Hypoglossal Stimulation for OSA: Pivotal Trial & Mechanisms

Kingman P Strohl M.D.

Professor of Medicine, Physiology & Biophysics, and Oncology

Center for sleep Disorders Research

Case Western Reserve University,
Cleveland OH, USA
Disclosures

Inspire Medical
  – Site PI for the STAR Trial
  – Consultant on FDA application

NIH and VA research Awards on Causes and Consequences of Sleep Apnea

Galleon Pharmaceuticals (Consultant Panel)

5i Sciences (Consultant)

DSMB, University of Illinois NIH Phase II Trial

Marinol (dronabinol) for OSA
Objectives

1. Describe the rationale for Hypoglossal stimulation as therapy for sleep apnea
2. Summarize Inspire STAR trial results and selection criteria for nerve stimulation
3. Consider mechanisms through which unilateral hypoglossal stimulation might operate.
Phenotype traits in OSA

- Oversensitive ventilatory control system (loop gain)
- Poor pharyngeal muscle response (gain and reflex)
- Small, collapsible upper airway (anatomy)
- Low arousal threshold (sleep mechanisms)

Obstructive Sleep Apnea

Younes, 2007; Wellman, 2011
Treatments for OSA

Obstructive Sleep Apnea

- Small, collapsible upper airway
- Poor pharyngeal muscle response
- Low arousal threshold
- Oversensitive ventilatory control system

CPAP

(Kribbs, 1993; Engelman, 2003)
Treatments for OSA

- Small, collapsible upper airway
- Oversensitive ventilatory control system
- Poor pharyngeal muscle response
- Low arousal threshold
- Anatomic surgery
  - Oral appliance
- Obstructive Sleep Apnea
Obstructive Sleep Apnea

Mechanical Properties of upper airway

ventilatory control system

Inadequate neural control

Drugs +/- Neurostimulation

arousal threshold

Obstructive Sleep Apnea

Decker et al 1993
Target the **Neuro**mechanically Unstable Upper Airway

Apneas occur in the context of a reduction in drive.

Strohl 1986
• Intraoperative direct stimulation for optimal placement

• Unilateral: ~1/3 of patients have temporary numbness

Second Generation System

Implanted Components

Inspire Programmer
- Adjust Therapy

Patient Programmer
- Therapy ON/OFF
- Adjust amplitude

Stimulation Lead

Implanted Pulse Generator (IPG)

Sense Lead
Effect of Stimulation Therapy ON Therapy OFF

EEG
EMG
Nasal Pressure
Thermo
Chest
Abdomen
SpO2

30 seconds
STAR Trial Design and Selection

**Inclusion:**
- Fail or intolerant to CPAP
- Moderate to severe OSA
  - AHI between 20 and 50 (screen)
- BMI ≤ 32 kg/m²

**Exclusion:**
- Complete concentric retropalatal collapse (DISE)
- Central sleep apnea (>25% of AHI)
- Positional OSA (AHI non-supine < 10)
Key Selection Criteria

Purpose: **Moderate or severe OSA**

- Have failed or have not tolerated CPAP
- BMI ≤ 32
- Do not meet the following pre-implant screening withdrawn criteria
  - AHI < 20 or AHI > 50
  - Central and mixed sleep apnea accounted for > 25% of all AHI events
  - Absence of significant apnea when sleeping in a non-supine position (AHI non-supine < 10)
  - Absence of any complete concentric collapse at the level of the soft palate (drug-induced sleep endoscopy)
DISE (drug induced sleep endoscopy)
Information from DISE

- Anatomic compatibility for INSPIRE
- If not.....
  - Mandibular advancement dental devices?
  - Other surgeries to alter airway?
Key Selection Criteria

Purpose: **Moderate or severe OSA**

- Have failed or have not tolerated CPAP
- BMI ≤ 32
- Do not meet the following pre-implant screening withdrawn criteria
  - AHI < 20 or AHI > 50
  - Central and mixed sleep apnea accounted for > 25% of all AHI events
  - Absence of significant apnea when sleeping in a non-supine position (AHI non-supine < 10)
  - Absence of any complete concentric collapse at the level of the soft palate (drug-induced sleep endoscopy)
Inspire Therapy System

- Inspire therapy:
  - Is fully implanted
  - Senses breathing
  - Delivers mild stimulation to key airway muscles
  - Turns on and off with a handheld remote
What was done for STAR Trial

** Point of emphasis

* 12- and 18-months
# Co-Primary Efficacy Endpoints

<table>
<thead>
<tr>
<th>Observed Responder Rate</th>
<th>Performance Goal</th>
<th>Lower 97.5% Confidence Level</th>
<th>p =</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AHI Responder</strong></td>
<td>66%</td>
<td>50%</td>
<td>57%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>ODI Responder</strong></td>
<td>75%</td>
<td>50%</td>
<td>67%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Graphs:**

**AHI**
- Baseline: 29.3
- 12 Month: 8.9
- 70% reduction in AHI

**ODI**
- Baseline: 25.4
- 12 Month: 7.2
- 72% reduction in ODI
Randomized withdrawal
1 week duration in the 13th month
n=23 remain “ON” vs 23 “OFF”

- **Endpoint**: demonstrate a difference in AHI increase in therapy ‘OFF’ group vs. therapy ‘ON’ group

- **Outcome**: Difference in mean AHI increase was 16.4 ± 12.0 events/hour between therapy ‘OFF’ and ‘ON’ groups, 95% CL of difference 9.3 to 23.6 (p < 0.0001)
18-month Effect in the Withdrawal Group

- Baseline
- 12 Month
- RCT
- 18 Month

AHI (Events/hr)

- Maintenance ('ON') Group
- Withdrawal ('OFF') Group

*p<0.05 vs. baseline; #, p<0.05 vs. 12 month; ##, p<0.05 vs. RCT. Mean and S.E.
No BMI Change

BMI (kg/m²)

Baseline: 28.4
12M: 28.5
18M: 28.5
Follow-up in the STAR Pivotal Trial

1. Safe
   - There were no device-related serious adverse events up to 18 month follow up period

2. Effective and Durable
   
   **AHI Responder Rate is 66%**
   - Therapy based on Pivotal Selection Criteria have shown sustained benefit to 18-months

3. Sleepiness, Snoring and/or Quality of Life
   - 85% showed significant improvement
Reduction in Snoring

Source: Inspire STAR pivotal trial (similar at 18 months)
Risk Considerations

First, pain, swelling, temporary tongue weakness, and infection are generally expected with any kind of surgery, and almost all resolve on their own or with medication within a period of weeks or at most months.

Once the therapy is turned on, some patients may experience discomfort from stimulation, tongue abrasion, mouth dryness, and discomfort from the presence of the device. The majority of these events resolve either on their own, with medication, or by adjusting the therapy settings.

Inspire may not work ideally, and there will be a need for reassessment.

Patients with Inspire therapy will not be able to have an MRI (unless shielded). Other imaging modalities are OK.
Mechanisms of Action

Moderate to severe OSA is most likely caused by a mixture of obstructive events in the oro- and/or naso-pharynx (Hudgel et al. 1988). Nasal endoscopy can visualize upper airway size and shape during wakefulness and “drug-induced sleep” (DISE) (DeVito et al. 2014).
Hypothesis for Inspire Effect

While we expect enlargement of tongue-base cross-sectional area (Oliven et al. 2007), we might not expect neural stimulation to affect the palatal area.
METHODS I

• **Subjects:** Enrolled in the Inspire III study for CPAP-refractory moderate to severe OSA (29+/− 7), BMI (28+/−1.7), and absence of concentric palatal collapse during DISE

• Video-endoscopic imaging of the **palatal** and **tongue-base** aperatures in the supine position
  – Awake (n=15) and DISE (mild sedation with propofol or midozalam, n =12)
Methods II: FES

Patient-specific inspiratory stimulation amplitude for:

- First sensation (AWAKE)
- Bulk tongue movement (AWAKE)
- PSG-titrated to abolish OSA events (ASLEEP)
- Sub-discomfort level while awake (AWAKE)

Image Analysis

- Cross-sectional area and dimensions reported as pixels or % total scope area
- Data is presented as mean ± standard deviation
Aperatures are reduced with DISE vs. Baseline

Naso-Pharynx

Oro-Pharynx

AWAKE

BASELINE

STIMULATION

AWAKE

BASELINE

STIMULATION

DISE

DISE
A-P and Lateral (LL) Dimensions with Stimulation

**Awake dimensions**
- RP-AP: *p=0.004, p=0.54, *p=0.001, *p=0.04
- RP-LL: *p=0.004, p=0.54, *p=0.001, *p=0.04
- RL-AP: *p=0.004, p=0.54, *p=0.001, *p=0.04
- RL-LL: *p=0.004, p=0.54, *p=0.001, *p=0.04

**DISE dimensions**
- RP-AP: *p=0.005, p=0.21, *p=0.002, *p=0.03
- RP-LL: *p=0.005, p=0.21, *p=0.002, *p=0.03
- RL-AP: *p=0.005, p=0.21, *p=0.002, *p=0.03
- RL-LL: *p=0.005, p=0.21, *p=0.002, *p=0.03

RP= retropalatal and RL = retrolingual
Retro-palatal and retro-lingual airway area enlarge with increasing stimulation amplitudes awake < DISE

(Palate>Tongue-base starts at a smaller size with DISE)
Stimulation of muscles or passive (direct or indirect) effects?

Arc of the oropharynx enlarges or does not change and A-P > lateral in nasopharynx.

1) Passive hyoid lift increases oropharyngeal and A-P naso-pharyngeal size in anesthetized dogs (Strohl et al 1986)
2) Maxillo-mandibular advancement increases oro- and naso-pharyngeal size (2012)
Responders were those with a reduction in AHI by >50% and an AHI <20/hr. (29 ± 3 at baseline to 8 ± 3/hr; p=0.02)

Non-responders were those with an AHI >20 or a fall in AHI <50%. (31 ± 10 to 43 ± 23/hour; p=0.30).

7 endoscopies of category were studied in wakefulness only.
(AWAKE) Percent (%) increase from Baseline to Therapeutic Stimulation
Responders (R) > Non-Responders (NR) in Retropalatal
Conclusions

Aperature areas are decreased from Awake to DISE. Airway area is increased in a dose-response manner in the AP and lateral directions at the retro-lingual region and in the AP direction in the retro-palatal region.

Effects on size and possibly stiffness of two critical sites can result from upper airway stimulation for OSA.

The success or failure of Inspire depends to some degree on this linkage between stimulation and palatal position.
Mechanism of Action

Baseline  Nasopharynx  Stimulation

Tongue-base

CT Scan

Courtesy: J. De Backer (unpublished)
Cross sectional area (mm²)

Distance from hard palate (mm)

NoStim
Stim

Courtesy : J. De Backer
(unpublished)
Current Model

OAT (Isono et al 1995; Chan et al, 2010) and MMA (Ryan et al 1999) increase retopatalal as well as retrolingual area in humans.

In animal models, forward motion of the hyoid arch opens the nasopharynx (van de Graaff et al 1984) to the same anatomic and flow resistive degree as stimulate drugs (Strohl et al 1986).

The working hypothesis is that...

- stimulation moves the hyoid arch anteriorly.
- nasopharynx effects are secondary to mechanical linkage with the outward motion to the nasopharynx
- Such linkage varies among patients
Inspire Therapy Process

Assessment

Sleep profile
Anatomy check

DISE
(Drug-Induced Sleep Endoscopy)

Sleep Study

Implant

Typically outpatient

Follow Up

Therapy activation

Therapy optimization

Routine annual follow up
Insurance/Cost Considerations

• Inspire therapy is FDA approved. Currently, the therapy is being reviewed by insurance companies on a patient-by-patient basis.

• The first step is to see if you qualify for the therapy and then the work with your insurance company on the Inspire implant.
Summary

Inspire therapy is a somewhat predictable treatment option for some…….

Who:
• Have moderate to severe OSA
• Struggle to get consistent benefit from CPAP
• Have a compatible airway anatomy profile
• Have a body mass index (BMI) <32

A team is best to determine if Inspire therapy (an invasive therapy) is right at this time for any given patient.
• The mechanism for AHI success is dependent upon its action on the nasopharynx.
## Acknowledgements: STAR Trial

<table>
<thead>
<tr>
<th>STAR TRIAL CENTERS</th>
<th>STAR TRIAL INVESTIGATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>St Lucas Andreas - Netherlands</td>
<td>DeVries</td>
</tr>
<tr>
<td>North Memorial - Minneapolis</td>
<td>Cornelius, Froymovich</td>
</tr>
<tr>
<td>UPMC</td>
<td>Strollo, Soose</td>
</tr>
<tr>
<td>University of South Florida</td>
<td>Padhya, Anderson</td>
</tr>
<tr>
<td>St Petersburg Sleep Disorders Center</td>
<td>Feldman</td>
</tr>
<tr>
<td>St Cloud ENT - Minnesota</td>
<td>Hanson, Payne</td>
</tr>
<tr>
<td>University of Mannheim - Germany</td>
<td>Maurer</td>
</tr>
<tr>
<td>University of Cincinnati</td>
<td>Steward, Surdulescu</td>
</tr>
<tr>
<td>University Hospital Case</td>
<td>Strohl, Baskin</td>
</tr>
<tr>
<td>Medical University of South Carolina</td>
<td>Gillespie</td>
</tr>
<tr>
<td>Medical College of Wisconsin</td>
<td>Woodson</td>
</tr>
<tr>
<td>UZA - Belgium</td>
<td>VanderVeken, Verbracken, Van de Heyning</td>
</tr>
<tr>
<td>Borgess Kalamazoo</td>
<td>Goetting, Szeles</td>
</tr>
<tr>
<td>Intersom Koln - Germany</td>
<td>Knaack, Mockel</td>
</tr>
<tr>
<td>California Sleep - Palo Alto</td>
<td>Roberson</td>
</tr>
<tr>
<td>Swedish - Seattle</td>
<td>Stolz, Yang</td>
</tr>
<tr>
<td>Advanced ENT - Atlanta</td>
<td>Mickelson</td>
</tr>
<tr>
<td>Wayne State - Detroit</td>
<td>Badr, Lin</td>
</tr>
<tr>
<td>Sleep Medicine Associates - Dallas</td>
<td>Jamieson, Williams</td>
</tr>
<tr>
<td>CHU de Bordeaux</td>
<td>Philip, Monteyrol</td>
</tr>
<tr>
<td>Foch Paris</td>
<td>Chabolle, Blumen, Hausser-Hauw</td>
</tr>
<tr>
<td>Bethanien Solingen - Germany</td>
<td>Randerath, Hohenhorst</td>
</tr>
</tbody>
</table>
Effect of Upper-Airway Stimulation for Obstructive Sleep Apnoea on Airway Dimensions

Safiruddin, Faiza; Vanderveken, Olivier M.; de Vries, Nico; Maurer, Joachim T; Lee, Kent; Ni, Quan; Strohl, Kingman

• Sint Lucas Andreas Hospital, Amsterdam, NETHERLANDS
• Department of Otorhinolaryngology, Head and Neck Surgery, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Antwerp, BELGIUM
• Faculty of Medicine and Health Sciences, University of Antwerp, Prinsstraat 13, 2000 Antwerp, BELGIUM
• University Medical Center Mannheim, Mannheim, GERMANY
• Inspire Medical Systems, Maple Grove MN, USA
• Case Western Reserve University, Cleveland OH, USA

Accepted in European Respiratory Journal