Intrathoracic Pressure Regulation
for the Treatment of Hypotensive Emergencies

April 30, 2012

Keith Lurie MD
Professor of Emergency Medicine and Internal Medicine
University of Minnesota
Cardiac Electrophysiologist, St. Cloud hospital
Chief Medical Officer
Advanced Circulatory Systems

The Other Side of Breathing

Understanding and Harnessing
Cardio-pulmonary-cerebral
Interactions for the Treatment of
Hypotension Secondary to Cardiac Arrest, Hemorrhage,
Traumatic Brain Injury, Sepsis, and
Orthostatic Hypotension

What’s the Problem?

Central Hypovolemia & Blood Pressure Regulation

Cardiac Arrest
- ~400,000 in- and out-of-hospital cardiac arrests annually
- ~5% to 10% survival to discharge prehospital, all
  rhythms, 15-20% in-hospital

Orthostatic Instability or Intolerance (Fainting)
- > 500,000 civilians
- > 10,000 unexplained cases of syncope in military annually

Hemorrhagic Shock due to trauma
- ~40% of civilian deaths
- ~85% of ‘potentially survivable’ deaths on the battlefield
Optimizing the Respiratory Pump: Harnessing Inspiratory Resistance to Treat Systemic Hypotension

Victor A Cornelisino MD, Kathy L Ryan PhD, Caroline A Bichkani PhD, Steven L Clancy MD, Ahmed H Idro MD, Demetris Yannopoulos MD, Anja Metzger PhD and Keith G Luce MD

Respiratory Care
June 2011
56: 846-857


Intrathoracic Pressure Regulation Therapy

ResQPOD: for CPR
ResQGARD: for hypotension in spontaneously breathing pts
CirQlator: for hypotension in apneic pts

All 3 devices cleared by FDA for clinical use
Cardiac Arrest

Compression

1. Increases intrathoracic pressure and blood flow out of the heart
2. Empties the left ventricle
3. Immediately increases intracranial pressure (ICP) thereby increasing resistance to brain flow
4. Pushes air/O2 out of the lungs
Decompression

- Refills the R and L ventricles
- Lowers ICP
- Pulls air/O2 into lungs

Decompression or Chest Wall Recoil

1. Lowers intrathoracic pressure relative to atmospheric pressure and the rest of the body
2. Pulls blood back into the right heart and helps refill the left ventricle
3. Draws air/O2 into the lungs
4. Lowers ICP, thereby lowering resistance to blood flow
5. Mimics the ‘gasping’ reflex

What about ventilation?
Effect of Positive Pressure Ventilation

1. Delivers air/O2 to lungs and re-inflates lungs, enabling gas exchange
2. Facilitates CO2 clearance
3. Lowers resistance to trans-pulmonary blood circulation (improves R to L flow)
4. Increases ICP, lower brain blood flow
5. Reduces venous blood return
6. Lowers cardiac output
7. Pushes blood out of lungs to left heart
8. Reduces interstitial fluid in lungs

Ventilation Strategies
Don't inadvertently hurt your patients!

Airway Pressure Waveforms

Large amplitude waves are ventilations.
Small amplitude waves are compressions.
Ventilation rate: 12/min
Compression rate: 78/min
Each strip records 16 seconds of time.
Death by Hyperventilation

Ventilation rate: 47 breaths / minute

Example: Prolonged Ventilations

Ventilation Duration: 4.36 seconds / breath
Ventilation Rate: 11 breaths / minute
% Positive Pressure: 80%
**Porcine Survival Study**

<table>
<thead>
<tr>
<th>Breaths/Minute</th>
<th>O₂/CO₂</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>100% O₂</td>
<td>6/7 (86%)</td>
</tr>
<tr>
<td>30</td>
<td>100% O₂</td>
<td>1/7 (14%)*</td>
</tr>
<tr>
<td>30</td>
<td>95% O₂/5% CO₂</td>
<td>1/7 (14%)*</td>
</tr>
</tbody>
</table>

*P<0.05

---

**Hyperventilation-Induced Hypotension During Cardiopulmonary Resuscitation**

Tomas P. Arfinsbo, MD, Gudar Siqueiros, MD, Ronald G. Pirrello, MD, MINSJ, Dimitrios Vayanos, MD, Scott McKinnon, BA, Chris von Broeck, BA, EMIT, Christian W. Sparks, EMT, Vaish J. Consul, RN, Tony A. Pavia, BA, EMT-P, Keith Y. Lant, MD

**Background**
A clinical observational study revealed that severe cardiopulmonary arrest patients undergoing cardiopulmonary resuscitation (CPR), including those who had a higher incidence of severe hypotension during CPR, had a significantly decreased mean arterial pressure and survival.

**Methods and Results**
- In humans, cardiopulmonary resuscitation (CPR) was electronically monitored by professional technicians, with 15 consecutive adult resuscitation cases included. Average ventilation rate was 10±2.5 breaths per minute, 15 to 40 breaths per minute. Average duration per breath was 1.2±0.97 per second. No patient survived. Hypotension was considered a major concern and increased with 30 breaths per minute. Survivors were then studied in 3 groups of 12 patients each, which was randomized with 12 breaths per minute (100% O₂), 18 breaths per minute (100% O₂), or 30 breaths per minute (100% O₂ 15% CO₂). In animals treated with 12, 20, and 30 breaths per minute: mean arterial pressures (MAP) and coronary perfusion pressures were high, whereas 7.18±0.7, 10.8±0.7, and 7.2±0.1 (P<0.001) and 10.4±0.1, 10.9±0.1, and 7.2±0.1 (P<0.001), respectively. Survival rates were 76.3%, 77.5%, and 79.7% with 12, 20, and 30 breaths per minute, respectively.

**Conclusion**
- Professional rescuers were observed to successfully ventilate patients during hospital CPR. Subsequent animal studies demonstrated that rapid reperfusion rates resulted in significantly increased intrathoracic pressures and markedly decreased coronary perfusion pressures and survival.

*Evolution, 20:4:12, 1980 (Vol.)*

---

**Index Case**

1987

Saved by a Household Plunger

San Francisco General Hospital
Goals

- Physiology of CPR: harnessing the intrathoracic pump
- Applications to Cardiac Arrest
- Physiology of Shock: new insights
  - Spontaneous ventilation
  - Assisted ventilation

Cardiac Arrest Today:
Nearly 2000 Americans die each day from cardiac arrest!! Why?

10 - 20% of normal blood flow to the heart
20 - 30% of normal blood flow to the brain

Active Compression Decompression CPR
NOT YET AVAILABLE IN THE USA
Founding Concept & Design

- **Concept**: Lower intrathoracic pressure during the decompression phase of CPR enhances venous return to the thorax.

- **Design**: Each time the chest wall recoils following a compression, the impedance threshold device (ITD) transiently blocks air/oxygen from entering the lungs, creating a small vacuum in the chest, resulting in improved preload.
Effect of Inspiratory Impedance During CPR on Airway Pressures

1. Lowers intrathoracic pressure
2. Mimics gasping reflex
3. Lowers ICP
4. Refills the heart
5. Doubles circulation

Conventional CPR

Conventional or ACD CPR with ITD

Enhanced Vacuum

Using an ITD: BLS & ALS

Lights flash @ 10/min to guide compression & ventilation rates

Human Data: Blood Pressure

*<p<0.05

n = 22

Clinical ITD Trials

Translational Research

Implementing the 2005 American Heart Association Guidelines and Use of the Impedance Threshold Device Improves Hospital Discharge Rates after Out-of-Hospital Cardiac Arrest

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>P-value</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROSC</td>
<td>30.4% (535/1757)</td>
<td>34.1% (586/1719)</td>
<td>0.022</td>
<td>1.18 (1.022, 1.366)</td>
</tr>
<tr>
<td>Hospital Discharge</td>
<td>9.7% (170/1757)</td>
<td>12.6% (216/1719)</td>
<td>0.007</td>
<td>1.34 (1.078, 1.671)</td>
</tr>
<tr>
<td>HD (VF)</td>
<td>19.0% (85/447)</td>
<td>31.1% (128/412)</td>
<td>&lt;0.001</td>
<td>1.91 (1.384, 2.667)</td>
</tr>
<tr>
<td>Normal Neurological Function</td>
<td>31.4% (11/35)</td>
<td>55.2% (32/58)</td>
<td>0.033</td>
<td>2.68 (1.027, 7.213)</td>
</tr>
</tbody>
</table>
Implementing the 2005 American Heart Association Guidelines and Use of the Impedance Threshold Device Improves Hospital Discharge Rates after In-hospital Cardiac Arrest

Hospital Discharge Rates Based on Initial Heart Rhythm

<table>
<thead>
<tr>
<th>HD</th>
<th>Control Phase</th>
<th>Intervention Phase</th>
<th>p-value: O.R. [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF:18/57 (31.6%)</td>
<td>21/48 (43.8%)</td>
<td>0.228: 1.68 [0.70, 4.04]</td>
<td></td>
</tr>
<tr>
<td>PEA:14/97 (14.4%)</td>
<td>27/91 (29.7%)</td>
<td>0.014: 2.50 [1.15, 5.58]</td>
<td></td>
</tr>
<tr>
<td>Asystole:10/87 (11.5%)</td>
<td>23/110 (20.9%)</td>
<td>0.087: 2.04 [0.86, 5.09]</td>
<td></td>
</tr>
<tr>
<td>Overall: 42/241 (17.4%)</td>
<td>71/249 (35.3%)</td>
<td>&lt;0.001: 2.59[1.63, 4.13]</td>
<td></td>
</tr>
</tbody>
</table>

Thigpen et al
J. Resp. Care 2010

PRIMING THE PUMP WITH ACD CPR + ITD

Blood Flow During CPR
(Porcine VF Model)

Witnessed VF not resuscitated with 3 initial shocks (n = 70)

ACD CPR + ITD in Humans

ResQTrial

The randomized, prospective, multicenter ResQTrial was a NIH-funded clinical trial conducted in the United States from 2005-2010 that compared ACD+ITD (n=840 patients) versus S-CPR (n=813) in patients with out-of-hospital cardiac of presumed cardiac etiology.*

*Aulderheide et al. Lancet 2011;377:301-311
ResQTrial: 2 CPR Methods Compared

<table>
<thead>
<tr>
<th>Standard CPR (S-CPR)</th>
<th>ACD CPR + ITD (ACD+ITD)</th>
</tr>
</thead>
</table>

**Results:**

**Primary Endpoint**

Survival to Hospital Discharge with Favorable Neurologic Outcome

- *53% improvement*
- \( P = 0.019 \)
- \( \text{OR} 1.58 \)
- \( \text{CI} (1.07, 2.36) \)

**Results:**

Time-Dependency of Interventions

Survival to Hospital Discharge with Favorable Neurologic Outcome

- 911 Call to Randomized CPR Treatment (min)
Results:

One-year Survival

<table>
<thead>
<tr>
<th></th>
<th>Control (N = 813)</th>
<th>Intervention (N = 840)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One-Year Survival</strong></td>
<td>48 (5.9%)</td>
<td>74 (8.8%)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

**Emotional:**
- Beck Depression Inventory (BDI)  
  Score range: 0 – 63
- **P-value:** 0.862

**Functional:**
- Disability Rating Score (DRS)  
  Score range: 0 – 29
- **P-value:** 0.358

**Cognitive:**
- Cognitive Abilities Screening Instrument (CASI)  
  Score range: 0 – 100
- **P-value:** 0.473

Greg was a little shaky and unsure at first but after passing his EP Boards this past year he is back in the saddle and doing great.

Hypotension in Spontaneously Breathing & Apneic Patients:

Harnessing the Thoracic Pump
Impedance Threshold Device (ITD-7)

Effect of Inspiratory Impedance During Spontaneous Respiration
1. Lowers intrathoracic pressure
2. Lowers ICP
3. Refills the heart
4. Increases cerebral and systemic circulation
5. Harnesses the sympathetic nervous system
6. Mimics stress response to central hypovolemia

Inspiratory Impedance Effect

- Increased intrathoracic vacuum
- Decreased intracranial pressure
- Increased cerebral blood flow
- Increased cardiac output
- Increased blood flow to vital organs
- Decreased resistance to forward blood flow
- Improved perfusion
Swine Model: Moderate Hemorrhage

Severe Blood Loss

Systolic Blood Pressure in Spontaneously Breathing Swine in Hemorrhagic Shock

Lurie et al, Critical Care Medicine, 2004
Spontaneous Breathing with sham ITD

Spontaneous Breathing with -7 ITD

Heat Stroke
Heat Stroke Animal Model
Systolic Aortic Blood Pressure

Yannopoulos et al, Aviat Space Environ Med 2008

Safety and Efficacy in Normal Subjects
Studies using a ITD in supine subjects

Orthostatic Intolerance
In Astronauts
Cerebral Blood Flow


Transcranial Doppler

Effects of ITD on Cerebral Blood Flow

Model of Hemorrhage at USAISR

Convertino and Cook, 2005
Inspiratory resistance as a potential treatment for orthostatic intolerance and hemorrhagic shock.

Convertino VA, Cooke WH, Lurie KG: Aviat Space Environ Med 76:319-325, 2005

Inspiratory resistance maintains arterial pressure during central hypovolemia: implications for treatment of patients with severe hemorrhage.


Muscle Sympathetic Nerve Activity
Clinical Experience with Hypotensive Patients

- Blood Bank
- Orthostatic Hypotension
- Dialysis
- Emergency Room
- EMS
- NASA Astronauts

ITD-7 in EMS
Effect of ITD in 331 hypotensive patients treated by BLS and ALS in Toledo OH

Conclusions

• The ITD-7 in humans increases SV, cardiac output, and organ perfusion.

• The ITD is well tolerated and can be used by sicker spontaneously breathing patients with mild to moderate hypovolemic hypotension.
Harnessing the Thoracic Pump in the Apneic Patient

Patients who Require Assisted Ventilation

Technology to optimize the thoracic pump mechanism by modulating intrathoracic pressure to treat intra-operative hypotension, cardiac arrest, sepsis, hemorrhagic shock and modulate intracranial pressure

Effect of Intrathoracic Pressure Regulators

1. Lowers intrathoracic pressure
2. Lowers ICP
3. Refills the heart
4. Increases cerebral and systemic circulation
Effect of ITPR on Tracheal Pressure and ICP in Apneic Pigs

Use in Hemorrhagic Shock
Use in Sepsis in Pigs

Use in TBI in Pigs

Effect of IPR on Tracheal, Aortic, Intracranial Pressures and ECG in Apneic Pigs
Sublingual Microcirculation (rectangles are 1025 x 750µm)

Clinical Experience – U of MN
(Drs. Loushin and Birch 2010)

Treatment of Intra-operative Hypotension
Abdominal Surgery

Consistent pulse pressure increase from 36mmHg to 46 mmHg (n=20, P<0.05)
Clinical Experience U of VA  
(Dr. Ed Nemergut 2010)

CABG pts (n=20):
Using TEE, a significant increase in cardiac output was observed (4.9 vs. 5.5 L/min, p=0.016). Since the device was not associated with a change in HR (68.7 vs. 69.4, p=0.708), the increase in cardiac output comes from an increase in stroke volume.

Neuro ICU (n=10):
To date there has been a consistent decrease in ICP from ~ 20 mmHg to 15 mmHg and an increase in cerebral perfusion pressure

Combined Results: ICP

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device 1</td>
<td>21%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device 2</td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Cyclic Changes in the Intrathoracic Pressure can be Harnessed to:

- Increase cardiac filling, stroke volume, and cardiac output.
- Lower ICP
- Increase arterial pressure, cerebral blood flow and orthostatic tolerance.
- Modulate sympathetic nervous activity and peripheral vascular constriction.
The Future of Respiratory Therapy

My prediction is that cardio-pulmonary-cerebral interactions and technologies that regulate the interactions will provide new and exciting opportunities for decades for you and your colleagues.

These interactions enable you to manipulate pressures in the airways and chest that control some of the most essential life processes.

Questions?

?