Neuromodulation for the treatment of asthma/migraine

Peter S. Staats, M.D., MBA., DABPM,FIPP
VP NJ SIPP
Adjunct Associate Professor
Dept of Anesthesiology and Critical Care
Johns Hopkins University
Premier Pain Centers

DISCLAIMER

Peter Staats, MD MBA
Partner: Premier Pain Centers
Adjunct Associate Professor
Department of Anesthesiology and Critical Care Medicine
The Johns Hopkins University School of Medicine

Member: Board of Directors ASIPP, VP NJ ASIPP
Past President NANS
Past President Southern Pain Society

Board of Directors/Stock Holder: Electrocore Medical
Several slides from Bruce Simon Electrocore medical
History of grant funding from NIH, Medtronic, Elan, Neurex and Pfizer
No active speakers bureau more than past two years
No Active Grants on Intraspinal Therapy
Off Label: I will discuss off label uses of peripheral nerve stimulation not currently approved for this indication by the FDA
Definition of Neuromodulation

Neuromodulation: is the electrical or chemical modulation of the peripheral or central nervous system to significantly reduce chronic pain or improve neurologic function.

Concept of Neuromodulation specialist
Neurostimulation Indications

- Pain
- Depression
- OCD
- Parkinsons disease
- Angina
- Obesity
- Airway reactivity/asthma
- Depression (VNS)
- Epilepsy (VNS)
- Vascular disease
- Vision
- Spasticity
- Hearing
- Ambulation
- Gene Induction
- Bladder incontinence
- Bowel incontinence
- Cystitis
- Headaches/migraine prevention

Robust Literature on sympathetic tone in Myocardial dysfunction/Interest in Autonomic NS and Stimulation
Benefits of Open Sympathectomy: Animal Models

• 42% smaller infarcts after LAD occlusion
• 200-400% greater regional blood flow by labeled microsphere perfusion scan (no difference in arterial pressure or heart rate)

Benefits of Open Sympathectomy: Humans

• 88 patients long term results: 1/3 symptom free and 1/3 significantly improved

Stimulation for angina--
references

• Murphy et al. Dorsal column stimulation for pain relief from intractable angina pectoris. Pain 1987, 28:365-368
• Foreman Demonstrates microcirculatory changes with electrical stimulation

Asthma

• Definition: Chronic long lasting inflammatory disease of the airways
• Increased airway reactivity, smooth muscle contraction causing the bronchoconstriction and release of mucus leads to narrowing airways
  » Coughing short of breath work of breathing, decrease FEV1
• Asthma affects over 34 million people in the United States each year
  » 9 million children
  » 2 million ED visits,
  » 1/2 million hospitalizations,
  » 4 thousand deaths each year
• Costs the American Economy 19.7 Billion dollars
Asthma Treatment

- Treatment: Steroids, Beta Agonists, Leukotriene receptor antagonists (block inflammation), Cromolyn (drugs that effect mast cells)
- Rationale for Use of neuromodulation:
  - Systemic local anesthetics affect airway reactivity
  - Neurally mediated
  - Anxiety can cause increased airway reactivity...possible central activity
  - Could we inhibit an constriction pathway or excite a relaxing pathway

Rationale for Treating Bronchoconstriction with Electrical Stimulation

- A large component of bronchoconstriction is due to a neurally mediated smooth muscle contraction
- The dominant neural pathways for controlling airway caliber are thought to utilize oppositional controls in the parasympathetic nervous system where cholinergic nerves mediate contraction and inhibitory, non-adrenergic, non-cholinergic (iNANC) nerves mediate relaxation
- It was hypothesized that an electrical signal could be developed that would:
  - Block efferent vagal action potentials causing bronchoconstriction, or
  - Selectively stimulate iNANC nerves to cause relaxation
  - Direct vagus nerve stimulation was optimized in a histamine guinea pig model
Animal Testing

- Worked with leading asthma researcher, Dr. Charles Emala, of Columbia University to develop a treatment for relief of bronchoconstriction
- Used a well-established Histamine Model for inducing and measuring airway pressure changes with direct nerve control of airway “tone”
- Used a standard model for Naturally Induced Anaphylaxis
- In 4 guinea pig studies, Electrical Stimulation showed significant effectiveness in reducing bronchoconstriction by 40% (and avoiding a fatal drop in blood pressure)
- Swine studies confirm effects with the same signal, and indicate alternate (safer and more effective) lead placement possible
Materials and Methods

- Used a Standard Guinea Pig Model for Measuring Airway Pressure Changes and Vagal Nerve Control of Airway Tone for Over 30 Years

- Airway cannula through tracheostomy to ventilator
- i.v. L jugular vein for succinylcholine
- To airway pressure transducer and DAQ
- Bilateral Electrodes on vagus nerves to stimulator

- i.v. R jugular vein to introduce histamine
- Carotid arterial Cannula to BP sensor And DAQ

Pulmonary Inflation Pressure (cm H2O)

16.0
17.5

Cholinergic vagal Nerve stimulations (20 V, 25 Hz, 0.2 msec for 7 s) Increase Airway Pressure

classic Use Of This Model To INDUCE Vagal Nerve Mediated Bronchoconstriction
Reduction in Acute Airway Resistance in a Guinea Pig Histamine Model

Histamine Control

Histamine + Stimulation

Histamine Control

Histamine Control

Histamine + Stimulation

Histamine + Stimulation

Histamine Control

Airway Pressure (cm H2O)

Time (min)

Guinea Pig Histamine Model

Change in Airway Resistance

Stimulation Resulted in Lower Resistance Across ALL Animals

Untreated

Treated

Change in Airway Pressure (cm H2O)

Animal Number

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

Stimulation Resulted in Lower Resistance Across ALL Animals
Swine Histamine Model
Reduction in Chronic and Acute Airway Resistance

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Histamine Control</th>
<th>Histamine + Stimulation</th>
<th>Histamine Control</th>
<th>Histamine + Stimulation</th>
<th>Histamine Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Stimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single Animal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stimulation Resulted in Lower Baseline AND Lower Resistance

Animal Procedure

- Urethane Anesthesia
- Ventilation through Tracheotomy
- Airway Pressure monitored via side port
- Both Jugular Veins accessed for Reagent Infusion
- Left Carotid Artery Cannulated for BP
- Both Vagus Nerves isolated and Electrodes attached
- Vagus Nerves selectively ligated to detect transmission direction
- Stimulation at 25Hz, 200µs, .5-3v

Figure adapted from Oh EJ, Mazzone SB, Canning BJ, Weinreich D. Reflex regulation of airway sympathetic nerves in guinea pigs. J Physiol 2006;573:549-564.
Neither iNANC Inhibitors nor Tying Vagal Nerves Caudal to Electrodes Affects Stimulation!!!!

Before Ligation

After Ligation

Tying Vagal Nerves Rostral to Electrodes Does Inhibit Effect of Stimulation

Before Ligation

After Ligation
**Propranolol, a Non-specific β-Blocker, Abolishes the Effect of Stimulation**

Before

After 1 mg/kg Propranolol

---

**Mechanism of Action**

- The mechanism does not involve iNANC stimulation or blocking of an efferent vagal signal.

- The effect can be completely blocked by the non-specific β-blocker, propranolol, suggesting a sympathetically mediated mechanism.

- Blocking efferent neural transmission has no effect on stimulation whereas blocking afferent conduction abolishes it.

- Thus, it now appears that we are inhibiting airway constriction through a parasympathetic-sympathetic reflex arc, whereby stimulation of an afferent vagal nerve causes an efferent sympathetically-mediated release of catecholamines, resulting in smooth muscle relaxation.

- Unknown if same mechanism operates in humans.
Feasibility Clinical Trial

- Percutaneous VNS for acute moderate to severe asthma exacerbation
- Standard of Care study: *Limited NON Sham control*

Primary Endpoints
- Change in FEV₁ at 60 min
- Self Assessment of Improved Work of Breathing

VNS Clinical Trial Design

**Bronchodilator Description:**
- External electrical signal generator plus temporary lead
- Percutaneous insertion into neck in the vicinity of the carotid sheath

**Enrollment**
- Study conducted under FDA IDE, IRB approval, and Patient Informed Consent
- Patients seen in Emergency Department with moderate to severe asthma (FEV₁ 25%-70%).
- Patients failed to respond to conventional pharmacologic therapy, including β2-adrenergic receptor agonists, anticholinergics and steroid treatments for one hour
- Enrolled 25 patients
**VNS Clinical Trial Procedure**

- Patients remained conscious and responsive
- Maintained in an upright position
- Required only a local anesthetic at the insertion site
- Procedure was quick, averaging 10.7 ± 1.3 minutes
- Assisted only by Ultrasound guidance
- Treatment consisted of 60 minutes of continuous electrical stimulation at 25 Hz, 200 μs pulse duration, 1-12 V (mean 5.5 V).

**FEV₁ Improvement**

![Graph showing FEV₁ improvement over time](image)

- Treatment vs Control
- p = 0.003
- p = 0.006
- p = 0.005
Work of Breathing Improvement for All Patients

Percent of Patients with a 50% Improvement in Work of Breathing
Patient Outcomes: Asthma Related Admissions to Hospital

![Graph showing patient outcomes](chart.png)

Summary of Clinical Feasibility Results

- Safe, quick, painless procedure
- Works when β-agonists have failed
- Clinically significant increase in WOB and FEV₁
- Acts quickly to alleviate constriction, within 15 – 30 minutes

Potential Clinical Benefits:

- Patients may leave ED sooner
- Decreased use of drugs, reduced morbidity
- Decreased hospital admissions

★ **BUT, it is an invasive procedure!**
Next Generation
Non-Invasive Vagus Nerve Stimulator 90 Second Treatment
TimeProprietary Signal and Treatment Head
to Provide Deep, Painless Stimulation

- High frequency signal to bypass skin capacitance and have minimal effect on pain sensors
- Unique electrode configuration for uniform electric field – no hot spots
- 90 second treatment time
- Placed on neck over the carotid sheath (parallel to vagus nerve)
- Nearly painless treatment with bronchorelaxation response within seconds.

Development of a Non-Invasive Vagus Nerve Stimulator (nVNS)
Inhibition of Methacholine-Induced Bronchoconstriction in a Hypersensitive Beagle Model

Effects of Propranolol

- Eliminated smooth muscle relaxation due to albuterol (positive control) and electrical stimulation!

Possible Mechanisms:

- Release of catecholamines from adrenal glands
- Release of norepinephrine (NE) from sympathetic nerve endings innervating bronchial smooth muscle (controversy in humans about extent of innervation)
- Blocks effect of NE from locus coeruleus (propranolol is membrane permeant). Mechanism could then be stimulation of iNANC, PGE$_2$, other.
How about Migraines?

- Many of the patients had resolution of migraines
- CE mark in Europe
- Patients are using for treatment and prevention of migraine
- FDA approved clinical trial approved now for prevention of migraine using vagal nerve stimulation

Classic Vagal Responses

- Why doesn't afferent vagal stimulation cause:
  a) bradycardia and lower blood pressure
  b) bronchoconstriction and make asthma worse?

- Aren’t anticholinergics given to asthmatic patients to block the negative effects of vagally mediated smooth muscle contraction?

- Answer: Our signal targets low threshold, large myelinated afferent fibers. It does not cause efferent vagal stimulation due to signal pulse parameters and very low amplitude.
High Voltage but NOT Low Voltage Induces Bradycardia

High Voltage but NOT Low Voltage Induces Bronchoconstriction
Conclusions

The nVNS device provides a non-invasive, painless signal to the vagus nerve which relieves acute bronchoconstriction due to reactive airway disease within minutes of treatment.

Potential Clinical Benefits:

- Works when β-agonists have failed
- Clinically significant increase in WOB and FEV$_1$
- Patients may leave ED sooner
- Decreased use of drugs, reduced morbidity
- Decreased hospital admissions

Conclusion

- Electrical Stimulation has been around for thousands of years in the treatment of pain
- Vagal nerve stimulation at a precise signal effectively blunts airway reactivity
- Works immediately
- Probably causes central mediation of release of endogenous beta agonists at the
- Paradigm shift in the treatment of asthma