

Apnea Risk Evaluation System (ARES): Summary of Scientific Evidence

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ARES Validation - Manuscripts

1. **Description and Validation of the Apnea Risk Evaluation System: A Novel Method to Diagnose Sleep Apnea-Hypopnea in the Home.** Westbrook PR, Levendowski DJ, Cvetinovic M, et al. *Chest* 2005 128:2166-2175.
ARES had a 0.96 correlation with PSG when recorded concurrently and 0.88 for in-home ARES vs. PSG. ARES demonstrated a sensitivity of 97.4 and a specificity of 85.6 in 284 subjects with data acquired concurrently with PSG, and a sensitivity of 91.5 and a specificity of 85.7 in 187 subjects when comparing in-home recordings to PSG. 32 of 35 of the in-home misclassifications were attributed to differences in the percent time supine. Twenty-percent of the subjects included in this study were healthy controls. The failure rate for the in-home comparisons was only 2%.
2. **Validation of a Self-Applied Unattended Monitor for Sleep Disordered Breathing,** Ayappa I, Norman R, Seelall V, Rapoport D. *J Clin Sleep Med* 2008 4(1):26-37.
The correlations between the ARES and PSG for simultaneously acquired recordings was 0.96 using an apnea/hypopnea index with a 4% desaturation (AHI-4%), and 0.93 using a respiratory disturbance index based on Chicago criteria (RDI). The diagnostic sensitivity of in-lab ARES RDI was 0.95 and the specificity was 0.94; comparable measures to PSG for the in-home ARES RDI values were 0.85 and 0.91.
3. **The Impact of Obstructive Sleep Apnea Variability Measured In-Lab versus In-home on Sample Size Calculations.** Levendowski D, Steward D, Woodson BT, et al. *Intl Archive Medicine* 2009 2:2
Thirty-six patients were tested by PSG with a 4-month test-retest interval and by ARES with a 6-month interval. The test-retest ARES apnea/hypopnea index (AHI) and apnea index (AI) were more highly correlated (0.65 and 0.68, respectively) as compared to PSG (0.56 and 0.58). The PSG AHI and AI showed a substantial bias toward increased severity at retest (8 and 6 events/hour), while there was no bias for ARES. Test-retest correlations in the percent time supine were 0.72 for ARES and 0.43 for PSG. The sample size required to power a study using PSG would be more than a 2 order of magnitude larger than ARES.
4. **Assessment of the test-retest reliability of laboratory polysomnography.** Levendowski DJ, Zack N, Rao S, et al. *Sleep Breath* 2009 13(2):163-167.
The correlations between PSG results from 20 patients with a 1-month retest interval without a treatment intervention for the AHI was only 0.44, and 0.52 for sleep efficiency, 0.69 for the supine AHI, 0.25 for the non-supine AHI and 0.70 for the percent time supine. There was a bias toward increased AHI severity when comparing the PSG at test vs. retest of 7 event/hour.
5. **Validation of Forehead Venous Pressure as a Measure of Respiratory Effort for the Diagnosis of Sleep Apnea,** Popovic D, King C, Guerrero M, et al. *J Clin Mon Comp* 2009 23(1):1-10.
Fifteen patients were studied during PSG with an esophageal balloon, respiratory effort belts and the FVP (from ARES). Kappa values showed all measures provided good overall agreement comparing obstructive apneas, hypopneas, flow limitation ventilation change and central/mixed events. Comparisons of inter-rater and intra-rater comparisons show that FVP is equivalent to effort belts in detecting events needed to provide the differential diagnoses of sleep disordered breathing.

6. **Impact of Clinical Assessment on Use of Data from Unattended Limited Monitoring as Opposed to Full-in lab PSG in Sleep Disordered Breathing.** Masdeu MJ, Ayappa I, Hwang D. *J Clin Sleep Med* 2010;6:51-58.

When presented with clinical data along with sleep data, sleep trained clinicians showed similar agreement on diagnoses and treatment recommendations whether the data was from full polysomnography or a portable ARES test. Differences in diagnosis and treatment recommendations appeared driven by SDB severity; good agreement was found in patients with high SDB indices and poorer agreement in patients with low SDB indices, regardless of the method by which the index was obtained.

7. **Assessment of Obstructive Sleep Apnea Risk and Severity in Truck Drivers: Validation of a Screening Questionnaire.** Levendowski D, Olmstead R, Popovic D et al. *Sleep Diagnosis and Therapy* 2007 2(2):20-26.

The sensitivity and specificity of the ARES Screener in predicting who will have an AHI > 5 was 0.94 and 0.79 in 850 subjects. 77% of the transportation workers predicted by ARES Questionnaire to have severe OSA had an AHI > 20.

8. **Prevalence of probable Obstructive Sleep Apnea Risk and Severity in a Population of Dental Patients.** Levendowski DJ, Morgan T, Montague J et al. *Sleep Breath* 2008 12(4):303-309.

Of 331 dental patients studied, 67% of the men and 28% of women were predicted to have an AHI > 5, 96% were confirmed to have sleep disordered breathing > 5 events/hour. 70% of patients predicted to have moderate or severe OSA by ARES Screener were found to have an AHI > 20.

9. **Validation study of a portable monitoring device for identifying OSA in a symptomatic patient population.** To Kw, Chan WC, Chan TO et al. *Respirology* 2009 14(2):270-275.

There were 141 patients who wore the ARES while undergoing a PSG study. Results of AHI from the ARES study were presented in the order of different scoring criteria--4% oxygen desaturation alone, obstructive events with 1% desaturation plus surrogate arousal criteria. The sensitivity was 0.84 (95% confidence interval (CI): 0.77-0.90) and 0.97 (95% CI: 0.94-0.99), respectively. The specificity was 1, and 0.63 (95% CI: 0.55-0.71), respectively. The receiver operating curve had an area of 0.96 and 0.98, respectively. The ARES device has reasonable sensitivity and specificity for diagnosing severe OSAS in symptomatic Chinese patients.

10. **Comparison of Two Limited-Channel Systems for the Diagnosis of Sleep Apnea/Hypopnea in the Home.** Westbrook PR, Dickel MJ, Nicholson D, Levendowski D, Zavara T, Simenovic V, Dalati R. *Sleep Diagnosis and Therapy* 2007 2(1):33-37.

The Kappa coefficients between the ARES vs. PSG were 0.88 for the ARES, and 0.69 and 0.66 for the NovaSom 4% and 2% respectively. The ARES provided greater sensitivity than the NovaSom 4% or 2% (100% vs. 78.6% and 85.7%, respectively). The NovaSom 4% provided better specificity than the ARES or NovaSom 2% (100% vs. 83.3% and 83.3% respectively). The positive predictive values of the ARES and NovaSom 4% and 2% were essentially equivalent (93.3%, 100% and 93.3%, respectively) while the ARES provided substantially better negative predictive values (100% vs. 66.7% and 71.4%, respectively).

- 11. Prevalence of Undiagnosed Obstructive Sleep Apnea Among Adult Surgical Patients in an Academic Medical Center.** Finkel KJ, Searleman AC, Tymkew H, et al. *Sleep Medicine*, 2009 10:753-758.
A large population of adult surgical patients (n=2877) were screened with the ARES questionnaire. The prevalence of OSA in 207 patients who screened at high risk and completed an ARES in-home sleep study was 82.1%. The estimated prevalence of OSA in the surgical population was 22% with over 70% undiagnosed.
- 12. Comparing the Berlin and ARES Questionnaires to Identify Patients with Obstructive Sleep Apnea in a Dental Setting.** Enciso R, Clark GT. *Sleep Breath* 2010, *in-press*.
Fifty-three moderate to severe OSA patients and 31 controls completed both the Berlin and ARES questionnaires and subsequently compared an ARES sleep study. Subjects predicted by ARES Questionnaire to have high risk of undiagnosed OSA were 7.9 times as likely to have OSA as subjects with low or no risk. Using a clinical cut-off AHI ≥ 10 , the ARES provided a sensitivity of 88%, a specificity of 58%, a positive predictive value (PPV) of 88% and a negative predictive value (NPV) of 58%. The Berlin provided a sensitivity of 68%, a specificity of 68%, a positive predictive value (PPV) of 88% and a negative predictive value (NPV) of 38%. The ARES questionnaire has better sensitivity, less specificity, similar PPV and better NPV than the Berlin.
- 13. Treatment Outcomes of Mandibular Advancement Devices in Positional and Non-Positional Patients.** Chung JW, Enciso R, Levendowski DJ et al. *Surg Oral med Oral Pathol Oral Radiol Endod*, 2009; *in-press*.
Forty-two positional and 30 non-positional OSA patient performed ARES sleep studies before and after treatment with a mandibular advancement device (MAD). Results showed that patients with positional OSA showed significantly greater reduction in AHI post-treatment. Age, BMI, gender and time supine were not factors associated with improved outcomes.

ARES Validation - Abstracts:

- 1. Accuracy of Automated Sleep Staging using Signals from a Single Forehead Site.** Popovic D, Ayappa I, Hauri P, et al. *Sleep* 2008 31:33.
Using actigraphy acquired from the forehead to detect sleep/wake provided an overall agreement of 91% with a sensitivity of detecting wave of 0.76. There was good agreement in estimating sleep latency, total sleep time and sleep efficiency and within clinically acceptable ranges.
- 2. Sleep/wake Classification using Head Actigraphy, Snoring and Airflow Signals.** Popovic D, Velimirovic V, Ayappa I, et al. *Sleep* 2008 32:379.
One-hundred and nine subjects wore the ARES Unicorder™ concurrent during laboratory polysomnography. The PSG records were staged for sleep according to the AASM criteria. Behavioral sleep/wake was derived using an algorithm that combined changes in actigraphy, snoring and airflow. On average there was an 85% agreement between the EEG and behavioral sleep/wake with mean Kappa scores of 0.52. The sensitivity and specificity of sleep/wake was consistent across RDI severities; the concordance between total sleep time and sleep efficiency improved when short/split-night PSG studies were excluded from analysis.

- 3. Feasibility of Portable Monitoring to Detect Obstructive Sleep Apnea In-home in Adolescents: Pilot study.** Daniel J. Levendowski, Carol L. Rosen, Timothy Zavora, et al. *Sleep* 2008 31:62.
There was a 0.96 correlation between the AHI values obtained from PSG and concurrently acquired ARES in 28 habitually snoring teens, and a 0.74 correlation between PSG and the in-home AHI values acquired with ARES. The ARES provided a sensitivity and specificity of 100% and 83% when worn concurrently during PSG using a clinical cut-offs of ≥ 2 events/hour, and 91% and 77% using a cut-off of ≥ 5 events/hr. The in-home ARES provided a sensitivity and specificity of 94% and 93% vs. PSG with a cut-off ≥ 2 events/hour and 82% and 94% using a cut-off ≥ 5 events/hour.
- 4. Impact of Age and Position on Severity of Gender-Specific Sleep Disordered Breathing.** Levendowski D, Berka C, Popovic D et al. *Sleep* 2009 32:203
A retrospective analysis of 529 males and 203 females stratified into a young (age 30-45) and old (age 55 – 70) patients, by gender differences in the percent time snoring and AHI and RDI were evaluated by and across positions were evaluated. There were no differences in neck size or BMI between gender specific groups. In males, the AHI and RDI severity increased with age across all positions. In females, the impact of age was only apparent in the increase in supine AHI and RDI severity. There was no difference in the percent time snoring between young and old males; older females snored significantly louder than younger females and equivalent to older males. This study suggests that the length of the pharyngeal airway may impact changes in OSA severity but not snoring as one ages.
- 5. Night to Night Variability in In-home Sleep Studies.** Westbrook P, Levendowski D, Zavora T, et al. *Sleep* 2007 30:184.
A study of 476 subjects with at least 4 hours of valid recording time in two separate nights acquired with the ARES Unicorder showed strong correlations in the AHI (0.90). An exponential equation used to identify clinically important differences in AHI revealed that there is substantial night to night variability in AHI in the range of 11 – 30 events/hour.
- 6. Comparison of Subjective Sleep Position Preference vs. Objective Ambulatory Data.** Rosenthal L, Dolan D. *Sleep* 2009 32:387.
Forty-nine subjects wore the ARES in-home for two nights to compare the subject's favored sleep position to an objective measure based on head position. The study confirmed that the preferred position during sleep reflected the differential time spent in the supine position during ambulatory recordings.
- 7. Timing of Changes in Oxyhemoglobin Saturation Resulting from Breath Holding.** Sasse S, Westbrook, P, Levendowski D, et al. *Sleep Medicine* 2006 7(2):261.
Co-oximetry results from arterial draws taken at 5-sec increments from 20 subjects were used to assess difference s in desaturation during 30-sec breath-holding at FRC. FRC was positively correlation with SaO2 level and negatively correlate with the maximum depth of desaturation. The percent change in SaO2 as a result of a 30-sec breath hold can be explained in part by FRC and FRC is related to BMI.

- 8. Timing of Changes in Oxyhemoglobin Saturation Resulting from Breath Holding.** Sasse S, Westbrook P, Levendowski D, et al. *Sleep Medicine* 2006 7(2):261.
Co-oximetry results from arterial draws taken at 5-sec increments from 20 subjects were used to assess differences in desaturation during 30-sec breath-holding at FRC. FRC was positively correlated with SaO₂ level and negatively correlated with the maximum depth of desaturation. The percent change in SaO₂ as a result of a 30-sec breath hold can be explained in part by FRC and FRC is related to BMI.
- 9. Predicting Effective Continuous Positive Airway Pressure (CPAP) based on Laboratory Titration and Auto-titrating CPAP.** Westbrook P, Levendowski D, Henninger D, et al. *Sleep Medicine* 2006 7(2):217.
The correlation between CPAP pressure obtained during laboratory titration vs. auto-CPAP over 30 days was only 0.65 with 21% of patients having a difference in CPAP pressure ≥ 3 cm H₂O. 96% of patients had an auto-PAP pressure within 2 cm H₂O after 3-nights vs. 30-nights. 85% of patients had a predicted CPAP pressure (derived using ARES sleep study data combined with anthropomorphic measures) within 3 cm H₂O vs. 3-nights of auto-PAP.
- 10. Impact of Clinical Assessment on the Difference Between Unattended Limited Monitoring and Full In-Lab PSG.** *Sleep*, 2008; 31:151.
Four sleep trained pulmonologists reviewed clinical history & physical information and full disclosure tracings from 85 subjects with the PSG and ARES studies reviewed > two-week apart. The goal was to assess agreement as to the primary diagnosis and treatment recommendations. The agreement between PSG and ARES-1% with a clinical cut-off of >15 was sensitivity = 80%, specificity = 92%, overall agreement for sleep disordered breathing = 86%. The overall diagnostic agreement across clinicians for PSG vs. ARES was 78%. Agreement for treatment recommendations was 75%.
- 11. Patient Preferences Comparing Use of Two Home Sleep Testing Devices.** Simmons M. *Sleep Breath* 2009;13:306.
This pilot study compared subject preferences and measurements from two well validated HST devices self-applied and worn simultaneously. Twenty subjects recruited from two dental offices were trained to apply device (A) ARES Unicorder Model 600 first and device (W) Watch-Pat Model-100 second at home just prior to sleep. Only about 50% of the subjects had a preference, and for those that did have a preference Device A was preferred for "Easiest to Apply"(3:1), Easiest to Remove"(7:1), "Comfortable During Sleep"(3:2), and "Immediate After Effects"(5:2). However Device W was preferred for "Preference of Report" (5:1). When given a choice as to which device they would "Prefer to Reuse subjects selected A (13:7), and in response to "Recommend to a Friend" A was preferred (9:4). For those indicating a preference, Device A was preferred on the average of 2:1. Device A failed in one case and device W failed in three cases. In 16 valid comparable studies there were no significant differences in total recording time, sleep time, and valid sleep time. Correlation between device A (AHI-4%) and device W (pAHI) measures validated against the Medicare AHI criteria was 0.78, however significant differences were observed (Device A AHI-4% 16 ± 3.4 vs. device W pAHI 27 ± 5.4 , p,0.01). There were also clinically important differences in Chicago criteria RDI in three cases and percent time SpO₂ below 90% in two cases.
- 12. Accuracy of Pulse Oximetry During Breath Holding.** *American Thoracic Society, San Diego, 2005*
Arterial blood was extracted at 5-sec intervals in 20 subjects during breath hold to FRC. The ARES and Nellcor forehead oximeters were more accurate than the Nonin finger oximeter in terms of the

root mean squared error and detection of the depth of desaturation vs. co-oximetry. The SaO₂ nadir point was significantly delayed using the finger oximeter relative to CoOx and forehead oximeters.

ARES – Assessing Treatment Outcomes

1. In-Home Evaluation of Efficacy and Titration of a Mandibular Advancement Device for Obstructive Sleep Apnea; Levendowski D, Morgan T, Patrickus J, et al. *Sleep Breath* 2007 11(3):139-147.

In a study of 30 patients (25 being CPAP failures) mandibular advancement devices (MAD) provided a 96% efficacy, reducing the AHI by at least 50% and in most cases reduced the AHI below 10 events/hour.

2. Impact of Time on the Treatment Efficacy of Mandibular Repositioning Devices (MRD).

Levendowski D, Morgan T, Montague J et al. *Sleep* 2009 32: 203.

Twenty-patients completed ARES sleep studies pre-treatment and at one-, two- three- and six-months subsequent to initiation of MRD therapy. Repeated ANOVA found a significant reduction in both AHI and RDI as a result of therapy, paired t-tests found no differences in the sleep disordered breathing (SDB) measures across treatment time points. No significant difference in the percent of time snoring pre- or post-treatment suggested it is not a reliable measure for assessing efficacious MRD outcomes.

3. Benefit of Mandibular Repositioning Device (MRD) Therapy in Patients with Moderate and Severe OSA. Levendowski D, Morgan T, Melzer V et al. *Sleep* 2009 32:203.

Fifty-nine patients identified with Moderate (AHI 15-29) or Severe (AHI $\geq$ 30) OSA based on an ARES in-home sleep study were retested to assess outcomes as a result of MRD therapy. Based on an AHI reduction $\geq$ 50%, 83% of the moderate and 96% of the severe OSA patients received an efficacious outcome. The percent of time SpO₂ < 90% was significantly reduced in both severity groups. Post-treatment changes in Epworth Scores, and Beck Depression and Comfort and Efficacy Indexes as well as the number of patients with normalized Epworth and Beck Depression scores resulting from therapy were significant.

4. Predicting Changes in AHI Resulting from Mandibular Repositioning Device Therapy. Levendowski D, Morgan T, Patrikus J et al. *Sleep Breath* 2009;13:308.

A comparison was made between pre- and post-treatment AHI and RDI values from 84 males and 38 females treated with a Tap or Herbst oral appliance. There is a strong positional component associated with the pre-treatment AHI and RDI and the overall post-treatment values. Neck size and Epworth scores for females were associated with the post-treatment values but not with males. The pre-treatment supine AHI and RDI were correlated with post-treatment values in males but not females, however the ratio between the supine and non-supine AHI was alternatively predictive only in females. A simple equation (divide the pre-treatment AHI by 5 and add 2) correctly predicted the post-treatment AHI resulting from MRD therapy within $\pm$ 6 event/hour in 89% of the 122 cases.

5. Predicted Prevalence of OSA in a Population of Dental Patients Undergoing Moderate Sedation Compared to a Cohort of General Dentistry Patients. Gagne R, Levendowski D, Scarfeo D, Westbrook P. *Sleep Breath* 2009;13:308.

A study of 98 consecutive cases found that females constituted a greater percentage of those who under parenteral sedation (62% vs. 38% for males). The prevalence of predicted OSA using the ARES Screener in the female sedation patient group was 46%, more than 60% greater than a comparable

female cohort from a general dentistry population. None of the 'at-risk' sedation females had been previously diagnosed with OSA. There was no difference in the predicted OSA prevalence in sedation vs. general dentistry males (>60%). The estimated prevalence in both females and males suggests that parenteral sedation practitioners should be aware of OSA prevalence and consider screening for OSA as a normal part of their pre-sedation work-up.

6. Assessing Change in OSA Severity During a Non-Treatment Wash-Out Period: Is There a Halo Effect. Levendowski D, Morgan T, Popovic D et al. *Sleep Breath* 2009;13:309.

Ten patients successfully being treated with Mandibular Repositioning Device (MRD) participated in a four-day wash-out study. Patients with primarily mild OSA by AHI and moderate by RDI criteria were studied with the ARES Unicorder™ at baseline (with the MRD) and for three consecutive nights without MRD therapy. For patients with AHI > 10, the return of sleep disorder breathing (SDB) to baseline occurred the first night without therapy. For patients with very mild SDB, a small but significant halo effect was apparent in the AHI on Nights 1 and 2 in the AHI and snoring for Night 1. The results suggest that a measure of pre-treatment OSA severity can be approximated with the temporary suspension of MRD therapy.

7. Assessing Changes in the AHI Resulting from Increased Vertical Dimension of Occlusion (VDO) of Mandibular Repositioning Devices. Levendowski D, Popovic D, Morgan T et al. *Sleep Breath* 2009;13:308.

Seventeen males and eight females, having completed three months of Mandibular Repositioning Device Therapy, were enrolled in a follow-up study to assess the change in AHI and RDI resulting from treatment with custom made Tap III appliance. Two lower trays were fabricated to provide either 7mm or 10mm VDO with approximately the same mandibular advancement. For males, the AHI and RDI trended toward improved efficacy or no change with increased VDO (94% and 84% respectively). With females, the opposite occurred with 100% showing an increase in AHI and RDI or no change as a result of 10mm VDO.

8. Factors Impacting Mandibular Repositioning Device Therapy at One-Month. Morgan T, Montague J, Melzer V et al. *Sleep Breath* 2009;13:307.

A dentist with 18-years experience fitted 20 patients with a Tap III and 26 patients with a Herbst oral appliance. A dentist with no prior experience in dental sleep medicine fitted 46 patients with the Tap III and using the expert's training manual. No differences in treatment efficacy were noted between the Tap III and the Herbst oral appliances or between a novice and expert dentist based on the AHI values. With a more subtle measure of sleep disordered breathing the TAP provided improved efficacy compared to the Herbst. The study showed that more consistent follow-up and coaching with the patient improved outcomes at one-month, and that a novice dentist can manage MRD complications without assistance with an appropriate training manual.

9. Oral Appliance Efficacy in Positional and Non-Positional OSA Patients. Chung J, Enciso R, Levendowski D et al. *Sleep Breath* 2009;13:303.

Seventy-nine patients treated with the Tap III or Herbst oral appliances were stratified into positional (n=44) and non-positional (n=35) OSA categories based on the supine to non-supine AHI ratio ≥ 2.0 . The percentage of patients with $\geq 50\%$ reduction in AHI was 89% for the positional group and 57% for the non-positional group. The percent time supine significantly increased in the positional group even as the AHI decreased. Oral appliances are more effective in positional OSA than non-positional OSA patients.

10. Using the ARES Screener and the Berlin Questionnaire to Predict SA. Enciso R, Clark G. *Sleep Breath* 2009;13:301.

39 OSA patients (AHI>15) and 23 controls (AHI<5) based on ARES home sleep testing were recruited. Each patient answered the Berlin Questionnaire and the ARES Screening Questionnaire. The Ares questionnaire performed better in most of the situations with a higher sensitivity, similar positive predictive value, higher negative predictive value, but lower specificity. The probable explanation is the ARES Screening Questionnaire was tailored to detect patients with an AHI>=5.