Predictive Modeling of Acute Blood Loss: The Compensatory Reserve Index (CRI)

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Disclosures

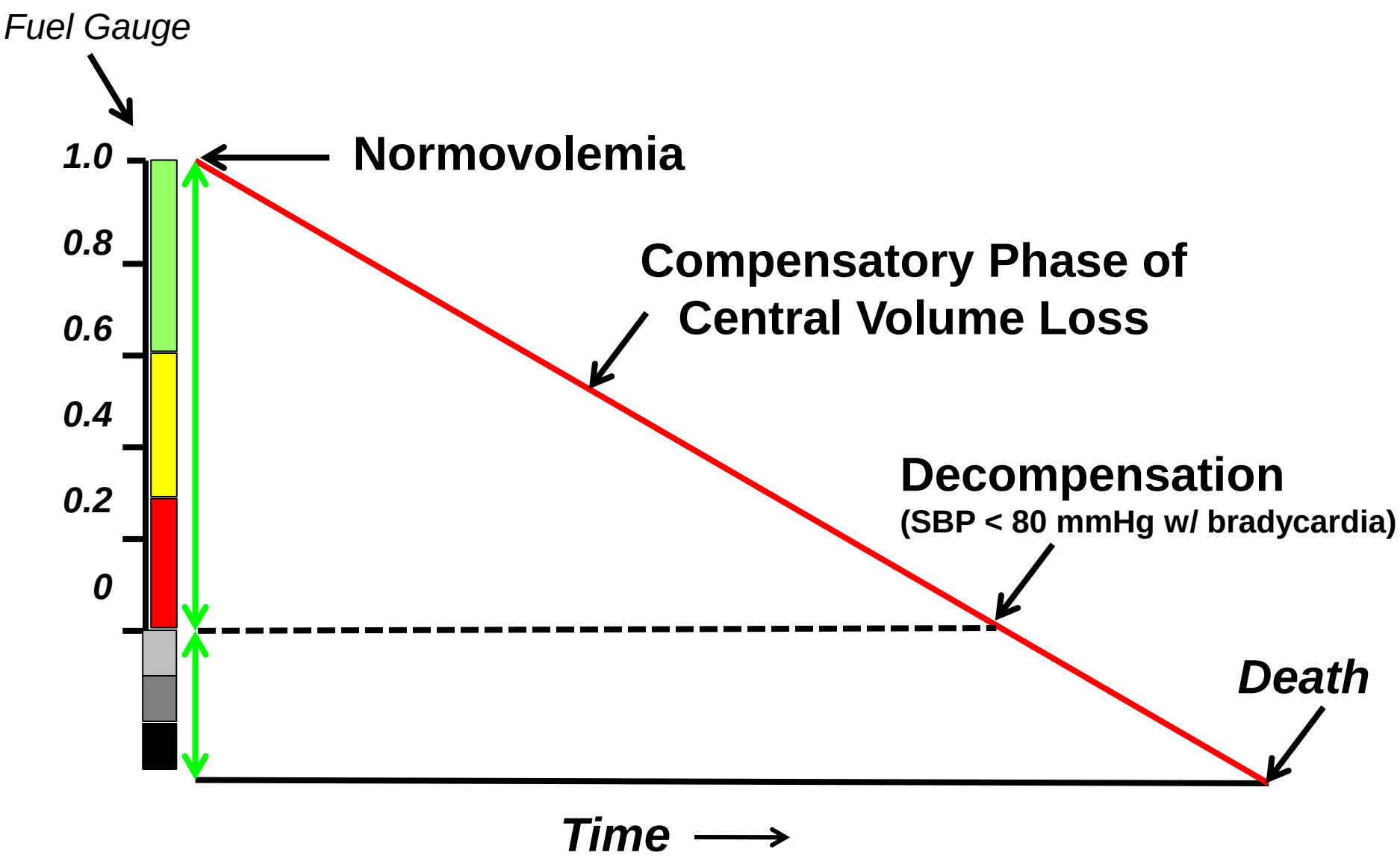
- Co-inventor of subject technology
  - All IP assigned to the Regents of the University of Colorado
- Co-founder/Consultant Flashback Technologies, Inc.
  - CU start-up; licensed technology from CU
- Research supported by:
  - US Army Grant Nos. W81XWH-09-C-0160, W81XWH-11-2-0091, W81XWH-11-2-0085, W81XWH-12-2-0112, W81XWH-13-CCCJPC6, W81XWH-13-C-0121
  - National Institutes of Health UL1 TR000154
  - State of Colorado Business Development Grant (BDEG)
  - Department of Surgery, University of Colorado

The technology under discussion is not approved by the FDA
There is nothing for sale

Overview

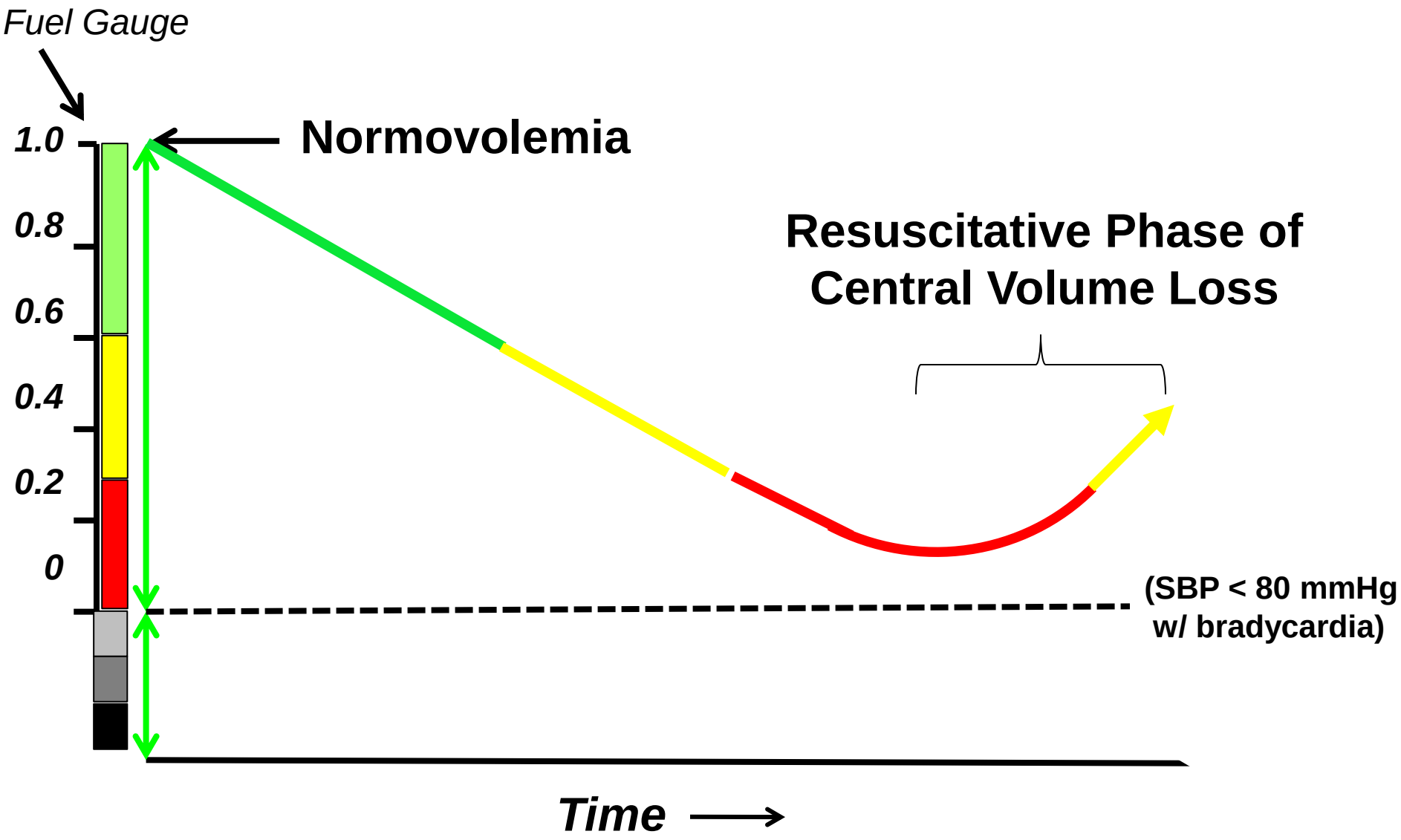
- An algorithm for monitoring the compensatory phase of hemorrhage
- Combination of technologies
  - To derive new knowledge from waveform data
  - nIBP or pulse ox (pleth) waveform
- Blood loss data
  - Primate
  - Human
- Demonstration

What if we had a technology that could identify and trend compensatory changes associated with progression toward **hemorrhagic shock** before any recognizable change in traditional vital signs?


Fuel Gauge
1.0
0.8
0.6
0.4
0.2
0
Normovolemia
Compensatory Phase of
Central Volume Loss
Decompensation
(SBP < 80 mmHg w/ bradycardia)
Death
Time

What if we had a technology that could

guide fluid resuscitation?


Fuel Gauge
1.0
0.8
0.6
0.4
0.2
0
Normovolemia
Resuscitative Phase of
Central Volume Loss
(SBP < 80 mmHg
w/ bradycardia)
Time

What Would It Take?

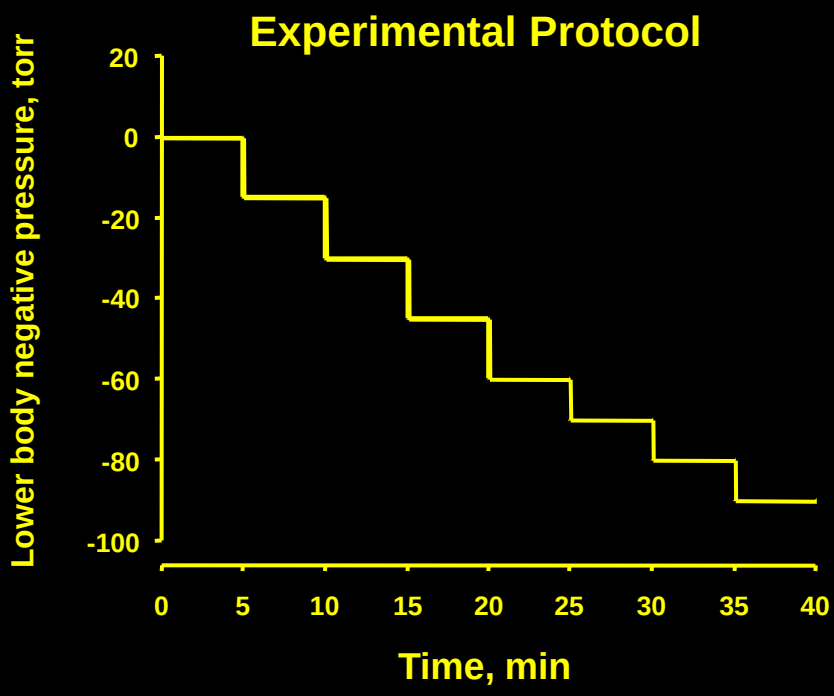
- Reproducible model of human hemorrhage
  - ✓ Generate and archive millions of waveforms
- Unbiased mathematical methods to:
  - ✓ Identify waveform features that correlate w/ compensation
  - ✓ Learn features that correlate with tolerance ***and*** intolerance to central volume loss
  - ✓ Build meaningful models that trend volume loss
- Data from primates and humans who are bled
- ***Diverse, dedicated group of scientists***

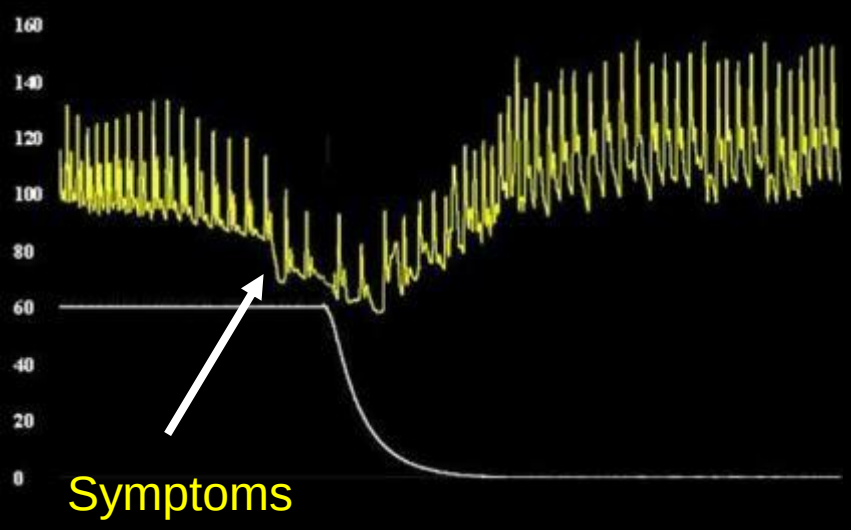
Reproducible Model of Human Hemorrhage

LBNP Model of Blood Loss

- Ethical constraints
- Lower body negative pressure
  - Simulate human hemorrhage
  - Focus on the early stages of hypovolemia
- Experimental set up
  - Males and females, 18 – 55 years old
  - Stepwise LBNP decompression at:

    -15, -30, -45, -60, -70, -80, -90, -100 mmHg
  - Waveform data at 500 Hz
  - > 250 LBNP experiments





Stop experiment for:

- Grey out
- SBP < 80 mmHg
- Completion of -100 mmHg level

or

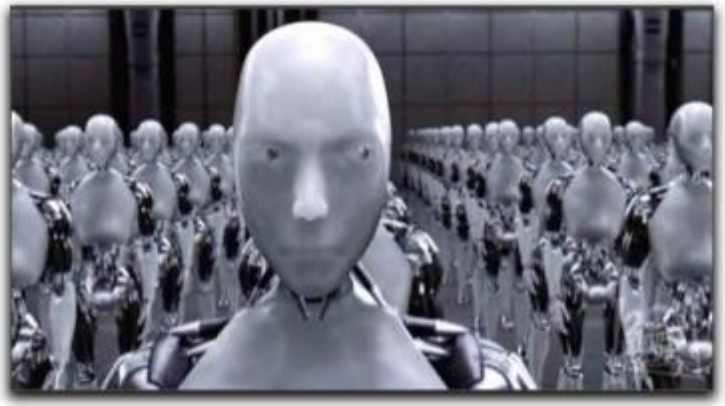
- Voluntary Subject termination

Unbiased Mathematical Methods to:

- ✓ Identify waveform features that correlate with compensation
- ✓ Learn features that correlate with tolerance ***and*** intolerance to central volume loss
- ✓ Build meaningful models that trend volume loss

Algorithm Development

Algorithms were developed by Grudic and Mulligan under DARPA* program "Learning Applied to Ground Robots (LAGR)"



*Defense Advanced Research Projects Agency (U.S. Government)

Algorithm Development

- Autonomous robot navigation
  - Goal: navigate from start position to GPS goal location through unknown terrain

- Grudic and Mulligan
  - Full spectrum ML:
    - Unsupervised learning
    - Semi-supervised learning
    - Active learning
    - Feature selection
    - Linear and nonlinear Regression and Classification
    - Reinforcement learning

  - <u>Learning platform</u> tightly integrated with <u>memory</u>
  - System grows increasingly more knowledgeable over time

Algorithm Development

- Clinicians learn to recognize the signs and symptoms (features) of bleeding
- Rely on experience and memory to predict clinical trajectory
- Anticipate patient needs, intervene early

Model Building Process

- Do vital sign waveforms from LBNP subjects contain info on physiology of compensation?
  - Which features of waveforms important?
  - Some more important than others?
  - More important at different levels of volume loss?

Feature extraction: dimensionality reduction
Machine learning: extract information

Unbiased analytical tools independently analyzed > 2 M waveforms and > 50,000's features within each waveform

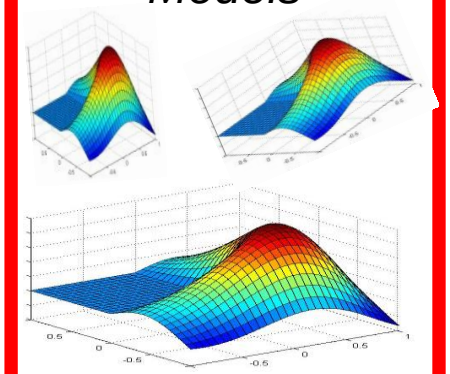
Model Building Process
Based on > 2 M Training Examples

Computational Machine Learning Engine
(aka LAGR navigation system)

Vital Sign Waveform Data

Autonomous Feature Extraction Algorithms

Produce Density Models



Define what is known

Autonomous Mathematical Modeling Algorithms

Analyze data from density models
Identify what is known, new and not known

Only new knowledge is added to the models

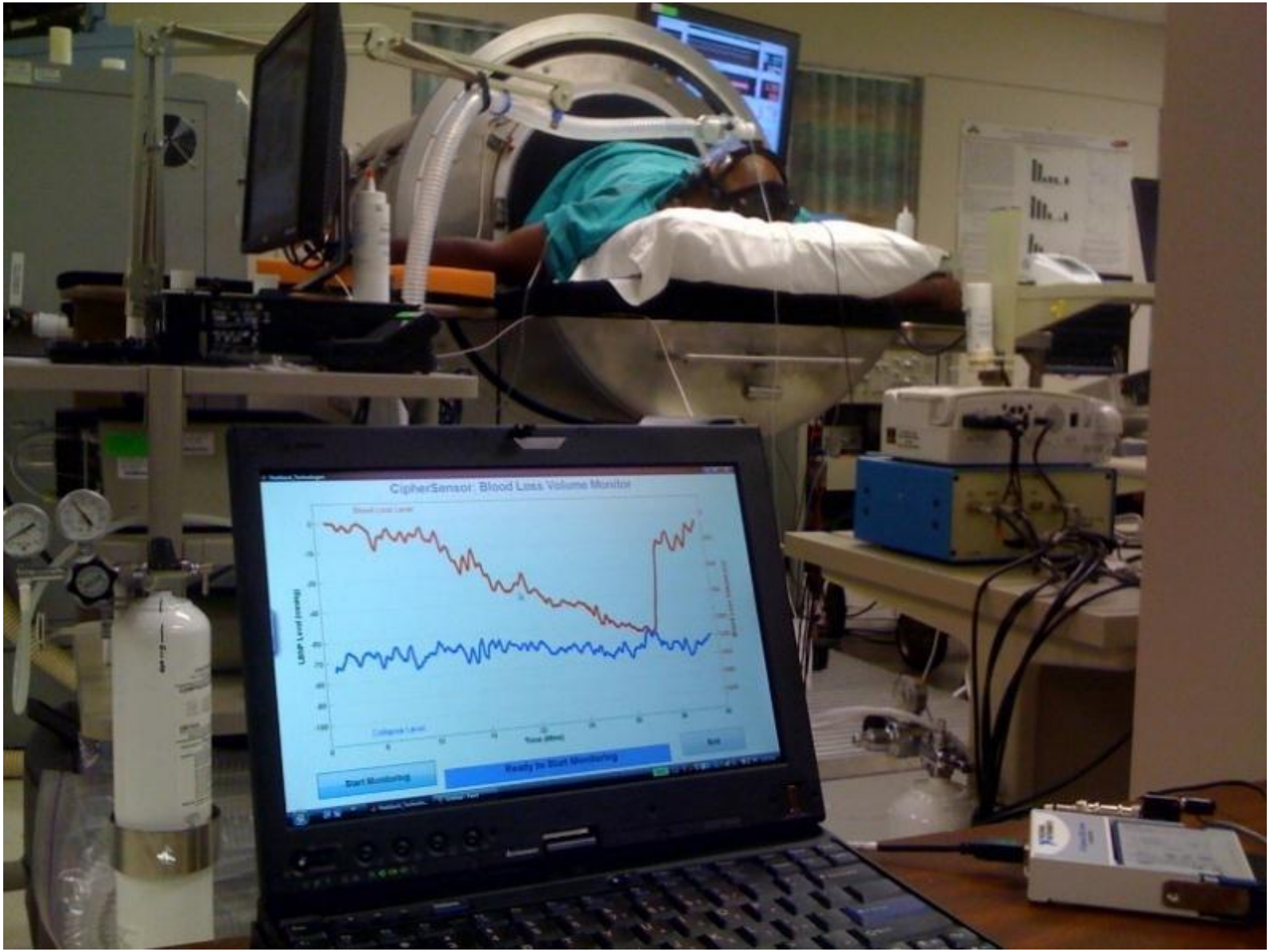
Only relevant parts of the models are modified

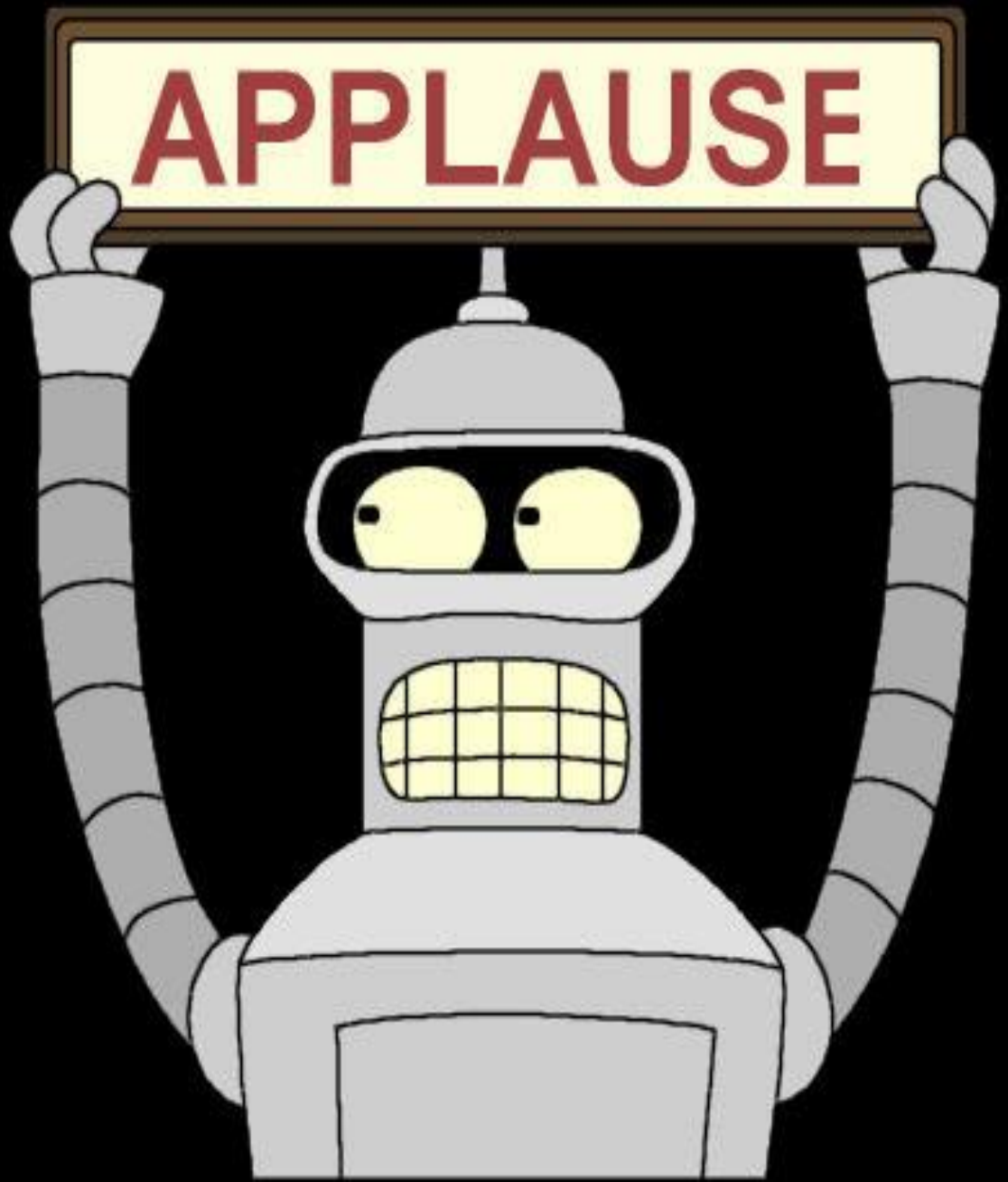
Define relevant mappings

Estimate

Predict

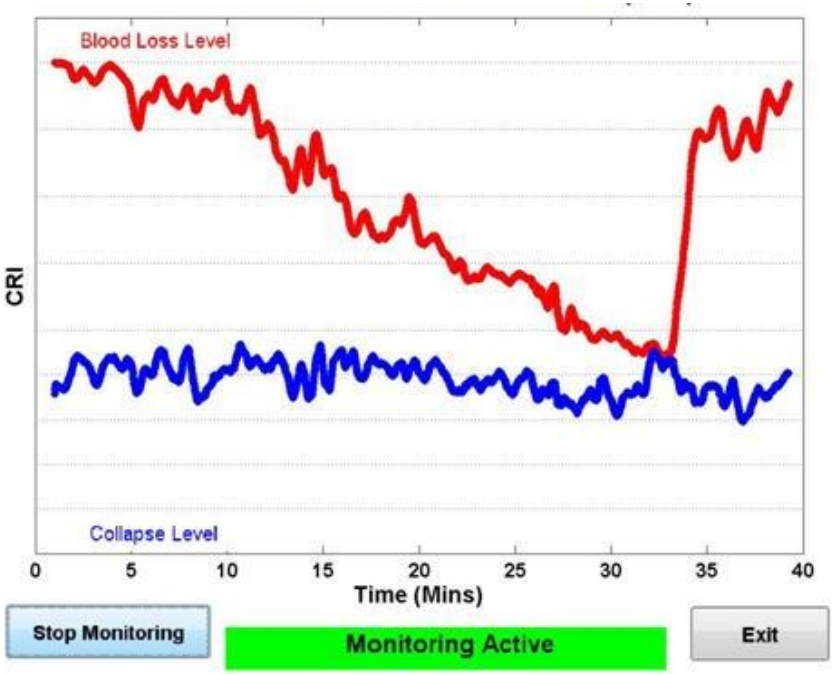
Real-time Testing in 2009




APPLAUSE

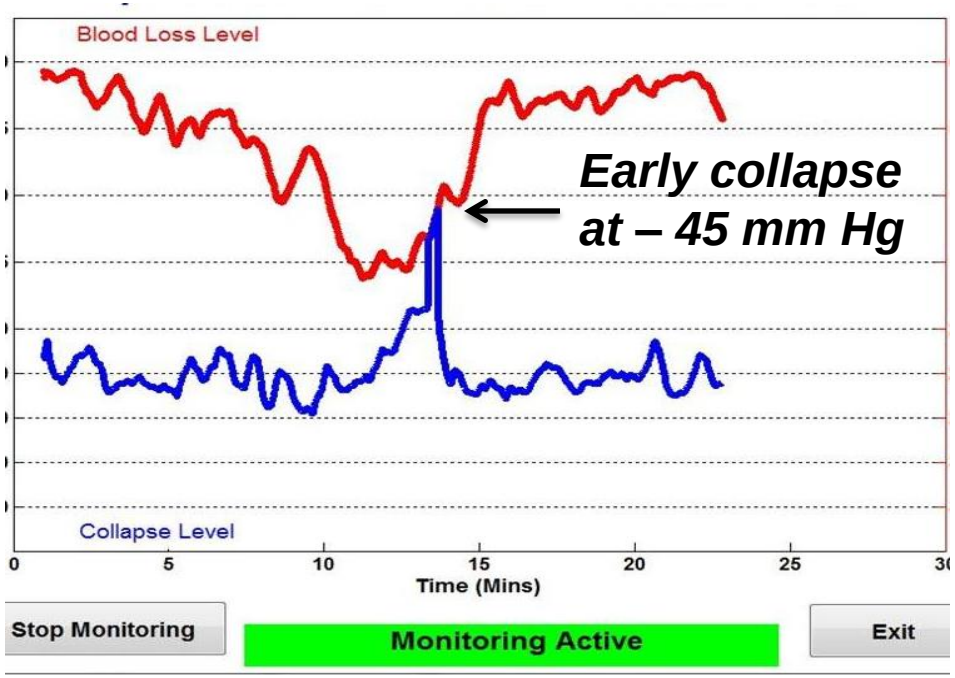
Results in 2009

Naïve Subjects 1-3



Naïve Subject 4

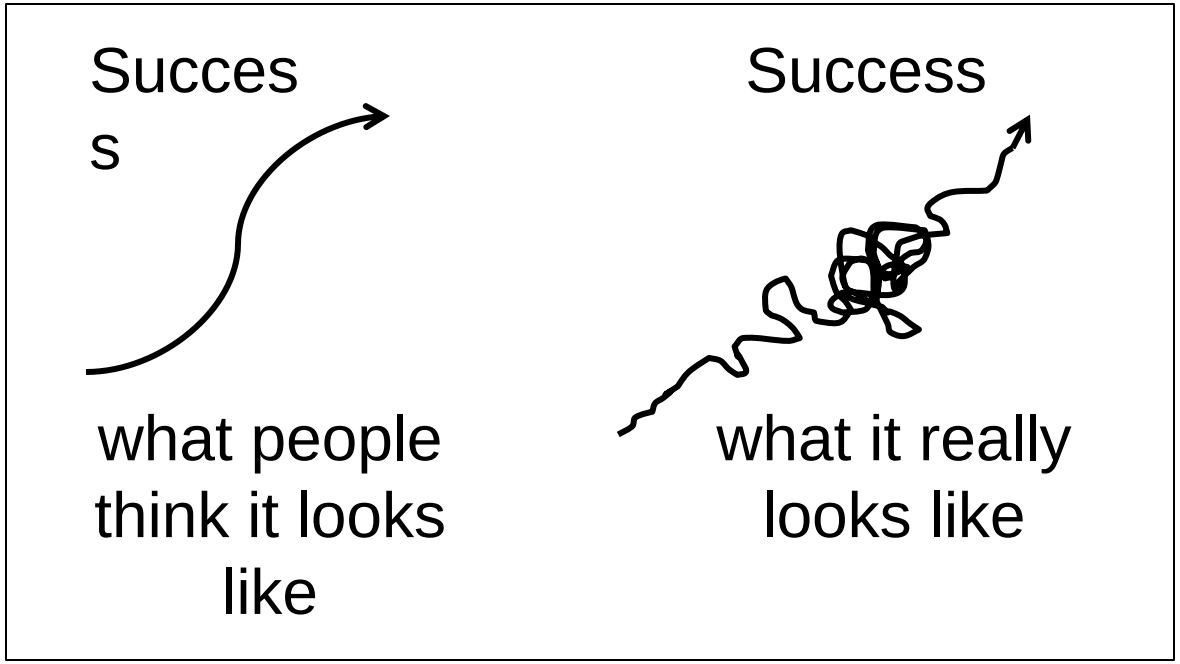
Low Tolerant Subject!

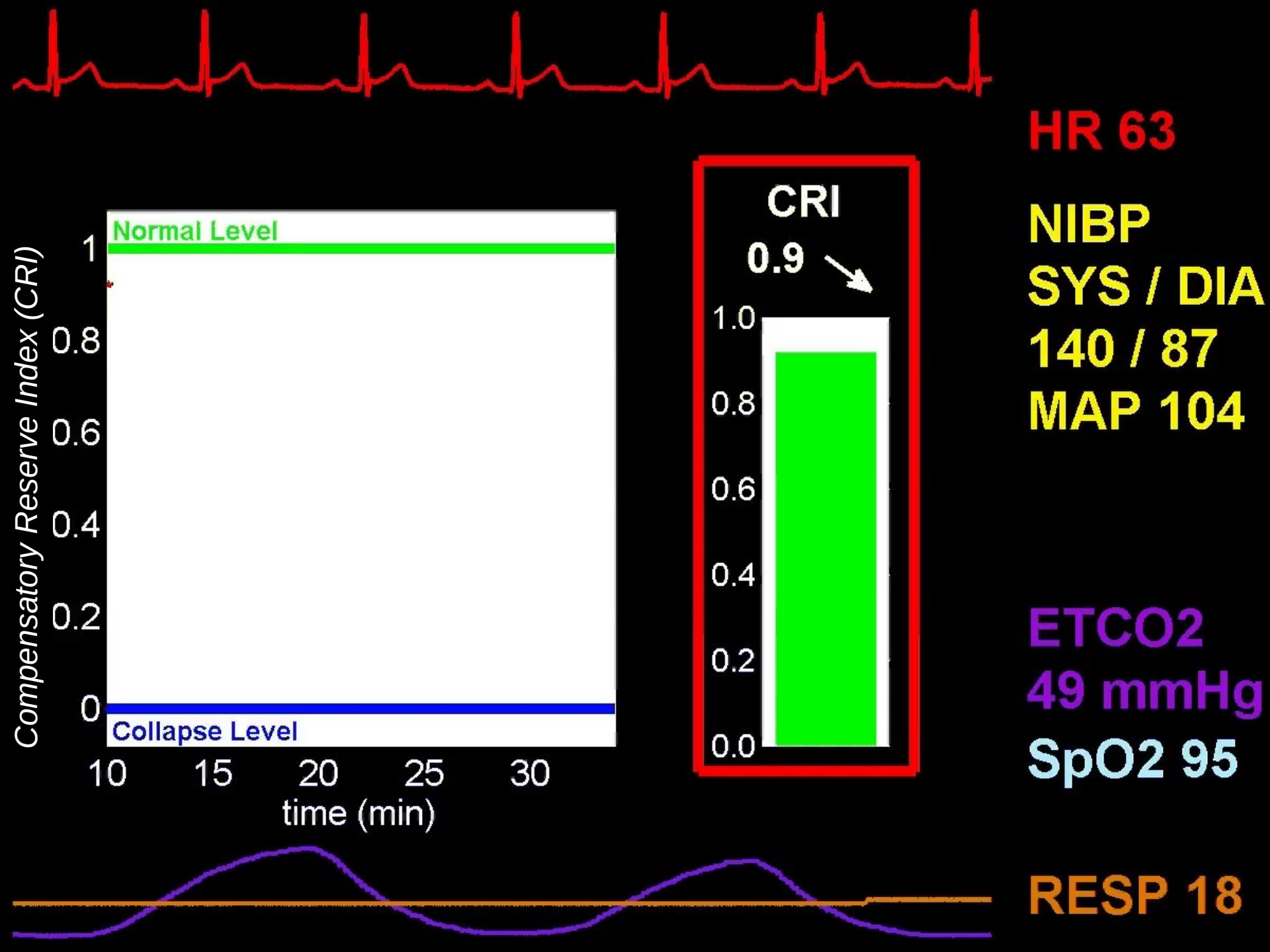


- ***Initial attempts at prediction of volume loss to the point of collapse***
- **Confounded by variable tolerance to blood loss**

Results in 2010

- CRI is an index
  - 1: Normovolemia
  - 0: CV collapse
  - Values 1 – 0 = patient's CRI




HR 63
NIBP
SYS / DIA
140 / 87
MAP 104
ETCO2
49 mmHg
SpO2 95
RESP 18
CRI
0.9
1.0
0.8
0.6
0.4
0.2
0.0
Normal Level
Collapse Level
Compensatory Reserve Index (CRI)
1
0.8
0.6
0.4
0.2
0
10
15
20
25
30
time (min)

Results 2011 - 12

- CRI algorithm trained by 180+ human LBNP experiments
- 30 heart beat initialization, then beat-to-beat
- 95% accurate at any stage of volume loss
- Ready for real-time testing…but what should we call “it”?

What Should We Call It?

- Hemodynamic Reserve Index (HDRI)

What Should We Call It?

- Hemodynamic Reserve Index (HDRI)
- Cardiovascular Reserve Index (CRI)

What Should We Call It?

- Hemodynamic Reserve Index (HDRI)
- Cardiovascular Reserve Index (CRI)
- Cardiopulmonary Reserve Index (CRI)

What Should We Call It?

- Hemodynamic Reserve Index (HDRI)
- Cardiovascular Reserve Index (CRI)
- Cardiopulmonary Reserve Index (CRI)
- Compensatory Reserve Index (CRI)

compensatory reserve index - Google Search - Windows Internet Explorer provided by Childrens Hospital Colorado IE 8

https://www.google.com/search?q=compensatory+reserve+index&hl=en&gbv=2&oq=&gs_l=

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About 69,200 results

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Past hour
Past 24 hours
Past week
Past month
Past year

All results
Verbatim

Scholarly articles for **compensatory reserve index**

Running on empty? The **compensatory reserve index** - Moulton - Cited by 12

Index of cerebrospinal **compensatory reserve** in ... - Kim - Cited by 28

... of power plant mortality on the **compensatory reserve** ... - Goodyear - Cited by 61

Running on empty? The **compensatory reserve index**.
www.ncbi.nlm.nih.gov/pubmed/24256681
The **compensatory reserve index**. Moulton SL(1), Mulligan J, Grudic GZ, Convertino VA. Author information: (1)From the Department of Surgery (S.L.M.), ...

The value of noninvasive measurement of the **compensatory reserve ...**
www.ncbi.nlm.nih.gov/pubmed/24667628
The value of noninvasive measurement of the **compensatory reserve index** in monitoring and triage of patients experiencing minimal blood loss. Nadler R(1) ...

CRI | Flashback Technologies

The Compensatory Reserve Index provides a way of getting ahead of shock : ems - Windows Internet Explorer provided by Childrens

http://www.reddit.com/r/ems/comments/1z4957/the_compensatory_reserve_index_provides_a_way_of/

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The Compensatory Reserve Index provides a way of ...

MY SUBREDDITS FRONT - ALL - RANDOM | GADGETS - SPORTS - GAMING - PICS - WORLDNEWS - VIDEOS - ASKREDDIT - AWW - MUSIC - FUNNY - NEWS - MOV

The Compensatory Reserve Index provides a way of getting ahead of shock (mrmc.amedd.army.mil)

3 submitted 1 year ago by will1984

3 comments share

all 3 comments

sorted by: best

[–] David_Parker 2 points 1 year ago

This looks fucking awesome. THIS. MORE OF THIS ON R/EMS.

permalink save give gold

[–] will1984 [S] 1 point 1 year ago

also: http://www.ncbi.nlm.nih.gov/pubmed/24256681

permalink save give gold

[–] climberslacker NY EMT-B, Collegiate EMS 1 point 1 year ago

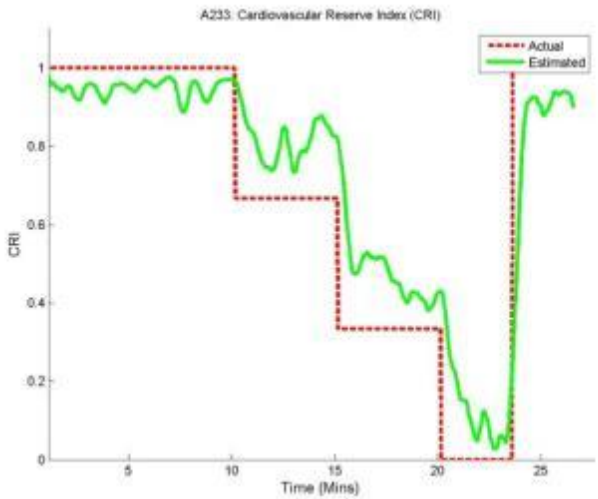
This is SICK!

Running on empty? The compensatory reserve index

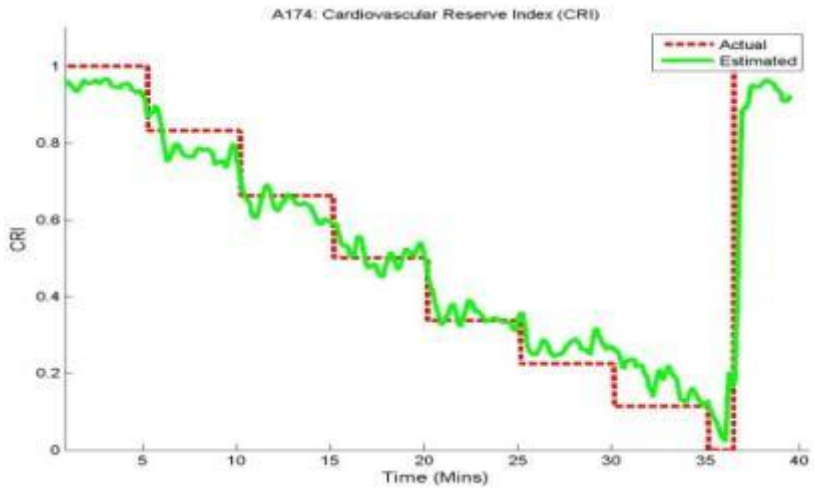
Steven L. Moulton, MD, Jane Mulligan, PhD, Greg Z. Grudic, PhD,
and **Victor A. Convertino, PhD,** *San Antonio, Texas*

J Trauma Acute Care Surg. 2013;75:1053-1059

CRI is individual specific; no baseline required



Low tolerance to LBNP



High tolerance to LBNP

Correlation between reference CRI (red) and the CRI monitor output (green) is $r^2 = 0.94$

Mean absolute difference between reference CRI (red) and the CRI monitor output (green) is 0.1 with std. dev. of 0.09

Limitations

- Ethical constraints limit modeling of severe human blood loss
- Direct comparisons between LBNP and human hemorrhage are not possible
- Models based on healthy subjects 18 – 55
- Might injury/pain alter waveform features?

Striking similarity between physiologic responses to LBNP and severe hemorrhage

Data from Primates Who are Bled

Validation of lower body negative pressure as an experimental model of hemorrhage

Hinojosa-Laborde C, et al. J Appl Physiol 2014 Feb 15;116(4):406-15

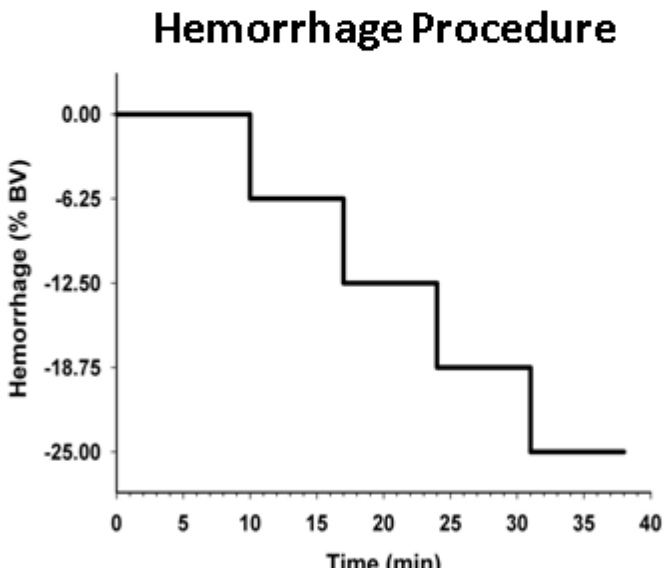
ANIMALS

Adult male baboons
N = 13
Age: 11 ± 0.5 years
Weight: 32 ± 2 kg
Blood volume: 71 ml/kg
Ketamine/Diazepam

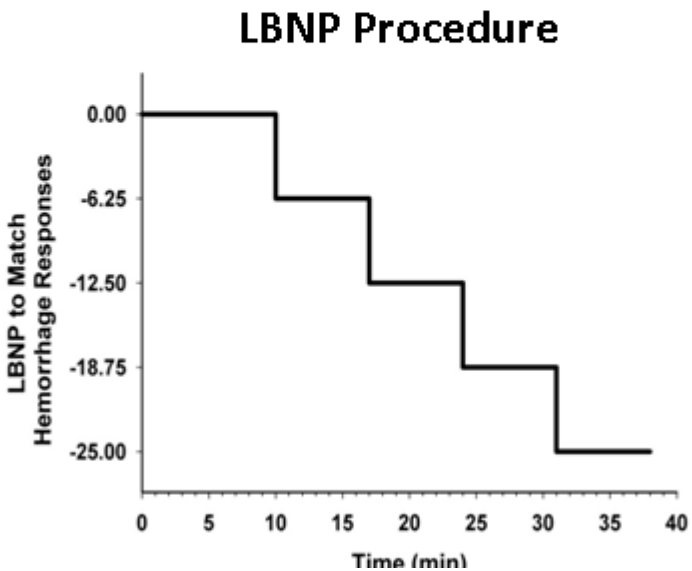
MEASUREMENTS

Lead II ECG
- Heart rate

Vascular catheters
- Arterial BP
- Pulse pressure
- CVP

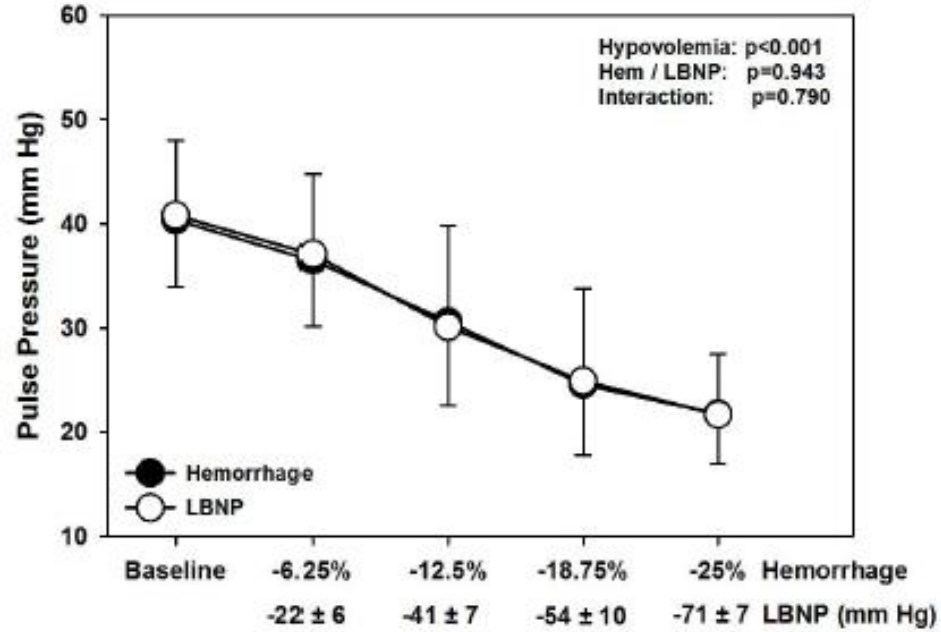


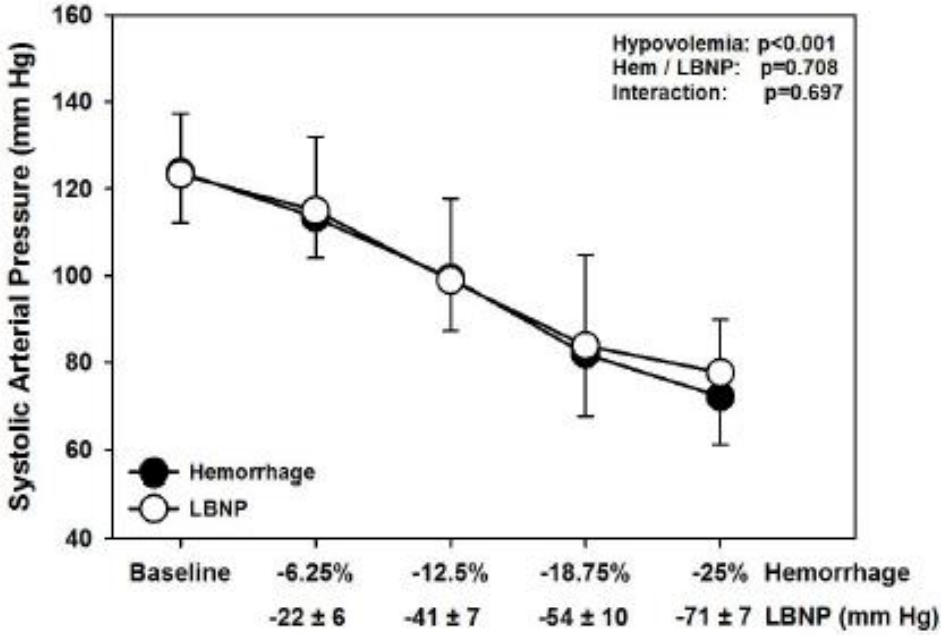
Four weeks

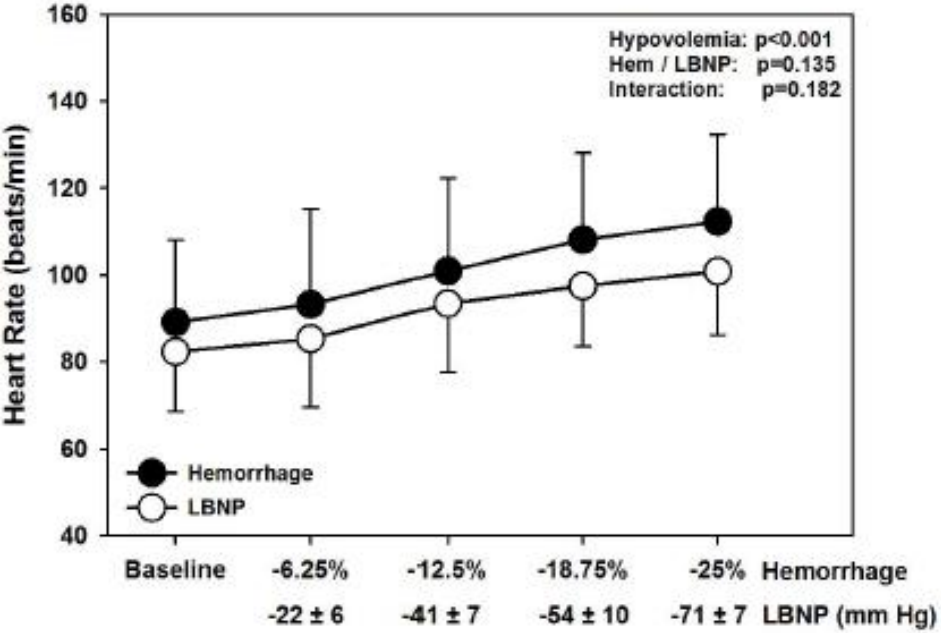


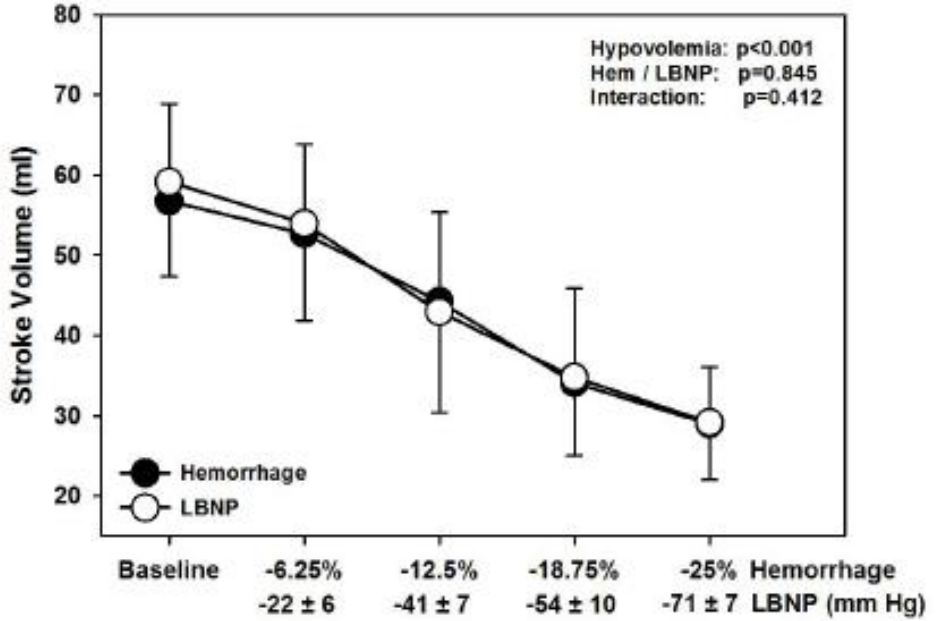
Maximum 25% total blood volume, four steps x 7min
Blood removed via femoral artery (50 ml/min)
Blood replaced at end of hemorrhage

Set 4 levels of LBNP to match CVP and/or PP during previous 4 step hemorrhage

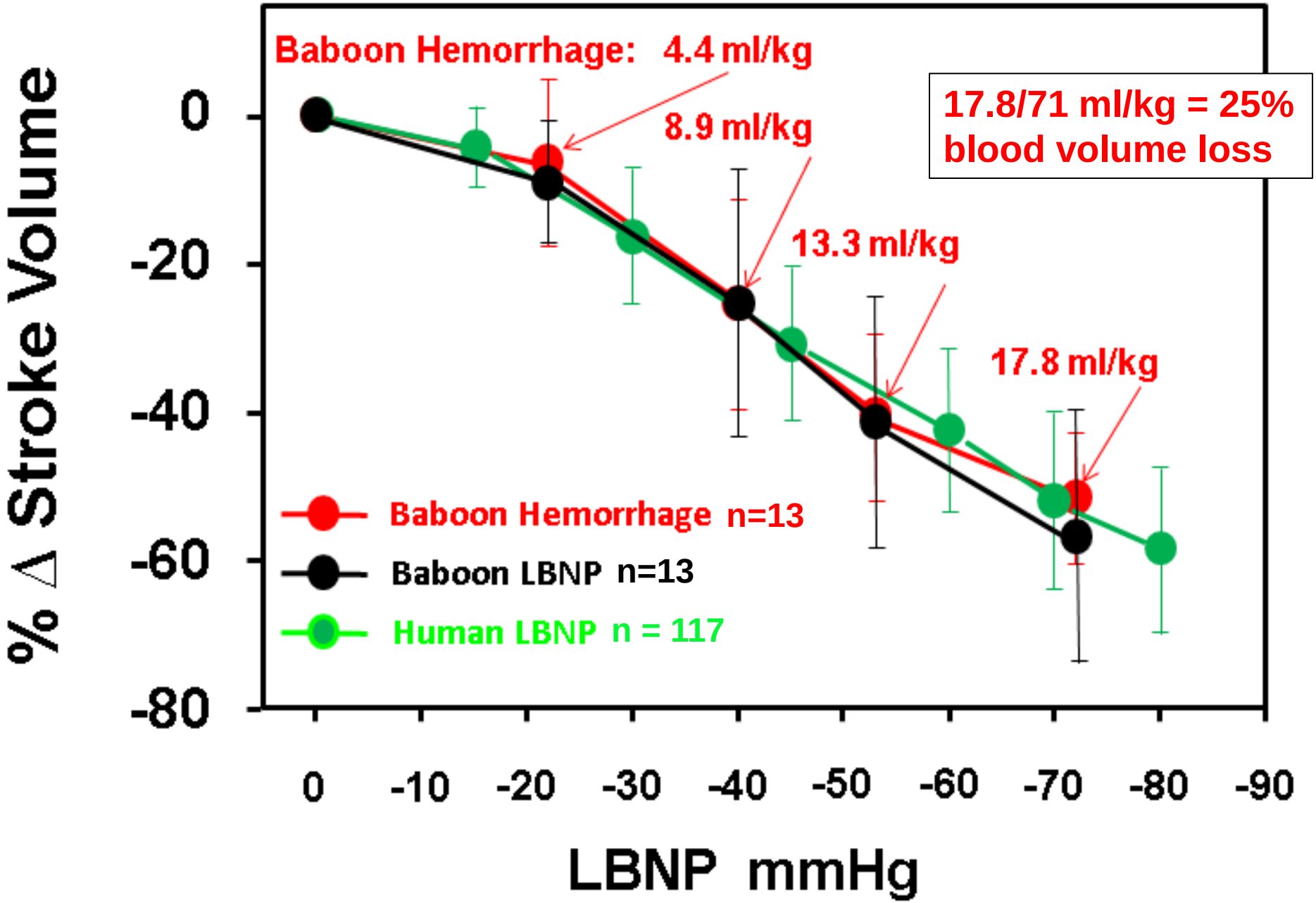




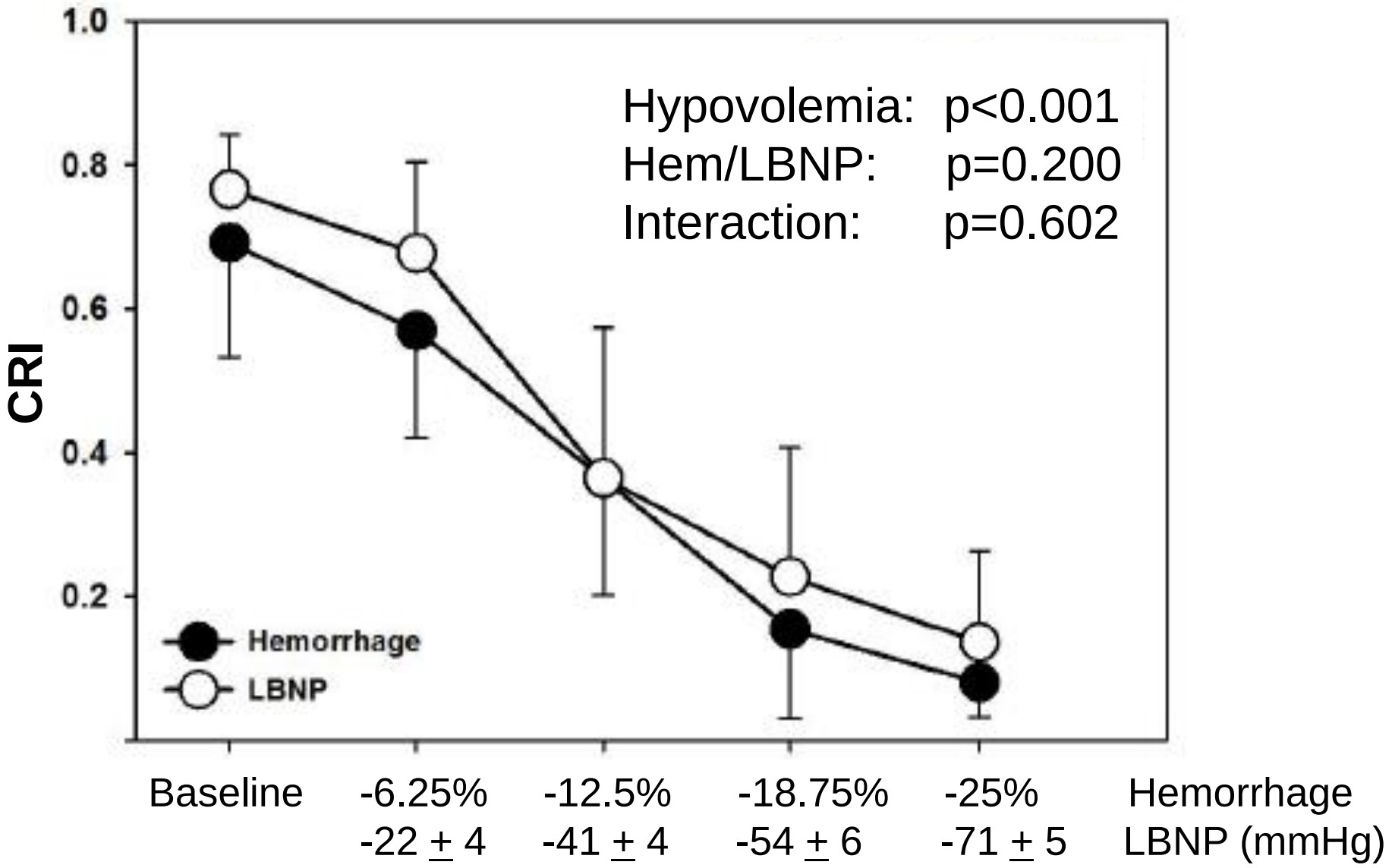




Hinojosa-Laborde C, et al. J Appl Physiol 2014 Feb 15;116(4):406-15

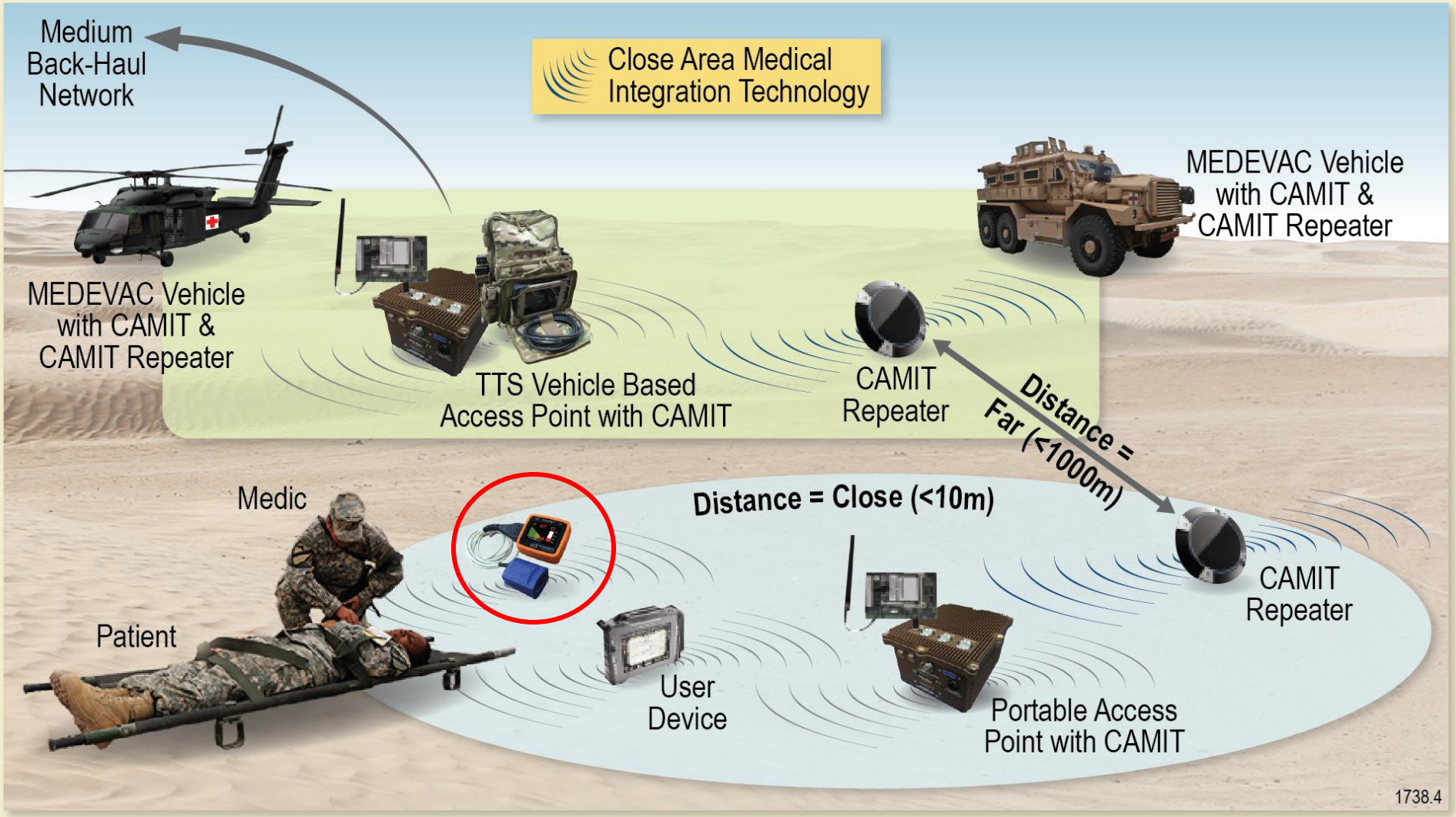


Hinojosa-Laborde C, et al. J Appl Physiol 2014 Feb 15;116(4):406-15

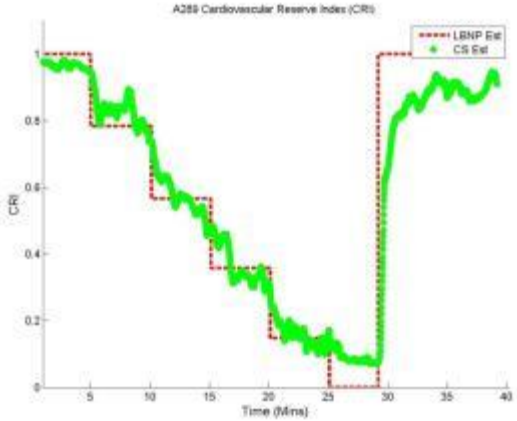


Hinojosa-Laborde C, Mulligan J, Grudic GZ, Convertino VA. Poster Presentation, MHSRS 2014

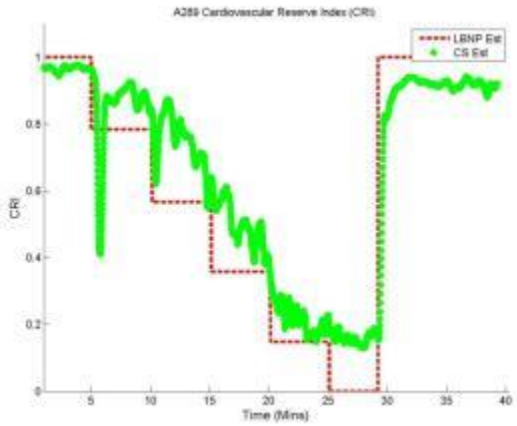
2014


Medium Back-Haul Network
Close Area Medical Integration Technology
MEDEVAC Vehicle with CAMIT & CAMIT Repeater
MEDEVAC Vehicle with CAMIT & CAMIT Repeater
TTS Vehicle Based Access Point with CAMIT
CAMIT Repeater
Distance = Far (<1000m)
Medic
Distance = Close (<10m)
CAMIT Repeater
Patient
User Device
Portable Access Point with CAMIT
1738.4

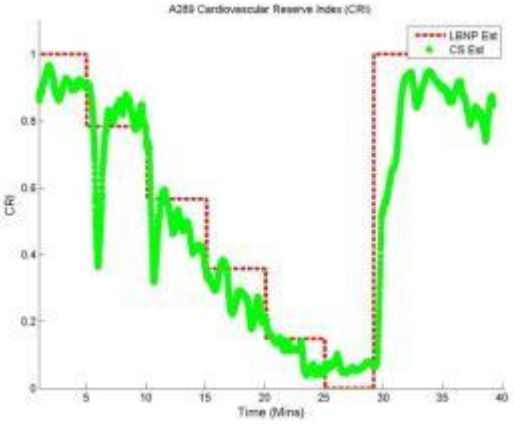
nIBP versus PPG Waveforms



Finometer nIBP



Nonin



Masimo

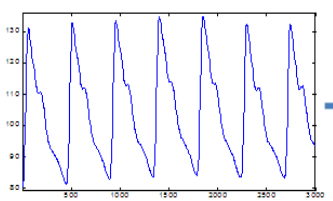
- Applied modeling technique to pulse ox PPG
- CRI accuracy results for 30 HT/LT
- CRI models for both pulse oximeters are similarly accurate
- CRI accuracy $\pm$ 0.1 w/ std. dev. 0.09

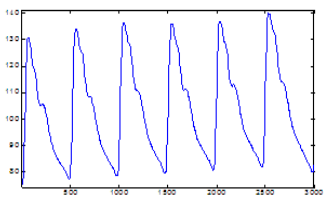
2014: How It Works

28 milliseconds

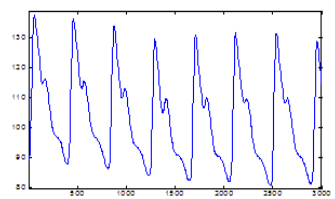
CRI Model + Library of Waveform Features

30 PPG waveforms

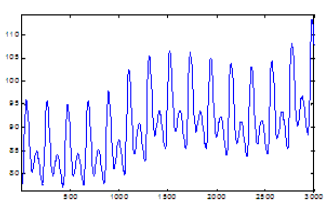




Features CRI=1



Features CRI=0.5



Features CRI=0

Normalized Sum of Matching Filters

Beat-to-Beat CRI Estimate

Data from Humans Who are Bled

Detection of low-volume blood loss: The compensatory reserve index versus traditional vital signs

Camille L. Stewart, MD, Jane Mulligan, PhD, Greg Z. Grudic, PhD, Victor A. Convertino, PhD, *and* Steven L. Moulton, MD, *Aurora, Colorado*

J Trauma Acute Care Surg 2014; 77:892-898

- **Hypothesis**: CRI can detect low volume blood loss with greater sensitivity and specificity than traditional vital signs
- **Method**: Record PPG waveforms and traditional vital signs while volunteers donate 1 unit of blood.

  - Compare sensitivity and specificity of CRI to traditional vital signs.

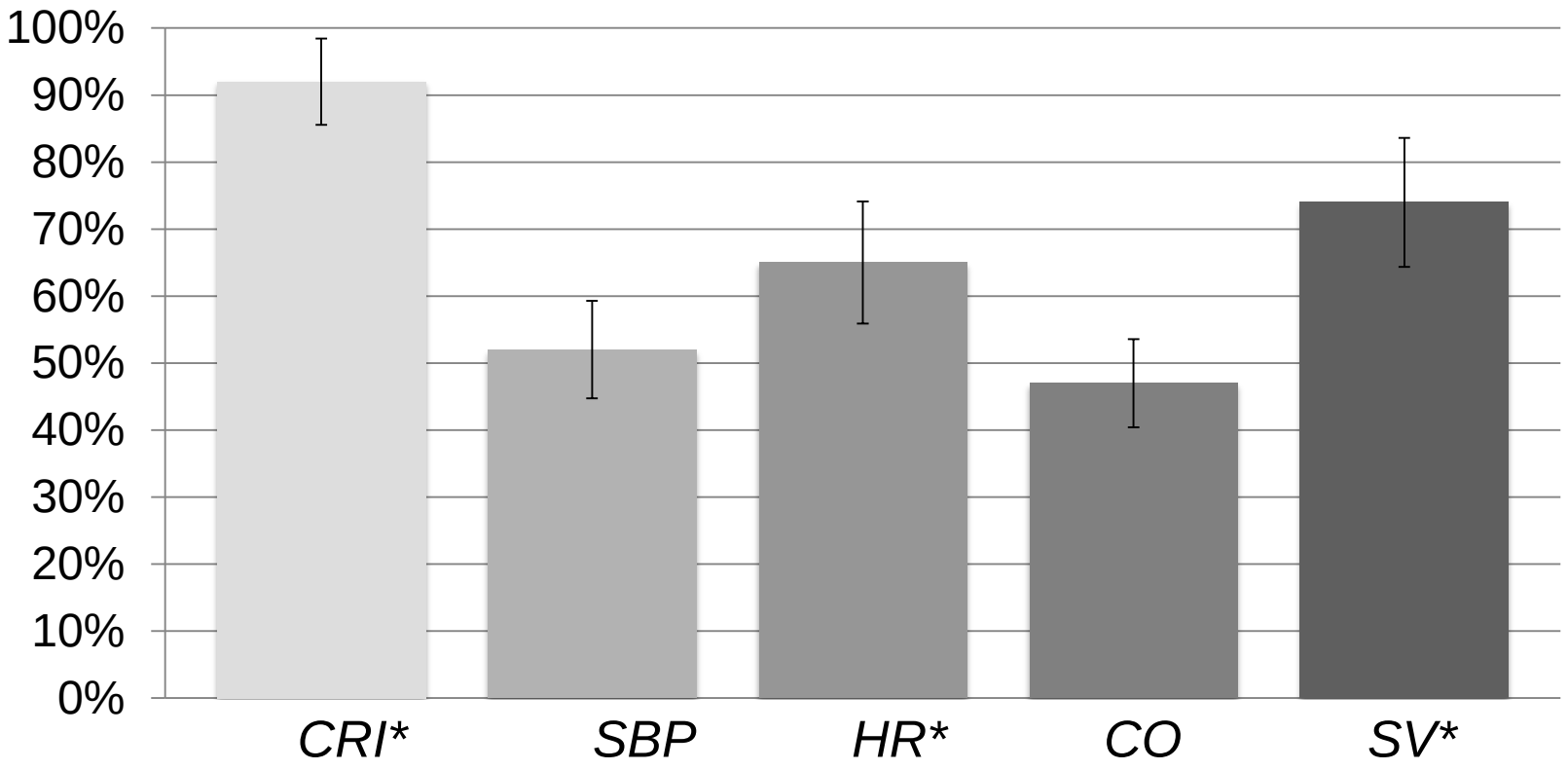
Methods

- 244 with adequate blood draw and PPG signal suitable for analysis
  - 204 also with traditional vital signs recorded
  - 122 with > 4 minutes of data prior to donation
- Gender: 79 males, 165 females
- Age: 40.1 ± 14.2 years (range 18 - 78)
- BMI: 25.6 ± 4.7 (range 17.2 - 46.4)
- Volume removed: 459 ± 9 mL (range 418 - 491)
- Duration of donation: 9 ± 2 min. (range 2 – 20)

Initial versus Final Values

Parameter	**Initial Mean (± STD)**	**Final Mean (±STD)**	**Two-sample t-test**
SBP (mmHg)	141 ± 22	138 ± 20	p=0.09
CO (L/min)	6.1 ± 1.5	5.9 ± 1.4	p=0.15
HR (bmp)	72 ± 11	75 ± 11	p<0.001*
SV (mL)	85 ± 18	78 ± 17	p<0.001*
CRI	0.78 ± 0.11	0.63 ± 0.15	p<0.001*

% Subjects with a Significant Change

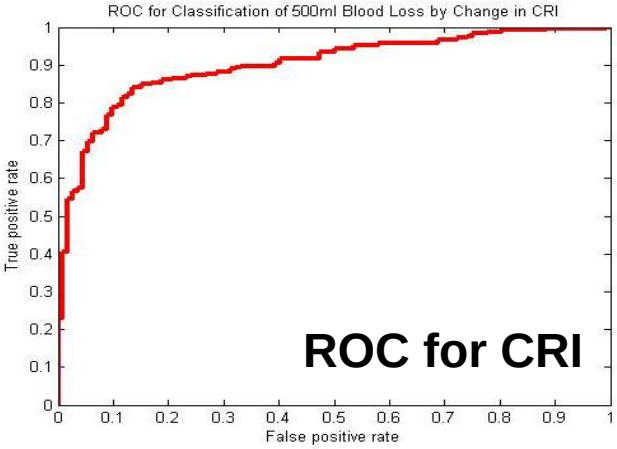


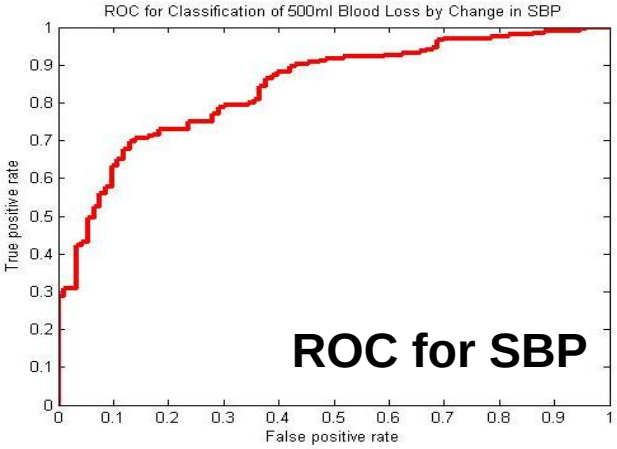
Significant change determined using a two-sided t-test with a power of 0.9 and α of 0.05

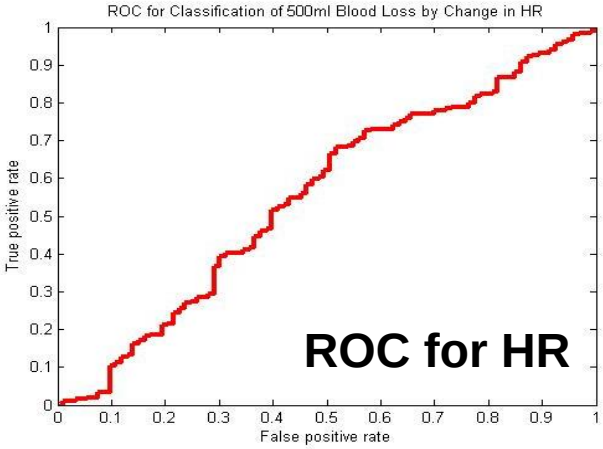
ROC AUC Analysis

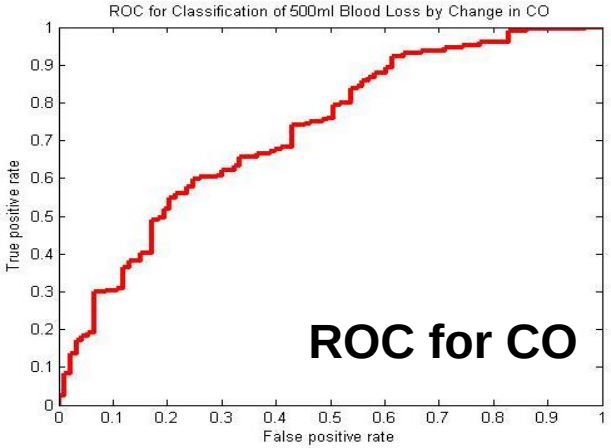
Parameter	Threshold (Δ)	ROC AUC	Sensitivity	Specificity
SBP (mmHg)	8	0.84	0.90	0.58
HR (bpm)	7	0.55	0.98	0.04
CO (L/min)	0.5	0.72	0.92	0.39
SV (mL)	2.7	0.78	0.92	0.42
CRI	**0.05**	**0.90**	**0.84**	**0.86**

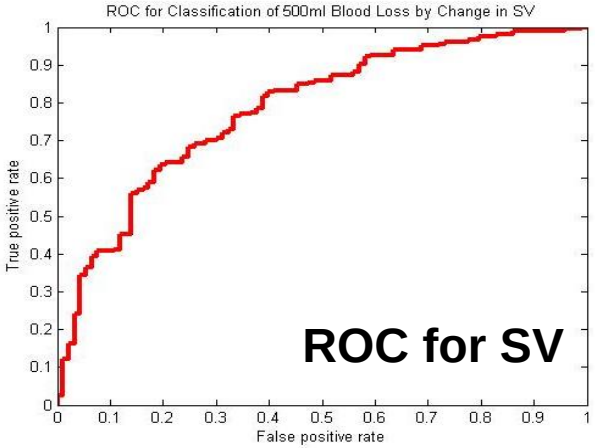
Comparison of ROC Curves





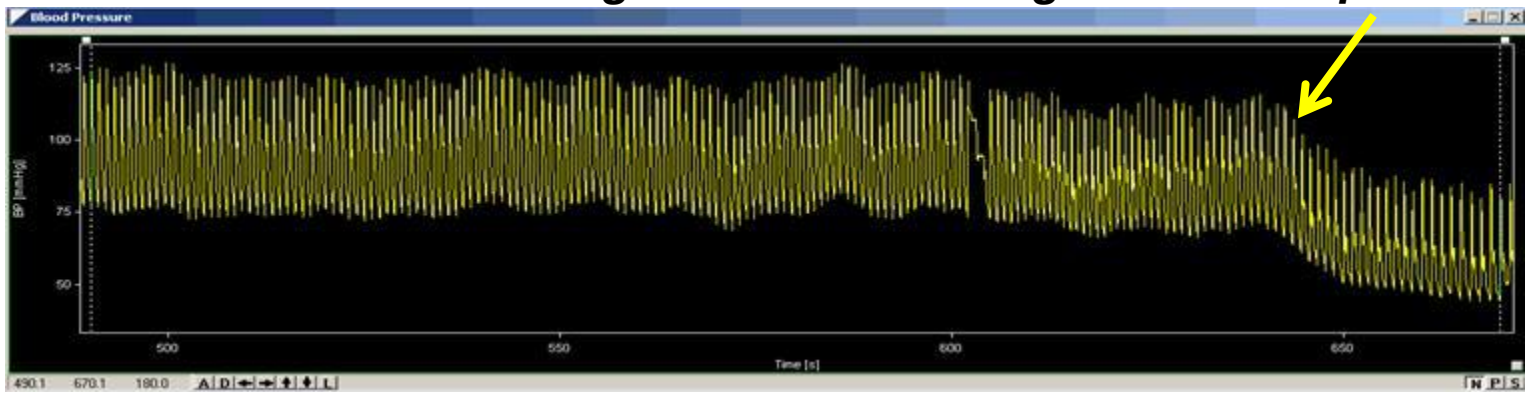




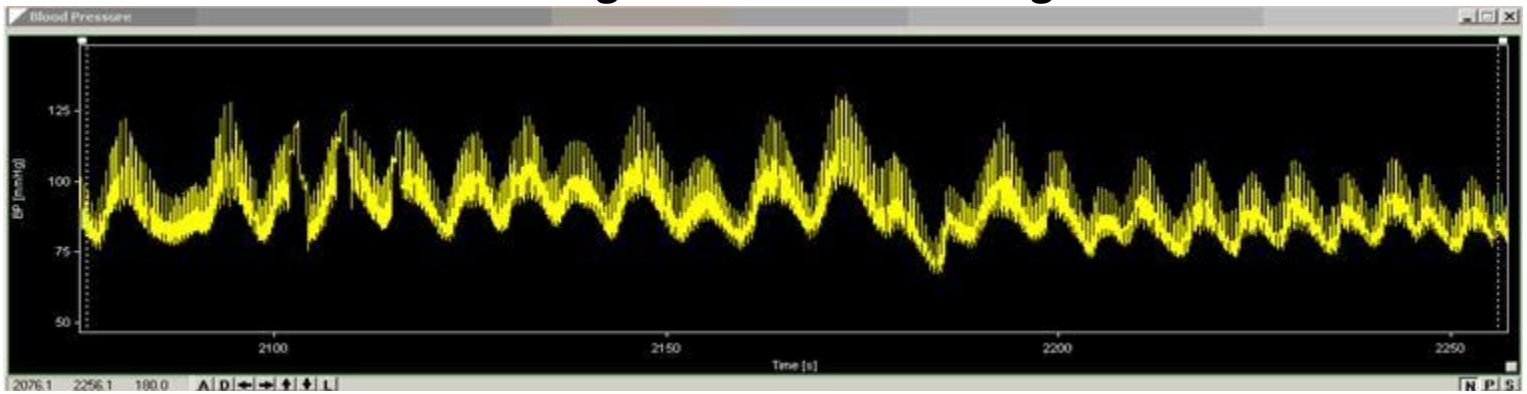


Speculation:
CRI is Better Because it is Individual Specific*

<u>Low Tolerant</u> (max LBNP = -30 mmHg)
Average SBP = 116 mmHg ***Decompensation***



<u>High Tolerant</u> (max LBNP = -80 mmHg)
Average SBP = 104 mmHg



*Convertino VA, Grudic GZ, Mulligan J, Moulton SL. J Appl Phys 2013;115(8): 1196-1202.

The Duke Study

One liter human blood loss study*

- Duke University (3/10/14 – 4/14/14)
- PI David McLeod, PhD

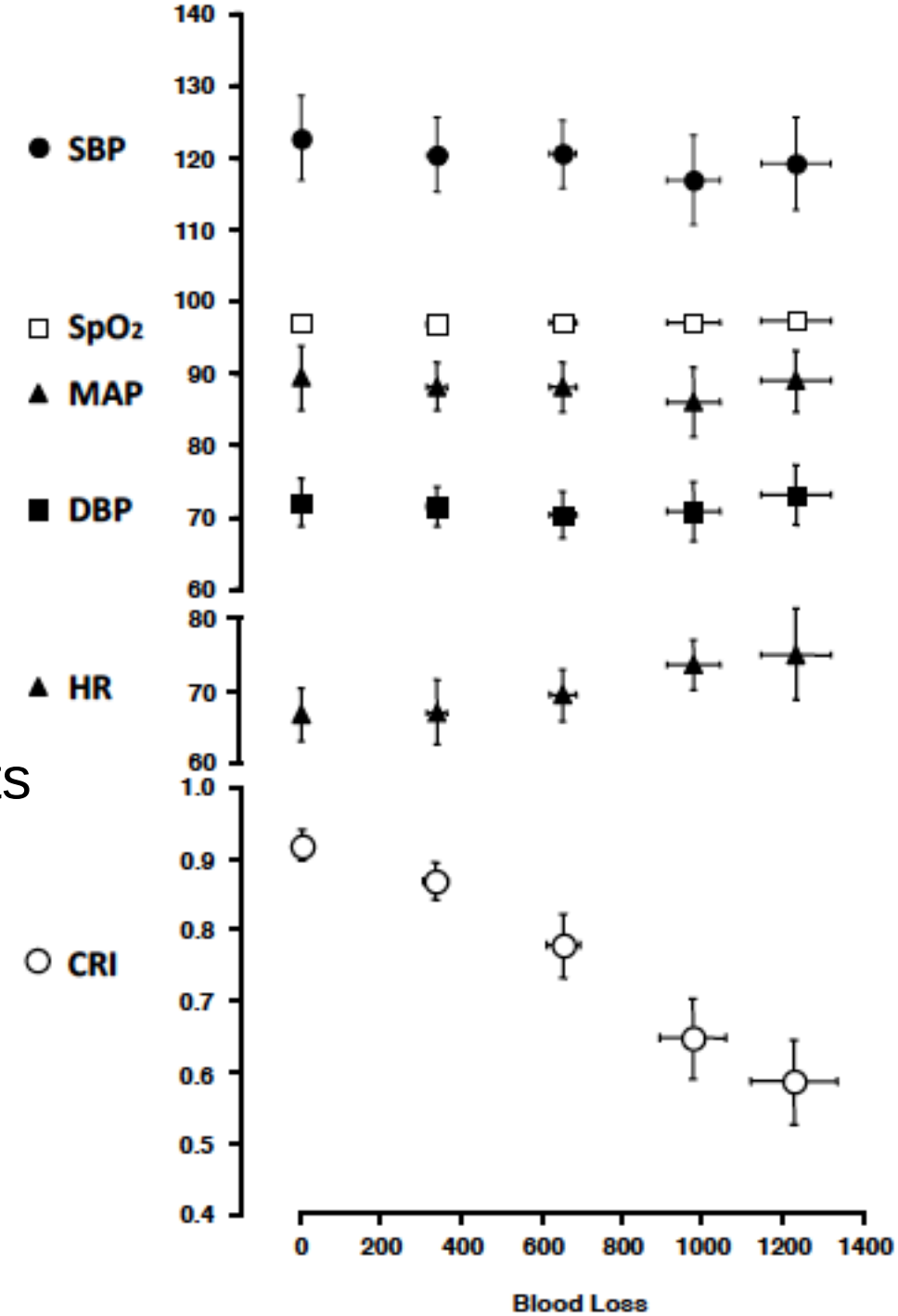
Protocol

- Healthy non-smoking adults 18 – 55 years old
- Nexfin (CRI and SV), Nonin PPG (CRI), EKG
- Large bore AC IV, 20% EBL at 333 ml/step
  - Males: 75 ml/kg Females: 65 ml/kg
  - 15 – 20 minute blood draw/step
  - Blood re-infused at conclusion of experiment

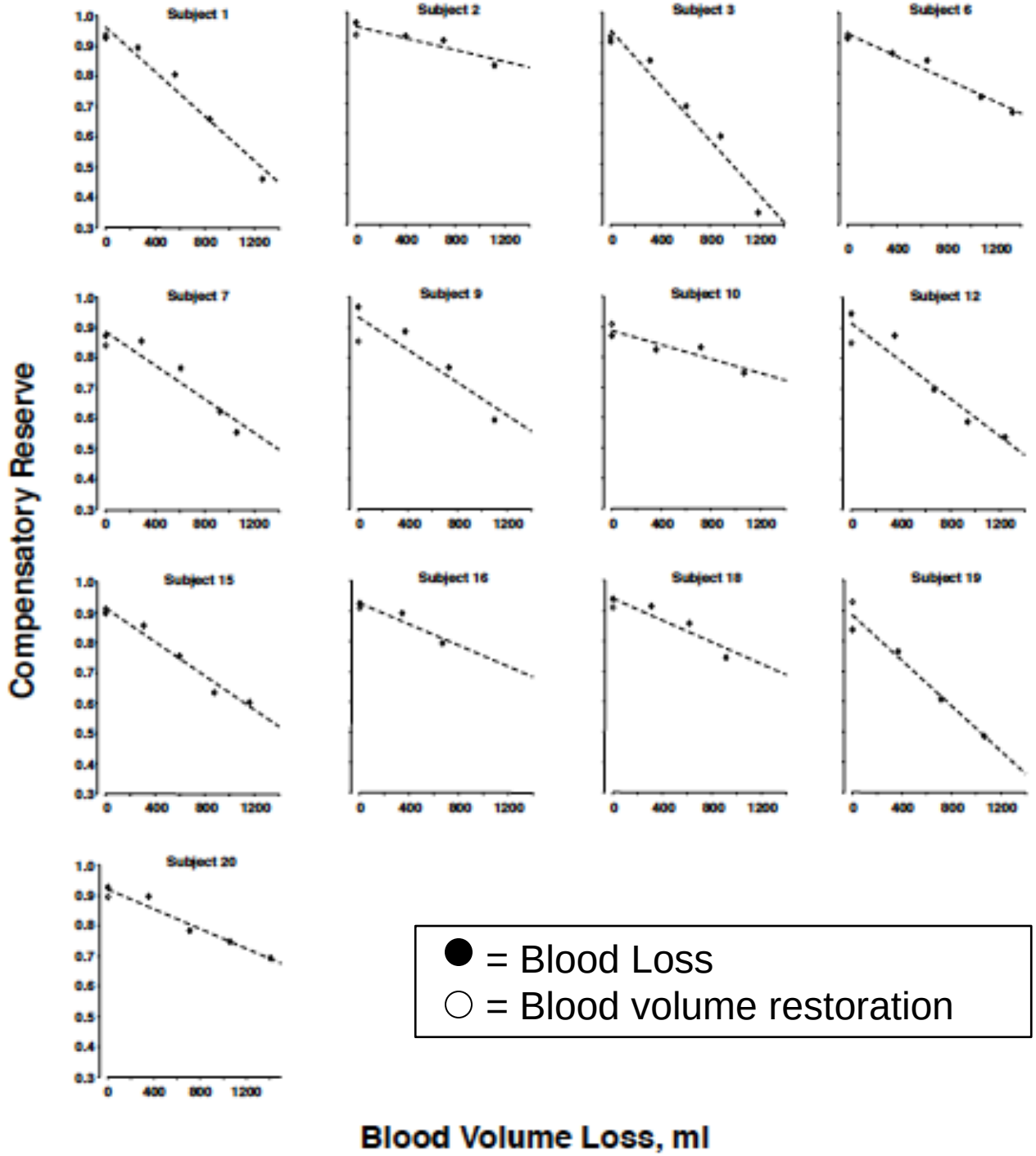
*Convertino VA et al. Individual-specific, beat-to-beat trending of significant human blood loss: the compensatory reserve. Shock 2015;44 Suppl 1:27-32.

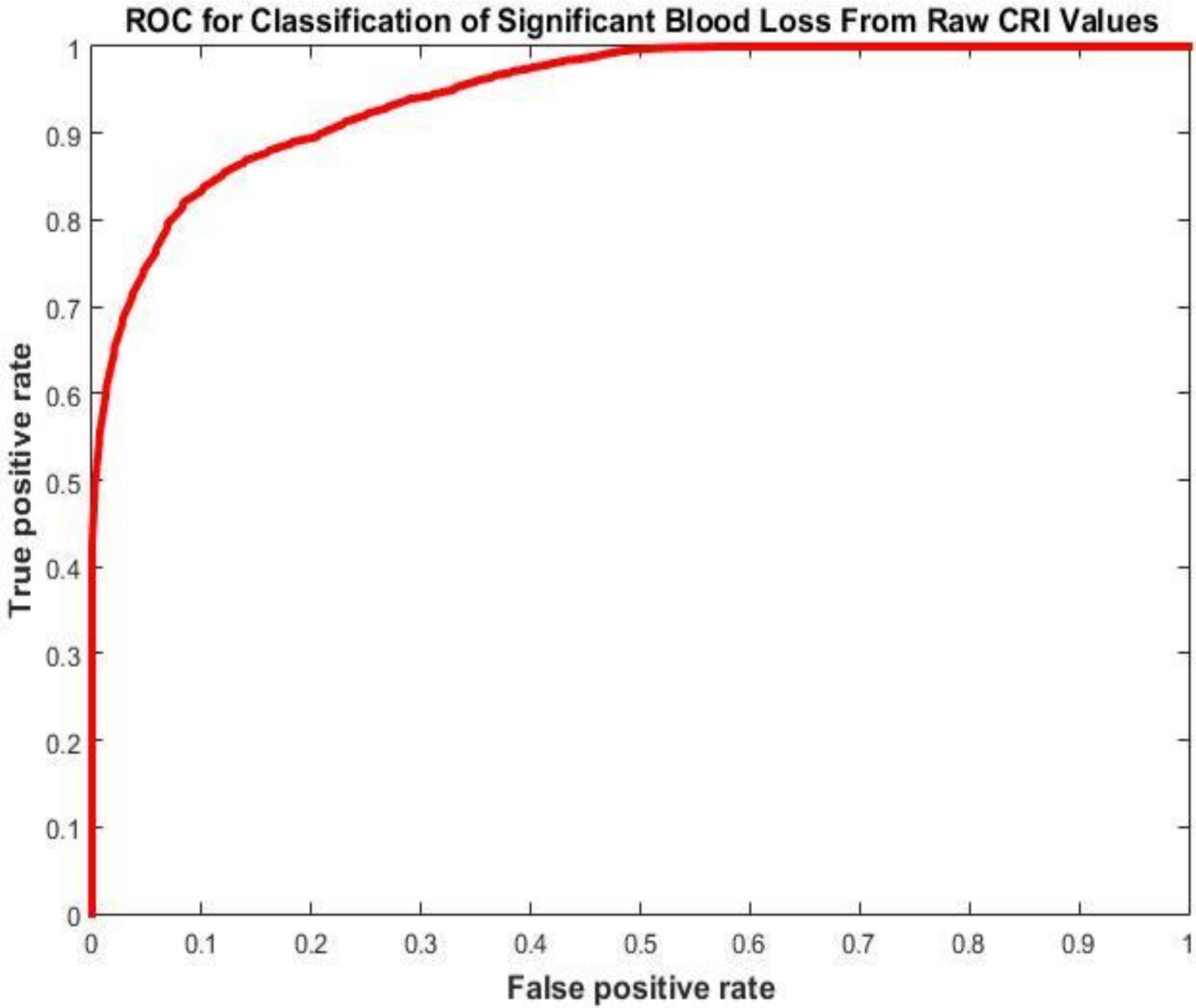
Results

- 20 patients recruited
  - 5 excluded
  - 15 completed
- BP and SpO2 unchanged
- HR increased last 2 stages
- SV decreased 15%
- CRI decreased 36%
- Linear correlation coefficients (r) for blood loss:
  - SV = 0.943
  - CRI = 0.954
- ROC AUC
  - SV = 0.7686
  - CRI = 0.9222



Results


Subject 1
Subject 2
Subject 3
Subject 6
Subject 7
Subject 9
Subject 10
Subject 12
Subject 15
Subject 16
Subject 18
Subject 19
Subject 20
Compensatory Reserve
Blood Volume Loss, ml
● = Blood Loss
○ = Blood volume restoration


ROC for Classification of Significant Blood Loss From Raw CRI Values
True positive rate
False positive rate
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1

Additional “Duke Data”

One liter human blood loss study

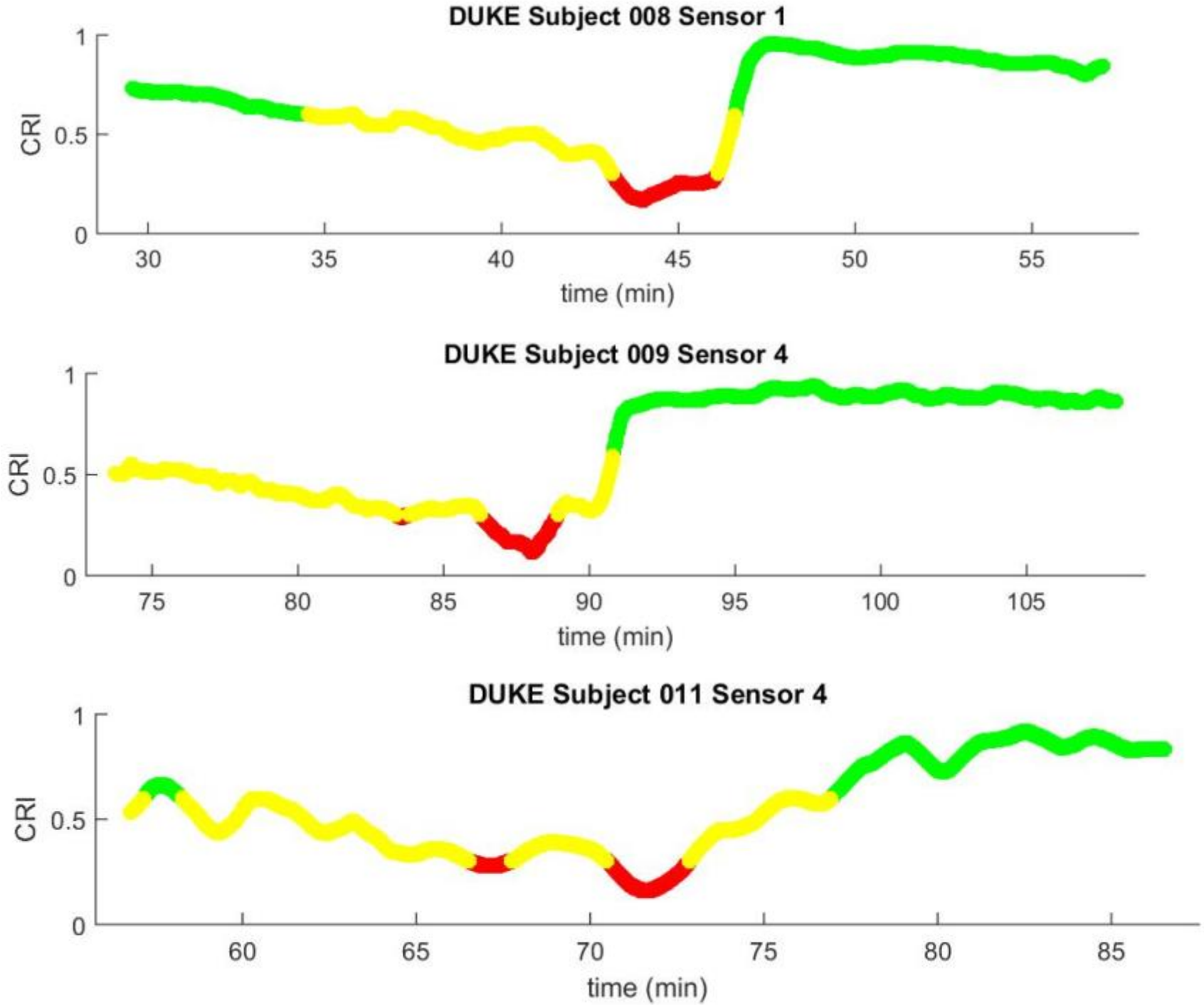
- Same protocol
- Additional 22 subjects (total = 42)

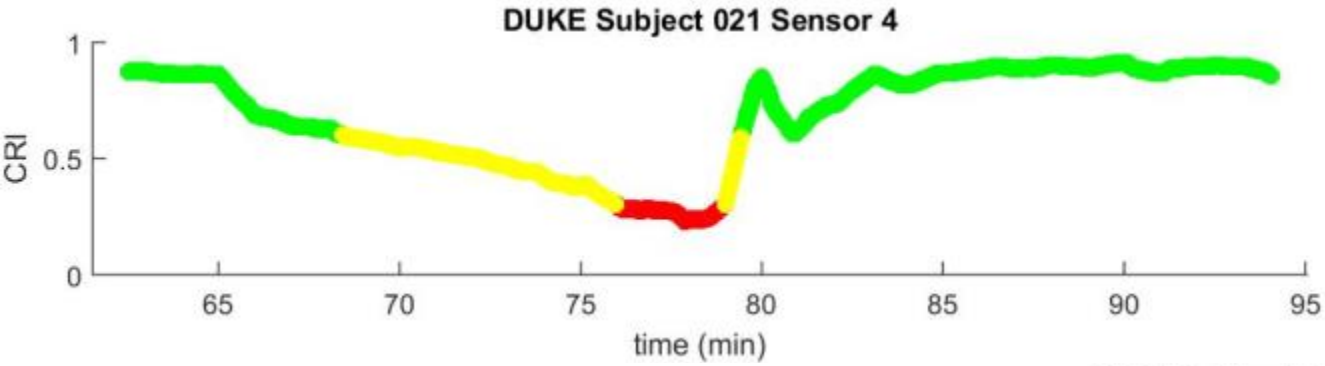
Results

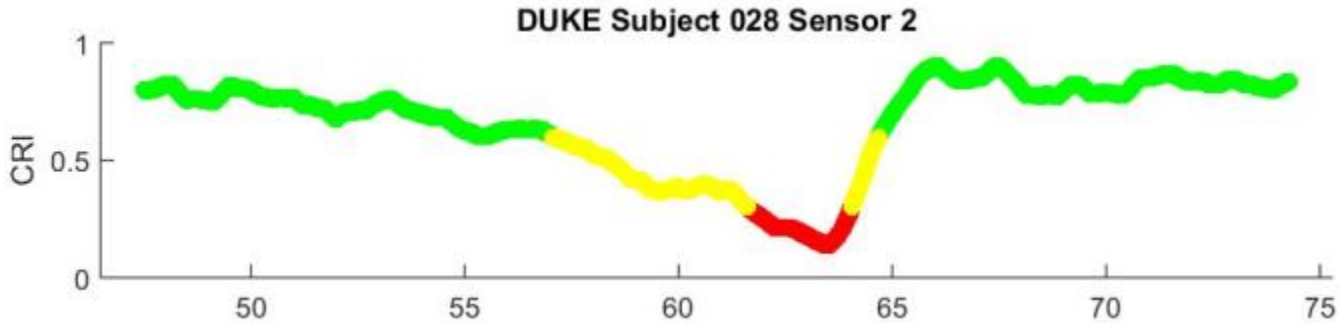
- **7/42 subjects decompensated (SBP < 80)**

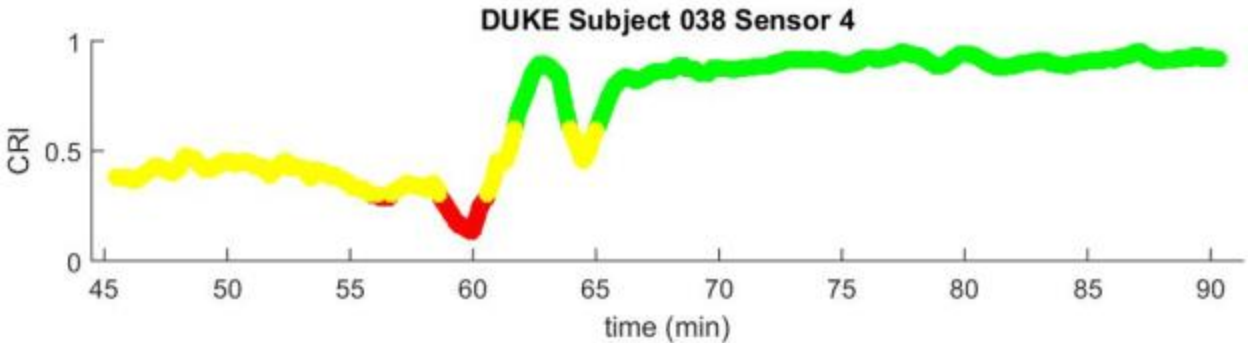
Symptomatic Subjects (n=7)	Baseline SBP mmHg	Baseline DBP mmHg	Symptoms SBP mmHg	Symptoms DBP mmHG	Symptoms MBP mmHg
8	118	74	78	45	56
9	118	71	62	38	46
11	118	72	68	50	56
21	121	73	68	42	50
28	117	72	61	37	44
38	118	71	64	36	45
39	119	74	78	44	54

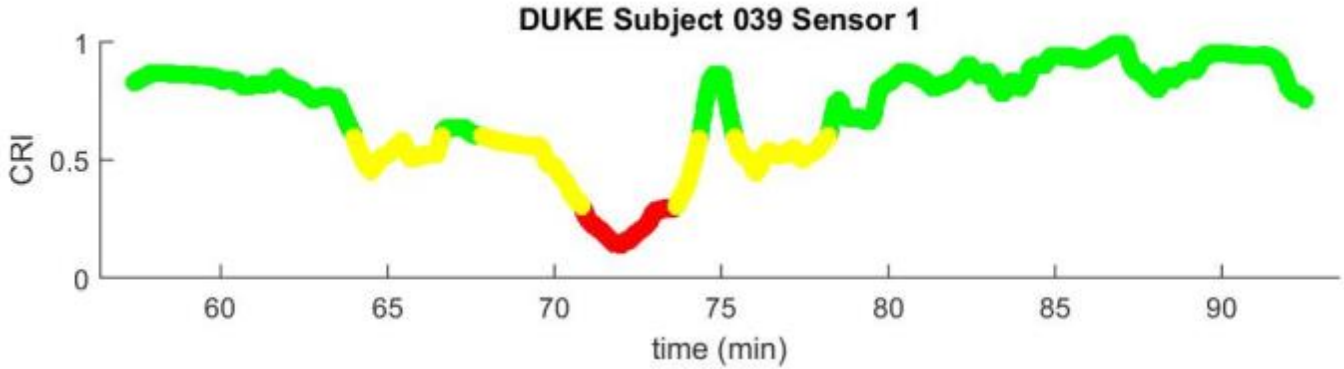
CRI	Pt's w/o Sx's Baseline n = 32	Pts w/o Sx's Max Blood Loss n = 32	Pts w/ Sx's at Max Blood Loss n = 7	Pt's w/o Sx's End n = 32
Mean CRI	0.880	0.592	0.197	0.880
Std. Dev.	± 0.083	± 0.166	± 0.071	± 0.074
Min. CRI	0.56	0.17	0.074	0.53
Median CRI	0.90	0.59	0.21	0.90
Max CRI	1.0	0.91	0.349	1.0


DUKE Subject 008 Sensor 1
CRI
1
0.5
0
30
35
40
45
50
55
time (min)
DUKE Subject 009 Sensor 4
CRI
1
0.5
0
75
80
85
90
95
100
105
time (min)
DUKE Subject 011 Sensor 4
CRI
1
0.5
0
60
65
70
75
80
85
time (min)


DUKE Subject 021 Sensor 4
CRI
1
0.5
0
65
70
75
80
85
90
95
time (min)

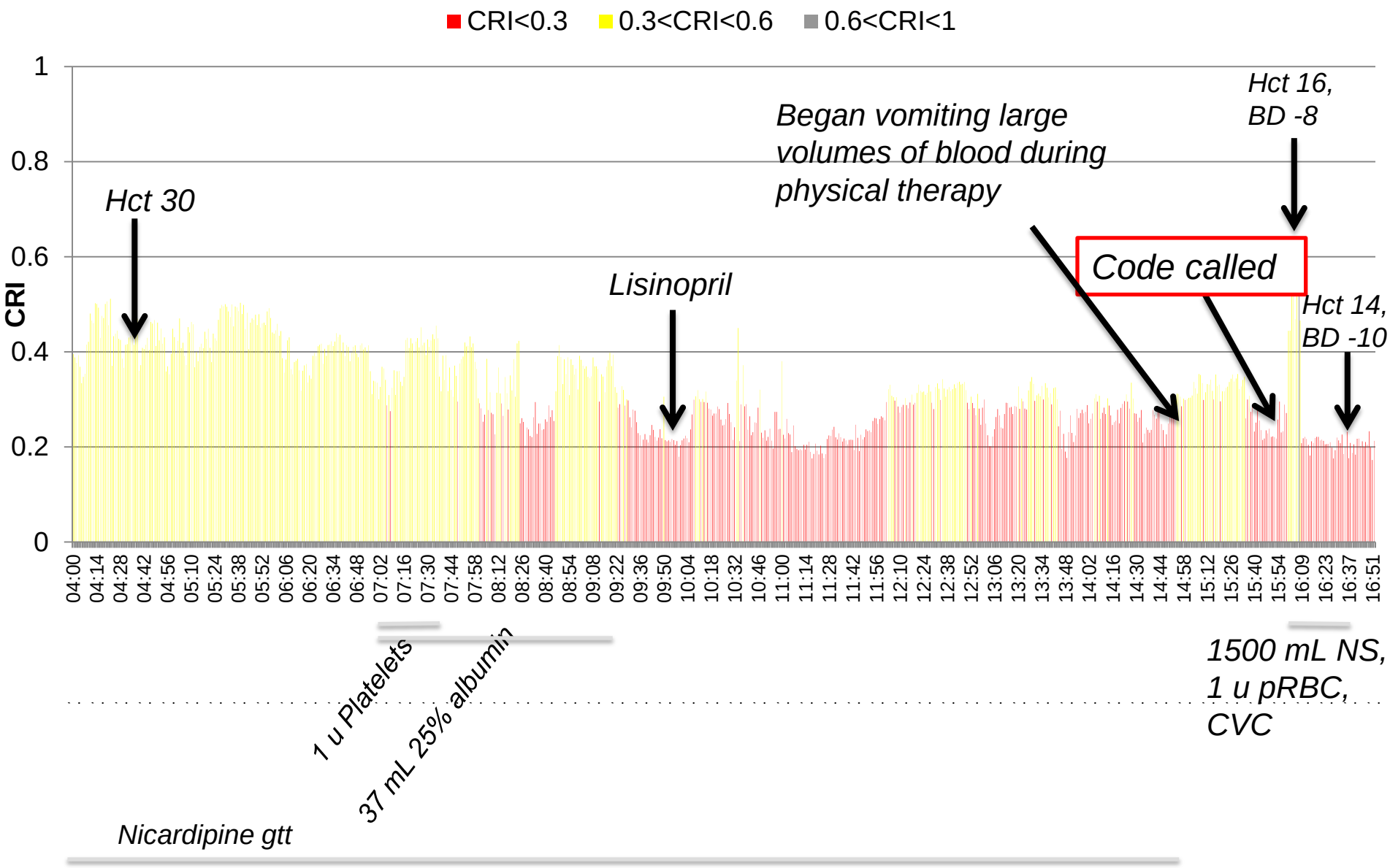

DUKE Subject 028 Sensor 2
CRI
1
0.5
0
50
55
60
65
70
75


DUKE Subject 038 Sensor 4
CRI
1
0.5
0
45
50
55
60
65
70
75
80
85
90
time (min)

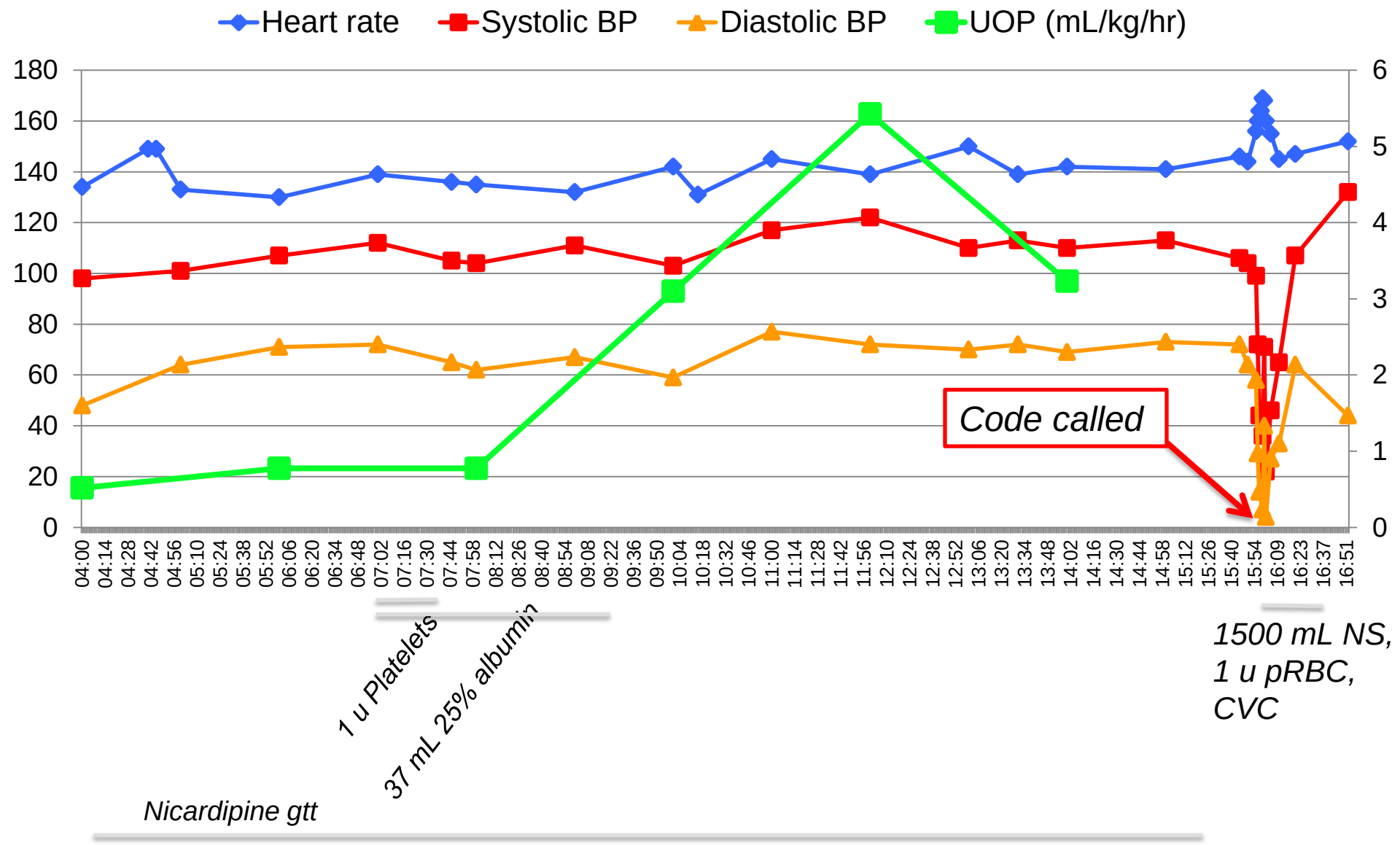

DUKE Subject 039 Sensor 1
CRI
1
0.5
0
60
65
70
75
80
85
90
time (min)

Clinical Data

12 y/o F with Lupus Nephritis, Massive Hematemasis



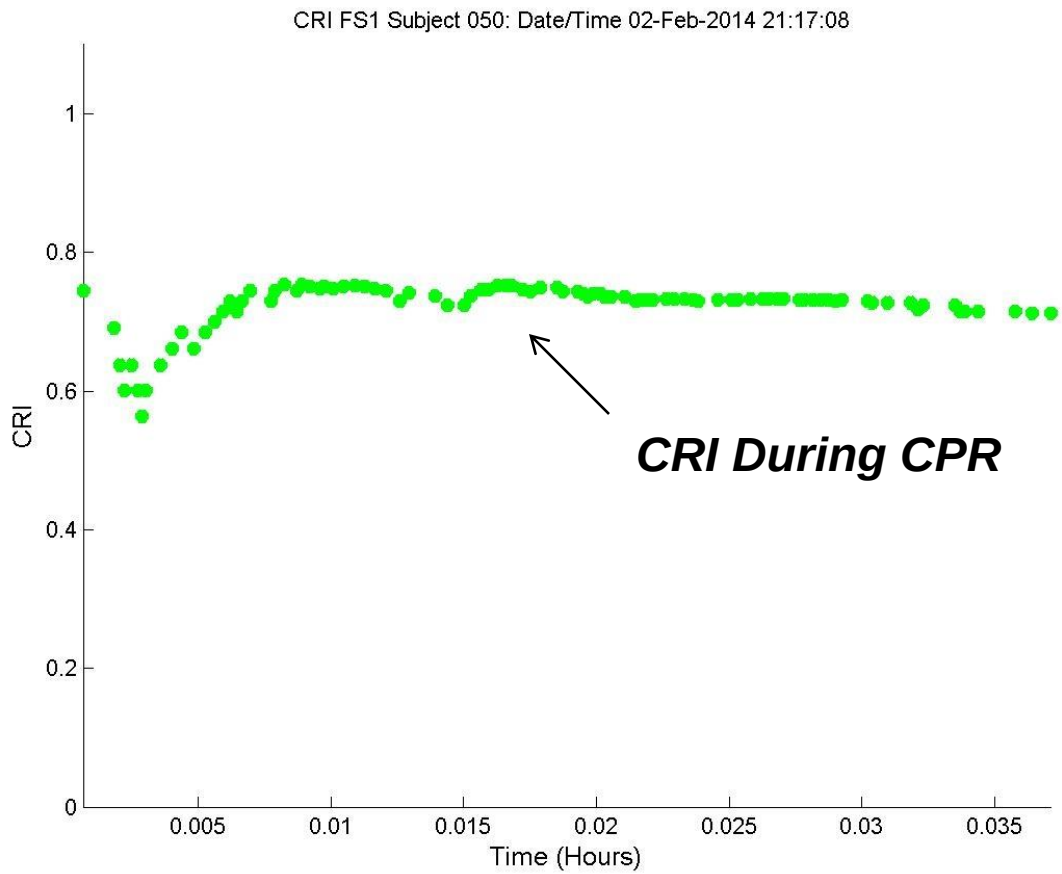
Traditional Vital Signs



CRI During Cardiopulmonary Resuscitation

57 year old male
Self-inflicted GSW chest
Arrived CPR in progress
Device placed
FAST
Patient declared dead
Device removed

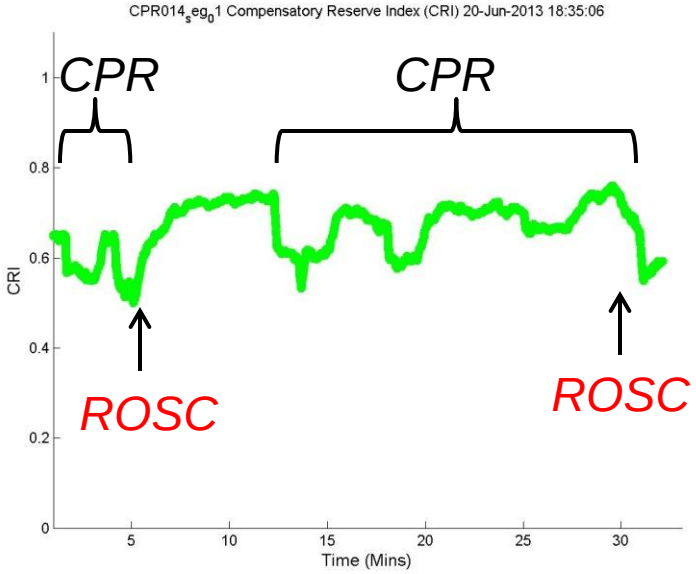
Waveform data run through CRI algorithm



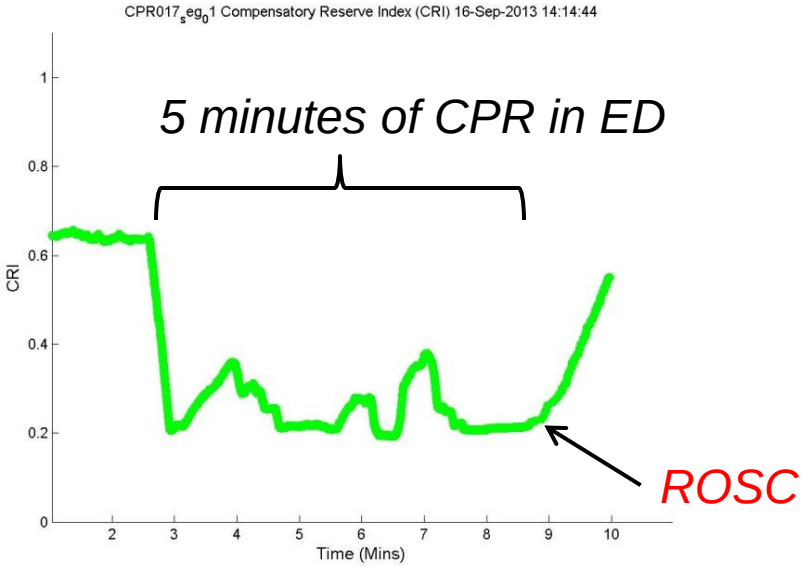
*Could CRI be a noninvasive measure of **CPR** effectiveness?*

CPR Data from Children's Hospital
2/17 Survivors in 2013 (shown)

3 month old male NAT victim
CPR started 4 minutes PTA
CPR 1838 – 1850
ROSC (return of spont. circulation)
CPR 1900-1920
ROSC



10 day old female
Critical coarctation of aorta
Cardiac arrest
CPR for 5 minutes, ROSC



Summary

- Computational algorithm for monitoring compensatory changes associated with central volume loss and gain:
  - Algorithm monitors nIBP <u>or</u> pulse ox waveforms
  - First CRI reading at 30 beats, each beat thereafter
  - Normovolemia → CV collapse → normovolemia
  - No baseline or convalescent data required
  - No specialized expertise to interpret result
  - Differentiates low from high tolerant subjects

Acknowledgment

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David McLeod, PhD

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Gary Muniz, BS

Questions?

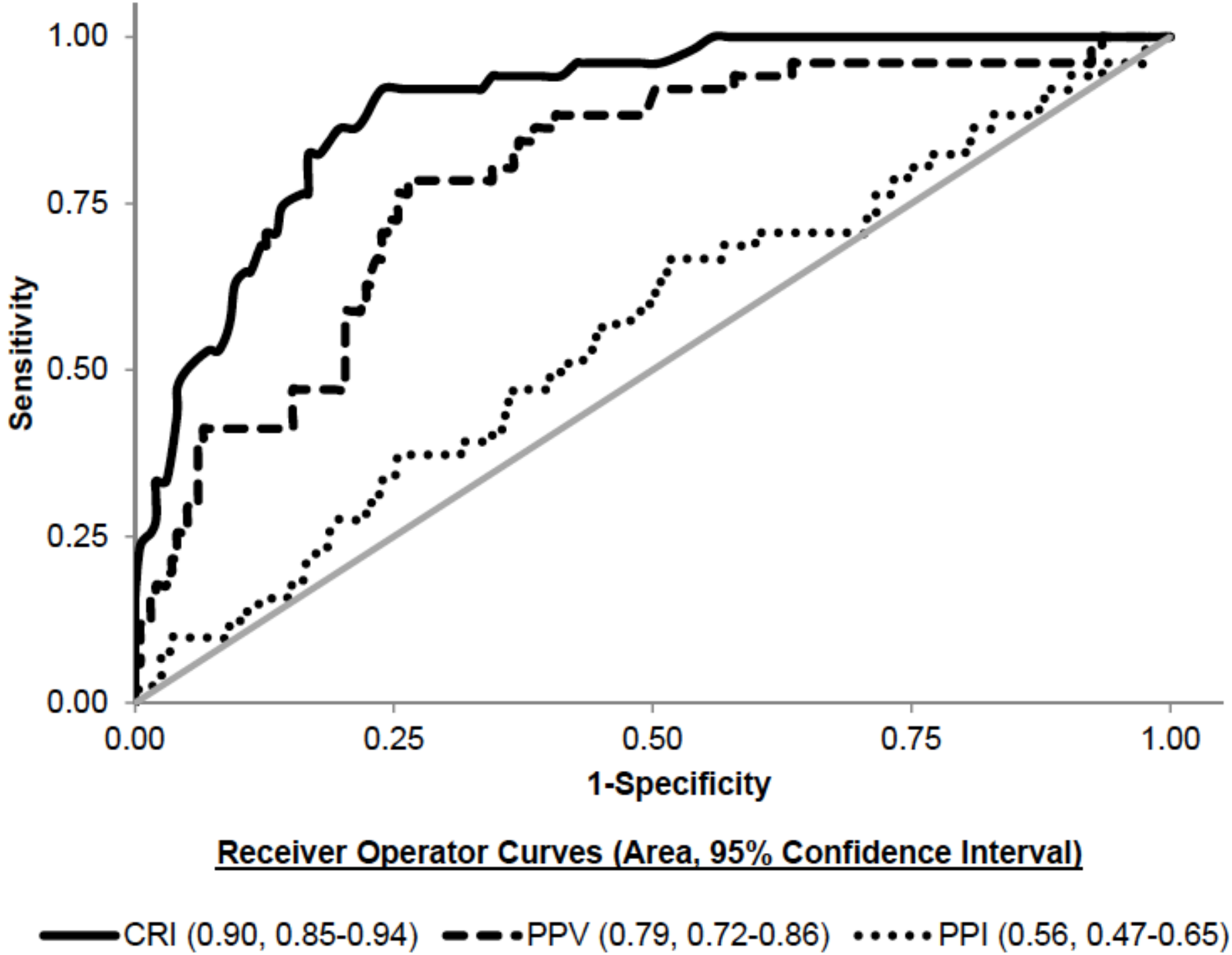
Comparison of PPI, PPV and CRI*

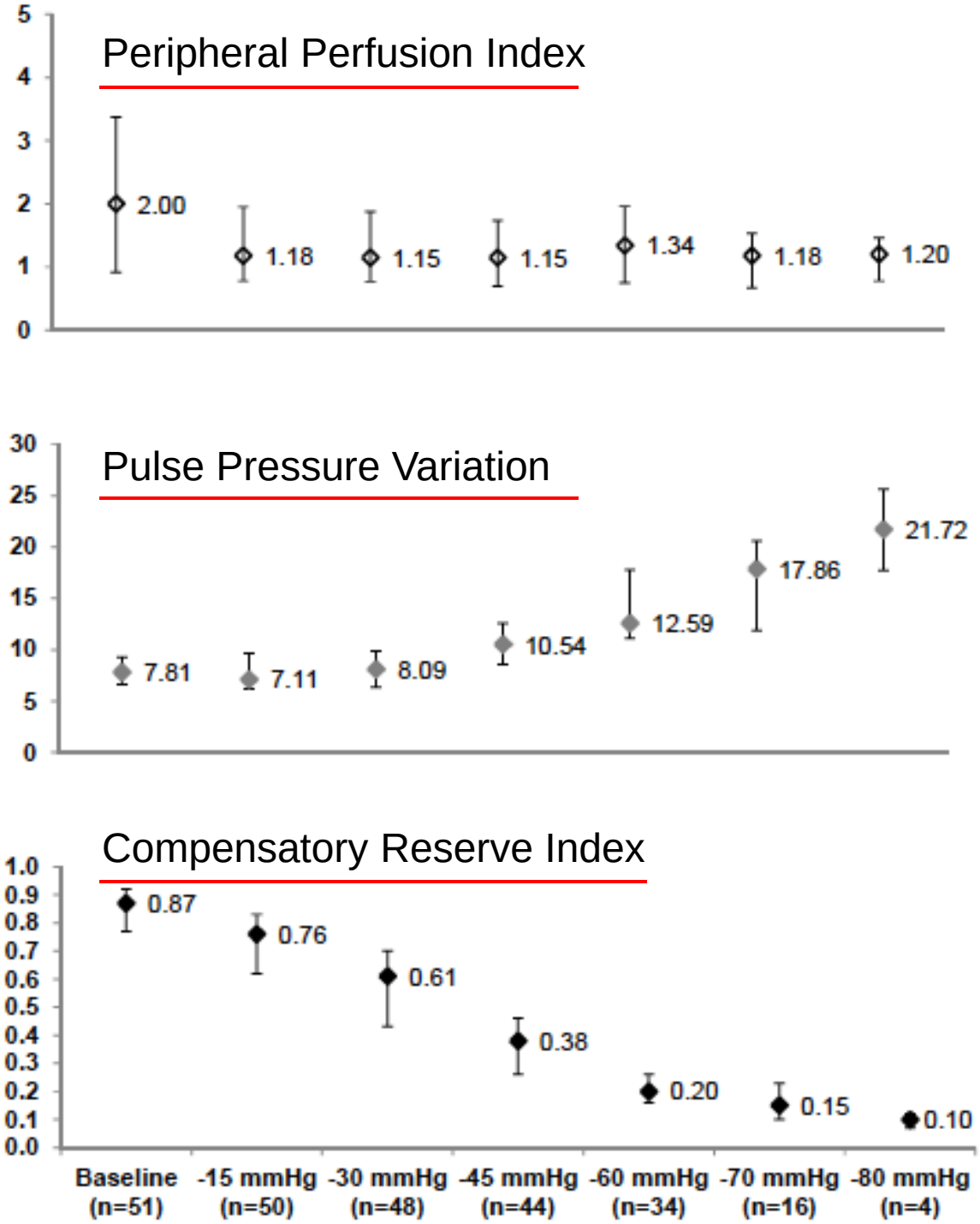
- Standard LBNP Protocol
  - 51 subjects
    - 28 men, 23 women
    - Average age 25 ± 1 years old
  - Compare sensitivity and specificity
    - PPV = pulse pressure variability
    - PPI = peripheral perfusion index
    - CRI = compensatory reserve index

*Janak JC, Howard JT, Goei KA, Weber RL, Muniz GW, Hinojosa-Laborde C, Convertino VA. Predictors of the onset of hemodynamic decompensation during progressive central hypovolemia. Submitted to Shock

Table 1. Vital Signs during Lower Body Negative Pressure Hemorrhage Simulation (n=51)

Vital Sign	Baseline	HD	ROC AUC (95% CI)	Chi-Square Test	p-value	Sensitivity	Specificity
PPI	2.00 (0.92-3.37)	1.06 (0.68-1.96)	0.56 (0.47, 0.65)	44.5	<0.0001	70.6	28.9
PPV	7.81 (6.62-9.30)	11.68 (10.86-19.18)	0.79 (0.72, 0.86)	14.6	0.0001	78.4	69.0
CRI	0.87 (0.77-0.92)	0.19 (0.11-0.32)	0.90 (0.85, 0.94)	Ref.	-	86.3	77.7


1.00
0.75
0.50
0.25
0.00
Sensitivity
0.00
0.25
0.50
0.75
1.00
1-Specificity
Receiver Operator Curves (Area, 95% Confidence Interval)
CRI (0.90, 0.85-0.94)
PPV (0.79, 0.72-0.86)
PPI (0.56, 0.47-0.65)


Peripheral Perfusion Index
5
4
3
2
1
0
2.00
1.18
1.15
1.15
1.34
1.18
1.20
Pulse Pressure Variation
30
25
20
15
10
5
0
7.81
7.11
8.09
10.54
12.59
17.86
21.72
Compensatory Reserve Index
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.87
0.76
0.61
0.38
0.20
0.15
0.10
Baseline (n=51)
-15 mmHg (n=50)
-30 mmHg (n=48)
-45 mmHg (n=44)
-60 mmHg (n=34)
-70 mmHg (n=16)
-80 mmHg (n=4)

Final Thoughts

The CRI algorithm ***estimates*** *the following:*

$$CRI = \frac{1 - EVL}{EVL_{HD}}$$

CRI is the proportion of compensatory reserve remaining

Where:

- EVL is the effective central volume loss
- EVL_{HD} is the effective central volume loss at which the patient will experience hemodynamic decompensation (HD)

Using the CRI Monitor

- Effective central volume changes with:
  - Postural changes
  - Heat
  - Exercise
  - Fatigue
  - Hydration
  - Blood loss
- Effective central volume is very dynamic and can change with every heartbeat
- <u>In a resting supine position</u>:
  - Central volume will normalize
  - *Low CRI or CRI trending down is a cause for concern*