

Title: APNEALINK™ PLUS WHITE PAPER

Project/Product:
APNEALINK PLUS DIAGNOSTIC DEVICE

Number: D2231-127

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Report on the validation of ResMed ApneaLink™ Plus diagnostic device for the correct scoring of hypopneas according to American Association Sleep Medicine (AASM) standards, differentiation of Apneas, and the usability evaluation of the new device features.

Study Objectives Recently, ResMed has expanded its resources of diagnostic systems introducing a new variant of ApneaLink, called ApneaLink Plus. The main difference between the existing and the upcoming system is the addition of a proprietary pneumatic effort sensor that allows the differentiation of Apneas into Central, Obstructive and Mixed events.

A new effort sensor technology coupled with a set of computer algorithms has been introduced to automatically classify apneas accordingly.

To reflect the most recent guidelines given by the AASM in 2007, the hypopnea algorithm has also been updated to correlate reductions in Respiratory Flow with Desaturation events in the SpO₂ channel.

The aim of this study to evaluate the feasibility and accuracy of the new device to fulfil the needs in clinical practice. The usability aspects of the newly introduced sensor as well as the modified Start/Stop function is also under investigation.

Specifically, the study aimed to:

- compare the ApneaLink Plus effort signal with the Gold standard Respiratory Inductance Plethysmography (RIP) and evaluate whether the ApneaLink Plus signal is adequate to differentiate the three types of apneas into obstructive, central and mixed events
- determine the accuracy of the ApneaLink Plus algorithms in differentiating Obstructive Apneas, Mixed Apneas and Central Apneas automatically
- determine the accuracy of ApneaLink Plus in scoring Hypopneas using the guidelines of the AASM in 2007
- determine whether patients can start and stop the recorder and attach the additional effort sensor by following the patient instruction sheet.

Study Design Overnight Polysomnograph (PSG) studies have been performed simultaneously with ApneaLink Plus recordings. Patients for this study have been recruited from individuals scheduled to undergo an overnight diagnostic PSG study in the SleepLab of Wangen, Allgäu, Germany. The Principal Investigator was Dr. Heribert Knape.

Study Inclusion Criteria

- Adult patients 18 years of age or older
- No alcohol consumption 12 hrs before and during the trial period
- Normally sleep more than 3 hours per night

Study Exclusion Criteria

- Pregnant
- Patients who use of Bilevel PAP or CPAP therapy during the PSG study
- Unsuitable for inclusion in the opinion of the investigator
- ApneaLink Plus evaluation time less than 4 hours

Demographics

- In total, 22 simultaneous recordings have been performed.
- 19 men and 3 women participated in the study.
- The average age was 53.73 years \pm 16.26 years.
- The average Body Mass Index (BMI) was 29.77 \pm 4.23.

Method

- A nasal cannula was used to generate the respiratory flow information. The nasal cannula signal fed into both systems using a T-piece connector allowed for synchronization of both recordings.
- The PSG system (Embla) used X-Tract RIP effort belts to detect respiratory excursions. ApneaLink Plus used a pneumatic measuring principle to detect respiratory excursions.
- For best comparability, both sensors (RIP and ResMed pneumatic effort sensor) have been attached simultaneously next to each other at patients' chest.
- To obtain information about the oxygen saturation of the patients, two SpO₂ sensors at patients' ring fingers were attached, one at the left hand (PSG) and one on the right hand (ApneaLink Plus). The saturation signals have been recorded with the corresponding systems.

Results

Data Analysis

The PSG studies have been manually scored in terms of apneas (obstructive, central, or mixed), Hypopneas and Desaturations according the 2007 AASM guidelines for scoring respiratory events (reduction of respiratory flow of at least 30% to baseline for at least 10 seconds accompanied by a desaturation event of at least 4%).

Processing of the ApneaLink Plus signals was done automatically after downloading the data from the recorder. The ApneaLink results were not visible to the investigators prior to having scored the PSG studies.

The ApneaLink Plus performance was summarized using:

- Visual comparison of the effort signals from both the reference RIP and ApneaLink Plus as well as Bland-Altman Analysis¹ of the raw signals of an arbitrary recording sequence
- Proportion of obstructive, central and mixed apneas over all Apneas out of 22 recordings included in this study
- Correlation² coefficients calculated from the PSG results and the ApneaLink Plus results for Apneas, Obstructive Apneas and Central Apneas
- Desaturations (correlation and Bland-Altman Analysis) as basis for adequate Hypopnea scoring according AASM guidelines
- Hypopnea scoring according AASM guidelines (Correlation Analysis and Bland-Altman Analysis)
- AHI analysis (Correlation and Bland-Altman Analysis)
- Classification of patients (True positives, True negatives, False positives, False negatives)
- Results of the usability questionnaire.

Recordings

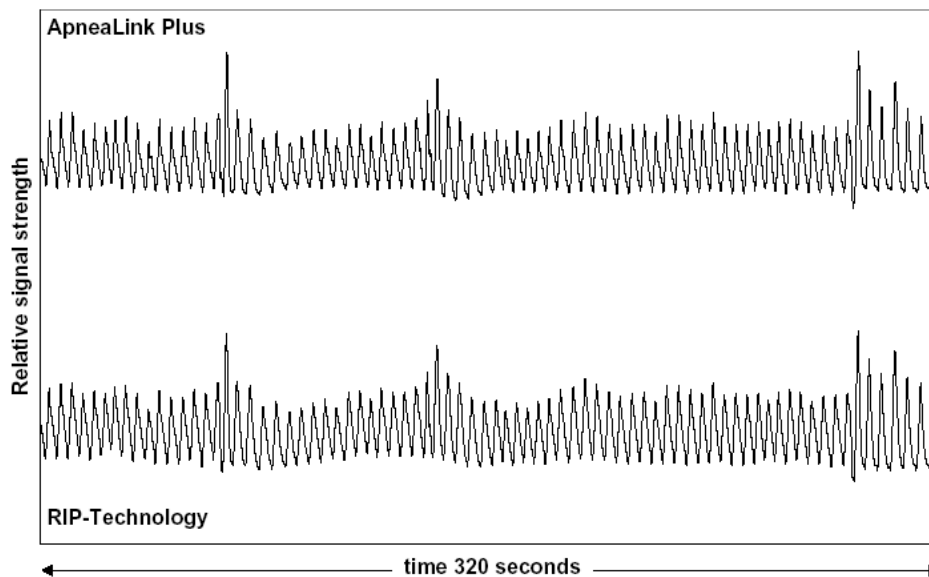
- The total recording time was 161:37:00 hours.
- 04:41:57 hours or 2.91% of the total recording time were affected by signal too small in the effort channel. Signal too small is scored automatically to exclude episodes with low signal strength as valid results of the automatic analysis cannot be guaranteed.
- At any time, the effort signal was strong enough to allow for differentiation of apnea events by visual inspection.

¹ The Bland-Altman plot is a graphic representation of the observed differences between paired measurements. The differences between the two measurements are plotted against the averages of the two measurements. The mean difference provides an estimate of whether the two methods of measurement, on average, return similar results. Results showing a mean difference close to 0 indicate little systematic bias.

² A correlation is a number between -1 and +1 that measures the degree of association between two variables. A result greater than $r = 0.75$ is considered to be indicative of good correlation between the two techniques.

Evaluation of the signal quality

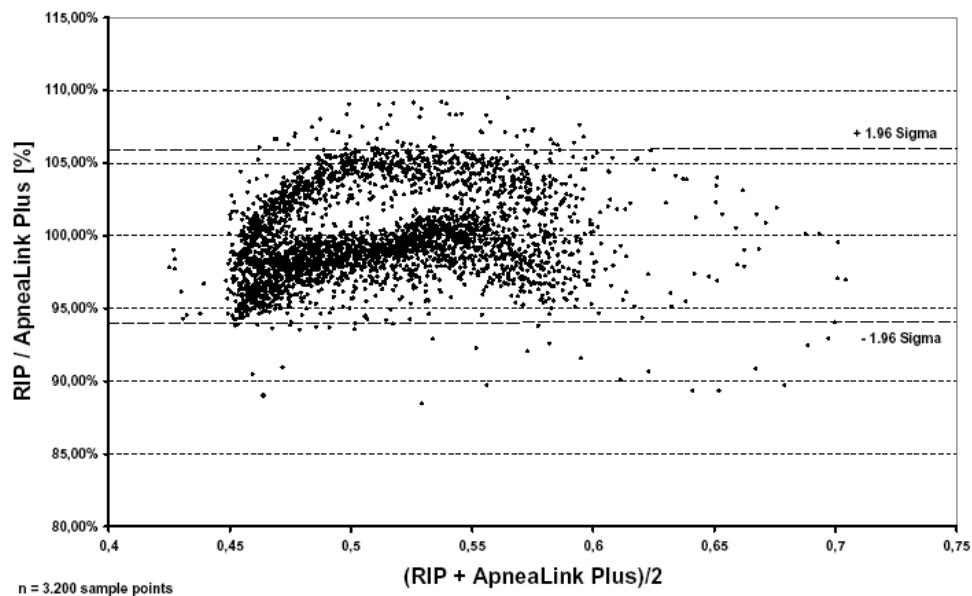
The signals from both RIP technology and ApneaLink Plus pneumatic principle have been visually compared. By visual inspection there was rarely a difference to observe.



The effort signals of both systems was exported into ASCII (data format) strings, normalized and corrected in their baseline. A Bland-Altman analysis was then performed.

Using 3,200 sample points each for both technologies proved the excellent characteristics of the new sensor compared to the gold standard RIP.

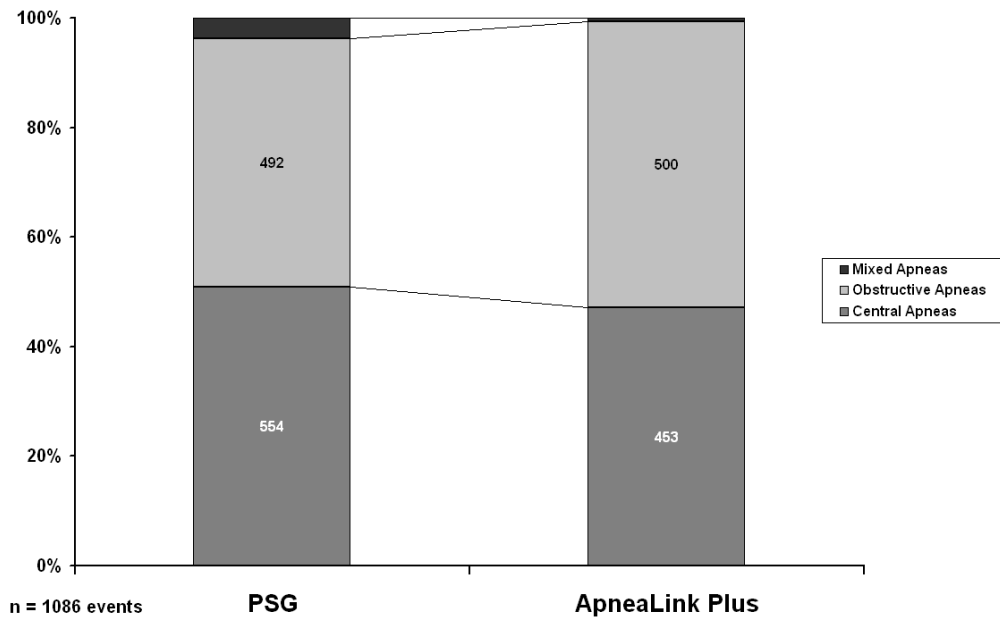
For normal breathing sequences as shown below, 95% of the raw sample points are located within a range of $\pm 5.2\%$.



Differentiation of Apneas

Within 22 PSG recordings included for this evaluation, 1,086 apneas and 702 hypopneas have been scored by visual scoring of the PSG. Within the group of Apneas the differentiation of the events into obstructive, central and mixed events showed only slight differences between PSG and ApneaLink Plus.

Apnea Classification



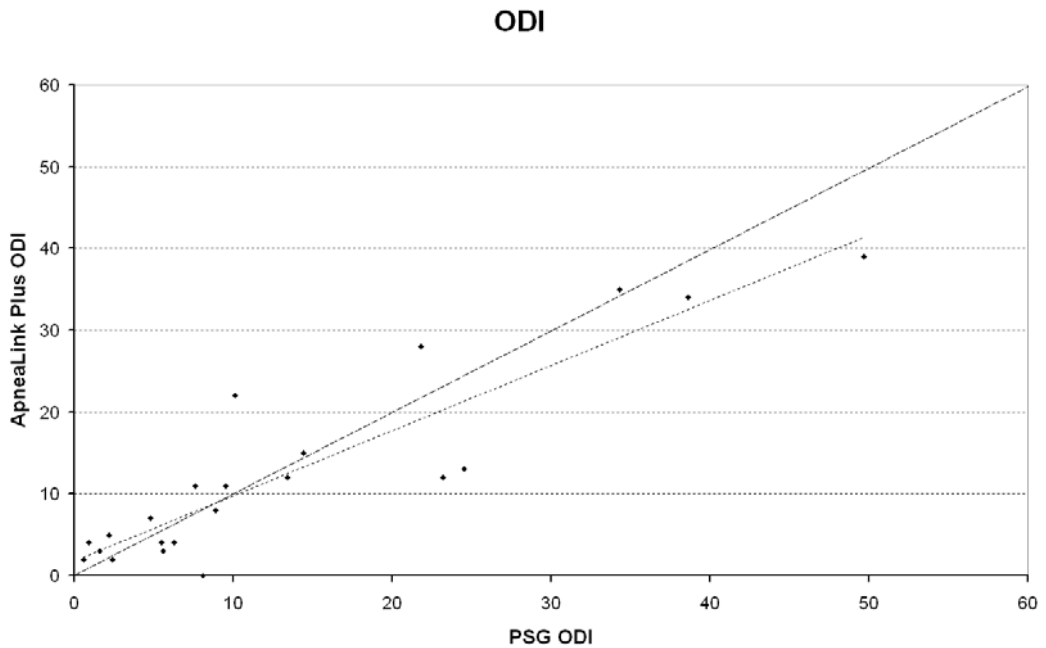
The corresponding correlation coefficients compared to the manually scored PSG results were:

| Event type | Correlation coefficient r |
|-------------------------------|---------------------------|
| Apnea Index (AI) | 0.935 |
| Obstructive Apnea Index (OAI) | 0.852 |
| Central Apnea Index (CAI) | 0.939 |

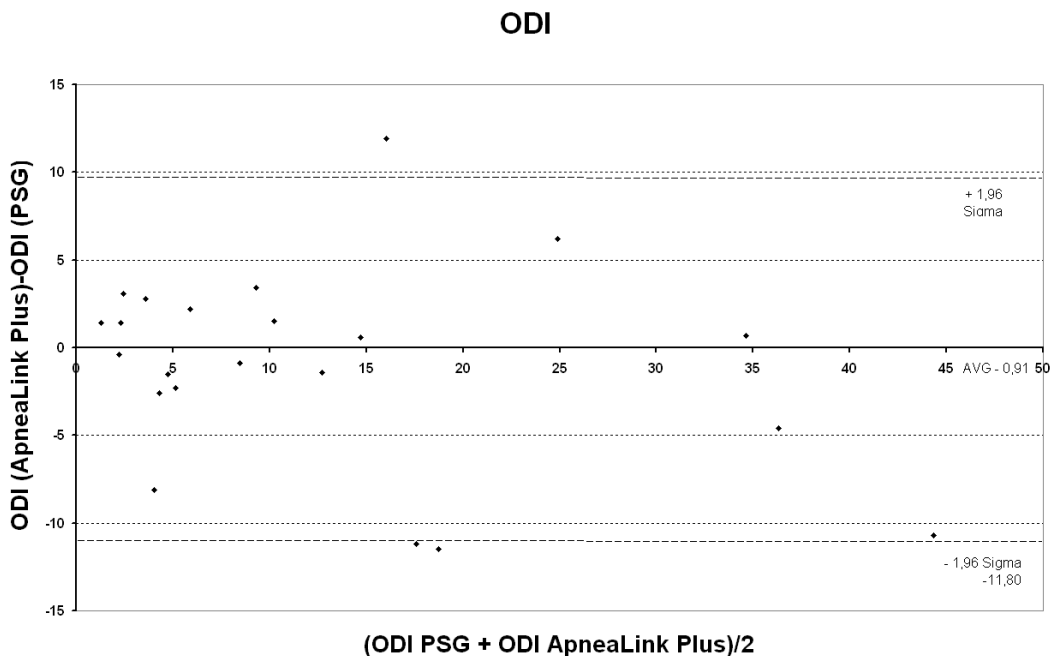
All correlation coefficients were statistically significant with p-values $p < 0.001$

Desaturations

As the correct scoring of desaturations directly affects the potential number of hypopneas to be scored, the desaturation events scored by ApneaLink Plus were compared with the corresponding PSG results. The default setting for desaturation scoring of 4% reduction from baseline was used.



The association between PSG and ApneaLink Plus significant correlation with a correlation coefficient of 0.905 for Oxygen Desaturation Index (ODI). The offset found when performing the corresponding Bland-Altman analysis was -0.91.



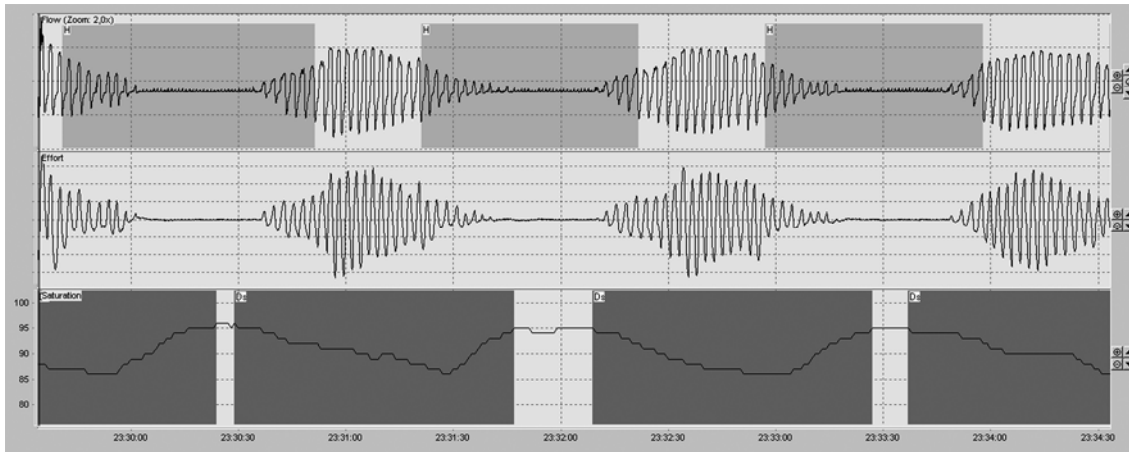
Hypopneas

Hypopnea Indicator (HI)

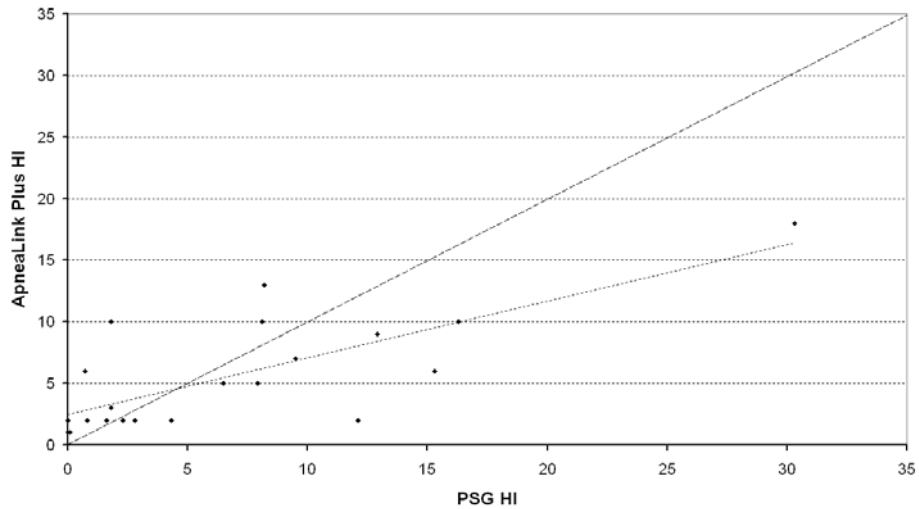
The guidelines for scoring Hypopneas according the 2007 AASM criteria are well reflected in ApneaLink Plus. As default criteria, a 30% reduction in flow for at least 10 seconds correlated with a 4% desaturation is set.

The algorithm to detect hypopneas works well with a correlation of 0.754; even in certain cases the algorithm tends to overestimate hypopneas against apneas.

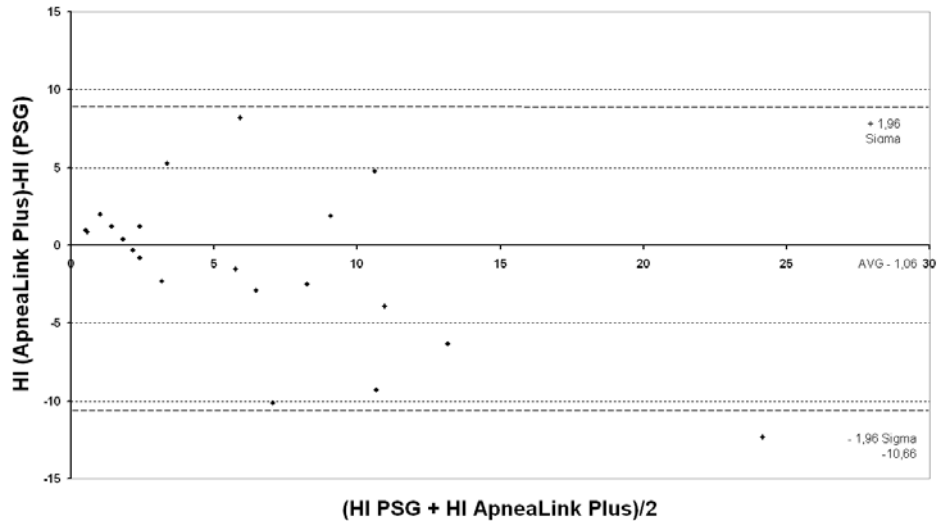
In one patient with typical Cheyne–Stokes (CS) breathing pattern, the detector scored hypopneas instead of central apneas in 80 situations, which negatively affected the overall positive results for scoring hypopneas. The CS algorithm implemented in ApneaLink Plus correctly reported that individual as CS positive.



HI



HI

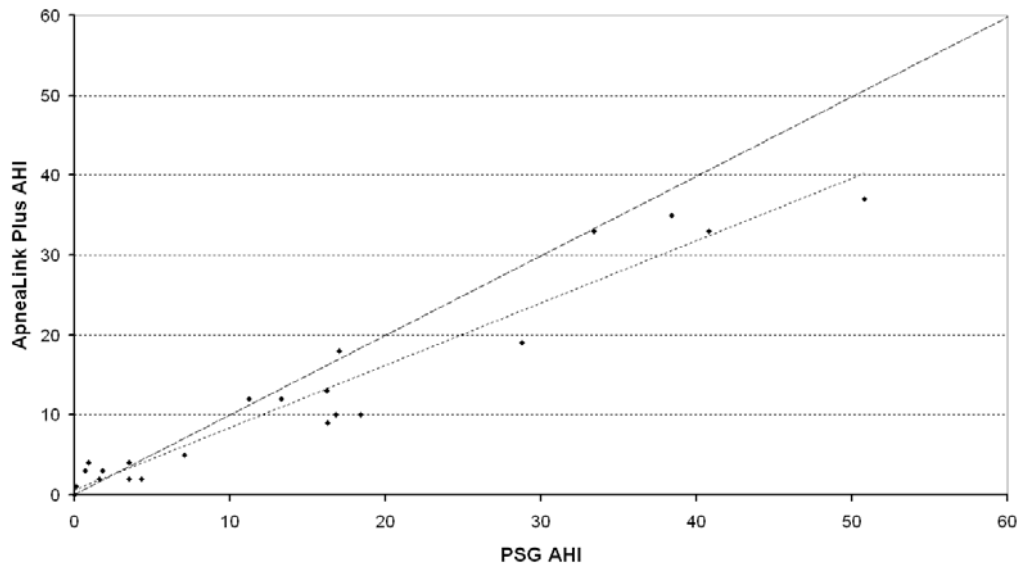


Apnea Hypopnea Index (AHI)

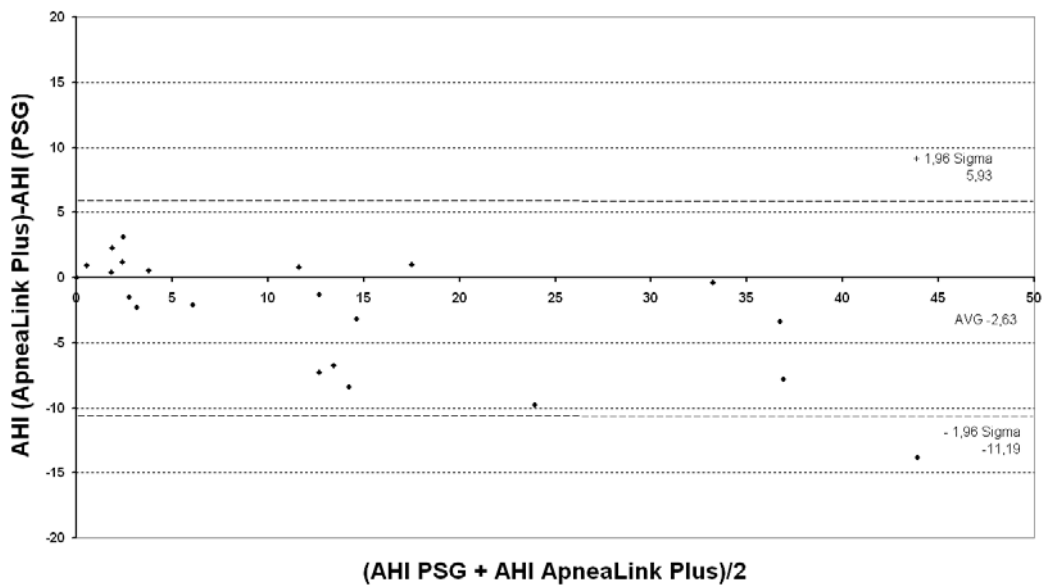
The AHI calculated by the PSG of 22 patients was compared with the AHI automatically calculated by ApneaLink Plus. The way of calculating the indices is different for both systems. As ApneaLink Plus does not have any sleep information, it is calculating the indices by dividing the number of events by the recording time reduced by 10 minutes. ApneaLink Plus automatically sets the first 10 minutes of the recording as analysis exclusion assuming the individual to be awake. Periods of bad signal quality will also be excluded automatically within the recording period.

To calculate indices per definition in the PSG, the number of events is divided by the total sleep time - which by definition must be equal or shorter than the recording time. It is expected that the PSG values will be higher than the ApneaLink indices.

AHI



AHI



The correlation between PSG AHI and ApneaLink Plus AHI has been calculated to be 0.968. As expected, the PSG AHI is slightly higher than the ApneaLink Plus AHI results (Offset in Bland-Altman Analysis was -2.63). The corresponding Bland-Altman analysis can be found above.

Classification of Patients

- Using the cut off value of AHI ≥ 5 events/hour suggested by the manufacturer, ApneaLink Plus classified all 13 positive studies as positives (true positives) and the 9 PSG negatives correctly as negatives (true negatives).
- Using the cut off value of AHI ≥ 10 events/hour often suggested to be the more reliable cut off, ApneaLink Plus classified 11 of 12 PSG positive studies as positive (true positives), 10 PSG negatives correctly as negatives (true negatives). One study was classified incorrectly as negative (false negative) by ApneaLink Plus.
- The false negative identified during this study is mainly introduced through the difference between Recording time and Total Sleep Time. When calculating the ApneaLink Plus false negative using the total sleep time instead of the Recording time, these patients would also be scored correctly as a true positive.

| AHI Cut Off ≥ 5 (n = 22) | True Positives | False Positives | True Negatives | False Negatives |
|-------------------------------------|----------------|-----------------|----------------|-----------------|
| Reference PSG | 13 | -- | 9 | -- |
| ApneaLink Plus | 13 | 0 | 9 | 0 |

| AHI Cut Off ≥ 10 (n = 22) | True Positives | False Positives | True Negatives | False Negatives |
|--------------------------------------|----------------|-----------------|----------------|-----------------|
| Reference PSG | 12 | -- | 10 | -- |
| ApneaLink Plus | 11 | 0 | 10 | 1 |

Usability

All patients participating in this study were asked to complete a questionnaire to find out whether the easy ApneaLink handling concept has been compromised by adding the effort sensor to ApneaLink Plus. The ratings range from 0 (poor) to 10 (excellent).

| Question | Average Patient Score | Median Patient Score |
|---|-----------------------|----------------------|
| <i>How easy/difficult was it to attach the recorder and effort sensor to your body?</i> | 8.5652 | 9 |
| <i>How intuitive/difficult was it to Start/Stop the recorder?</i> | 9.7826 | 10 |
| <i>How comfortable/uncomfortable did you feel during the night recording?</i> | 9.6957 | 10 |

Conclusion

- The device has been recognized by the patients to be easy to use and set up with a high degree of comfort.
- The ApneaLink Plus does not interfere with sleep during home testing.
- The signal quality provided by the sensor was robust and stable throughout the entire study.
- All evaluable correlation coefficients were statistically significant with p-values $p < 0.001$.
- Compared with the Gold standard RIP using single use RIP belts, the information provided by the ApneaLink Plus pneumatic effort sensor is absolutely comparable.
- The application of the ApneaLink Plus effort sensor appears to be much simpler.
- The new ApneaLink Plus algorithm clearly helps to identify and differentiate different kinds of sleep apnea in patients suffering from SDB.
- The algorithms to detect respiratory events worked properly and reliably throughout the entire study.
- The correlation between PSG results and ApneaLink Plus results was significant at any time.
- The differentiation between the Apnea event types showed a good correlation compared to manual Apnea scoring in the PSG.
- The automatic detection of desaturations worked properly, which is important for the overall Hypopnea scoring.

References

1. Erman M, Stewart D, Einhorn D, Gordon N, Casal E; Validation of the ApneaLink™ for the Screening of Sleep Apnea: a Novel and Simple Single-Channel Recording Device; *Journal of Clinical Sleep Medicine*, Vol. 3, No. 4, 2007.
2. American Academy of Sleep Medicine; *AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specification*; www.aasmnet.org