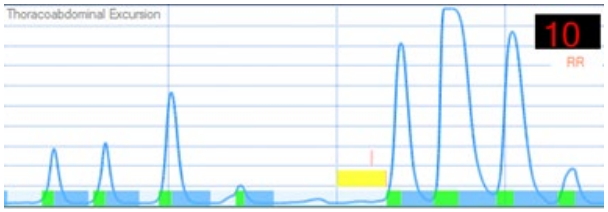
WhisperSom™

Technology for the REST of your life™




# Early Sleep Apnea Termination by Acoustic Neuromodulation Reduces Oxyhemoglobin Desaturation Magnitude and Duration and Reduces EEG Arousal Frequency and Duration, in those with Obstructive Sleep Apnea Syndrome (OSAS) and Central Sleep Apnea (CSA)

Draft – Confidential – Not for Distribution

The Science of Acoustic Neuromodulation for Sleep Apnea

Revision 5.2

# Early Sleep Apnea Termination by Acoustic Neuromodulation Reduces Oxyhemoglobin Desaturation Magnitude and Duration and Reduces EEG Arousal Frequency and Duration, in those with Obstructive Sleep Apnea Syndrome (OSAS) and Central Sleep Apnea (CSA)

***Extracts – Acoustic stimulation without waking***

"The presence of transient electrocortical arousal in the current study appears to be able to influence respiration consistent with termination, or early resolution, of obstructive apneas in patients with OSA. Furthermore, such non-respiratory afferent stimulation appears to be able to influence apnea resolution without involving ascending arousal systems. Resolution of the apnea after stimulation was generally associated with qualitatively increased submental EMG compared with the EMG during the apnea whether electrocortical arousal occurred, suggesting a similar mechanism of response to tones *irrespective of cortical involvement*." (201)

"The current findings suggest that strategies of induced arousal, at an intensity level stimulating respiration while avoiding recruitment of the ascending arousal system and its potential effects of sleep disruption, could have potential application as a therapeutic modality in patients with OSA." (201)

"…tones delivered relatively early and late in the apnea were equally likely to be associated with resolution of the apnea. These data indicate that transient arousal, induced by non-respiratory stimulation, influences the resolution of obstructive apneas during sleep…the tendency for the stimulus to resolve the apnea within 2s of the tone.…the current study appears to be able to influence respiration consistent with termination, or early resolution, of obstructive apneas in patients with OSA. Furthermore, such non-respiratory afferent stimulation appears to be able to influence apnea resolution without involving ascending arousal systems." (14)

"…it may be possible to significantly modulate respiratory drive via non-respiratory afferent stimulation (in this research it is acoustic stimulation) without causing a significant sleep fragmentation or restriction. This may have potential therapeutic implications for disorders such as sleep-related hypoventilation and sleep apnea syndrome". (14)

"…The apnea index, the number of times per hour that SaO2 dropped below 85% ($SaO_2$< 85%/hour), and the total apnea duration expressed as a percentage of total sleep time during stimulation nights decreased to approximately 50% of the corresponding values on the control night." (5)

"…five of the six subjects completed questionnaires the morning after acoustic stimulation. All underestimated the number of tones they recalled receiving ranged from 2 to 8, whereas each subject actually received >20 tones". (5)

This would be a 75% arousal free rate of respiratory recovery if the number of stimuli was 20. By comparison, the questionnaires completed to date by independent volunteers, indicate a 96% arousal free recovery rate with WhisperSom acoustic neuromodulation therapy.

In an experiment (69) tone induced arousals were found to have approximately the same duration as spontaneous arousals (spontaneous arousals happen in all humans and are not related to sleep apneas and lasting approximately 7 seconds) wherein those produced in conjunction with an apnea had a mean length of 12. 6 seconds (70, 74) [an 80% increase in arousal duration].

The magnitude of changes to Blood Pressure varied significantly between degrees of arousal (15, 16, 17, 23, 50, 64, 85) with non-cortical activations (<3s) having a much lower diastolic than that of an EEG/Cortical arousal (>10s). Other studies show that even with acoustically induced EEG/Cortical arousals the magnitude of Blood Pressure changes is less than those that occur when an apnea self-extinguishes (17, 77). It is a conclusion of O'Driscol *et al.* (26) that the cardiovascular response occurring at the end of an obstructive apnea is almost double that of which happens after a spontaneous arousal.

Guilleminault *et al.* (18) concluded that the activation of the brainstem can lead to autonomic nervous system response without objective consequences the next day.

A controlled arousal via a CNS (Central Nervous System) impact upon sleep continuity can be as little as <3 seconds. In comparison a study by Schwartz *et al.* (92) found that that cortical arousals (e.g. coincidental with an apnea), many of which are greater than 15 seconds in duration,….constituted 18.4% of all arousals and accounted for 37.5% of the total arousal time.

According to Halasz *et al.* (200), a respiratory challenge (such as an apnea) can be resolved without involving a cortical arousal at all.

Simply put, stimulus does not automatically lead to wakening's; for instance, Non-invasive ambulatory blood pressure monitoring (i.e. APBM or ABP (24 hr blood pressure monitors used in the home)). "Sleep is often disturbed by blood pressure monitoring but that "86.4% of subjects did not perceive an appreciable sleep deprivation during overnight ABP monitoring despite a frequency of measurements set to 1 every 15 minutes over the entire 24-hour period" (20). The results of that study closely mirrored those reported by Parati *et al.* (21).

"An additional decrease of event durations is expected with associated reduction in the amount of nocturnal hypoxia. Indeed, as cardiovascular and metabolic consequences of OSA are mainly related to the severity of nocturnal intermittent hypoxia1; shortening the mean event duration to less than 8 to 10 seconds will reduce the burden of deleterious consequences. "Although patients and physicians were aware of the on and off treatment periods, the PSG core laboratory was blinded to the occurrence of stimulation during a respiratory event. No stimulation artifact on the respiratory or electroencephalogram waveforms was noted on the scored PSG signals."(202)

Ball *et al.* (6) addressed the fact, that while sleeping, people can and do ignore smoke detector alarms. The same holds true for people living in the flight paths near airports. Anecdotally it is known that people fall asleep while listening to music or the TV.

***Extracts - The importance of reducing the number and length of apneas***

- **Hypoxemia (oxyhemoglobin desaturation)**
- **Sympathetic outflow (fight or flight metabolic processes and inflammation)**
- **Sudden changes in heart rate and blood pressure**
- **Motor vehicle accidents**
- **Diabetes**
- **Cardiovascular Disease**
- **Cancer**
- **Stroke**
- **Hearing loss**
- **Glaucoma**
- **Alzheimer's Disease**

In a study of 1,478 individuals with sleep apnea, the authors conclude, “Our study provides strong evidence that untreated OSA increases the risk of MVA [motor vehicle accidents]…by a factor of 2.5…” The study also found that CPAP intervention reduced risk of MVA by 70%. (1)

There exists a number of compelling reasons to avoid an apnea (10, 25). Perhaps the most important is to **maintain normalized blood gases**. This was supported in two studies by Hudgel *et al*. (87, 88) in which it was concluded that changes in the amount of inspired $CO_2$ and $O_2$ had a dramatic impact on the duration of apneas (i.e. normal blood gases lead to shortened apneas).

During an apnea the $SpO_2$ levels decline (for instance, for a 26 second apnea the decrease was 9.2% (52, 85)), leading to intermittent oxyhemoglobin desaturation (hypoxia or hypoxemia). Hypoxia by itself has been causally linked to many morbidities. However, the role of hypoxia in the characteristic **increase in Blood Pressure and Heart Rate at the end of an apnea episode** remains contested with it being supported as a causative agent in some studies (61, 65, 67, 68, 78, 90). A recently released study by Lusina *et al.* (27) found “that 10 daily exposures to isocapnic hypoxia in humans can increase sympathetic outflow during acute hypoxia and recovery” (such as from an apnea event). ***The significance of increased sympathetic outflow is that it seems to be directly responsible, at least in part, for the acute Blood Pressure changes that occur at the end of a self-extinguishing apnea event*** (28, 29, 91). It is the conclusion from a study by Leuenberger *et al.* (30) that “these findings strengthen the rationale that preventing intermittent hypoxia, a goal that is presently best achieved with continuous positive airway pressure therapy, is crucial to prevent the adverse neurocirculatory and cardiovascular consequences of sleep apnea.” Another study that links intermittent hypoxia to increased sympathetic outflow was performed by Leuenberger *et al.* (75).

According to Miliauskas *et al*. (83) “Hypoxemia depth at night is an important factor for **daytime sleepiness** ...” aka Excessive Daytime Sleepiness (EDS) which effect perhaps half of those with OSAS.

It is a conclusion of a study that prior sleep apnea events increase the arousal threshold to upper airway occlusion on subsequent nights and prolongs the apnea events (45). **Decreasing the quantity and duration of apneas may break that positive feedback cycle** (76). Indeed, according to De Backer *et al.* (57) that “any intervention that stabilizes the breathing pattern will ultimately also lower the tendency to collapse.”

From Stoohs *et al*. (52) it was determined that hypoxia is a significant mediating agent in changes to **Stroke Volume, and Heart Rate**. That view is partially supported by a study by C. P. O’Donnell *et al*. (66).

The magnitude of changes to **Blood Pressure** varied significantly between degrees of arousal (15, 16, 17, 23, 50, 64, 85) with non-cortical activations (<3s) having a much lower diastolic than that of an EEG/Cortical arousal (>10s). Other studies show that even **with acoustically induced EEG/Cortical arousals the magnitude of Blood Pressure changes is less than those that occur when an apnea self-extinguishes** (17, 77). It is a conclusion of O'Driscol *et al.* (26) that the cardiovascular response occurring at the end of an obstructive apnea is almost double that of which happens after a spontaneous arousal.

In a similar vein, hypoxia has been implicated as a risk factor in **silent cerebral infarct** in a study by Eguchi *et al.* (7).

A study by Punjabi *et al.* (42) concluded that the frequency of hypopneas associated with a 4.0–4.9% oxyhemoglobin desaturation was associated with **prevalent cardiovascular disease** after adjusting for the frequency of hypopneas with oxyhemoglobin desaturations above 5%.

Intervention will minimize changes to intrathoracic pressure. Continued respiratory effort after an obstruction leads to increases in negative intrathoracic pressure. Negative intrathoracic pressure encourages venous return to the right ventricle, increases after load on the left ventricle, which causes **ventricular hypertrophy and results in congestive heart failure** (34).

**Alzheimer's Disease**. Untreated sleep apnea has also been linked to the onset of Alzheimer's Disease according to analyses of the data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). (203) These analyses found: Sleep disordered breathing accelerated the accumulation of brain β-amyloid both in cognitively normal individuals and individuals with mild cognitive impairment Obstructive sleep apnea (OSA) was associated with increased brain β-amyloid deposition, decreased cerebrospinal fluid (CSF) levels of β-amyloid and increased tau protein levels.

The analyses reported by investigative teams at Wheaton College in Wheaton, Illinois, at AAIC 2017 examined sleep patterns among participants in ADNI to characterize potential effects of sleep disordered breathing (SDB) and OSAS on brain changes associated with mild cognitive impairment and Alzheimer's disease.

Brain β-amyloid-42 accumulation was studied in a cohort of 516 cognitively normal subjects and it was found that those with SDB had higher levels in CSF at baseline and more rapid accumulation over time. They found no interactive effect between OSAS and the Alzheimer's risk gene APOE- e4. This suggests that OSAS may be independently associated with brain amyloid burden.

Similar analyses were performed to assess the effects of OSAS in 798 subjects with mild cognitive impairment (MCI). As with the cognitively normal cohort, both baseline β-amyloid-42 levels and the rate of accumulation were higher in subjects with OSAS. While MCI does not always lead to dementia, a person with MCI is at an increased risk of developing Alzheimer's or another dementia. These results suggest that SDB may be an independent risk factor for Alzheimer's and raises the possibility that interventions aimed at treating SDB may also reduce Alzheimer's risk.

In a secondary analysis of the Age-Well clinical trial (204), 127 participants were analyzed for Alzheimer's Disease biomarkers associated with sleep disordered breathing (SDB). The analysis showed that SDB-associated brain changes in older adults who are cognitively unimpaired include greater amyloid deposition and neuronal activity in Alzheimer disease-sensitive brain regions, notably the posterior cingulate cortex and precuneus. These results support the need to screen and treat for SDB, especially in asymptomatic older populations, to reduce Alzheimer disease risk.

**Hearing loss**. In a study of almost 14,000 U.S. participants, untreated sleep apnea was observed to be linked to hearing loss (205, 210, 212, 213). The studies all seem to agree that while there does seem to be a correlation between Sleep Apnea and hearing loss, none have defined a mechanism by which it occurs. Postulates include damage to hearing structures from Snoring (212), Oxygen desaturations (213), and/or restrictions of blood flow.

In a study (210), there was evidence for a dose-response relationship between the increasing apnea/hypopnea index and any hearing impairment. Findings showed that "sleep apnea was independently associated with a 31% increase in high-frequency hearing impairment, a 90% increase in low-frequency hearing impairment and a 38% increase in both."

People with moderate sleep apnea had a 22% increased risk of hearing impairment, while severe sleep apnea was associated with a 46% increased risk. The association between sleep apnea and hearing loss was significant and independent of symptoms such as snoring, exposure to external noise and conductive hearing loss.

It is plausible to suggest that improving oxyhemoglobin values will, at the least, halt further damage to structures within the ear and just may lead to improvement in cases of hearing loss.

Also reducing the amount and amplitude of snoring may be a positive step forward in that regard.

There is provocative study (206) that concludes that “CPAP treatment for at least 6 months in OSAS patients can improve unilateral hearing ability (average, low, and medium tone). There is not any benefit to CPAP therapy in high tone SNHL. CPAP short-term treatment (3 months) cannot benefit SNHL, either”.

However, the use of CPAP has been implicated in causing hearing issues. Sleep Apnea and CPAP can cause inflammation in the air passages. Swelling can lead to prevention of proper equalization of the air pressure between the middle ear and the outside air. If the pressure is higher in the middle ear, the eardrum will bulge out. This reduces the contact it has with the malleus (hammer bone) in the middle ear. The ear will feel "full" and speech will sound muffled. The result will be some degree of a temporary conductive hearing loss until the air pressure equalizes and hearing returns to normal again (210).

The constant flow of air in the mouth and nose can dry out the mouth and nose and also cause congestion. When congestion occurs, the airway is partially blocked and thus more work is required because it becomes harder to breathe (210).

If the user adjusts the airflow on their CPAP machine to increase the air flow so that they can breathe easier, it may cause barotrauma to their ears. Barotrauma is when damaging levels of air pressure build in the middle ear (210). While middle ear barotrauma can cause enough inflammation within the middle ear to result in conductive hearing loss, it may also be transmitted to the inner ear, causing a sensorineural hearing loss (210).

This inner-ear barotrauma may result when the Eustachian tubes open and air rushes in. This brisk inward movement of air pushes on the oval window just like a very loud sound would and with the same results. It may be so violent that it ruptures the thin oval-window membrane and permits an inner ear fluid (perilymph) to leak out (what doctors call a perilymph fistula). This results in a sudden sensorineural hearing loss (210).

When using a CPAP device typically there is an increase in middle-ear pressure. This occurs when one swallows and momentarily open the Eustachian tubes. Rather than equalizing the air pressure in the middle ear with the outside air pressure, when using a CPAP machine, this results in increased middle ear pressure. This increase in pressure is directly proportional to the pressure delivered by the CPAP machine. There has been a case wherein a man ruptured both of his eardrums from the CPAP pressure (210).

**Diabetes.** In a commentary entitled, “The Effect of OSA Therapy on Glucose Metabolism: It’s All about CPAP Adherence!”, (207) the authors write, **“**In recent years, evidence has accumulated to indicate that **obstructive sleep apnea (OSA) is both a risk factor for the development of T2DM (type II diabetes mellitus**) [2–4] and an exceptionally frequent comorbidity with an adverse effect on glycemic control.[5–8] Multiple studies, including approximately 1,400 patients with T2DM, have shown that the prevalence of OSA (assessed by polysomnography) ranges between 58% to 86%.[5,7,9–14] There is a significant association between increasing OSA severity

and reduced glycemic control and this association persists after controlling for multiple potential confounders.[5,7,8] Therefore, based on current estimations, of the nearly 30 million people in the United States with T2DM, approximately two-thirds may have OSA. Given these important associations, it seems appropriate to consider OSA as a modifiable risk factor in patients with prediabetes and T2DM."

**Glaucoma**. In a review of 49 studies, it was concluded that OSAS is the major risk factor for developing glaucoma. (216). Similar to hearing loss, a study concluded that patients with OSA demonstrated significant 24-hour interocular pressure (IOP) fluctuations, with the highest values at night. CPAP therapy causes an additional IOP increase, especially at night. Regular screening of visual fields and the optic disc is warranted for all patients with OSA, especially those treated with CPAP. (217).

An article by two Harvard Medical School Professors entitled, Sleep apnea: a common mechanism for the deadly triad--cardiovascular disease, diabetes, and cancer?" (208) suggests there exists a number of studies that link nocturnal hypoxemia resulting from apneas to the development of a number of comorbidities, including but not limited to Cancer, Diabetes, Cardiovascular disease, and changes to the brain with an impact on cognition and memory.

[Clinically significant indicators of sleep apnea and WhisperSom field trial observations begin on the next page.]

## Clinically Significant Indicators of Sleep Apnea

1. **Oxygen desaturation index (ODI) –** Oxygen ($O_2$) desaturation **events / hour**
   - **4% oxygen desaturation under baseline indicates sleep apnea if > 5 events / hr**
   - **ODI** tracks up and down with **apnea events / hour** – the Apnea Hypopnea Index (**AHI**)
   - ODI or AHI > 5 / hour indicates **Sleep Disordered Breathing**
     - **ODI or AHI of 5 – 15 / hour indicates Mild Sleep Apnea**
     - **ODI or AHI of 15- 30 / hour indicates Moderate Sleep Apnea**
     - **ODI or AHI of > 30 / hour indicates Severe Sleep Apnea**

2. **Oxygen desaturation duration** indicates degree of hypoxemia and hypoxic load
   - **Percent of time in oxygen desaturation** best describes nocturnal hypoxemia
   - PO3 and PO4 are the percentages of sleep time at >3% and >4% below baseline $O_2$
   - **ODI and PO3** are the measures that the literature cites as being most closely associated with poor clinical outcomes resulting from untreated sleep apnea
   - **Nocturnal oxygen desaturation is associated with day-time fatigue**

## OBSERVATIONS FROM WHISPERSOM FIELD TRIALS USING ACOUSTIC NEUROMODULATION

- 42 in-home test nights - unobserved in an ecologically valid test environment.

- Seven (7) independent male and female test volunteers with AHI 16 – 28/hr (moderate) mixed obstructive and central sleep apnea.

- 2,470 apneas recorded: 1,281 Therapy OFF (Baseline); 1,216 Therapy ON.

    1. Significantly reduced apnea duration, and fewer apneas –
       3 seconds average respiratory recovery time

    2. Significantly reduced oxygen desaturation –
       ODI 4% < 5

    3. More restful sleep –
       33% less motion, 96% arousal-free treatment

*While not a statistically significant test population, the effects of WhisperSom Therapy with each volunteer were clinically significant and remarkably similar.*

## Data from testing to date

An early PoC version (V2.5L) yielded this data-

**5 test subjects observed over 33 nights**

**WhisperSom therapy OFF:** 65 seconds for 99% of apneas to resolve naturally using normalized data (orange dots).

**WhisperSom therapy ON:** 99% of apneas were resolved within 14 seconds using normalized data (blue dots), a 76% improvement over baseline.

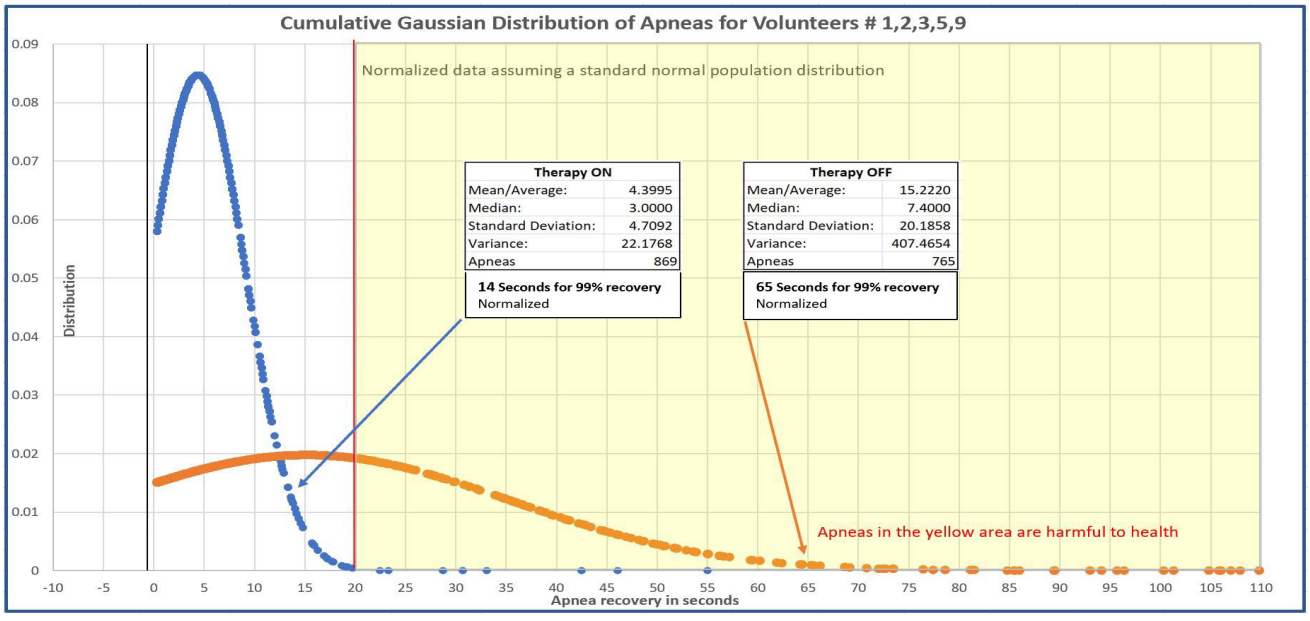
**Average time to respiratory recovery after the first stimulus was 4.4 seconds.**

Test subjects reported sensing 0-5 stimuli per night, and 49 total instances out of the 869 treated apneas and 2,000+ stimuli delivered – a **94% raw arousal-free treatment rate**.

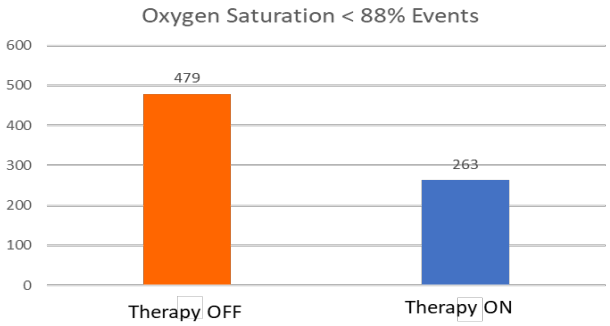
**1,634** total apneas detected:

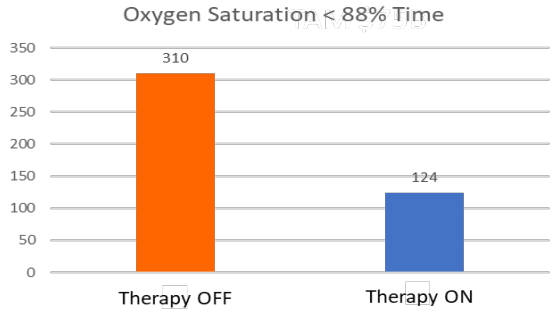
**869** with WhisperSom® Therapy ON - (blue dots)
**765** with WhisperSom® Therapy OFF - (orange dots)

**76%** improvement in respiratory recovery time with WhisperSom Therapy ON, over baseline



## Reduced Oxygen Desaturation




45% improvement over baseline

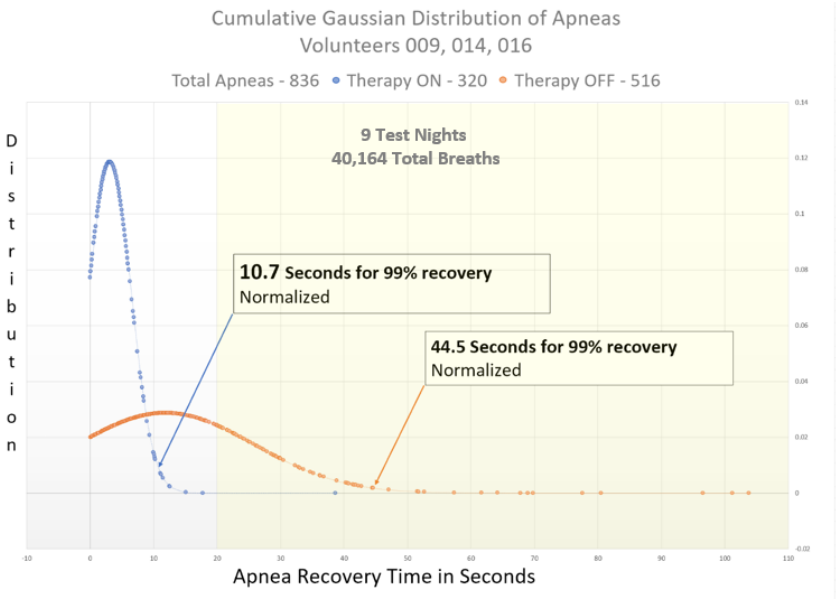
60% improvement over baseline

**A later generation PoC V6.M**, a much more sophisticated device with additional sensors yielded the following improved results

**Sensors data stream from the V6.M PoC**

**Click HERE for playback**

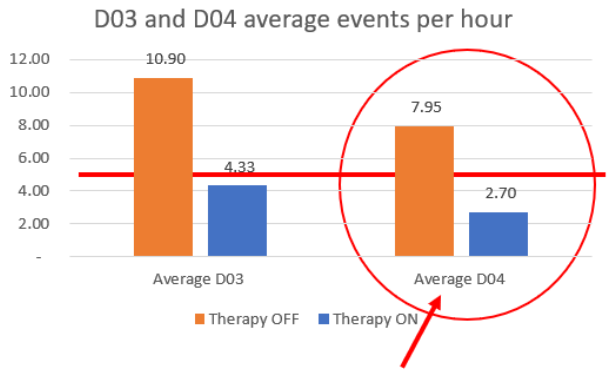
# Apnea Duration Reduced - V6 Pooled Results

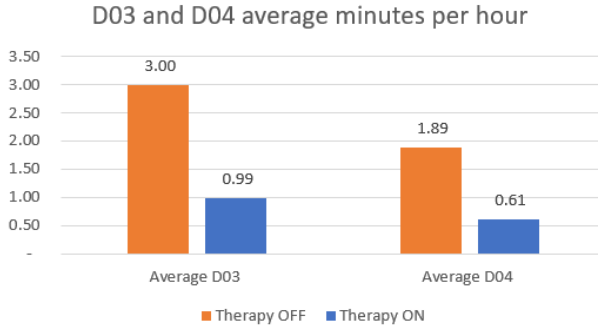



- **Clinically significant reduction in apnea duration**
- **76% improvement** based on normalized data
- **3 seconds** average recovery time with Therapy ON
- **96%** effective without waking

# Sleep Disordered Breathing Eliminated

**Significant reduction in both the number of oxygen desaturation events per hour (ODI) and the time spent in desaturation with WhisperSom Therapy ON**
**Need for CPAP eliminated**

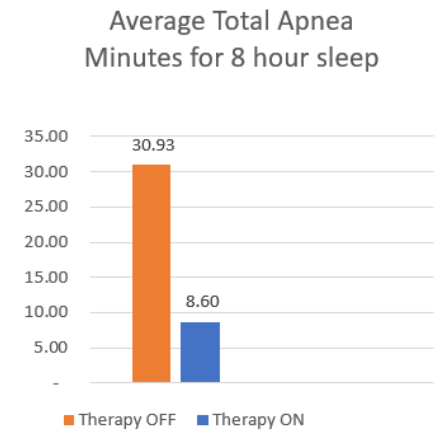


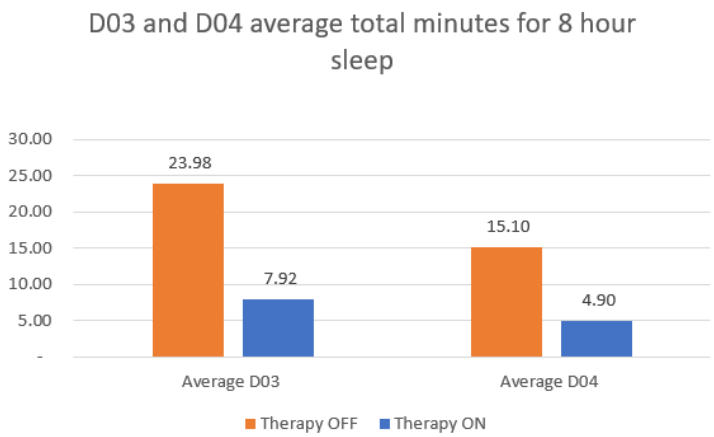

The Oxygen Desaturation Index (ODI) measures the number of times that the oxygen level in blood drops 4% or more during sleep. **ODI or AHI > 5/hr indicates Sleep Apnea and Sleep Disordered Breathing.**

# Time in Apnea and Oxygen Desaturation Reduced

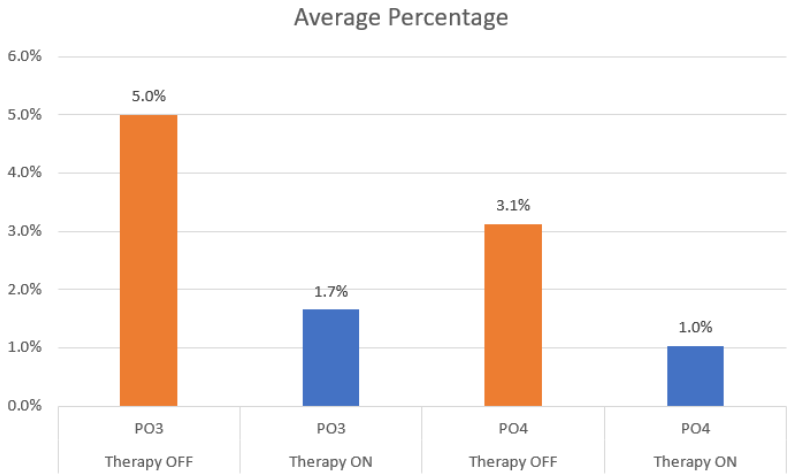
## Clinically significant reduction in time spent in apnea




## Clinically significant reduction in time spent in hypoxia




# Nocturnal Hypoxemia Reduced



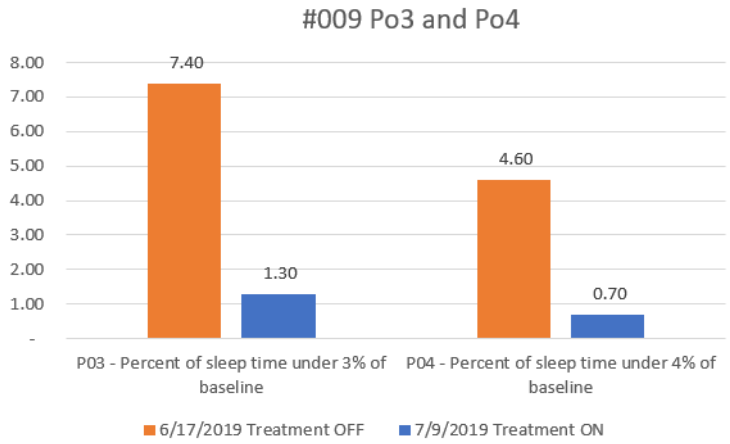

- **Clinically significant reduction in oxygen desaturation observed**
- **With WhisperSom Therapy nightly, CPAP would not be indicated or prescribed**

**PO3- Percentage of sleep time 3% under baseline**

**PO4- Percentage of sleep time 4% under baseline**

## Effective for Obstructive and Central (Mixed) Sleep Apnea

### Time spent in oxygen desaturation was significantly shortened in a test subject with moderate mixed apnea



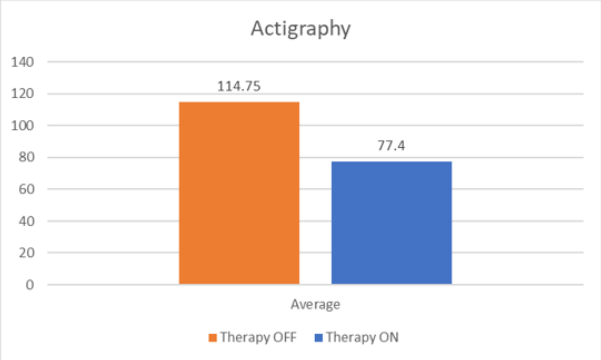

**Volunteer Age:** 58
**Sex:** Female
**BMI:** 28
**AHI:** 17.2/hr*
**oAHI:** 6.3/hr*
**cAHI:** 9.8/hr*

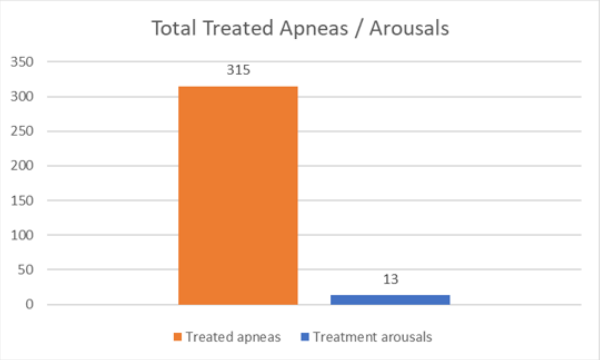
*Weinmann Home Sleep Test
AHI – apnea/hypopnea events
oAHI – obstructive apneas
cAHI – central apneas

**85%** improvement in PO3 **87%** improvement in PO4

## Sleep Quality Improved

### Movement / Arousals




**Movement during sleep is associated with arousals. Less movement while sleeping is associated with improved sleep quality. WhisperSom therapy was observed to reduce movement by 33% from baseline.**

**With WhisperSom therapy ON 96% of apneas were resolved without causing an arousal resulting in an 'awake button press' or recall the following morning.**

## Test Volunteer Demographics

| Volunteer ID # | 001 | 002 | 003 | 005 | 009 | 014 | 016 |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| **Gender** | Female | Male | Male | Male | Female | Female | Male |
| **Age** | 68 | 75 | 62 | 57 | 68 | 48 | 54 |
| **Height** | 6' 0" | 5' 11" | 5' 11" | 5' 7" | 5' 5" | 5.3" | 5.9" |
| **Weight** | 245 | 201 | 164 | 160 | 165 | 205 | 180 |
| **BMI** | 33 | 28 | 23 | 25 | 28 | 36 | 27 |
| **Shirt Collar Size** | | 16 | 16 | 15 1/2 | | 17.5 | 15.5 |
| **Diagnosed OSA** | 2004 | 2001 | 2017 | No | 2011 | 2019 | |
| **AHI (Mild, Moderate, Severe)** | Moderate /Severe | Severe | Moderate | N/A | Moderate | Mild | |
| **Respiration** | | | | | | | |
| AHI | n/a | 28.5 / h | 16.4 / h | 14.5 / h | 17.2 / h | | 26 / h |
| AI (apnea index) | n/a | 22.1 / h | 13.9 / h | 9.3 / h | 14.0 / h | | |
| HI (hypopnea index) | n/a | 6.8 / h | 2.6 / h | 5.2 / h | 3.4 / h | | |
| Longest Apnea | n/a | 55 s | 58 s | 29 s | 24 s | | |
| Mean Apnea Duration | n/a | 27s | 31 s | 15 s | 15 s | | |
| oAHI (obstructive AHI) | n/a | 20.3 h | 13.2 / h | 6.7 / h | 6.3 / h | | 14 / h |
| cAHI (central AHI) | n/a | 2.9 / h | 2.7 / h | 6.6 / h | 9.8 / h | | 11 / h |
| | | | | | | | |
| **Epworth Sleepiness Scale** | N/A | N/A | 7 | 7 | 8 | 10 | |
| | | | | | | | |
| **PAP use:** | | | | | | | |
| Hours per night | 8 | 5 | 8 | N/A | 0 | | |
| Nights per week | 7 | 1 | 7 | N/A | 0 | | |
| **PAP Type (CPAP, APAP, biPAP)** | CPAP | CPAP | N/A | N/A | CPAP | | |
| **Mandibular Advancement Device** | | No | No | No | No | No | |
| **Number Frank Awakenings per Night** | | 1 - 2 | 2 - 3 | 4 - 5 | 1 - 3 | 0-1 | |

[References begin on the following page.]

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