Heart rate characteristics monitoring to detect neonatal sepsis

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METHOD

- Pick the right problem.

Little babies are dying.
Neonatal Sepsis: A Major Public Health Problem

• Of 4 million births each year, 56,000 are very low birth weight infants (VLBW, <1500 grams; about 3.5 lbs)

• Risk of sepsis is high
  – 21 - 40% of VLBW infants develop sepsis while in the neonatal intensive care unit (NICU)

• Significant mortality and morbidity (NICHD 2002)
  – In VLBW infants, sepsis more than doubles the risk of dying
  – Length of stay is increased by 3 weeks
  – Health care costs are increased
Is this baby septic?

• The diagnosis of neonatal sepsis is difficult
• The outcome of sepsis is potentially catastrophic
• Leading physicians to:
  – obtain lab tests
  – administer antibiotics early and often
METHOD

- Pick the right problem.
- Look at the data.

We observed reduced variability and transient decelerations prior to clinical illness and death.
Hours prior to death

>150

<24
Normal heart rate characteristics

Histogram of heart rates

many small decelerations

many small accelerations

decelerations  accelerations
Abnormal heart rate characteristics

- many large decelerations
- few or no accelerations

Histogram of heart rates

- decelerations
- accelerations
CONVENTIONAL HRV measures do not detect reduced variability and transient decelerations, so we made some up.
HRC algorithm development

• Mathematical analysis of reduced variability and transient decelerations
  – standard deviation
  – sample asymmetry
  – sample entropy

• Biostatistical analysis of HRC prior to clinical diagnosis of neonatal sepsis
  – multivariable logistic regression

• Result: an on-line continuous estimate of the risk of sepsis in the next 24 hours, based on the degree of reduced variability and transient decelerations
Predictive model – study design

CRASH = Cultures, Resuscitation, & Antibiotics Started Here

Epochs were defined as “well” (more than 24 hours prior to CRASH event), “sick”, or a 14-day “blackout” period that was not analyzed.
The **HRC index** is derived from regression modeling and uses HRC measures of *standard deviation* (S.D.), *Sample Asymmetry* (R1 and R2), and *SampEn* to estimate the risk of upcoming sepsis and sepsis-like illness.

The formula for the **HRC index** is:

\[
\text{HRC index} = \frac{\exp(A)}{1+\exp(A)}
\]

where:

\[
A = \text{intercept} + \beta_1(\text{S.D.}) + \beta_2(\text{R1}) + \beta_3(\text{R2}) + \beta_4(\text{SampEn})
\]

We derived the intercept and coefficients $\beta$ using UVa data, and then calculated the **HRC index** for WFU data.
HRC INDEX PREDICTS SEPSIS AT 2 NICUs

TRAIN AT UVa:
316 infants;
155 events in 101 infants

TEST AT WFU:
317 infants;
118 events in 93 infants

result: formula for HRC index

HRC index is associated with sepsis and sepsis-like illness
p<0.0001

HRC index adds significantly to BW, GA and days of age
p<0.0001
Fold-increase in risk

HRC index, as percentile

HeRO 2 or more
*High risk* – top 10%

HeRO 1 to 2
*Intermediate risk* – 70 to 90%

HeRO 1 or less
*Low risk* – bottom 70%
HRC index rises prior to sepsis

Term infant

Premature infant

Fold-increase in risk

Days post-natal

Fold-increase in risk

Days post-natal

CRASH
Symptoms: none
Labs: normal
BC: *Serratia marcescens*
HRC rises before illness score

HRC index (fold-increase)

Clinical score

Time relative to event (days)
Fate of HRC (VLBW infants)
# A neonatal sepsis risk scorecard

<table>
<thead>
<tr>
<th>Clinical score</th>
<th>HRC index</th>
<th>Not measured</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not measured</td>
<td>1.0</td>
<td>0.5</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.7</td>
<td>0.5</td>
<td>1</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
METHOD

• Pick the right problem.
• Look at the data.
• Assume nothing.
• Do a randomized trial.

1 R01-HD 048562-01
“Impact of neonatal heart rate characteristics”
ClinicalTrials.gov identifier NCT 00307333
Does HRC display improve outcomes in the NICU?

admission to NICU

\[\downarrow\]

randomize

\[\leftarrow\quad \leftarrow\]

HRC display    no HRC display

outcome measures:
• ventilator-free days during first 120 days of life (primary)
• days in hospital
• days on antibiotics
• in-hospital mortality
Mathematical analyses of neonatal heart rate

• Empirical cumulative distribution functions and the Kolmogorov-Smirnov two-sample test (Cao)
  – Neonatal HR is non-stationary, and even less so prior to sepsis.

• Nearest-neighbor analysis and tournaments of models (Xiao)
New data point

healthy neighbor

septic neighbor

neighborhood

WBC

Day of age

Birth weight

New data point

healthy neighbor

septic neighbor
Are the biggest pessimists the best predictors of sepsis?
Results

- Nearest-neighbor analysis added independent information to logistic regression \((p<0.05)\).
- HRC index was the most predictive individual finding, but tournaments of models led to the best predictions.
Mathematical analyses of neonatal heart rate

- Empirical cumulative distribution functions and the Kolmogorov-Smirnov two-sample test (Cao)
- Nearest-neighbor analysis and tournaments of models (Xiao)
- Deceleration detection using wavelet transform analysis (Flower)
Wavelet transform analysis of decelerations
Wavelet transform analysis of decelerations

Raw data with fitted wavelet templates superimposed

Baseline heart rate variability

+ 

Detected decelerations
Some infants had storms of decelerations

BW 1285 g, GA 29 weeks
Day 18 of life
2 hours before
*Klebsiella* sepsis

BW 1005 g, GA 27 weeks
Day 21 of life
7 hours before
*Pseudomonas* sepsis
These storms were highly predictive of sepsis.
Decelerations add information to the HRC index

<table>
<thead>
<tr>
<th>predictor 1</th>
<th>predictor 2</th>
<th>ROC</th>
<th>p1</th>
<th>p2</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.D. of RR intervals</td>
<td></td>
<td>0.70</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>S.D. of RR intervals</td>
<td>number of decelerations</td>
<td>0.75</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>HRC index</td>
<td></td>
<td>0.75</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>HRC index</td>
<td>number of decelerations</td>
<td>0.77</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

S.D. = standard deviation; $p_1$ is for significance of predictor 1; $p_2$ is for added information of predictor 2; * = <0.05.
Mathematical analyses of neonatal heart rate

• Empirical cumulative distribution functions and the Kolmogorov-Smirnov two-sample test
• Nearest-neighbor analysis and tournaments of models
• Deceleration detection using wavelet transform analysis
• Entropy estimation:
  – ApEn is biased, but Sample Entropy (SampEn) is less so (Richman).
  – Low values of entropy can arise from spikes in the data (Lake).
  – Atrial fibrillation detection based on entropy requires only short records (Lake, Xiao).
  – Closed form estimates of the variance of SampEn (Richman, Lake)…
  – …allow optimization of $m$ and $r$ (Lake, Rushton, Xiao).
Entropy estimation

bars are $r(S.D.)$

$A = \text{match of length } m+1$

$B = \text{match of length } m$

Sample Entropy $= -\ln \frac{\Sigma A}{\Sigma B}$

Approximate Entropy $\approx \Sigma -\ln \frac{1+\Sigma A}{1+\Sigma B}$

For regular, repeating data, $\Sigma A / \Sigma B$ nears 1 and entropy nears 0.
Toward improved entropy estimates

- Signal $x_1, x_2, \ldots, x_n$
- $X_i(m) = (x_{i-m+1}, \ldots, x_i)$ template $i$ of length $m$
- $B_i =$ number of matches with $X_i(m)$
- $A_i =$ number of matches with $X_i(m+1)$
- $B = \sum B_i =$ number of matches of length $m$
- $A = \sum A_i =$ number of matches of length $m+1$
- Conditional probability: $p = A / B$
- SampEn = $-\log(p)$
Conditional probability variance

\[ \sigma_p^2 = \frac{1}{4B^2} \left( \sigma_A^2 - 2p\sigma_{AB}^2 + p^2\sigma_B^2 \right) \]

\[ \sigma_A^2 = n \sum_{i=1}^{n} (A_i - \bar{A}/n)^2 + 2n \sum_{h=1}^{K} \sum_{i=1}^{n-h} (A_i - \bar{A}/n)(A_{i+h} - \bar{A}/n) \]

\[ \sigma_{AB}^2 = \text{Cov}[A,B] = n \sum_{h=-K}^{K} \sum_{|i-j|=h} (A_i - \bar{A}/n)(B_j - \bar{B}/n) \]

- Factor of 4 needed to account for counting each match twice
- \( K \) selected based on correlation length of signal and \( m \)
- Conservative estimate is maximum value among all \( K \)
Estimated SampEn Standard Error

• Above estimate more accurate and generally smaller than that previously reported (Lake et al, 2002) and available on Physionet

• Estimate motivated by more accurate U-statistic approach of Richman (Ph.D. dissertation 2005)

• New estimate requires less computation and agrees favorably on MIT-BIH NSR data base

• Standard error of SampEn is approximately standard error of $p$ divided by $p$
Relative error of the SampEn estimate

Atrial fib  Normal sinus rhythm  CHF

ROC areas
AF vs NSR  AF vs CHF  NSR vs CHF
Acknowledgments

University of Virginia
• Doug Lake
• Boris Kovatchev
• Frank Harrell/Doug Wagner
• Hanqing Cao (Susan)
• Abby Flower
• Yuping Xiao
• Ben Rushton

MPSC
• Will King
• Scott Booth

Wake Forest
• Mike O’Shea

UAB
• Wally Carlo

Wm&Mary
• John Delos

George Beller
John Kattwinkel
Brian Duling
CIT, CMC, AHA, NIH