Improving Weaning:

Weaning and Variability Evaluation (WAVE) Study

Canadian Critical Care Forum 2013

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Ottawa Hospital Research Institute, University of Ottawa
Disclosure

• Academic disclosure
  – Variability analysis = personal academic passion

• Financial disclosure
  – Therapeutic Monitoring Systems Inc.
  – I am Founder & Chief Science Officer
  – I hold patents and equity in TMS

• Aim: Improve efficiency and quality of care
Improving Weaning?
Focus on decision to extubate

• Depends on:
  1. “Will the patient be able to sustain spontaneous ventilation following tube removal?”
  2. “Will the patient be able to protect his or her airway after extubation?”

• Spontaneous Breathing Trial
  – Addresses first question only
  – Multiple “weaning parameters” evaluated
Weaning Parameters

- **Rapid Shallow Breathing Index (RSBI) = RR/TV**  

- **Tidal Volume (TV), Respiratory Rate (RR)**  

- **(Normalized) Airway Occlusion Pressure 0.1s after Inspiratory Onset (P0.1, P0.1/Pmax)**  
  Capdevila XJ, Perrigault PF, Perey PJ et al. (1995) *Chest*

- **Increase in B-type natriuretic peptide**  

**Combination Parameters:**

- **Peak Expiratory Flow and RSBI**  

- **Integrated effort Quotient**  
  Milic-Emily J. Is weaning an art or a science? (1986) *Am Rev Resp Dis*

- **CROP = Dynamic Compliance x Max Insp Press x (PaO2/pAO2)/ resp rate**  

- **Integrated Weaning Index (IWI) = Static Compliance x PaO2/RSBI**  
  Nemer SW, Barbas CSV, Caldeira JB et al (2009), *Crit Care*
Yet Weaning is an Unresolved Problem


“Extubation failure occurs in 10% to 20% of patients and is associated with extremely poor outcomes including high mortality rates of 25% to 50%.”

Failed Extubation is a major problem

- Definition: Re-intubation within 48 hours
- Incidence: average 15% (5-20%)

- Failed extubation associated with increased ICU & hospital mortality & length of stay, tracheostomy, cost, long term & rehab care

- Need for improved prediction of extubation failure
Novel approach

• Complex systems research paradigm
  – Accept emergence: focus on whole system
  – Accept uncertainty: focus on monitoring/time
  – Utilize variability to track whole system/time

• Quantitative approach
  – Variability analysis: characterize degree and character of variation over intervals in time
  – Predictive modeling: machine learning to derive robust predictive model
Variability Metrics

- Characterize patterns of variation over intervals in time
- Domains of analysis
  - Statistical, geometric, energetic, informational, & invariant.
- One parameter alone inadequate – multivariate comprehensive variability approach required


Review and classification of variability analysis techniques with clinical applications

Methods derived from nonlinear dynamics for analysing heart rate variability

Andreas Voss, Steffen Schulz, Rico Schroeder, Mathias Baumert and Pere Caminal

*Phil. Trans. R. Soc. A* 2009 367, 277-296
Studies to date

Pattern of spontaneous breathing: potential marker for weaning outcome
Spontaneous breathing pattern and weaning from mechanical ventilation

Breathing pattern variability: a weaning predictor in postoperative patients recovering from systemic inflammatory response syndrome

Changes of Heart Rate Variability During Ventilator Weaning
Hsiu-Nien Shen, Lian-Yu Lin, Kuan-Yu Chen, Ping-Hung Kuo, Chong-Jen Yu, Huey-Dong Wu and Pan-Chyr Yang

Reduced breathing variability as a predictor of unsuccessful patient separation from mechanical ventilation*

Lower Interbreath Interval Complexity Is Associated With Extubation Failure in Mechanically Ventilated Patients During Spontaneous Breathing Trials

Biosignal analysis techniques for weaning outcome assessment
Weaning and Variability Evaluation (WAVE) Study

Andrew JE Seely, Andrea Bravi, Christophe Herry, Geoffrey Green, André Longtin, Tim Ramsay, Dean Fergusson, Lauralyn McIntyre, Dalibor Kubelik, Anna Fazekas, Donna E. Maziak, Niall Ferguson, Sam Brown, Sangeeta Mehta, Claudio Martin, Gordon Rubenfeld, Frank J Jacono, Gari Clifford, John Marshall
WAVE: Weaning and Variability Evaluation Study

• **Hypothesis:**
  – Altered HRV and/or RRV during Spontaneous Breathing Trials (SBTs) is associated with and predicts subsequent extubation failure

• **Design:**
  – Prospective, multicenter, waived consent, observational, derivational study

• **Methods:**
  – Continuous ECG and CO2 capnograph waveform recording prior to & during SBTs

• **Analysis:**
  – Statistical analysis (Wilcoxon rank-sum) and machine learning (LR ensemble model)

• **Subjects:**

• **Funding:**
  – TOH AFP Innovation (2009), CIHR (2010)
**Inclusion criteria:**
- ventilation for >48 hours
- SBTs for assessment for extubation
- normal sinus rhythm
- PS ≤ 14 cm H₂O, PEEP ≤ 10 cm H₂O
- SpO₂ ≥ 90% with FiO₂ ≤ 40%
- hemodynamically stable
- stable neurological status
- intact airway reflexes (cough & gag)

**Exclusion criteria:**
- order not to re-intubate
- anticipated withdrawal
- severe weakness
- tracheostomy
- prior extubation

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**For each SBT**

1. **Attach etCO₂ module**
2. **Pre-SBT Observation (30 min)**
3. **Spontaneous Breathing Trial (30 min)**
4. **Post-SBT Observation (30 min)**

**SBT CRF: Data collection: 5 points in time**

**ECG & CO₂ data download, and remove etCO₂ module**

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**Clinical CRF completion 5 days post extubation**

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**Extubation CRF**

Prior to Extubation

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**CRF** = Case Report Form

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**SBT** = Spontaneous Breathing Trial
## Multi-center Wave Enrolment

<table>
<thead>
<tr>
<th>City</th>
<th>PI</th>
<th>RC</th>
<th>Hospital</th>
<th>Enrolling since</th>
<th># Patients Enrolled</th>
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</thead>
<tbody>
<tr>
<td>Ottawa</td>
<td>Andrew Seely</td>
<td>Irene watpool</td>
<td>General Hospital</td>
<td>9-Nov</td>
<td>384</td>
</tr>
<tr>
<td>Ottawa</td>
<td>Jon Hooper</td>
<td>Tracy McArdle</td>
<td>Civic Hospital</td>
<td>10-Feb</td>
<td>89</td>
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<tr>
<td>Ottawa</td>
<td>Peter Wilkes</td>
<td>Denyse Winch</td>
<td>Heart Institute</td>
<td>9-Nov</td>
<td>45</td>
</tr>
<tr>
<td>London</td>
<td>Claudio Martin</td>
<td>Eileen Campbell</td>
<td>LHSC</td>
<td>11-Jan</td>
<td>41</td>
</tr>
<tr>
<td>Toronto</td>
<td>Geeta Mehta</td>
<td>Maedean Brown</td>
<td>Mt Sinai</td>
<td>11-Jul</td>
<td>61</td>
</tr>
<tr>
<td>Ann Arbor</td>
<td>James Blum</td>
<td>Elizabeth Jewell</td>
<td>University of Michigan</td>
<td>11-Aug</td>
<td>7</td>
</tr>
<tr>
<td>Cleveland</td>
<td>Frank Jacono</td>
<td>David Haney</td>
<td>University VA Hospital</td>
<td>11-Oct</td>
<td>42</td>
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<tr>
<td>Lebanon NH</td>
<td>Athos Rassias</td>
<td>Sara Metzler</td>
<td>Dartmouth</td>
<td>11-Nov</td>
<td>4</td>
</tr>
<tr>
<td>Vancouver</td>
<td>Peter Dodek</td>
<td>Betty Jean Ashley</td>
<td>UBC</td>
<td>12-Jan</td>
<td>27</td>
</tr>
<tr>
<td>Billings MT</td>
<td>Rob Merchant</td>
<td>Pam Zinnecker</td>
<td>Billings Clinic</td>
<td>12-Jan</td>
<td>6</td>
</tr>
<tr>
<td>Utah</td>
<td>Samuel Brown</td>
<td>Tracy Burbback</td>
<td>University of Utah</td>
<td>12-Jul</td>
<td>5</td>
</tr>
<tr>
<td>Toronto</td>
<td>John Marshall</td>
<td>Orla Smith</td>
<td>St. Michael's</td>
<td>12-Sep</td>
<td>10</td>
</tr>
</tbody>
</table>

N=721
WAVE Patient flow-chart

Enrolled Patients N=721

Included Patients: N=517

Failed Extubation: N=62
Passed Extubation: N=455

Enough samples for variability calculations?

Failed Extubation: N=58
Passed Extubation: N=427

Variability quality cleaning

Failed Extubation: N=51
Passed Extubation: N=383

Excluded failed N=4
Excluded passed N=28

Excluded failed N=7

Excluded Patients: N=204

Excluded

Protocol Violations: N=97
Missed last SBT: N=18
Directly to trach: N=18
No SBT: N=17
Incl./Excl. criteria: N=15
Intubation < 48hrs: N=11
Missing clinical info: N=2
Other: N=16

Technical Violations: N=107
Missing waveform: N=49
No upload: N=45
Corrupt file: N=6
Incomplete: N=7
## Population demographics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>61.6 ± 15.1 y.o. (range 16-92)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male: 50.5%; Female: 49.5%</td>
</tr>
<tr>
<td><strong>Apache score</strong></td>
<td>20.5 ± 7.5</td>
</tr>
<tr>
<td><strong>ICU admission diagnoses</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>N=152 (25.4%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>N=124 (20.7%)</td>
</tr>
<tr>
<td>Infections</td>
<td>N=80 (13.4%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>N=52 (8.7%)</td>
</tr>
<tr>
<td>Head</td>
<td>N=45 (7.5%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>N=42 (7.0%)</td>
</tr>
<tr>
<td>Renal</td>
<td>N=22 (3.7%)</td>
</tr>
<tr>
<td>Trauma</td>
<td>N=12 (2.0%)</td>
</tr>
<tr>
<td>Overdose</td>
<td>N=11 (1.8%)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>N=8 (1.3%)</td>
</tr>
<tr>
<td>Hepatobiliar</td>
<td>N=4 (0.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>N=47 (7.8%)</td>
</tr>
</tbody>
</table>
Patient monitoring record containing:

- ECG and CO₂ waveforms

Waveform Analytics

- Median variability pre & during BT

Predictive Modeling

- Automated HRV and RRV for high quality intervals

- Average Predictive Capacity (ROC AUC) per model

Univariate Logistic Regression models

Multivariate LR ensemble model

Training / validation

Randomly split population data

1/3

2/3

Repetitive randomized sub-sampling

Test set

Predictive Performance
Univariate Statistical Analyses

Population differences

- Statistical analysis of all variability metrics, comparing extubation success (ES) vs. extubation failure (EF)
- P-values determined by Wilcoxon Rank-Sum test
- Result p-value histogram displays spectrum of differences between populations

Each bar represents a different measure of variability.

Multiple comparison correction was done through the false discovery rate, imposing a 5% of false positives.
Statistically significant variability measures (during SBT Only)

<table>
<thead>
<tr>
<th>Variability Domain</th>
<th>Measure name</th>
<th>Passed (n=383)</th>
<th>Failed (n=51)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical</td>
<td>HRV Mean of the differences</td>
<td>$1.4 	imes 10^{-6}$ (-9.4 $10^{-7}$, 3.7 $10^{-6}$)</td>
<td>$-8.4 	imes 10^{-6}$ (-1.5 $10^{-5}$, -1.9 $10^{-6}$)</td>
<td>0.00278</td>
</tr>
<tr>
<td>Geometric</td>
<td>RRV RQA: average diagonal line</td>
<td>0.0057 (0.0054, 0.0060)</td>
<td>0.0044 (0.0038, 0.0053)</td>
<td>0.00011</td>
</tr>
<tr>
<td></td>
<td>RRV RQA: maximum diagonal line</td>
<td>0.021 (0.020, 0.022)</td>
<td>0.016 (0.015, 0.018)</td>
<td>0.00004</td>
</tr>
<tr>
<td></td>
<td>RRV RQA: maximum vertical line</td>
<td>0.017 (0.016, 0.018)</td>
<td>0.012 (0.011, 0.014)</td>
<td>0.00017</td>
</tr>
<tr>
<td></td>
<td>RRV RQA: trapping time</td>
<td>0.0048 (0.0046, 0.0050)</td>
<td>0.0038 (0.0030, 0.0042)</td>
<td>0.00009</td>
</tr>
<tr>
<td>Informational</td>
<td>RRV Fano factor distance from a Poisson distribution</td>
<td>-0.12 (-0.12, -0.11)</td>
<td>-0.15 (-0.17, -0.12)</td>
<td>0.00166</td>
</tr>
<tr>
<td>Energetic</td>
<td>RRV Hjorth parameters: activity</td>
<td>11.1 (10.4, 11.8)</td>
<td>7.8 (6.0, 10.7)</td>
<td>0.00406</td>
</tr>
<tr>
<td>Scale-Invariant</td>
<td>HRV Power Law (based on frequency) x intercept</td>
<td>15.8 (14.8, 17.3)</td>
<td>10.0 (4.5, 13.9)</td>
<td>0.00255</td>
</tr>
<tr>
<td></td>
<td>RRV Largest Lyapunov exponent</td>
<td>1.02 (1.00, 1.02)</td>
<td>1.07 (1.03, 1.14)</td>
<td>0.00151</td>
</tr>
<tr>
<td></td>
<td>RRV Power Law (based on histogram) y intercept</td>
<td>-2.17 (-2.21, -2.10)</td>
<td>-2.35 (-2.59, -2.15)</td>
<td>0.00259</td>
</tr>
</tbody>
</table>

RQA: Recurrence quantification analysis;
Ensemble of Univariate Logistic Regression

Machine Learning Analysis Summary

• **Training**: parameter identification for each logistic regression
  – Randomized balanced sampling, 500 times repeated

• **Validation**: determine best combination of logistic regression models
  – Feature selection using “greedy” approach to pick optimal ensemble average of 5 univariate Logistic regression models

• **Test** – unbiased performance estimation
  – Repeated 100 times, providing mean and 95% CI of ROC AUC

<table>
<thead>
<tr>
<th>Feature</th>
<th>Median of ROC AUC distribution (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRV</td>
<td>0.56 (CI: [0.50, 0.61])</td>
</tr>
<tr>
<td>HRV and RRV</td>
<td>0.66 (CI: [0.62, 0.69])</td>
</tr>
<tr>
<td>RRV</td>
<td>0.69 (CI: [0.66, 0.73])</td>
</tr>
<tr>
<td>RSBI</td>
<td>0.61 (CI: [0.57, 0.67])</td>
</tr>
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</table>
Final Model Identification

• To be used for subsequent validation study
  – 90% data – training
  – 10% data – validation, feature selection

• Test on derivation cohort
  – Useful to highlight sub-group analyses
  – Evaluate complementary value
WAVE score

- WAVE score correlates with probability of extubation failure

- Goal: Identify low risk and high risk patients

- Provide clinical decision support, not decision-making
WAVE score: Complementary Value

**RSBI<105**
- Risk of failing extubation
- 351 Passed, 45 Failed

**RSBI≥105**
- Risk of failing extubation
- 20 Passed, 6 Failed

**Low/Average risk**
- 298 Passed, 32 Failed

**High risk**
- 33 Passed, 12 Failed
Interpretation & Next Steps

• Altered HRV and RRV during last SBT is statistically associated with extubation failure.
  – P-values range from 0.00004 to 0.004

• Predictive algorithms using RRV alone superior to all other measures to predict extubation outcomes
  – Added sensitivity, better discrimination in high risk patients
  – Complimentary to RSBI and clinical impression of risk

• Multicenter validation study is required to evaluate predictive model in an independent cohort.
Physiologic Significance: What does altered RRV mean?

- Diminished RRV = diminished capacity to tolerate increased workload of breathing.

Dyspnea and Decreased Variability of Breathing in Patients with Restrictive Lung Disease

Thomas Brack, Amal Jubran, and Martin J. Tobin
Division of Pulmonary and Critical Care Medicine, Edward Hines Jr., Veterans Affairs Hospital; and Loyola University of Chicago, Stritch School of Medicine, Hines, Illinois

Restrictive Lung Disease

Controls

Am J Respir Crit Care Med  Vol 165. pp 1260–1264, 2002
Strengths and Limitations

• **Strengths:**
  – Large multicenter study: 721 patients, 12 centers
  – First to perform entirely automated analysis (no inspection)
  – Compelling signal: both statistical association and prediction
  – Pragmatic: all patients; all ages, comorbidities, diagnoses
  – Observational: no control ventilation, sedation, decisions

• **Limitations:**
  – Single center predominance; 28% patients excluded
  – Under-powered for multivariate prediction
  – Pragmatic: may dampen signal (lower pre-test prob. of EF)
  – Observational: test-referral bias (incl. only extubated pts)
Future

• Aim: develop clinical decision support to assist with extubation decision making to improve care
  – Standardized process (duration SBT, vent, sedation, etc)
  – Standardized checklists (SBT and Extubation checklists)
  – Optimal prediction (RRV and existing measures)

• Next steps
  – **Clinical**: WAVE validation study (initiate in 2014)
  – **Technical**: make waveform quality determination and variability analysis openly accessible and transparent ([www.cimva.org](http://www.cimva.org))
  – **Physiological**: improved understanding of independent dimensions to variability analysis (*in silico* and *in vivo* experiments)
# Acknowledgements

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<thead>
<tr>
<th>Canadian Critical Care Trials Group</th>
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<tr>
<th>Ottawa Hospital Research Institute Collaborators</th>
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<tr>
<td>T Ramsay, D Fergusson, L McIntyre, P Wilkes, J Hooper, D Maziak</td>
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<th>Dynamical Analysis Lab team &amp; Collaborators</th>
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<tr>
<td>A Bravi, C Herry, D Townsend, G Clifford</td>
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<td>A Fazekas, I Watpool, R Porteous, T McArdle</td>
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<th>Therapeutic Monitoring Systems</th>
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<td>G Green, W Gallagher, S Goulet, D Longbottom, J Stiff</td>
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What’s so great about the Critical Care Canada Forum?

Check out the video at www.criticalcarecanada.com

- “Focused, engaging, challenging discussions, stimulating, informative, world-renown speakers, international flavour, ground breaking research, exciting, educational, innovative science, high quality program”
- “Goldilocks Conference – not too small, enough people to meet and greet; and not too big such that you can’t elbow your way to the front to ask a question”
- “It is the best critical care conference in the world!”
Controversies

• Optimal level of vent support during a SBT?
  – T-piece vs. 5 PS / 5 PEEP vs. PS 7?
    • Bien MY et al, *Crit Care Med*, 2011

• Optimal duration of SBT?
  – High degree of variation of practice
    • Soo Hoo GW, Park L. *Chest* 2002.

• What goes into an integrated assessment’ re a patient readiness to extubate?
  • RSBI, patient trajectory, cough, patient opinion, grip strength, ...

• Prediction controversies
  – What level of ‘added value’ in prediction is clinically meaningful?
<table>
<thead>
<tr>
<th>Gender:</th>
<th>Passed extubation (N=383)</th>
<th>Failed extubation (N=51)</th>
<th>p-value*</th>
</tr>
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<tbody>
<tr>
<td>Male, n (%)</td>
<td>186 (48.6)</td>
<td>29 (56.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>191 (49.9)</td>
<td>21 (41.2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Age (95% CI)</td>
<td>63 (61, 64)</td>
<td>65 (58, 69)</td>
<td>0.86</td>
</tr>
<tr>
<td>APACHE score (95% CI)</td>
<td>19 (19, 20)</td>
<td>20 (18, 23)</td>
<td>0.21</td>
</tr>
<tr>
<td>Level of sedation (95% CI)</td>
<td>0 (0, 0)</td>
<td>0 (-1, 0)</td>
<td>0.78</td>
</tr>
<tr>
<td>ICU Admission Diagnoses</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardiovascular, n (%)</td>
<td>112 (25.4)</td>
<td>12 (20.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Respiratory, n (%)</td>
<td>87 (19.7)</td>
<td>18 (30.0)</td>
<td>0.05</td>
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<td>Infections, n (%)</td>
<td>62 (14.1)</td>
<td>10 (16.7)</td>
<td>0.54</td>
</tr>
<tr>
<td>Gastrointestinal, n (%)</td>
<td>34 (7.7)</td>
<td>3 (5.0)</td>
<td>-</td>
</tr>
<tr>
<td>Surgery, n (%)</td>
<td>33 (7.5)</td>
<td>3 (5.0)</td>
<td>-</td>
</tr>
<tr>
<td>Head, n (%)</td>
<td>36 (8.2)</td>
<td>1 (1.7)</td>
<td>-</td>
</tr>
<tr>
<td>Renal, n (%)</td>
<td>18 (4.1)</td>
<td>2 (3.3)</td>
<td>-</td>
</tr>
<tr>
<td>Trauma, n (%)</td>
<td>8 (1.8)</td>
<td>1 (1.7)</td>
<td>-</td>
</tr>
<tr>
<td>Overdose, n (%)</td>
<td>9 (2.0)</td>
<td>1 (1.7)</td>
<td>-</td>
</tr>
<tr>
<td>Pancreatitis, n (%)</td>
<td>3 (0.7)</td>
<td>1 (1.7)</td>
<td>-</td>
</tr>
<tr>
<td>Hepatobiliary, n (%)</td>
<td>5 (1.1)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>34 (7.7)</td>
<td>8 (13.3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Comorbidities:</td>
<td></td>
<td></td>
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<tr>
<td>None, n (%)</td>
<td>237 (61.9)</td>
<td>28 (54.9)</td>
<td>0.34</td>
</tr>
<tr>
<td>Lung, n (%)</td>
<td>90 (23.5)</td>
<td>15 (29.4)</td>
<td>0.35</td>
</tr>
<tr>
<td>Heart, n (%)</td>
<td>81 (21.1)</td>
<td>13 (25.5)</td>
<td>0.48</td>
</tr>
<tr>
<td>Both, n (%)</td>
<td>25 (6.5)</td>
<td>5 (9.8)</td>
<td>0.39</td>
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<tr>
<td>Ventilation Settings Pre-SBT:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEEP (95% CI) [cmH2O]</td>
<td>10 (8 10)</td>
<td>8 (8 10)</td>
<td>0.90</td>
</tr>
<tr>
<td>PS (95% CI)</td>
<td>10 (10 10)</td>
<td>10 (10 10)</td>
<td>0.14</td>
</tr>
<tr>
<td>FiO2 (95% CI)</td>
<td>30 (30 30)</td>
<td>30 (30 30)</td>
<td>0.04</td>
</tr>
<tr>
<td>Ventilation Settings During-SBT:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEEP (95% CI)</td>
<td>5 (5 5)</td>
<td>5 (5 5)</td>
<td>0.46</td>
</tr>
<tr>
<td>PS (95% CI)</td>
<td>5 (5 5)</td>
<td>5 (5 5)</td>
<td>0.01</td>
</tr>
<tr>
<td>FiO2 (95% CI)</td>
<td>30 (30 30)</td>
<td>30 (30 30)</td>
<td>0.11</td>
</tr>
<tr>
<td>Perceived risk of failure:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A, n (%)</td>
<td>53 (13.8)</td>
<td>7 (13.7)</td>
<td>0.98</td>
</tr>
<tr>
<td>Low, n (%)</td>
<td>117 (30.5)</td>
<td>6 (11.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Average, n (%)</td>
<td>180 (47.0)</td>
<td>26 (51.1)</td>
<td>0.59</td>
</tr>
<tr>
<td>High, n (%)</td>
<td>33 (8.7)</td>
<td>12 (23.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Respiratory rate: [breaths/min]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-SBT (95% CI)</td>
<td>16.0 (16.0, 18.0)</td>
<td>18.0 (15.0, 22.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>During-SBT (95% CI)</td>
<td>18.4 (17.9, 19.0)</td>
<td>21.7 (18.7, 25.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>RSBI: [breaths/min/L]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-SBT (95% CI)</td>
<td>34.1 (31.8, 36.4)</td>
<td>40.0 (32.5, 50.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>During-SBT (95% CI)</td>
<td>42.7 (39.3, 45.6)</td>
<td>46.6 (40.0, 67.5)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
RAAS Scores (All Patients)
Weaning and Variability Evaluation (WAVE) Prediction of Extubation Failure

Inter-Breath Interval

Wavelet AUC

Standard Deviation

Pass
Fail

ΔHRV
ΔRRV

ΔRRV Cut point -1.4
ROC AUC 0.78
Pos LLR 2.25 (1.3-3.8)

Mean ± SEM; * p < 0.05
• First study to evaluate RRV during SBTs on 5 cm H₂O PS
• N=78 patients: abdominal surgery with SIRS, no pre-existing lung disease, short period ventilation (57 passes and 21 failed)
• Reduced respiratory variability (CoV and Poincaré SD1 & SD2) associated with extubation failure
• ROC AUC 0.75-0.80, equivalent to RSBI
Reduced breathing variability as a predictor of unsuccessful patient separation from mechanical ventilation*

Marc Wysocki, MD; Christophe Cracco, MD; Antonio Teixeira, MD, MSci Biostat; Alain Mercat, MD; Jean-Luc Diehl, MD; Yannick Lefort, MD; Jean-Philippe Derenne, MD; Thomas Similowski, MD, PhD

- First multicenter study (4 units)
- N=51 (“success” in 32, “failure” in 14)
- Visual inspection of the data; removal artifact, non-stationarity
- SBT with ≤ 5 cm H₂O PS
- “Breathing variability is greater in patients successfully separated from ET tube”.

![Graph showing successful and unsuccessful separation](image-url)
Comparisons of predictive performance of breathing pattern variability measured during T-piece, automatic tube compensation, and pressure support ventilation for weaning intensive care unit patients from mechanical ventilation

Maou-Ying Bien, PhD, RRT, RPT; You Shui Lin, PhD; Chung-Hung Shih, MD, PhD;
You-Lan Yang, PhD, RRT; Hui-Wen Lin, PhD; Kuan-Jen Bai, MD; Jia-Horng Wang, MD; Yu Ru Kou, PhD

**Conclusions:** Since 100% inspiratory automatic tube compensation with 5 cm H$_2$O positive end-expiratory pressure and 5 cm H$_2$O pressure support ventilation with 5 cm H$_2$O positive end-expiratory pressure reduce the predictive performance of breathing pattern variability, breathing pattern variability measurement during the T-piece trial is the best choice for predicting extubation outcome in intensive care unit patients. (Crit Care Med 2011; 39:2253–2262)

- Small study (n=68) with elevated (34%) extubation failure rate
- Absolute variability recorded
- ROC values: 0.73±0.07 for T-piece, 0.67±0.07 for 5 cm H$_2$O PS, 0.67±0.07 for 5 cm H$_2$O PS/5 cm H$_2$O PEEP
Waveform Processing

Patient Monitoring Record containing:
- ECG
- CO₂

Waveform Preprocessing

Event Detection

Artifact Removal

Event Time Series

Variability Calculation

Variability Metrics
- 97 HRV, 82 RRV metrics

Analysis Windows
- 5 min HRV, 15 min RRV

Quality Assessment

Quality Measurements
- Detect disconnection
- Non-physiologic data filters
- Abnormal beats/breaths
- Degree of nonstationarity
- Rank waveform quality

CIMVA analysis matrix (one row/interval)
Input Data:

- PASS n=383
- FAIL n=51

82 RRV measures

Split Data

- TRAIN/VALIDATE (345P, 46F)
- TEST (38P, 5F)

Repeat 4 times

Repeat 500 times

Repeat 500 times

Repeat 100 times

Repeat 500 times

Train

- Train (35P, 35F)
- Validate (310P, 11F)

Fit LR model for each measure

Derive P(failure) for each pt using each LR model

Get ROC AUC for each measure

Select measure with highest median (ROC AUC + min(PPV, Sens))

Evaluate other measures for performance increase when used in ensemble average; choose best

5 best measures

V1 V2 V3 V4 V5

Fit univariate LR model for V1, V2, V3, V4 and V5

Distribution of LR parameters for each measure

Select parameters with highest median

Univariate LR models specified

Evaluate test set performance using ensemble average of univariate LR models

Distribution of ROC AUCs with median providing robust estimation of average performance
Discussion: Learning

- Process of enrolment & analysis = voyage of learning and discovery
- Observational design = no consent & protocols facilitates enrolment, yet may dampen signal
- Heterogeneous patient inclusion = widely applicable, yet may dampen signal
- Sample size calculation for univariate statistics ≠ sample size required for predictive model

- Variability signal is present, superior to conventional means, worth pursuing.
Random Forest results

Analysis Summary
• 50 time-repeated 10-fold stratified cross-validation
• Models:
  – 300 trees, no pruning
  – Within training: 2/3 training; out of bag test set: 1/3 dataset

<table>
<thead>
<tr>
<th>Variables of the model</th>
<th>ROC AUC</th>
<th>Sensitivity*</th>
<th>Specificity*</th>
<th>PPV*</th>
<th>NPV*</th>
<th>F1 measure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate, heart rate and RSBI (during)</td>
<td>0.61</td>
<td>0.48</td>
<td><strong>0.67</strong></td>
<td>0.16</td>
<td>0.91</td>
<td>0.24</td>
</tr>
<tr>
<td>Only HRV (during)</td>
<td>0.58</td>
<td>0.56</td>
<td>0.55</td>
<td>0.14</td>
<td>0.91</td>
<td>0.23</td>
</tr>
<tr>
<td>Only RRV (during)</td>
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<td>0.59</td>
<td>0.16</td>
<td>0.16</td>
<td>0.91</td>
<td>0.25</td>
</tr>
<tr>
<td>Both HRV and RRV (during)</td>
<td>0.63</td>
<td><strong>0.60</strong></td>
<td>0.59</td>
<td>0.16</td>
<td><strong>0.92</strong></td>
<td>0.25</td>
</tr>
</tbody>
</table>

* Used 0.12 as cutoff for the output probability of failure
Univariate Logistic Regression

Analysis Summary

- 50 time repeated, stratified 10-fold cross-validation. For each fold:
  - training on 500 randomly sampled balanced subset (all Fail, same number of pass)
  - Logistic regression for that fold is average over the 500 trained models
- Sensitivity, Specificity, Negative Predictive Value, Positive Predictive Value and F1-Measure based on a threshold of 12%

<table>
<thead>
<tr>
<th>Variables</th>
<th>ROC AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>F1 measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRV RQA: maximum diagonal line</td>
<td>0.67</td>
<td>0.76</td>
<td>0.49</td>
<td>0.17</td>
<td>0.94</td>
<td>0.27</td>
</tr>
<tr>
<td>RRV RQA: trapping time</td>
<td>0.67</td>
<td>0.67</td>
<td>0.49</td>
<td>0.15</td>
<td>0.92</td>
<td>0.24</td>
</tr>
<tr>
<td>RRV RQA: average diagonal line</td>
<td>0.67</td>
<td>0.68</td>
<td>0.51</td>
<td>0.16</td>
<td>0.92</td>
<td>0.25</td>
</tr>
<tr>
<td>RRV RQA: maximum vertical line</td>
<td>0.66</td>
<td>0.77</td>
<td>0.47</td>
<td>0.16</td>
<td>0.94</td>
<td>0.27</td>
</tr>
<tr>
<td>RRV Largest Lyapunov exponent</td>
<td>0.64</td>
<td>0.57</td>
<td>0.63</td>
<td>0.17</td>
<td>0.92</td>
<td>0.26</td>
</tr>
<tr>
<td>RRV Fano factor distance from a Poisson distrib</td>
<td>0.64</td>
<td>0.54</td>
<td>0.68</td>
<td>0.18</td>
<td>0.92</td>
<td>0.27</td>
</tr>
<tr>
<td>HRV Mean of the differences</td>
<td>0.63</td>
<td>0.31</td>
<td>0.79</td>
<td>0.18</td>
<td>0.90</td>
<td>0.22</td>
</tr>
<tr>
<td>RRV Power Law (based on histogram) y intercept</td>
<td>0.63</td>
<td>0.54</td>
<td>0.65</td>
<td>0.17</td>
<td>0.92</td>
<td>0.26</td>
</tr>
<tr>
<td>HRV Power Law (based on frequency) x intercept</td>
<td>0.63</td>
<td>0.36</td>
<td>0.80</td>
<td>0.19</td>
<td>0.90</td>
<td>0.25</td>
</tr>
<tr>
<td>RRV Hjorth parameters: activity</td>
<td>0.62</td>
<td>0.66</td>
<td>0.47</td>
<td>0.14</td>
<td>0.91</td>
<td>0.23</td>
</tr>
<tr>
<td>RRV Grid transformation feature: grid count</td>
<td>0.62</td>
<td>0.51</td>
<td>0.64</td>
<td>0.16</td>
<td>0.91</td>
<td>0.24</td>
</tr>
<tr>
<td>RR Mean rate</td>
<td>0.62</td>
<td>0.55</td>
<td>0.68</td>
<td>0.19</td>
<td>0.92</td>
<td>0.28</td>
</tr>
<tr>
<td>RSBI @ end of SBT</td>
<td>0.61</td>
<td>0.47</td>
<td>0.72</td>
<td>0.18</td>
<td>0.91</td>
<td>0.26</td>
</tr>
</tbody>
</table>
Multivariate Logistic Regression

Analysis Summary

• 50 time-repeated 10-fold stratified cross-validation
• Models:
  – Clinical variables only (Heart rate, respiratory rate, RSBI)
  – Feature selected model:
    • Top performing AND uncorrelated variability measures
      – Top 5 univariate logistic regression performers that are NOT strongly correlated (corr coeff<90%)
      – Variables: RRV dlmax, RRV dlmean, RRV v1max, RRV LLE, HRV Power Law X-intercept (frequency-based)
    • Most frequently selected variability measures
      – Top 5 most frequently selected measures from internal cross-validation of ensemble model, that are NOT strongly correlated
      – Variables: RRV LLE, RRV dlmax, RRV v1max, RRV mDiff, HRV Power Law X-intercept (frequency-based)

<table>
<thead>
<tr>
<th>Variables of the model</th>
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<th>Specificity*</th>
<th>PPV*</th>
<th>NPV*</th>
<th>F1 measure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical variables: respiratory rate, heart rate and RSBI</td>
<td>0.59</td>
<td>0.46</td>
<td>0.69</td>
<td>0.17</td>
<td>0.91</td>
<td>0.24</td>
</tr>
<tr>
<td>Top performing AND uncorrelated variability measures</td>
<td>0.68</td>
<td>0.61</td>
<td>0.63</td>
<td>0.18</td>
<td>0.92</td>
<td>0.28</td>
</tr>
<tr>
<td>Most frequently selected variability measures</td>
<td>0.70</td>
<td>0.65</td>
<td>0.62</td>
<td>0.18</td>
<td>0.93</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Research Program

• Develop multiorgan variability monitoring as a means to track emergent properties of the complex systemic host response, in applications where it is clinically useful.

• Seek to understand the clinical insights provided by irreducible emergence, irreducible unpredictability, fractals & power laws, order creation and entropy production.
1) Research Program
Research Paradigm

Complex Systems Science

What insights are useful for care & research?

1. **Emergence**: whole is greater than sum of its parts
2. **Uncertainty**: irreducible inability to predict future
3. **Dissipation**: self-organizing stable non-equilibrium
4. **Non-duality**: opposing forces both present
5. ...
• Accept emergence
  — Requires evaluation of the system as a whole

• Accept uncertainty
  — Requires continuous evaluation of system over time

Hypothesis:
Continuous evaluation of multiorgan variability provides evaluation of whole system over time

Seely AJE, Christou NV. *Crit Care Med*, 2000
Seely AJE, P Macklem, *Crit Care*, 2004
Value of Uncertainty

• The value of embracing uncertainty
  – health-care practice, health-care management, physician-patient communication, basic science and clinical research
    • Seely AJE, Perspect Biol Med. 2013; 56:65

• The value of underestimating uncertainty
  – “Principle of the Hiding Hand”
    • “apt to take on and plunge into new tasks because of the erroneously presumed absence of a challenge—because the task looks easier and more manageable than it will turn out to be.”
SBT Analysis
## Variability Metrics

### Description of the domains of variability

<table>
<thead>
<tr>
<th>Types of domain</th>
<th>Description</th>
<th>Example of measures</th>
</tr>
</thead>
</table>
| **Statistical** | Descriptors of the data distribution | • Standard deviation  
• Kurtosis |
| **Geometric**   | Descriptors of the geometry in a reference space | • Poincaré plots features  
• Recurrence plot features |
| **Informational** | Degree of complexity, i.e. distance from periodicity and stochasticity | • Sample entropy  
• Shannon entropy |
| **Energetic**   | Descriptors of the energy of the signal | • LF/HF Ratio  
• Multiscale time irreversibility |
| **Invariant**   | Descriptors of those properties that are invariant, i.e. not supposed to change over either time or space. | • Detrended fluctuation analysis  
• Largest Lyapunov exponent |

> 100 published variability metrics in medical literature

**Bravi A et al, Biomed Eng, 2011**

**REVIEW**

Review and classification of variability analysis techniques with clinical applications

Andrea Bravi, André Longtin and Andrew JE Seely
Software Development: CIMVA Universal
Quality Analysis

A. Waveform quality
   a. Disconnection
   b. Saturation
   c. Gross amplitude changes

B. Physiological Filtering
   a. Event time series
   b. Physiological cleaning

C. Event Filtering
   a. Event characterization through parameters
   b. Classification

D. Variability calculations on cleaned event time series

E. Stationarity Assessment
   Spike, step events and Linear trend events

F. Quality Measures
   Waveform, event & stationarity quality measurements

G. Overall Quality Index, QI
   [High, Intermediate, Low]

H. Display

1) Quality Report
2) Quality of intervals for variability analysis
3) Variability / time
4) Visible clinical Events
5) Waveform review