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Master of Science Degree

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Assessment of the Oxygen Desaturation Index during Treatment of Obstructive Sleep Apnea by Limited Mandibular Advancement

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Advanced Education in General Dentistry Program, Fort Bragg, NC

TABLE OF CONTENTS

ABSTRACT

Study Objectives: Oral appliance therapy (OAT) has gained increasing recognition as a treatment of obstructive sleep apnea (OSA) in holding the mandible to in anterior position. Currently, appliances are titrated based on patient's reports of improvement in symptoms with reduction in snoring and daytime sleepiness. Oxygen Desaturation Index (ODI) has the potential to provide objective insight into the therapeutic effect of incremental advancement in oral appliance therapy.

Methods: Participants were identified through electronic health record as having undergone a sleep study, diagnosed with OSA, and referred for OAT. Participants were fitted for oral appliances in comfortable protruded positions and were assessed for improvement of ODI compared to baseline values. Means and associated standard deviations (SD) were used to summarize continuous data.

Results: A total of 5 individuals were included in the analyses. Means and associated standard deviations (SD) were used to summarize continuous data. Numerically, both ODI minimal SpO_2 improved with mandibular advancement. Average ODI improvement over titration was -13% (SD 5%, Range -8% to -21%).

Conclusion: Oxygen Desaturation Index (ODI) collected periodically during the oral appliance titration has the potential to provide objective measure of treatment efficacy of obstructive sleep apnea in the military population. Further research is needed to validate the improvement in ODI to reduction in AHI with oral appliance therapy.

INTRODUCTION

Obstructive Sleep Apnea (OSA) is a chronic condition characterized by repetitive partial (hypopnea) or complete (apnea) collapse of the upper airway during sleep. These repetitive events of decreased airflow result in episodic oxygen hemoglobin desaturations. The burden of this chronic condition and lack of sufficient sleep includes increased risk of cardiovascular morbidity, motor vehicle crashes, occupational accidents as well as all-cause mortality.[1,2] OSA is a major sleep disorder that has an estimated prevalence of 24% of men and 9% of women.[13] OSA is a growing health concern in civilian and military populations. The incidence of OSA diagnosis in the active component of the US military was 3.3-fold higher in 2015 compared to 2004.[13] Much of this increase can be attributed to more completeness of evaluations as well as an increase to access of sleep specialty clinics. As our capabilities to diagnose OSA increase, it is imperative to meet those needs with predictable therapies.

While Continuous Positive Airway Pressure (CPAP) remains the gold standard in treatment of OSA, oral appliance therapy (OAT) has gained increasing recognition as an alternative for patients with mild and moderate OSA conditions. Oral appliance therapy holds the mandible in an anterior and inferior position. This protrusion of the mandible passively advances attached soft tissue to increase upper airway patency, specifically the lateral dimension of the velopharynx.[3]

It was traditionally believed that greater advancement would provide a greater therapeutic effect. More recent studies have demonstrated that mandibular advancements greater than 50% of the patient's protrusive range did not significantly influence the success rate of treatment.[4] Another study that remotely controlled the advancement of the mandible during a sleep study demonstrated therapeutic mandibular advancement (AHI <10 and 50% reduction from baseline) was achieved with as little 6% of protrusive range with the median being 68% of protrusive range.[5]

Currently, custom and adjustable oral appliances provide this low level of advancement. The amount of mandibular advancement is often increased based on improvement in symtomns with reduction in snoring or daytime sleepiness reported by the patient. Proper titration of appliances using this method is a challenge in that excessive sleepiness defined as an Epworth Sleepiness Scale greater than 10 is

reported in 12% to 47% of OSA patients.[6,7,8] Furthermore, the amount of mandibular advancement in OAT is often a weighted compromise of therapeutic effect with a decrease in respiratory events versus undesirable side effects. The American Academy of Sleep Medicine guidelines recognize that development of a temporomandibular disorder (TMD) is the primary reason for interrupting OAT therapy.[4] Other undesirable side effects include sore teeth, gum problems, sore jaw muscles, excessive salivation, dry mouth and changes in occlusion.[9] Therefore, it would be clinically beneficial to objectively assess the effectiveness of oral appliance therapy in order to achieve a minmially advanced therapeutic mandibular position to reduce the risk of these side effects.

This objective measure could be obtained through nocturnal pulse oximetry with peripheral capillary oxygen saturation (SpO_2) readings. Oxygen desaturation index (ODI) utilizes this parameter by recording a 3% drop in baseline oxygen saturation that lasts at least 10 seconds to identify a hypopnea event.[10,11] To our knowledge, there is no study that observes at home nocturnal pulse oximetry and corresponding ODI values with each increment of mandibular advancement throughout treatment. This objective data combined with the subjective reports of the patient can provide the clinician valuable insight to maximize medical benefit to their patient.

The aim of this investigation is to evaluate the feasibility of recruitment and procedures in implementation of oxygen desaturation index (ODI) for assessment of incremental mandibular advancement and in US Army personnel diagnosed with obstructive sleep apnea.

MATERIALS AND METHODS

This was a prospective, single-armed cohort pilot study designed to assess Oral Appliance Therapy efficacy during titration as measured by ODI. Criteria for patient acceptance were active duty patients who have received a medical diagnosis of obstructive sleep apnea with an AHI of 10 or greater from a board-certified sleep physician, and have been referred for oral appliance therapy. Consented participants followed the following research protocol:

STEP A consisted of an initial evaluation and records in accordance with June 2017 US Army Dental Care System Clinical Practice Guideline. The clinical evaluation included mandibular range of motion measured with a George Gauge through maximum voluntary protrusion as well as full retrusion.

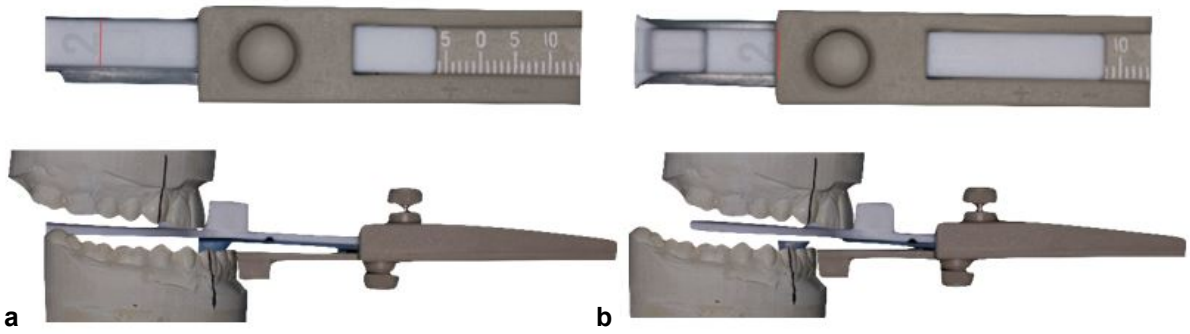


Figure 1: George gauge in a) maximum protrusion and b) full retrusion

Variables of interest included age, gender, and Body Mass Index (BMI), and neck circumference were collected. Participants completed an Epworth Sleepiness Scale (ESS) questionnaire to document and assess baseline daytime sleepiness score with a maximum score 24. At this appointment, records were made for fabrication of a interlocking style mandibular advancement sleep appliance, a multi-tray system capable of 1mm incremental advancements. Utilizing the George Gauge, the initial oral appliance position was set at approximately 50% of the participant's range of motion subject to variation based on comfortable protrusion.

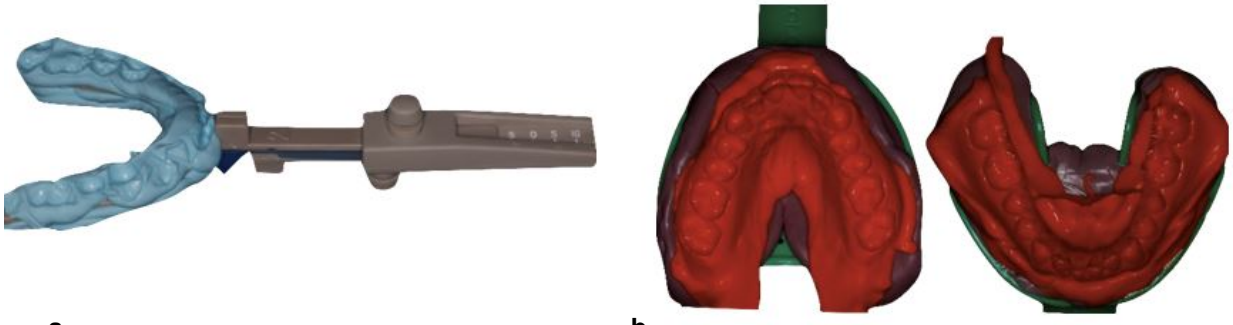


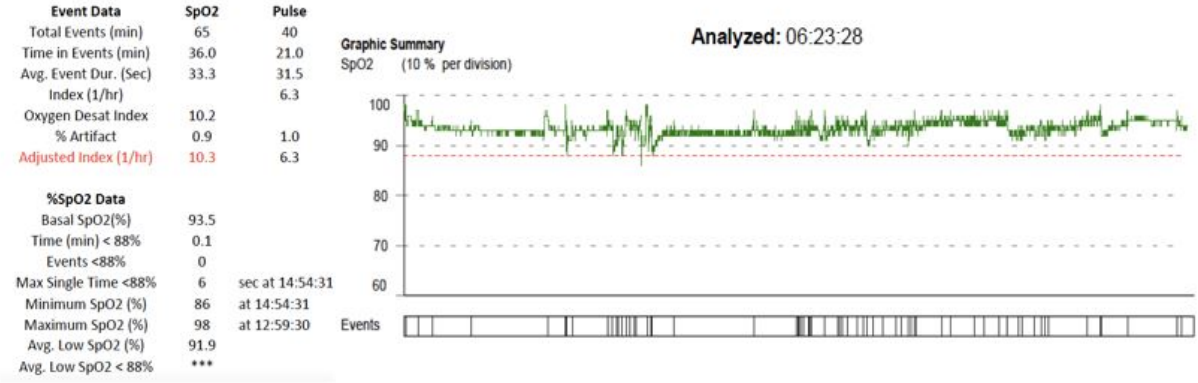
Figure 2: a) Bite registration and b) full dental arch impressions

A WristOx2 Model 3150 Home-based nocturnal pulse oximeter was provided during the visit along with instructions on its use. The participant was instructed to wear the pulse oximeter throughout the night for seven consecutive nights to collect baseline oxygen saturation data during the period in which the oral appliance was being fabricated.

Figure 3: WristOx2 Model 3150 Home-based nocturnal pulse oximeter

S

STEP B consisted of baseline ODI data collection and fitting of oral appliance. As in current practice of care, all participants returned to the dental clinic once the oral appliance was fabricated and prepared for use. At this appliance delivery appointment, the initial pulse oximetry data from the pulse oximeter was retrieved and designated as



Event Data	SpO2	Pulse
Total Events (min)	65	40
Time in Events (min)	36.0	21.0
Avg. Event Dur. (Sec)	33.3	31.5
Index (1/hr)		6.3
Oxygen Desat Index	10.2	
% Artifact	0.9	1.0
Adjusted Index (1/hr)	10.3	6.3

%SpO2 Data		
Basal SpO2(%)	93.5	
Time (min) < 88%	0.1	
Events <88%	0	
Max Single Time <88%	6	sec at 14:54:31
Minimum SpO2 (%)	86	at 14:54:31
Maximum SpO2 (%)	98	at 12:59:30
Avg. Low SpO2 (%)	91.9	
Avg. Low SpO2 < 88%	***	

Figure 4: Pulse oximetry data and graphic summary

the baseline data in the NVision data management software as seen in Figure 4. ODI was measured in accordance with the AASM recommendation of 3% decrease from basal arterial oxygen saturation lasting for 10 or more seconds.[10] The pulse oximeter was then returned to the participant for continued monitoring for seven consecutive nights with the oral appliance in place.

STEP C consisted of oral appliance titration with the participant returning to the dental clinic at a target of one to two week intervals for follow up and re-evaluation. At

each visit, the clinician evaluated for therapeutic success based on improvement in symptoms with reduction in snoring or daytime sleepiness reported by the participant completing an updated Epworth Sleepiness Scale questionnaire. Pulse oximetry data from the pulse oximeter was retrieved. If the participant did not achieve therapeutic success, the participant was fitted with the appropriate tray combination to advance their mandible an additional 1-millimeter from that position.

Figure 5: Prosomnus Iterative Advancement MicrO_2 oral appliance system

Follow-up appointments with mandibular advancement and ODI data collection continued until a therapeutic position was achieved as determined by improvement in symptoms.

STEP D consisted of a follow up sleep study. Consistent with current practice, participants underwent a titration sleep study with WAMC sleep medicine clinic to evaluate therapeutic efficacy of oral appliance therapy. The final therapeutic mandibular position was recorded to correlate with percent of mandibular range of motion.

The Regional Health Command- Atlantic (RHC-A) IRB approved this study and informed consent was obtained from all participants. Descriptive statistics were used to present the available data. Means and associated standard deviations (SD) were used to summarize continuous data. Due to the limited sample size, no inferential statistics were performed.

RESULTS

A total of 5 participants (n=5) meeting the inclusion criteria were recruited in the 12-week duration of this study. All participants were male and all completed steps A through C with exception of one participant electing to discontinue OAT titration due to successfully being fitted with a new CPAP mask that was well tolerated (subject 02). Two participants completed protocol through step D (subject 01 and 04).

Table 1: Participant Clinical Characteristics, n =5

Variable	Mean (SD)	Range
OSA (Mild/Moderate/Severe)	3/1/1	
Mandibular range of motion, mm	12 (1.5)	11-15
Demographics		
Age	38 (6)	31 – 47
Anthropometry		
Body Mass Index, kg/m^2	29.8 (3.3)	25.1 – 33.4
Neck Circumference, in	16 (1)	15 – 18
Sleep Apnea		
AHI	18.6 (13.3)	10 – 41.5
Baseline ESS	8 (5)	4 – 17

Participants averaged four nights of complete data when using pulse oximeter for seven consecutive days. All participants improved in daytime sleepiness as measured by ESS (Avg 2.2, SD 1.1, Range 1-4) and reported eliminating of snoring. Figure 6 demonstrates percent change in ODI values according to mandibular position with 0% representing baseline.

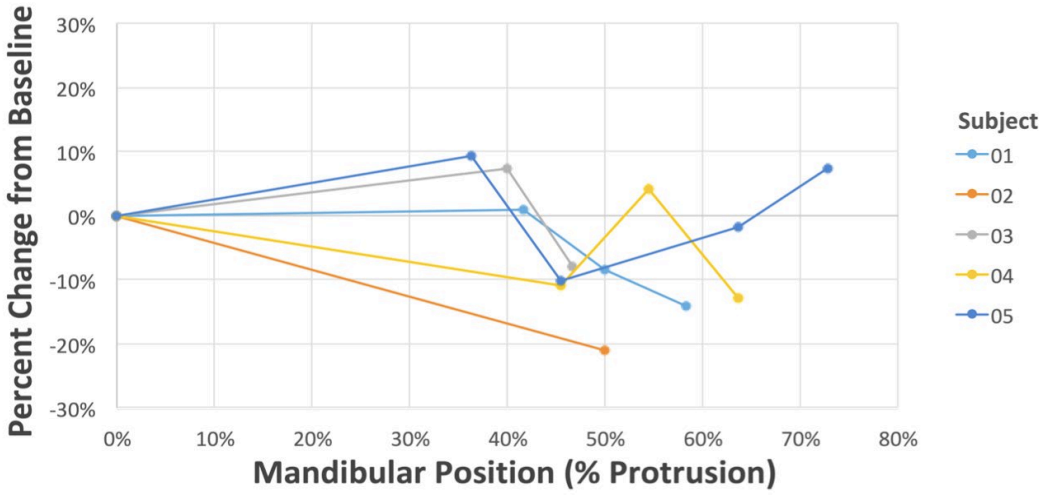


Figure 6: Change in ODI from baseline by mandibular position

Participants that completed Step D had a final AHI of 3.0 (19 baseline) at 42% mandibular protrusion and 1.9 (12 baseline) at 64% mandibular protrusion with corresponding ODI percent change of +1% and -13%, respectively. Average ODI improvement over titration was -13% (SD 5%, Range -8% to -21%). Along with ODI, Minimum SpO2 % also trended improvement with mandibular advancement. Figure 7 demonstrates minimum SpO_2% values according to mandibular position with 0% representing baseline.

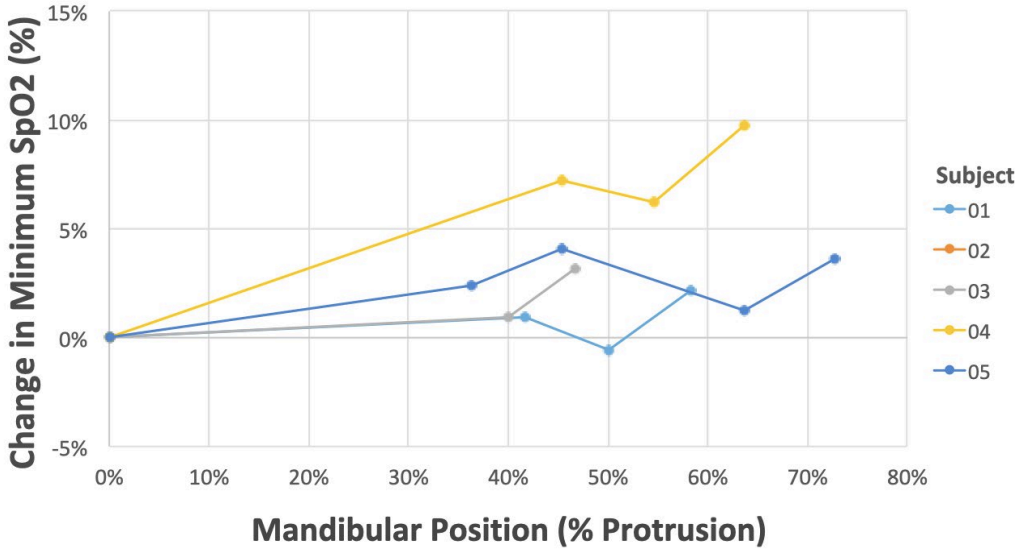


Figure 7: Change in minimum SpO_2 from baseline by mandibular protrusion.

Participants that completed Step D had a final AHI of 3.0 (19 baseline) at 42% mandibular protrusion and 1.9 (12 baseline) at 64% mandibular protrusion with corresponding minimum SpO_2 percent change of +1% and +10%, respectively. Average minimum SpO_2 percent improvement over titration was +4% (SD 4%, Range 0% to 10%).

DISCUSSION

The primary purpose of this study was to assess the feasibility of recruitment and procedures in implementation of ODI for assessment of incremental mandibular advancement and in US Army personnel diagnosed with obstructive sleep apnea. All participants enrolled were able to comply with the research protocol without adverse

events. Based on current recruitment rates and using five nocturnal pulse oximeter devices, it will take 126 weeks to collect the projected 69 participants required for inferential statistical analysis. The amount of individuals meeting inclusion criteria available for recruitment was the limiting factor of this study.

An important observation in the measured improvement in pulse oximetry values to include ODI as well as baseline SpO_2 is identifying patients that are successfully responding to OAT. In evaluating the general therapeutic response of patients using OAT, approximately one third of OSA patients will show a complete response with a treatment AHI of <5, one third will have a greater than 50% reduction in AHI although still >5 events per hour, and one third will not achieve a > 50% reduction in AHI.[14] In this study, subjects 01 and 04 had improvement in symptoms measured with ESS as well as objective improvement in pulse oximetry values. These measures provide insight into the patient successfully responding to oral appliance therapy, which were validated in subjects 01 and 04 achieving a final AHI < 5.

A strength of the present study is the prospective design. The greatest limitation is the sample size, participants were only male and the limited age range. Additionally, there was significant variation in reported pulse oximetry data each night with as great as a two-fold difference between ODI values on consecutive nights. A possible explanation for this variation could be due to the multifactorial nature of OSA.

CONCLUSION

Recruitment and procedures in implementation of ODI were successful in objectively assessing incremental mandibular advancement in US Army personnel diagnosed with OSA. All recruited individuals elected to participate in the study. Due to the small sample size of this pilot study, formal predictive conclusions in correlating ODI with the effective therapeutic position are not warranted at present. However, pulse oximetry does show promise to be an objective measure of improvement in effectiveness of oral appliance therapy. Recommendation for conducting this study on a larger scale would be to supplement ODI data with minimum SpO_2%, and to collect

additional data points for a more accurate average value in subjects exhibiting high night-to-night variation.

AUTHOR CONTRIBUTIONS

L. Stanford, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript. T. Beltran, contributed to design and data interpretation, drafted and critically revised the manuscript. R. Allred, contributed to conception, design, data acquisition and critically revised the manuscript. D. Shaha, contributed to conception, design and data acquisition.

DECLARATION OF CONFLINCTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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DEFINITIONS

Apnea Hypopnea Index (AHI): The average number of apnea or hypopnea events per hour determined through a polysomnography (PSG) sleep test to diagnose obstructive sleep apnea (OSA). Mild: $\geq$5 and <15, Moderate: $\geq$ 15 and < 30, Severe: $\geq$ 30.

Oxygen Desaturation Index (ODI): The average number of blood oxygen desaturations of 3% from baseline that lasts for at least 10 seconds per hour.

REFERENCES

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: A population health perspective. *AM J Respir Crit Med*. 2002; 165(9):1217-39.

2. Marshall NS, Wong KK, Liu PY, et al. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. *Sleep*. 2008; 31 (8): 1079-85.

3. Chan A, Sutherland K, Schwab R, Zeng B, Petocz P, Lee R, Darendeliler M, Cistulli P. The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. *Thorax*. 2010; 65: 726-32.

4. Bartolucci M, Bortolotti F, Raffaelli E, D'Antò V, Michelotti A, Bonetti A. The effectiveness of different mandibular advancement amounts in OSA patients: a systematic review and meta-regression analysis. *Sleep and Breathing*. 2016; 20(3): 911-919.

5. Remmers J, Charkhandeh S, Grosse J, et al. Remotely controlled mandibular protrusion during sleep predicts therapeutic success with oral appliances in patients with obstructive sleep apnea. *Sleep*. 2013;36(10):1517-1525A. Published 2013 Oct 1. doi:10.5665/sleep.3048

6. Fietze I, Laharnar N, Obst A, et al. Prevalence and association analysis of obstructive sleep apnea with gender and age differences - Results of SHIP-Trend. *J Sleep Res*. 2019;28(5):e12770. doi:10.1111/jsr.12770

7. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med*. 2015;3(4):310-318. doi:10.1016/S2213-2600(15)00043-0

8. Kapur VK, Baldwin CM, Resnick HE, Gottlieb DJ, Nieto FJ. Sleepiness in patients with moderate to severe sleep-disordered breathing. *Sleep*. 2005;28(4):472-477.

9. Ramar K, Dort L, Katz S, Lettieri C, Harrod C, Thomas S, Chervin R. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. *J Clin Sleep Med*. 2015; 11(7), 773-827. doi:10.1093/sleep/28.4.472

10. Dumitrache-Rujinski S, Calcaianu G, Zaharia D, Toma CL, Bogan M. The Role of Overnight Pulse-Oximetry in Recognition of Obstructive Sleep Apnea syndrome in Morbidly Obese and Non Obese Patients. *Journal of Clinical Medicine*. 2013; 11(3), 237-242.

11. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American

Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;8(5):597-619. Published 2012 Oct 15. doi:10.5664/jcsm.2172

12. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993; 328 (17): 1230-5.

13. Rogers A, Stahlmn S, Hun D. Obstructive Sleep Apnea and Associated Attrition, Active Component, U.S. Armed Forces, January 2004-May 2016. *Medical Surveillance Monthly Report*. 2016; 23(10): 2-11.

14. Sutherland K, Phillips C, Cistulli P. Efficacy versus Effectiveness in the Treatment of Obstructive Sleep Apnea: CPAP and Oral Appliance. *Journal of Dental Sleep Medicine.* 2015; 2(4): 175-181.

ATTACHMENTS

NVision Baseline Data Example

Nvision Data Example.pdf

Model 3150 Wrist Ox2 Pulse Oximeter Operator’s Manual

3150 Operator's Manual.pdf

nVision Software User Guide

nVision User Guide.pdf