Revenge of the Iron Lung: The development of a novel Transvenous Phrenic Nerve Pacer and the return of assisted negative pressure ventilation

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Dr. S. Reynolds Disclosure

- Relevant financial relationships with commercial interest:
  - co-inventor in a transvenous pacing patent application
  - Covidien, research support
Positive pressure mechanical ventilation is the cornerstone upon which the ICU has been built.

It’s the basis of how we care for the sickest patients who would otherwise die.
Prior to 1952 negative pressure ventilation was applied through the use of Iron Lung and Cuirass ventilators.
During the Polio epidemic of 1952 the mortality of patients with bulbar polio was 90% and iron lungs and cuirass ventilators were in short supply.

A locum anesthetist at a Copenhagen hospital, Dr. Bjorn Ibsen, proposed the unconventional idea of performing a tracheostomy and applying positive pressure ventilation.
BACK WHEN KIDS WERE SAFE FROM THE DANGERS OF VACCINES...

THOSE WERE THE DAYS...
2.8% of all patients admitted undergo mechanical ventilation.

40.5% are ventilated for greater than 96 hours.

Although it's somewhat difficult to estimate, mechanically ventilated patients consume 12% of hospital budgets ($27 billion in the US and $2.5 billion in Canada) which is 0.5% of the national GDP.

34.5% of patients who are ventilated die in hospital.

Wunsch et al. 2010, Boles et al. 2006, Carson et al. 2007
The Harms of Positive Pressure Ventilation- the evil “V”s

* Ventilator acquired pneumonia (VAP)
* Ventilator induced lung injury (VILI)
  * Volutrauma
  * Atelectotrauma
  * Biotrauma
* Ventilator induced diaphragmatic dysfunction (VIDD)
Rapid Onset of Specific Diaphragm Weakness in a Healthy Murine Model of Ventilator-induced Diaphragmatic Dysfunction

Relevance of Ventilator-induced Diaphragm Dysfunction in ICU Patients

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Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically Ventilated Humans


Diaphragm fiber atrophy in brain dead donors kept on MV for 18-69 h (case subjects) vs. surgery patients kept on MV for only 2-3 h (control subjects) showed a 57% and 53% decrease in fiber CSA of slow twitch and fast twitch fibers respectively.
How do we mitigate these harms?

- Target specific metabolic pathways?
- Tank ventilators?

- Functional Electrical Stimulation (FES) to activate the diaphragm through stimulation of the phrenic nerve
Figure 1: Illustration of Lungpacer™ diaphragm pacing system
Potential Impact of Phrenic nerve pacing

- **AVOID** Ventilator Induced Diaphragmatic Dysfunction
- **TREAT** Ventilator Induced Diaphragmatic Dysfunction
- **AVOID** Ventilator Induced Lung Injury
- **REDUCE** Atelectasis
3 groups of pigs; 6 never ventilated animals (control), 6 were ventilated for 60 hours (MV) and 6 were ventilated for 60 hours and received phrenic nerve pacing (MV-P).

Upon sedation and initiation of MV, each ventilated pig received a Lungpacer IntraVenous Electrode (LIVE) catheter in the left subclavian vein. (MV and MV-P groups only)

The MV-P group was paced in synchrony with MV on alternate breaths, reducing ventilator pressure by a target 20-30%.

The subjects in the MV group were only briefly stimulated to assess diaphragm output at the start and the end of the study.
Phrenic Nerve Pacing
Paced vs. Non-paced breaths
Diaphragm pacing contribution to ventilation

Ventilator Pressure was Consistently Reduced with Phrenic Nerve Pacing

During the paced breaths, we observed:

- EMG confirmation of bilateral activation (D, E)
- Unchanged air flow (K) and tidal volume (L)
- Consistently reduced positive pressure (A)
- Increased abdominal excursion (F, G)
- Esophageal, gastric and trans-diaphragmatic pressures resembling physiological norm (H-J)
Cross-sectional area results

- Control subjects (median = 24.6 µm²/kg, IQR = 21.6 – 26.1) had a significantly greater CSA than MV subjects (median = 17.8 µm²/kg, IQR = 15.3 – 23.7) \((p=0.001)\).

- There was no significant difference in CSA between MV-P subjects (median = 24.9 µm²/kg, IQR = 16.6 – 27.3) and both Control (median = 24.6 µm²/kg, IQR = 21.6 – 26.1) \((p=0.205)\) and MV subjects (median = 17.8 µm²/kg, IQR = 15.3 – 23.7) \((p=0.189)\).
Our interpretation is that the findings support that PNP:

- Prevents muscle atrophy
- May protect the human diaphragm from VIDD
- May offer protection from VILI
- Promising intervention and worthwhile to progress to clinical trials to evaluate PNP as a means to shorten time to wean, improve patient outcomes and reduce cost of prolonged care in the ICU
13 patients were sedated and intubated for an elective Atrial Septal Defect closure procedure. For up to 90 minutes prior to their procedure they underwent:

- subclavian placement of the pacing catheter
- mapping of optimal electrode pairs for phrenic nerve capture and diaphragm activation
- determination of activation threshold (in mAmp) of optimal pairs
- stimulation of the diaphragm in conjunction with MV.
The diaphragm was paced in synchrony with alternate ventilator breaths.

Fluoroscopy and ventilator waveform analysis revealed the extent of diaphragmatic participation.

The pacing contribution was assessed as the Inspiratory Pressure-Time-Product (PTP) for paced vs. un-paced breaths.
Fluoroscopy of Diaphragm Pacing
Of the 13 patients recruited, 1 could not proceed to testing.

Of the remaining 12 patients 92% had bilateral capture. (23/24 phrenic nerves)

Only the LPN was captured in Subject 4

Pt has a left-sided SVC that precluded bilateral capture.

the anatomical variant of left sided SVCs occur in much higher frequency in patients with ASD than the normal population (4% vs 0.3%).

1 Burnery K 2007 clinical radiology
Mean reductions in the PTP during paced breaths ranged from 9.8% to 35.1% between patients.

The extent of PTP reduction could be adjusted by varying the phrenic nerve stimulation intensities.

Variability of degree of capture was noted over time, likely due to cardiac oscillations and its impact on the SVC.
12 patients tolerated the experimental procedures well.

Catheter was removed in all patients uneventfully.

Follow up at 24 hours and two weeks demonstrated no adverse events, including the patient in whom the procedure was aborted.
Conclusion

* A temporary, transvenous phrenic nerve pacer can safely and effectively yield a diaphragm contraction in humans thereby reducing the pressure required to produce a set tidal volume on a MV.
Next steps

* Clinical trials in;
  * Prevention;
    * Patients who will be a complex wean from the ventilator
    * Patients who have a high cervical cord injury but may regain diaphragm control
  * Treatment;
    * Patients who have established respiratory muscle weakness
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Histology Showed Significant Differences

- Muscle fiber areas normalized by pig weight (μm²/kg): Paced (47.8 μm²/kg) > Control (28.4 μm²/kg); P < 0.05

- Stronger effect on left side (52.7 vs. 25.9 μm²/kg; P < 0.05) than on right side (43.0 vs. 30.8 μm²/kg; N.S.)
Diaphragm pacing contribution to ventilation

The time-varying changes in reduction of the pressure-time product (blue traces) and peak airway pressure (red traces) achieved during paced breaths are shown for the 4 paced subjects over the entire duration of each experiment.