Difficult Weaning
Is there a role for PAV?

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Disclosure

- CIHR-industry partnered operating grant with Covidien (Medtronic) as the industry partner
  - PAV+
  - Investigator-initiated and sponsored
  - Institution receives funding
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Outline

1. How MV may contribute to difficult weaning
2. Why PAV might help
3. Recent evidence
4. Current research
The Problem

- ~30% of ICU patients experience **difficult or prolonged weaning** from mechanical ventilation (MV)
- Mortality and morbidity increases with increasing duration of MV
- MV costs approximately $2000 CDN per day
- Patients receiving prolonged MV account for 13% of all ventilated patients but consume 37% of ICU resources
Task Force: Weaning from MV

Statement of the Sixth International Consensus Conference on Intensive Care Medicine

• For difficult or prolonged weaning, choose mode which:
  • Maintains a favourable balance between respiratory system capacity and load
  • Attempt to avoid diaphragm muscle atrophy
  • Aids in the weaning process

• Use of nonfatiguing modes such as PSV or A/C
Critical Illness

Mechanical Ventilation

Sedation and muscle relaxants

Malnutrition and electrolytes disorders

Immobilization/ bedrest

Muscle breakdown, atrophy, weakness
VIDD: Ventilator-Induced Diaphragm Dysfunction

- Diaphragm biopsy specimens from adult brain-dead organ donors ventilated for 18-69 hrs vs. control patients undergoing thoracic surgery ventilated for 2-3 hrs

**VIDD**

- Complete diaphragm inactivity during CMV results in diaphragm muscle fiber atrophy and contractile dysfunction with reduced force-generating capacity

- Partial modes of support favoured over CMV

- PSV is the most commonly used mode for patient-triggered spontaneous breath delivery

- High levels of PSV can also induce significant diaphragm atrophy and weakness in rats randomized to 12 and 18 hours of PSV, CMV or control (no MV)

Overuse injury and fatigue

• Excessive workload may induce diaphragmatic injury due to fatigue


• Clinical distress, myocardial ischemia, lactic acidosis

• High transpulmonary pressures leading to VALI

• Negative intrathoracic pressure swings impact cardiac function

## Patient-Ventilator Asynchrony

<table>
<thead>
<tr>
<th></th>
<th>Patient Breath</th>
<th>Ventilator Breath</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triggering Problem</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ineffective Efforts (IE)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Autotriggering (AT)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Cycling off Problem</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double Triggering (DT)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Delayed Cycling (DC)</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Asynchrony Index (AI)

• % of breaths that are asynchronous

\[
\text{AI} = \frac{\text{Number of Asynchrony Events}}{\text{Total Respiratory Rate}} \times 100
\]

\[
= \frac{\text{IE}_{E} + \text{IE}_{I} + \text{DT} + \text{AT}}{\text{Ventilator breaths + Ineffective efforts}} \times 100
\]

• Asynchrony Index ≥ 10% → High


Outcomes of Patients AI >10%

Patients with high level of asynchrony (AI >10%):

- Longer duration of MV
- Less likely to successfully wean from MV
- Longer ICU LOS
- Longer Hospital LOS
- Less likely to be discharged home

- Higher ICU and hospital mortality

*De Wit, Critical Care Medicine (2009) 37: 2740-45*

# Patient-Ventilator Asynchrony

<table>
<thead>
<tr>
<th>Type</th>
<th>Correction</th>
</tr>
</thead>
</table>
| **Ineffective triggering**  | Decrease trigger threshold  
- weak inspiratory effort  
- High PEEPi (COPD)  
Reduce sedation  
Reduce the potential for intrinsic PEEP  
(decrease $V_T$, $V_E$, increase $T_E$) |
| **Delayed Cycling**  | Increase cycling criterion (Esens)  
- Low elastic recoil (emphysema)  
- High resistance (COPD)  
Decrease Ti |
| **Auto-triggering**  | Increase trigger threshold  
- cardiogenic oscillations or circuit leaks  
- absence of patient effort  
Switch from flow to pressure triggering  
Avoid hyperventilation |
| **Double-triggering**  | Aim for ways to reduce ventilatory demand.  
Is $V_T$ too small? $T_I$ too short?  
Decrease cycling criterion ($E_{sensitivity}$) |

*Respir Care. 2011;56(1):61–72*
Patient-Ventilator Interaction

\[ P_{\text{vent}} + P_{\text{mus}} = (\text{Flow} \times \text{Resistance}) + (\text{Volume} \times \text{Elastance}) \]

**Optimal Patient-Ventilator Interaction:**

- Neural Ti = Ventilator Ti
- Level of assistance is proportional to level of need

**Suboptimal Patient-Ventilator Interaction:**

- Asynchrony
  - Wasted energy, inefficient energy use
- Over-assistance
  - Disuse atrophy, Central apneas
  - PEEPi
  - Ineffective efforts
PAV

\[ \text{Pmus} = \text{Pres} + \text{Pel} = \text{Flow} \times \text{Rtot} + \text{Vt} \times \text{Est} \]

**Proportional Assist Ventilation**

- Instantaneously measures flow and volume being “pulled in” by the patients
- Ventilator knows the respiratory resistance and elastance
- Therefore calculates instantaneous Pmus
- Provides assistance in proportion to Pmus
Invention to Commercialization

- The PAV algorithm was invented by Dr. Magdy Younes, MD, PhD, University of Manitoba, Canada.
- Original Winnipeg Ventilator, 1986
- Patented 1990
- Initial versions of PAV:
  - Evita 4, XL, V500 Ventilators in Proportional Pressure Support Mode (Dräger, Lubeck, Germany)
  - BiPAP Vision Ventilator in PAV Mode (Respironics, Murrayville, Pennsylvania, USA)
- Closed-loop PAV (PAV+) is a software package for the Puritan-Bennett 840, 980 ventilator (Covidien, Boulder, Colorado, USA)
- Released in Canada 2005

Photos courtesy of Dr. Magdy Younes
## PAV: Clinical studies

<table>
<thead>
<tr>
<th>Result on PAV</th>
<th>Versus</th>
<th>Condition (n)</th>
<th>Duration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved synchrony</td>
<td>PSV</td>
<td>Acute respiratory failure (13, 50, 208)</td>
<td>&lt; 48 hr</td>
<td>Bosma (1,2), Xiouchaki, Ranieri, Wysocki Georgopoulos, Younes</td>
</tr>
<tr>
<td>Averted risk of over-assistance, ↓Vt, ↓Ppeak, ΔP &lt;15 cmH₂O</td>
<td>PSV</td>
<td>Mild, moderate ARDS (12), ARDS (64)</td>
<td>&lt; 1 hr, &lt;48 hr</td>
<td>Kondili, Georgopoulos</td>
</tr>
<tr>
<td>Increased breathing pattern variability</td>
<td>PSV</td>
<td>Medical ICU (14,15)</td>
<td>&lt; 1 hr</td>
<td>Varelmann, Ranieri</td>
</tr>
<tr>
<td>Improved cardiac index, Maintains gas exchange</td>
<td>PSV</td>
<td>Mild, moderate ARDS (12)</td>
<td>&lt; 1 hr</td>
<td>Kondili</td>
</tr>
<tr>
<td>Improved sleep quality</td>
<td>PSV</td>
<td>Acute respiratory failure (14)</td>
<td>&lt; 24 hr</td>
<td>Bosma(1)</td>
</tr>
<tr>
<td>Safe and tolerated</td>
<td>PSV/--</td>
<td>Acute respiratory failure (50, 56)</td>
<td>PSV Trial to extubation</td>
<td>Bosma(2), Carteaux</td>
</tr>
</tbody>
</table>
A Pilot Randomized Trial Comparing Weaning From Mechanical Ventilation on Pressure Support Versus Proportional Assist Ventilation

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With special thanks to: Tracey C. Bentall, Mona Madady, Chris Harris, Delores Tack, Dr. Robert Coke, Ronald H. VanderHeide, Anita Plat-Kuiken, RRTs of University Hospital MSICU

Funded by: Western University Department of Medicine, Program of Experimental Medicine (POEM), Critical Care Western Program, Lawson Health Research Institute, and Covidien ISR Grant
Purpose of Pilot Study

- The purpose of this study was to compare the physiologic and clinical performance (failure rate), safety and feasibility of protocols utilizing daily SBT plus PSV vs. PAV until ventilation discontinuation.
Methods

• **Study Design:** Single centre, prospective RCT

• **Study Site:** MSICU, University Hospital, London, Canada

• **Study Participants:** Adult patients intubated >36 hrs meeting eligibility criteria for weaning and tolerating PSV ≥30 minutes

• **Interventions:** Patients randomized to PSV or PAV weaning algorithm (PAV+™, Puritan Bennett 840, Covidien, Boulder, USA). Both algorithms utilized progressive decreases in level of assistance as tolerated coupled with daily assessment for SBTs. A/C was used for rescue in both arms.
Methods

\[ P_1 - P_2 = R \cdot V' \]

\[ \int_{0}^{t} V' \cdot dt = V \]

![Image of method setup and equipment]
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>PAV</th>
<th>PSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean ± SD</td>
<td>63 ± 14</td>
<td>67 ± 12</td>
</tr>
<tr>
<td>Gender, female, n (%)</td>
<td>15 (56)</td>
<td>10 (43)</td>
</tr>
<tr>
<td>APACHE II score at admission</td>
<td>27 ± 9</td>
<td>26 ± 8</td>
</tr>
<tr>
<td>APACHE II score at randomization</td>
<td>19 ± 7</td>
<td>20 ± 5</td>
</tr>
<tr>
<td>Duration of MV at randomization, d, median (IQR)</td>
<td>6.3 (4.1-7.9)</td>
<td>5.2 (3.9-10.2)</td>
</tr>
<tr>
<td>Hospital Admission Type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>19 (70)</td>
<td>19 (83)</td>
</tr>
<tr>
<td>Surgical</td>
<td>8 (30)</td>
<td>4 (17)</td>
</tr>
</tbody>
</table>
Safety and Feasibility

• No adverse events linked to study protocol
  • Arrhythmias, pneumothorax, death

• Use of daily checklists reduced protocol violations
  • 2\textsuperscript{nd} audit found complete adherence to study protocol on 254/292 (90\%) study days

• Recruitment rate 1.3 patients per month
  • Over a 42 month enrolment period, 706 patients were screened of whom 80 met eligibility criteria for enrolment and 54 were randomized
PAV Failure Rate

• All patients tolerated the weaning protocol modes
  • Ventilated on study mode on average of 18.1 ± 5.9 hours/day in the PAV group and 18.8 ± 5.0 hours/day in the PSV group, p=NS

• RRTs increased level of ventilator support for respiratory distress more frequently on PSV
  • 124/295 (42%) of study days vs. 76/232 (33%) on PAV, p=0.002

• Changes to A/C mode equal frequency in groups
  • 66/232 (28%) of study days on PAV vs 90/295 (30%) study days on PSV, p=NS
Time from Randomization to Successful Extubation

3.9 (2.8-8.4) PAV vs. 4.9 (2.9-26.3) PSV, P=NS

Results
Time from Randomization to ICU Discharge

7.3 (5.2-11.4) PAV vs. 12.4 (7.4-30.8) PSV  
$p = 0.03$

Results

![Graph showing time from randomization to ICU discharge with Kaplan-Meier curves for two modes. The graph includes the number of patients at risk at different time points for each mode. The graph shows that Mode 1 has a lower proportion of patients at risk compared to Mode 2, indicating a shorter time to ICU discharge for Mode 1. The table below the graph indicates the number of patients at risk at each time point for both modes.]

<table>
<thead>
<tr>
<th>time (days)</th>
<th>Mode 1</th>
<th>Mode 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>20</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>25</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

Number at risk

P = 0.03
Conclusions

- Weaning protocols are safe, tolerated by patients
- Adherence to protocols enhanced with daily checklists for RRTs
- Enroll 1 patient for every 10 screened; 1.3 patients/month in a 20 bed MSICU
- Need multicentre RCT to verify if there is a difference between PAV + SBT vs. PSV + SBT weaning protocols
Bedside Adjustment of Proportional Assist Ventilation to Target a Predefined Range of Respiratory Effort

Guillaume Carteaux, MD\textsuperscript{1,2}; Jordi Mancebo, MD, PhD\textsuperscript{3}; Alain Mercat, MD, PhD\textsuperscript{4}; Jean Dellamonica, MD, PhD\textsuperscript{5,6}; Jean-Christophe M. Richard, MD, PhD\textsuperscript{7,8}; Hernan Aguirre-Bermeo, MD\textsuperscript{3}; Achille Kouatchet, MD\textsuperscript{4}; Gaetan Beduneau, MD\textsuperscript{7,9}; Arnaud W. Thille, MD, PhD\textsuperscript{8}; Laurent Brochard, MD\textsuperscript{10,11}

\[
PTP_{\text{mus}} = \frac{P_{\text{mus,Peak}} \times Ti}{2} \times RR
\]
The PROMIZING Study

Proportional Assist Ventilation for Minimizing the Duration of Mechanical Ventilation

Karen Bosma and Laurent Brochard
Research Question

• Does PAV+, set to maintain a workload of breathing within the normal range, improve clinical outcomes in weaning from mechanical ventilation compared to the current standard of care using PSV?
Mechanism Hypothesis

• Maintaining Pmus within normal range will shorten duration of MV by
  – Preventing diaphragmatic atrophy and/or
  – Rehabilitating deconditioned respiratory muscles

• Study design does not directly test this mechanistic hypothesis but:
  – Need to capture patients at risk of prolonged weaning early in their critical illness
  – Need to ensure adequate exposure to intervention (several days on MV post randomization)
Summary

1. How MV may contribute to difficult weaning
   - VIDD, VALI, asynchrony

2. Why PAV might help
   - Diaphragm active, decreased driving pressure, decreased asynchrony, increased variability, improved hemodynamics

3. Recent evidence
   - Physiologic benefits in real world setting; tolerated until extubation

4. Current research ➔ the PROMIZING Study
Questions?

KarenJ.Bosma@lhsc.on.ca
References (1)


Is there a role for PAV and NAVA?
References Continued (3)

22. Delisle S et al. Respir Care 2013, 58:745-753