriction

- Hypothesis:
  - Fluorescence rate-of-rise correlates with cardiac output after rapid bolus injection

Measurement of Cardiac Function

- 2D echocardiography
- Well characterized in mouse
- LF function:
  - FS
  - EF

Fluorescence Distribution Protocol

- CA/CPR
  - 2h
  - 24h
- Inject ZW800-1
  - Rapid NIR imaging
  - 1 image/s*10m
- Analysis
  - 7 ROI
  - Correlate with TTE
Fluorescence Distribution Example

No CA/CPR

2h after CA/CPR

1 frame/1 second total 120 seconds
false color indicates signal intensity
Summary

- ZW800-1 is renally cleared, with plasma quenching
- Compensation for plasma quenching yields replicable measurement of GFR
- Well tolerated in critically ill animals
- ZW800-1 clearance compares favorably with Inulin GFR

Summary

- ZW800-1 fluorescence uptake correlates with FS
- Additional data analysis underway
- Promising minimally invasive technique in rodents
- Regulatory, IP challenges for this technology

Future Directions

- Scientific
  - Complete current data analysis and publish
  - Continue collaboration with Choi lab
- Technology
  - Identified need and desire for realtime monitors of renal function
  - Significant interest in perioperative community
  - 2 additional, derivative technologies in very early stages
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