# EFFECT OF CPAP ON GWI SYMPTOMS

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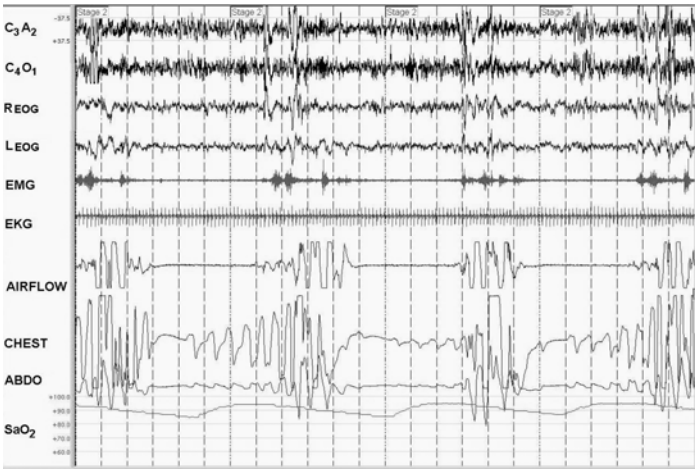
**The PI report no conflict of interest. This research funded by a DVA Career Development Award**

## Background

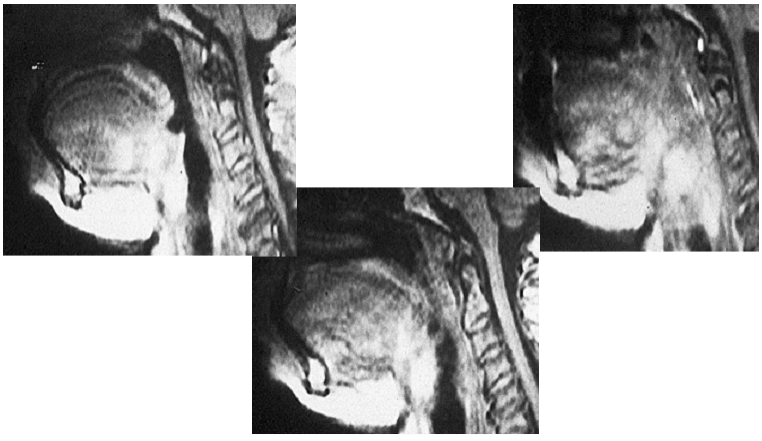
- Veterans of the first Gulf War experience the symptoms of the *Functional Somatic Syndromes* , including: headaches, widespread pain, cognitive difficulties, fatigue and gastrointestinal complaints.
- My involvement with this research began with the recognition that *Sleep Disordered Breathing* plays a role in the symptoms of the functional somatic syndromes.

## Obstructive Sleep Apnea

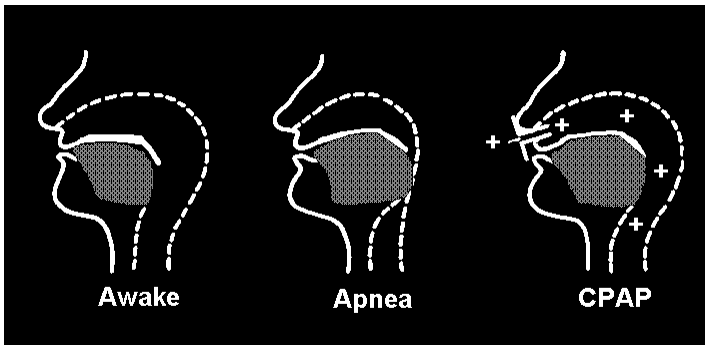



*2 minutes of sleep in severe obstructive sleep apnea*

## Pharyngeal Collapse

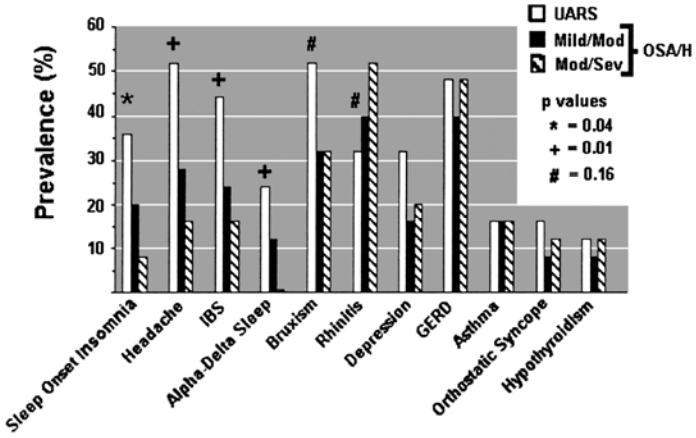


## Nasal Continuous Positive Airway Pressure (CPAP)




## Upper Airway Resistance Syndrome (UARS)

## Functional Somatic Syndromes symptoms among 25 Sleep Disordered Breathing patients

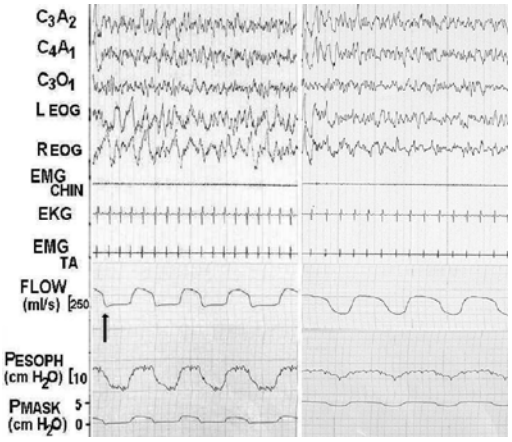



*Gold AR and associates. CHEST 2003; 123:87–95.*

## Inspiratory Airflow Dynamics During Sleep in Fibromyalgia

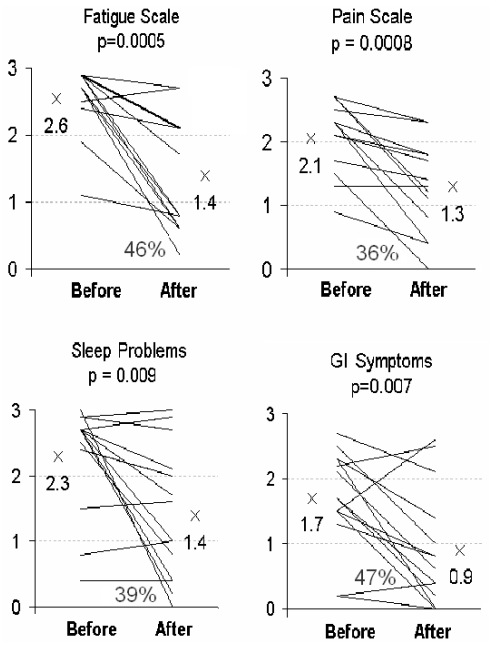
*Gold AR and associates. Sleep 2004; 27(3):459–66.*

27 of 28 female fibromyalgia patients had pharyngeal collapse with inspiratory flow limitation (IFL), defined as a continued increase in inspiratory effort with a plateau or decrease in inspiratory airflow.




*A 30 y/o non-snoring female. BMI = 19 kg/m$^2$*

The effect of 3 weeks of nasal CPAP upon the symptoms of 14 fibromyalgia patients.




*Gold AR and associates. Sleep 2004; 27(3):459–66.*

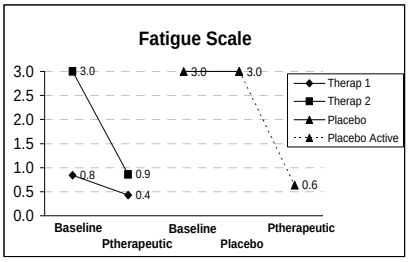
**Does pharyngeal collapse during sleep underlie the symptoms of GWI?**

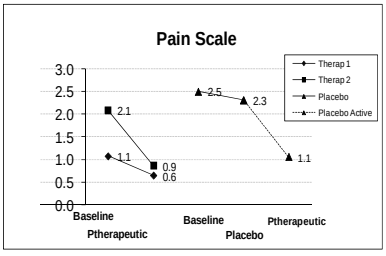
# Pharyngeal collapse with IFL in a Veteran with GWI

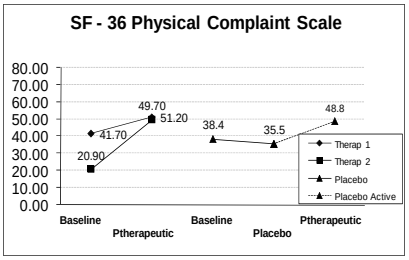
4 veterans with GWI studied, 3 had UARS and one had OSA.

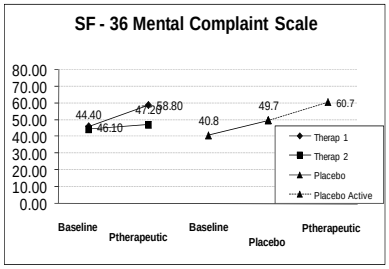

The arrows mark the start of pharyngeal collapse with IFL

# Effect of 3 weeks of nasal CPAP on 3 GWI veterans



## Career Development Award

***Hypothesis*** :

GWI veterans have Inspiratory Flow Limitation (IFL) during sleep, its correction will result in an improvement of sleep complaints and other functional symptoms.

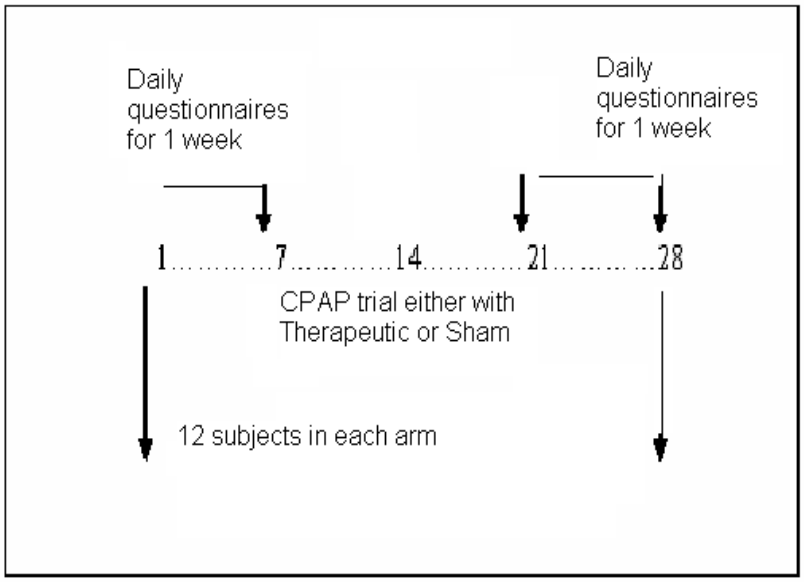
***Objectives*** : Demonstrate that :

1. GWI veterans have increased IFL during sleep compared to asymptomatic Gulf War veterans (cross sectional study).
2. Relief of IFL with CPAP results in improvement of GWI patient's symptoms (longitudinal study).

## Study Protocol

1. Initial enrollment and verification of GWI status.
2. First standard polysomnogram (PSG) to document IFL and obtain baseline parameters.
3. Second PSG with supra - glottic pressure catheter and pneumotachograph to measure effort & flow / CPAP titration.
4. Randomization to receive either therapeutic CPAP or sham for 3 weeks (compliance monitored by software in the CPAP units).
5. Third PSG after 3 weeks on their assigned treatment.

## CPAP Trial and Patient Reported Outcomes




## Patient-Reported Outcomes

- Questionnaires administered at baseline and during the third week on assigned treatment:

1. Daily **cognitive VAS** to evaluate ability "to think" "to concentrate" and "memory".
2. **FSS** to measure fatigue over one week.
3. Daily **pain VAS**.
4. **Pittsburgh Sleep Quality Index (PSQI)** to measure sleep quality over one week.
5. **SF36** to measure general and mental health.

## Recruitment / Inclusion Criteria

By advertisement, participants must have been deployed to the Persian Gulf between 8/90 and 8/91 and have the following 3 symptoms beginning after 8/90, lasting at least 6 months and meeting the clinical threshold of validated instruments:

1. **Fatigue** that limits usual activity measured by **Fatigue Severity Scale** (**FSS**): assessing impact of fatigue on daily activity.
2. **Musculoskeletal pain** involving 2 or more regions of the body measured by visual analogue scale with increasing pain recorded as 0-10.
3. **Cognitive symptoms** (memory, concentration, or attention difficulties) measured by **Cognitive Failure Questionnaire** assessing frequency of difficulties with memory, attention, action and perception.

All **3** symptoms must be unexplained by any clearly defined organic illness.

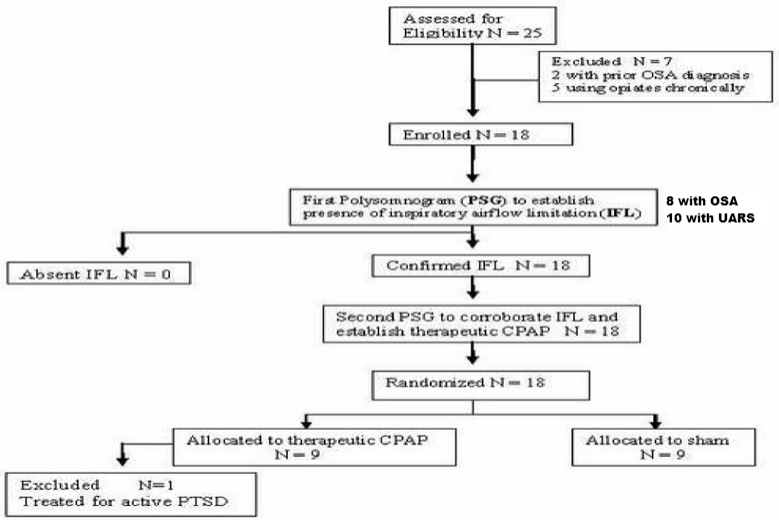
Sleep complaints were not part of the inclusion criteria to avoid a sampling bias.

## Exclusion Criteria

1. Alcoholism:
   screened by Rapid Alcohol Problem Screen.
2. *Uncontrolled* Depression:
   screened by Beck Depression Inventory.
3. *Uncontrolled* PTSD:
   screened by PTSD check list.
4. Current opiate use.

To facilitate matching with healthy controls (in the cross-sectional arm of the study), all subjects were male.

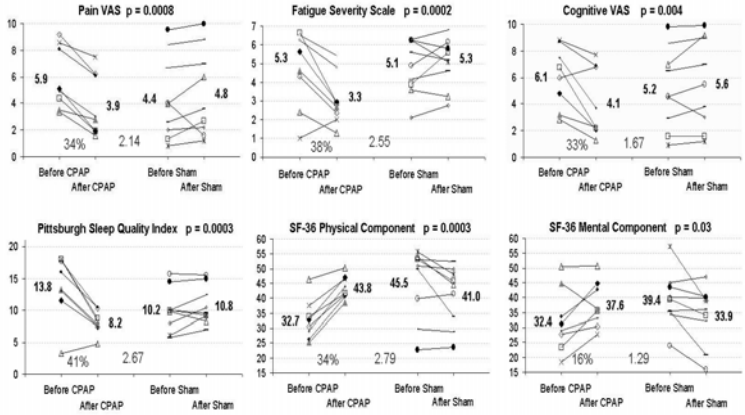
# Flow Chart for Participants




# Baseline Patient-Reported Data

| | Therapeutic CPAP (N=8) mean ± SD | Sham CPAP (N=9) mean ± SD | P-Value |
|---|---|---|---|
| Pain VAS | 5.9 ± 2.4 | 4.4 ± 3.1 | 0.28 |
| FSS | 5.3 ± 1.5 | 5.1 ± 1.1 | 0.74 |
| Cognitive VAS | 6.1 ± 2.3 | 5.2 ± 3.1 | 0.50 |
| PSQI | 13.8 ± 5.0 | 10.2 ± 3.5 | 0.11 |
| SF-36 Physical | 32.7 ± 6.9 | 45.5 ± 12.0 | 0.02 |
| SF-36 Mental | 32.4 ± 10.6 | 39.4± 9.1 | 0.16 |

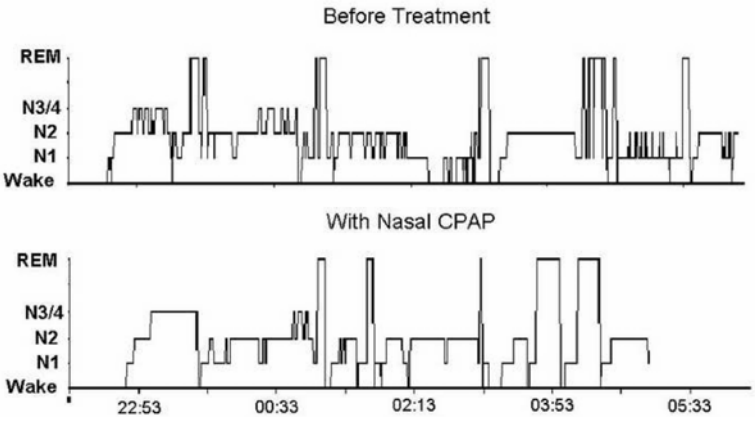
# The Effect of Treatment on Patient-Reported Outcomes



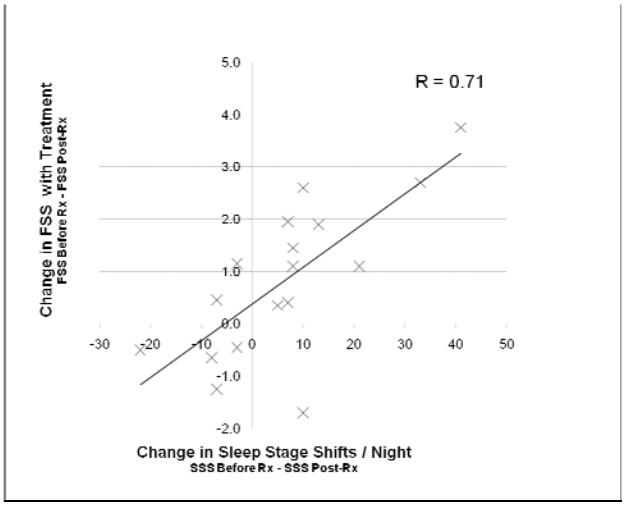

# Post-Treatment Polysomnographic Data

| Polysomnographic Parameter | | Therapeutic CPAP mean ± SD | Sham CPAP mean ± SD | p value |
|---|---|---|---|---|
| **AHI** (events/hr) | before | 22.7 ± 31.0 | 17.5 ± 20.4 | **p = 0.0009** |
| | after | 0.5 ± 0.7 | 11.1 ± 7.0 | |
| **Sleep Stage Shifts** | before | 43.9 ± 15.8 | 36.0 ± 7.0 | **p = 0.002** |
| | after | 26.3 ± 5.7 | 39.1 ± 9.4 | |
| **Slp Stg Shift Idx** | before | 6.6 ± 2.6 | 8.2 ± 4.3 | **p = 0.026** |
| | after | 4.4 ± 0.8 | 7.5 ± 3.0 | |

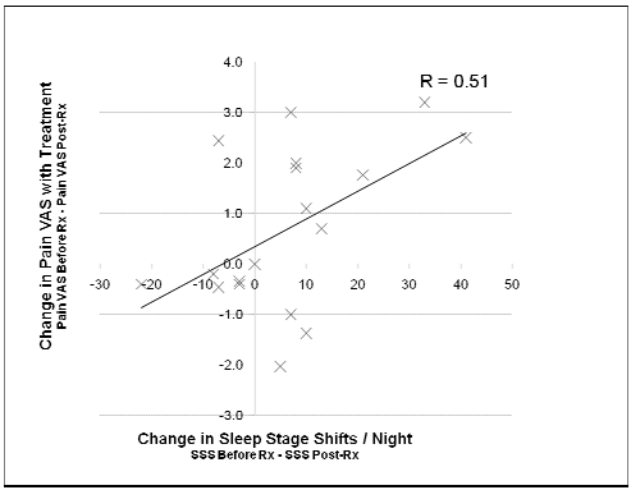
# THE EFFECT OF NASAL CPAP UPON SLEEP STAGE SHIFTS




# Correlation of the Change in SSS with the Change in Fatigue



## Correlation of the Change in SSS with the Change in Pain




## CONCLUSIONS

1. Our findings in this pilot study suggest that pharyngeal collapse during sleep is common among veterans with GWI, and contributes to their symptoms.

2. These findings are similar to the previous findings among fibromyalgia patients.

## ACKNOWLEDGEMENT

**CDA Mentoring Committee**:
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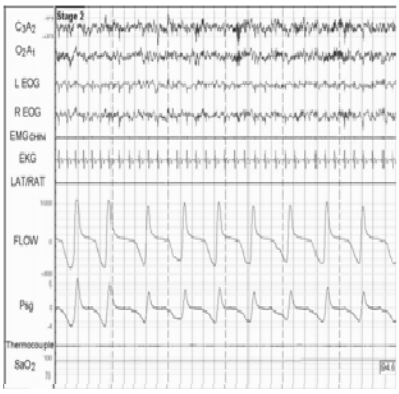
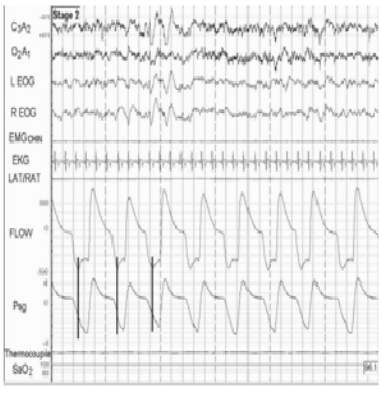
Dr. Norman Edelman
Dr. Joan Broderick

Respironics Inc. supplied the hardware and compliance software CPAP and sham units

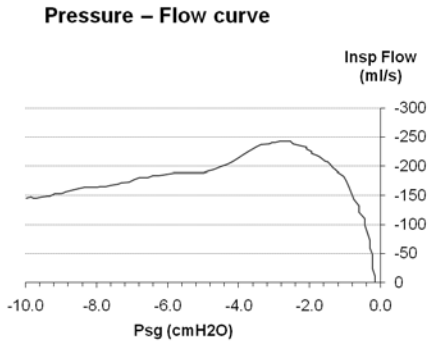



**Control**

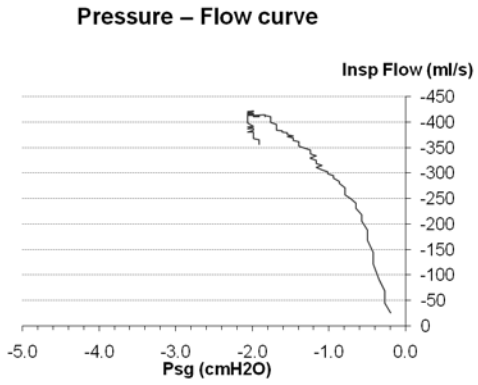



**GWI Participant**

# FLOW LIMITED BREATH




# FLOW NON LIMITED BREATH



| | Age years | BMI kg/m² | % flow-Limited |
|---|---|---|---|
| 1 | 43 | 24 | 100 |
| 2 | 37 | 26 | 100 |
| 3 | 45 | 27 | 83 |
| 4 | 43 | 29 | 89 |
| 5 | 41 | 30 | 100 |
| 6 | 41 | 30 | 97 |
| 7 | 43 | 30 | 92 |
| 8 | 47 | 32 | 100 |
| 9 | 40 | 32 | 98 |
| 10 | 39 | 33 | 89 |
| 11 | 45 | 33 | 97 |
| 12 | 38 | 33 | 100 |
| 13 | 46 | 33 | 94 |
| 14 | 44 | 34 | 100 |
| 15 | 37 | 34 | 100 |
| 16 | 42 | 34 | 100 |
| 17 | 50 | 35 | 100 |
| 18 | 41 | 36 | 94 |
| **Mean** | **42** | **31** | **96** |
| **SD** | **4** | **3** | **5** |

**GWI**

| | Age years | BMI kg/m² | % flow-Limited |
|---|---|---|---|
| 1 | 47 | 22 | 65 |
| 2 | 41 | 27 | 0 |
| 3 | 34 | 30 | 13 |
| 4 | 39 | 31 | 0 |
| 5 | 46 | 33 | 44 |
| 6 | 33 | 33 | 32 |
| 7 | 37 | 36 | 47 |
| 8 | 38 | 36 | 65 |
| **Mean** | **39** | **31** | **33** |
| **SD** | **5** | **5** | **27** |

**GW controls**

## VOSS'S HYPOTHESIS

- Sleep stage shifts protect an organism from threats
  - Predators have more continuous sleep than their prey
  - Monkeys in captivity sleep longer, deeper, with fewer interruptions and with more REM sleep than when they sleep in the wild
  - Humans have increased sleep stage shifts during their first night of sleep in a new environment (*the first night effect*)
- An organism sleeping under stress adapts by increasing its sleep stage shifts

*Voss U. Functions of sleep architecture and the concept of protective fields. Reviews in the Neurosciences 15: 33-46 (2004)*

Stress of War

↓

**Activation of Hypothalamic Pituitary Adrenal axis:**

1. Increased secretion of stress hormones

2. Increase sympathetic tone

↓

**Neural Sensitization**

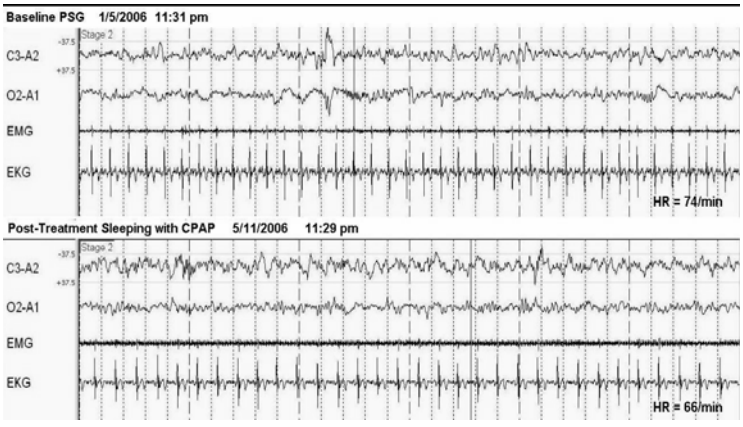
**Pharyngeal Collapse during Sleep as Stressor** ← **Pharyngeal Collapse during Sleep in Asymptomatic Soldier**

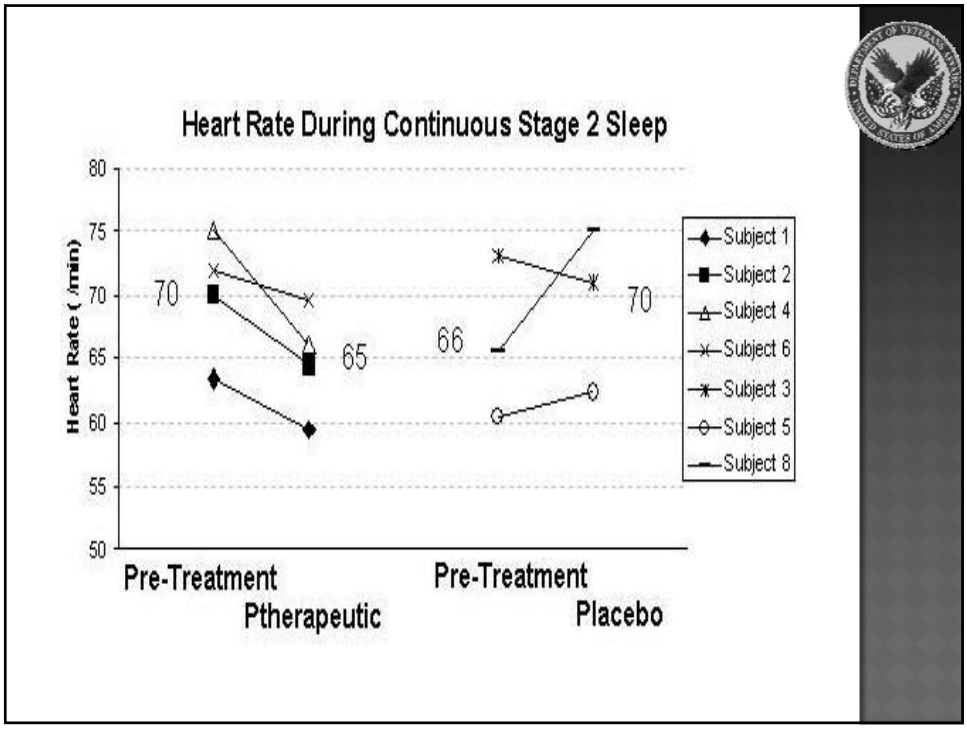
↓

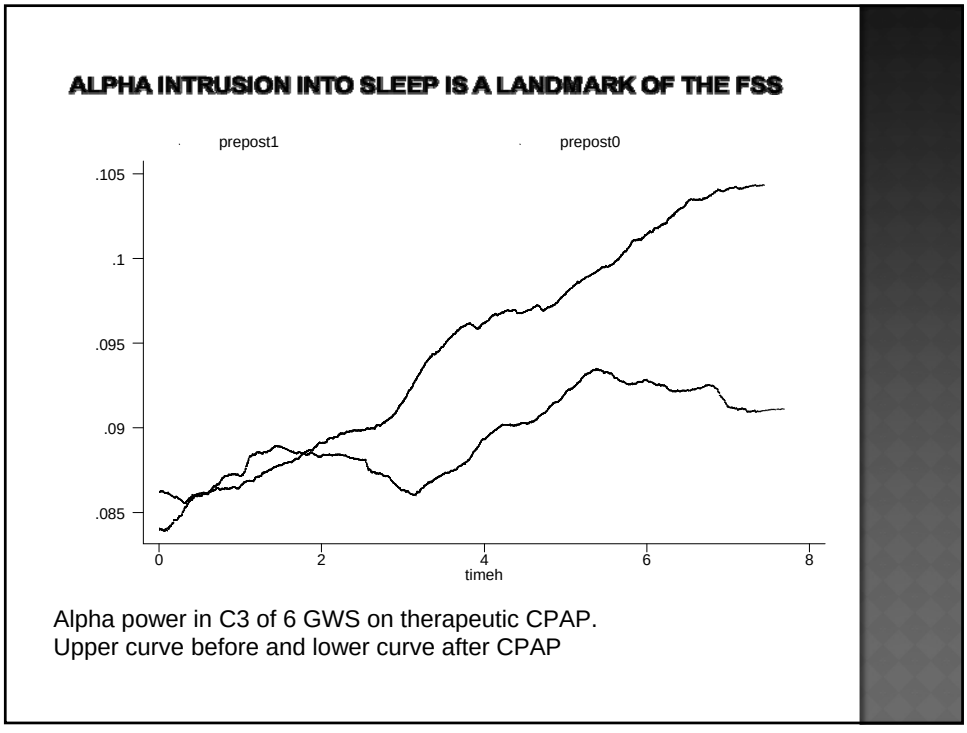
**Activation of Hypothalamic Pituatary Adrenal axis**

1. Bell IR, Baldwin CM, Fernandez M, Schwartz GE. Neural sensitization model for multiple chemical sensitivity: overview of theory and empirical evidence. Toxicol Ind Health 1999;15:295-304.
2. Fiedler N, Giardino N, Natelson B, et al. Responses to controlled diesel vapor exposure among chemically sensitive Gulf War veterans. Psychosom Med 2004;66:588-98.

# HR DURING STAGE 2






Alpha power in C3 of 6 GWS on therapeutic CPAP.
Upper curve before and lower curve after CPAP

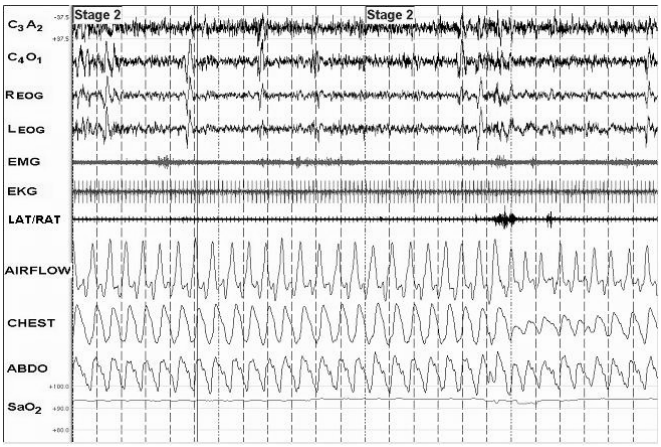
# ANTHROPOMETRIC AND SLEEP DATA

| Participant | Age | BMI | Snoring | AHI | RERA/hr | P therapeutic | Assignment |
|---|---|---|---|---|---|---|---|
| 1 | 46 | 33 | + | 9 | 6 | 7 | Sham |
| 2 | 43 | 24 | - | 10 | 25 | 7 | Sham |
| 3 | 41 | 30 | - | 10 | 37 | 11 | Sham |
| 4 | 42 | 34 | + | 60 | 11 | 10 | Sham |
| 5 | 44 | 34 | + | 45 | 2 | 8 | Sham |
| 6 | 45 | 33 | - | 2 | 9 | 7 | Sham |
| 7 | 47 | 32 | + | 8 | 7 | 8 | Sham |
| 8 | 41 | 30 | - | 5 | 11 | 9 | Sham |
| 9 | 37 | 26 | - | 9 | 15 | 9 | Sham |
| 10 | 39 | 33 | + | 7 | 19 | 11 | Active |
| 11 | 37 | 34 | + | 47 | 27 | 13 | Active |
| 12 | 50 | 35 | + | 91 | 14 | 12 | Active |
| 13 | 41 | 36 | + | 10 | 29 | 10 | Active |
| 14 | 43 | 29 | - | 10 | 13 | 7 | Active |
| 15 | 43 | 30 | - | 5 | 23 | 9 | Active |
| 16 | 40 | 32 | + | 9 | 4 | 8 | Active |
| 17 | 45 | 27 | ? | 6 | 8 | 9 | Active |
| 18 | 38 | 33 | - | 3 | 7 | 9 | Active |
| **Mean + SD** | **42 ± 4** | **31 ± 3** | | **19 ± 25** | **15 ± 10** | **9 ± 2** | |

# Post treatment symptoms

| Questionnaire | Therapeutic CPAP (N=8) mean ± SD | Sham CPAP (N=9) mean ± SD | Correlation with SSS (p-value) |
|---|---|---|---|
| **Pain VAS Post** | **3.9 ± 2.3** | **4.8 ± 3.3** | **0.51 (0.037)** |
| **Change from Baseline** | **-2.0 ± 0.9** | **0.4 ± 1.2** | |
| | | | |
| **FSS Post** | **3.3 ± 1.3** | **5.3 ± 1.1** | **0.71 (0.002)** |
| **Change from Baseline** | **-2.1 ± 0.9** | **0.2 ± 1.0** | |
| | | | |
| **Cognitive VAS Post** | **4.1 ± 2.6** | **5.6 ± 3.4** | **0.64 (0.006)** |
| **Change from Baseline** | **-2.0 ± 1.7** | **0.4 ± 1.0** | |
| | | | |
| **PSQI Post** | **8.2 ± 1.8** | **10.8 ± 3.2** | **0.59 (0.016)** |
| **Change from Baseline** | **-5.7 ± 3.5** | **0.6 ± 1.7** | |
| | | | |
| **SF-36 Physical Post** | **43.8 ± 4.0** | **41.0 ± 10.0** | **-0.41 (0.104)** |
| **Change from Baseline** | **11.1 ± 3.9** | **-4.5 ± 5.9** | |
| | | | |
| **SF-36 Mental Post** | **37.6 ± 7.8** | **33.9 ± 9.9** | **-0.58 (0.015)** |
| **Change from Baseline** | **5.3 ± 7.3** | **-5.5 ± 7.0** | |

# Upper Airway Resistance Syndrome (UARS)




*2 minutes of sleep in upper airway resistance syndrome*

# 30 seconds of UARS