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Clinical Use of Loop Gain Measures to Determine CPAP Efficacy in Patients with Complex Sleep Apnea: A Pilot Study

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MS,KR, WC, WD, SS and AM contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. MS takes responsibility for the content of the manuscript, including the data and analysis.

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Abstract

Rationale: Measures of unstable ventilatory control (loop gain) can be obtained directly from the periodic breathing duty ratio on polysomnography in patients with Cheyne-Stokes respiration/central sleep apnea and can predict the efficacy continuous positive airway pressure (CPAP) therapy.

Objectives: In this pilot study, we aimed to determine if this measure could also be applied to patients with complex sleep apnea (predominant obstructive sleep apnea, with worsening or emergent central apneas on CPAP). We hypothesized that loop gain was higher in patients whose central events persisted 1 month later despite CPAP treatment versus those whose events resolved over time.

Methods: We calculated the duty ratio of the periodic central apneas remaining on the CPAP titration (or second half of the split night) while patients were on optimal CPAP with the airway open (obstructive apnea index <1/h). Loop gain was calculated by the formula: $LG = 2\pi/[(2\pi DR - \sin(2\pi DR)]$. Patients were followed on CPAP for 1 month. Post-treatment apnea hypopnea index (AHI) and compliance data were recorded from smart cards.

Results: 32 patients with complex sleep apnea were identified and 17 patients had full data sets. 8 patients continued to have a total of >5/h (11.8 ± 0.5/h) (non-responders). The remaining 9 patients had an AHI <5/h (2.2 ± 0.4/h) (responders). Loop gain was higher in the non-responders versus responders (2.0 ± 0.1 vs. 1.7 ± 0.2, p =0.026). Loop gain and the residual AHI 1 month after CPAP were associated (r = 0.48, p= 0.02). CPAP compliance was similar between groups.

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Conclusions: In this pilot study, loop gain was higher for patients with complex sleep apnea in whom central apneas persisted after 1 month of CPAP therapy (non-responders). Loop gain measurement may enable an *a priori* determination of those who need alternative modes of PAP.

Obstructive sleep apnea (OSA), a disorder characterized by collapse of the upper airway during sleep, is caused by a combination of loss of upper airway muscle tone, collapsible pharyngeal anatomy and increased loop gain of the ventilatory control system (more unstable).[1, 2] By contrast, central sleep apnea (CSA) is characterized by a cessation of breathing that does not require upper airway collapse and is a driven primarily by increased respiratory system loop gain.[3, 4]

In patients with OSA and higher loop gain, the acute treatment of OSA with continuous positive airway pressure (CPAP) resolves the obstructive events. [5] However, residual CSA emerges or worsens from baseline, a phenomenon that has been referred to as complex sleep apnea[6-8] Such patients pose a challenge clinically, because CPAP treatment resolves the central events over time in some patients, but in others the central events persist and can be associated with concurrent sleepiness or insomnia. [9-11]

There is currently no means to predict which patients may need additional therapy for persistent central apneas beyond CPAP. Available evidence suggests that CPAP treatment resolves central events over time by improving ventilatory control system stability (lowers loop gain) over time. In patients with heart failure, CPAP reduces residual central sleep apneas over time[12] indicating that loop gain is gradually reduced with ongoing treatment. In OSA patients without heart failure, the ventilatory chemoreflex response to CO2 (a key component of ventilatory stability) is normalized with approximately 4 weeks of CPAP treatment.[13, 14]

Since a reduction in loop gain below the critical threshold value of 1 is required for stable breathing to occur, we propose that patients with a high loop gain at baseline (loop gain well above 1 on initial CPAP titration) will still have persistent ventilatory instability manifest as

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residual central events over time despite CPAP therapy. By contrast, those with low loop gain (loop gain closer to 1 at CPAP titration) will be more likely to have their breathing stabilized over time.

In the present study, we aimed to measure loop gain in a group of patients with complex sleep apnea to determine if we could detect patients who would later be found to be responsive to CPAP therapy. Loop gain was measured by assessing the ventilatory pattern of central sleep apnea.[15] Specifically, we assessed the duty ratio (DR) of the central sleep apnea, defined as the ratio of the duration of the ventilatory phase (time from the end of one apnea to the start of the next) to the total cycle duration (time from the end of one apnea to the end of the next). We then calculated loop gain using the formula: Loop gain = $2\pi/[2\pi DR - \sin(2\pi DR)]$. The method has been used in patients with heart failure and Cheyne-Stokes respiration on a baseline sleep study to predict whose who will respond to CPAP,[15] an outcome that has been associated with excess morbidity and mortality.[16-18] We tested the hypothesis that patients with persistent apneas after 1 month of CPAP would have a higher loop gain on their CPAP titration night than patients with resolved apneas.

Methods

We reviewed 3247 patient's baseline polysomnograms or diagnostic portions of split studies to find individuals with predominant obstructive sleep apnea (AHI>15/h) as well as the presence of central apneas (0<CAI<5/h; CAI, central apnea index) (Table 1). 168 patients satisfied these criteria and also attended for a CPAP titration study (or had a split night). From this group we

found 32 patients exhibited complex sleep apnea, defined as persistent and exacerbated central apneas upon exposure to CPAP (CAI>5/h), accompanying the resolution of obstructive events.

Measures of the duty ratio (loop gain) were recorded from stable periods of NREM sleep on optimal CPAP with no residual obstructive apneas. There had to be at least 10 duty cycles available for the calculation of loop gain and thus at least 10 min of stable NREM was observed.

We recorded demographic, polysomnographic variables and determined the duty ratio (DR) from a minimum of 10 periodic breathing cycles remaining on the CPAP titration (or second half of the split night), while on optimal CPAP with the airway presumably open (obstructive apnea index <1/h). All patients were followed on CPAP for 1 month. Post-treatment AHI and compliance data were recorded from modem/smart cards.

ANOVA was used to compare data from the baseline polysomnograms, CPAP titration nights, and after 1 month of PAP use. Duty ratios, loop gain, and compliance data were compared between responders (residual AHI<5/h) and non-responders (residual AHI>5/h) using t-tests. Simple regression was used to determine the relationship between loop gain measures and residual AHI after 1 month of CPAP therapy with normality of the data distribution evaluated using Shapiro-Wilk test.

This study was approved by the Rhode Island Hospital Institutional Review Board, project number 444551-2.

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Results

32 patients with complex sleep apnea were identified from the cohort (male 23, female 9, mean age = 61.2 years, mean BMI =32 kg/m^2, mean Epworth 9.8/24). 18 patients were treated with CPAP and follow-up PAP device downloads were available from 17 patients (Table 1 and Figure1). There were few patients in this cohort with congestive heart failure (n =2) or chronic opiate use (n = 2) and they were split evenly among the responders and non-responders to CPAP (Table 1).

We repeated the analysis without the heart failure and opiate use patients. There was no difference between responders and non-responders in terms of loop gain (mean ± SEM, 1.73 ± 0.1 vs 2.12 ± 0.2, p = 0.03). There was a slight change in the regression analysis (r= 0.43, p= 0.024) but not substantially. CPAP was effective in reducing the number of obstructive events during the titration night and at 1 month and although PAP reduced the number of central events at one month of therapy there were some individuals where the central apneas persisted at 1 month (Table 1 and 2). The mean AHI of responders was 2.2 ± 0.4 events/h versus non-responders of 11.8 ± 0.5 events/h (p= 0.03), with no difference in the mixed apnea index (mixed apnea index, 1.5 ± 1.2 for the responders vs. 1.4 ± 1.3 for the non-responders).

Much of the residual AHI in the non-responders was due to residual central events (central apnea index of 10.7 ± 5.9 events/h. By contrast, the responders exhibited a central apnea index of just 1.6 ± 1.5 events/h (Table 1). In addition, the ratio of central apnea index to obstructive apnea index was higher in the non-responders compared to responders at 1 month.

Figure 2 reveals raw data from one patient on CPAP of 13cm H_2O during a CPAP titration showing emergent central events with the airway patent (i.e. no obstructive apneas seen). This figure illustrates how the duty ratio is calculated using the ventilatory pattern of CSA. 8 patients (non-responders) exhibited a total AHI of >5/h on CPAP therapy at 1 month, whereas the remaining 9 patients (responders) had an AHI <5/h. Loop gain was higher on the CPAP titration in those who became non-responders versus responders (Table 2). CPAP

Compliance was not statistically different between groups (Table 2), although we acknowledge a trend towards increased compliance in responders versus non-responders (+0.8 hours/night, +9% of nights of CPAP use >4 hours).

Linear regression showed a relationship between loop gain and the residual AHI one month after CPAP ($r = 0.48$, $p = 0.04$), Figure 3. The relationship between duty ratio and loop gain is shown in figure 4 with the mean value for non-responders versus responders.

Discussion

The major findings of this pilot study are: 1) loop gain (measured during the CPAP titration) is higher in patients with complex sleep apnea in whom central apneas persisted after 1 month of CPAP therapy (non-responders) compared to those who respond to CPAP; and 2) the number of residual apneas on therapy is predicted by this loop gain measure. Thus, OSA patients who exhibit persistent CSA on CPAP have a more unstable ventilatory control system than those whose CSA resolves over time. We speculate that estimating loop gain from the duty cycle or

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other available methods may help determine *a priori* those whose sleep apnea requires alternative modes of PAP for an effective treatment.

The prevalence of complex sleep apnea is variable but is estimated to occur in approximately 5-15% of patients being evaluated in university sleep lab settings.[6, 10, 19] Known risk factors for persistent central events on CPAP included those with central events on the baseline sleep study, CHF/atrial fibrillation and chronic opiate use. [10, 19] Randomized trials have shown that those with persistent central events show better control on adaptive servo-ventilation PAP devices. [9, 20, 21]The downside of this adaptive-PAP therapy is that these devices are quite costly compared to CPAP with which many patients do well. However, like patients with Cheyne-Stokes respiration[18, 22] there are a group of patients with complex sleep apnea who do not respond to standard CPAP, remain symptomatic with their residual central events.

Our study identified a group of patients with more significant control system instability (higher loop gain) who do not experience resolution of all their respiratory events on CPAP. In addition the number of residual respiratory events is predicted by how unstable ventilation is on the CPAP titration night (Figure 3). These patients may respond to other therapies like Adaptive/Auto servo ventilation (ASV), O2, oral appliances or combinations of therapy including acetazolamide, and further studies are necessary. Recent findings regarding concern for safety of ASV in patients with congestive heart failure may encourage alternative strategies to avoid ASV in complex sleep apnea unless necessary.[23]

We did not set out to identify a threshold level of loop gain above which CPAP is ineffective but based on this data set a level of greater than or equal 2 is reasonable to consider. Further studies to validate this threshold are underway.

The fact that there was not a difference in compliance between the responders and non-responders deserves mention. Some authors have suggested that a poor initial experience with PAP therapy due to residual disease may lead to long term non-adherence with PAP in some patients.[24] [20, 21] Such a finding would theoretically support the concept of early intervention (perhaps with a newer ASV device) in such patients to avoid long term non-adherence. This concept is currently being studied[20], but our data do not support the use of ASV in an early intervention strategy for the purposes of improving adherence. Whether there are implications for sleep apnea symptoms and cardiovascular outcomes remains to be fully determined.

Several limitations of this pilot study deserve mention. Loop gain may change from night-to-night, for example, based on fluid shifts or changes in medications.[25] Thus, our finding that loop gain explains some proportion but not all of the variance in residual apnea is not surprising. Individual differences regarding the size of the reduction in loop gain over time may explain further variability in residual AHI. Possible mechanisms include the following:

a) Improved oxygenation may reverse the effects of apnea-induced intermittent hypoxia on chemoreflex sensitivity. [26, 27]
b) Reversal of apnea-induced sympathoexcitation with CPAP may also contribute to reducing chemoreflex sensitivity.[28]
c) Patients may adapt to CPAP over time and achieve a greater sleep depth during the night, and may therefore be less susceptible to the effects that lighter sleep and arousal may have on ventilatory instability.[29, 30]

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d) Changes in plant gain or circulatory delay could also occur, for example, with reduced circulatory delay or reversal of edema-related reduction in lung volume and thus oxygen/CO2 stores. These effects may be more important in some patients than others.

Our goal was to conduct a clinical study rather than a physiology experiment. Thus, a number of physiological variables were not measured. For example, we assume pharyngeal airway patency on optimal CPAP but did not measure resistance or critical closing pressures. Differences in upper airway anatomy are unlikely since responders and non-responders had similar BMI and were on similar CPAP levels. Similarly, we did not measure PaCO2 which might be important in understanding the mechanism of increased loop gain and persistent events in the non-responders.[31]

We followed a relatively small cohort of patients for only one month on CPAP, a time duration which may not be long enough for all the central events to resolve. However, we note that 1 month is considered sufficient to normalize the effects of sleep apnea on loop gain.[13, 14] Hence, available evidence suggests that at 1 month it is reasonable to reconsider the use of alternative strategies with a greater scope for resolving ventilatory instability (e.g. ASV).[18] However, as noted recent findings regarding concern for safety of ASV in patients with congestive heart failure may encourage alternative strategies to avoid ASV in complex sleep apnea, until ongoing studies are completed.[23]

In conclusion, we demonstrate that patients whose central sleep apnea persists on CPAP at 1 month had a more unstable ventilatory control system (higher loop gain) than those whose central sleep apnea resolved with treatment over time. This finding is consistent with the

notion that when loop gain is far above 1 at baseline, it is more challenging for treatments to reduce it below 1 to enable stable breathing. Measures of ventilatory instability from the ventilatory pattern (duty ratio) in patients with complex sleep apnea may help to identify a group for which CPAP may be less effective. Recognizing patients at higher risk of treatment failure with CPAP may be helpful in the future identifying those more likely to need alternative therapies, such as possibly adaptive servo devices or pharmacological agents to stabilize breathing. [32, 33]

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Table 1. Baseline Demographics, Sleep disordered breathing severity for the responders, non-responders during the Baseline sleep study, CPAP titration night and 1 month after CPAP therapy (group mean ± SEM); central apnea index (CAI), obstructive apnea index (OAI), total apnea hypopnea index (AHI) (events/h) between Responders (residual AHI<5/h) versus Non-Responders (residual AHI>5/h) after therapy with positive airway pressure (PAP), (mean ± SEM)

Baseline Demographics	**Responders (n=9)**	**Non-Responders (n=8)**	**p**
Epworth	9.6 ± 0.9	9.8 ± 0.8	0.47
Age (y)	60.9 ± 2.4	63.1 ± 2.7	0.32
BMI (kg/m2)	30.1 ± 1.6	31.0 ± 1.7	0.57
Opiates (n)	1	1	ns
Benzodiazepines (n)	2	1	ns
CVA (n)	0	0	ns
CHF (n)	1	1	ns
CPAP (cm H20)	10.7 ± 1.2	10.4± 1.6	0.45
PSG Baseline			
AHI	47.0 ± 4.9	43.9 ± 6.3	0.33
OAI	28.1 ± 4.7	32.2 ± 5.1	0.09
CAI	5.9 ± 2.6	5.7 ± 1.7	0.47
CPAP Titration			
AHI	20.2 ± 3.0 *	22.0 ± 2.5 ¥	0.37
OAI	5.2 ± 1.6 ¶	4.9 ± 1.9 £	0.18
CAI	13.0 ± 2.3	15.1 ± 6.1	0.25
1 mo CPAP			
AHI	2.2± 0.4 *	11.8 ± 0.5 ¥	0.02
OAI	0.5 ± 0.7 ¶	0.8 ± 1.5 £	0.23
CAI	1.5 ± 1.5	10.2 ± 5.9	0.02
*p<0.001 AHI Baseline vs titration and 1 mo CPAP			¥ p< 0.001 AHI Baseline vs titration vs 1 mo CPAP
¶p<0.001 OAI Baseline vs titration and 1 mo CPAP			£ p<0.001 AHI vs Baseline vs 1 mo CPAP
p<0.001 CAI Baseline vs titration and 1 mo CPAP			

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Table 2. Comparisons of Duty Ratio with Total Cycle Duration, Ventilation Duration, Apnea duration; Loop Gain measures and Compliance data between Responders (residual AHI <5/h) versus Non-Responders (residual AHI >5/h) after therapy with CPAP (mean ± SEM).

	Responders (n=9)	Non-Responders (n=8)	p
Duty Ratio	0.58 ± 0.02	0.51 ± 0.03	0.038
Total Cycle Duration	39 ± 1.7	37.7 ± 1.9	0.12
Apnea Duration	16 ± 1.8	19 ± 2.1	0.03
Ventilation Duration	23 ± 1.7	18.7 ± 2.3	0.02
Loop Gain	1.73 ± 0.16	2.02 ± 0.11	0.026
% time >4 hours CPAP	77.4 ± 4.5	68.6 ± 11.5	0.47
CPAP hours/night	5.7 ± 0.23	4.9 ± 0.60	0.21

Figure Legends

Figure 1. Flow chart of inclusion/exclusion of patients from the sleep study cohort. From the 3247 patient's baseline or split studies, 168 patients with primarily obstructive and some central events on the diagnostic evaluation (sleep study) were identified. Of these 32 patients (pts) with Complex Sleep Apnea defined as persistent or emergent central events occurring during CPAP titration were identified. Of these 18 patients were treated with CPAP and 17 patients had 4 week (wk) compliance downloads available for review. After 1 month of CPAP 9 patients had AHI<5/h (responders) and 8 patients had AHI>5/h (non-responders).

Figure 2. Raw polysomnographic data from a single patient with complex sleep apnea, during a CPAP titration, showing persisting central apneas (but no obstructive apneas) while on optimal CPAP of 13 cm H_2O (left), with an inset (right) showing a magnification of the flow/effort channels from the same patient, exhibiting how duty ratio is measured (duty ratio is defined as the ventilation duration/cycle duration). 30 second epochs are denoted by the vertical blue lines.

Figure 3. Regression analysis showing the relationship between residual apnea hypopnea index (AHI, events/h) and loop gain after CPAP therapy

Figure 4. Mathematical relationship between loop gain and duty ratio illustrating mean data for responders and non-responders. Note the non-responders are 40% further from stable breathing (loop gain <1.0) than responders.

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FIGURE 1

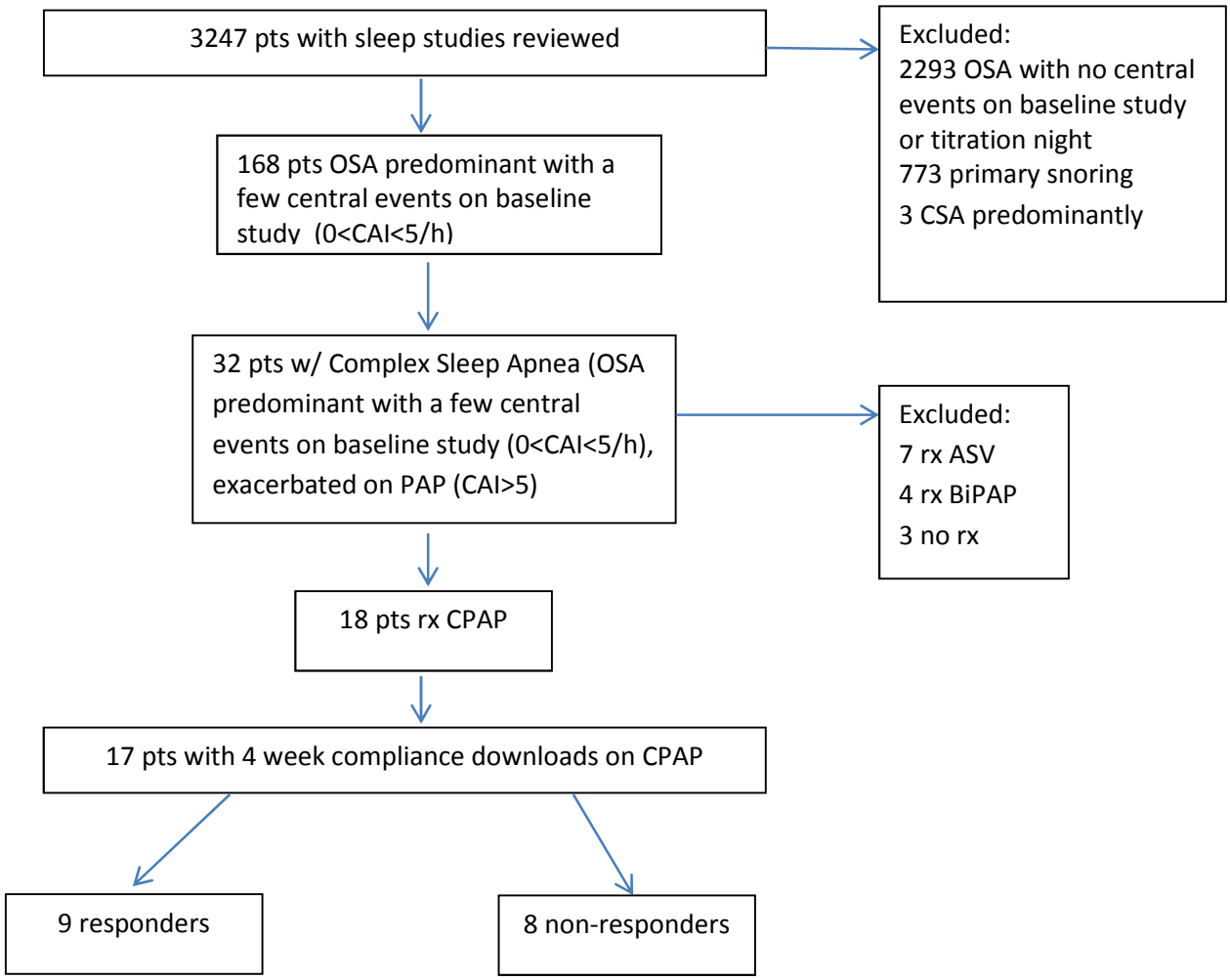

FIGURE 2

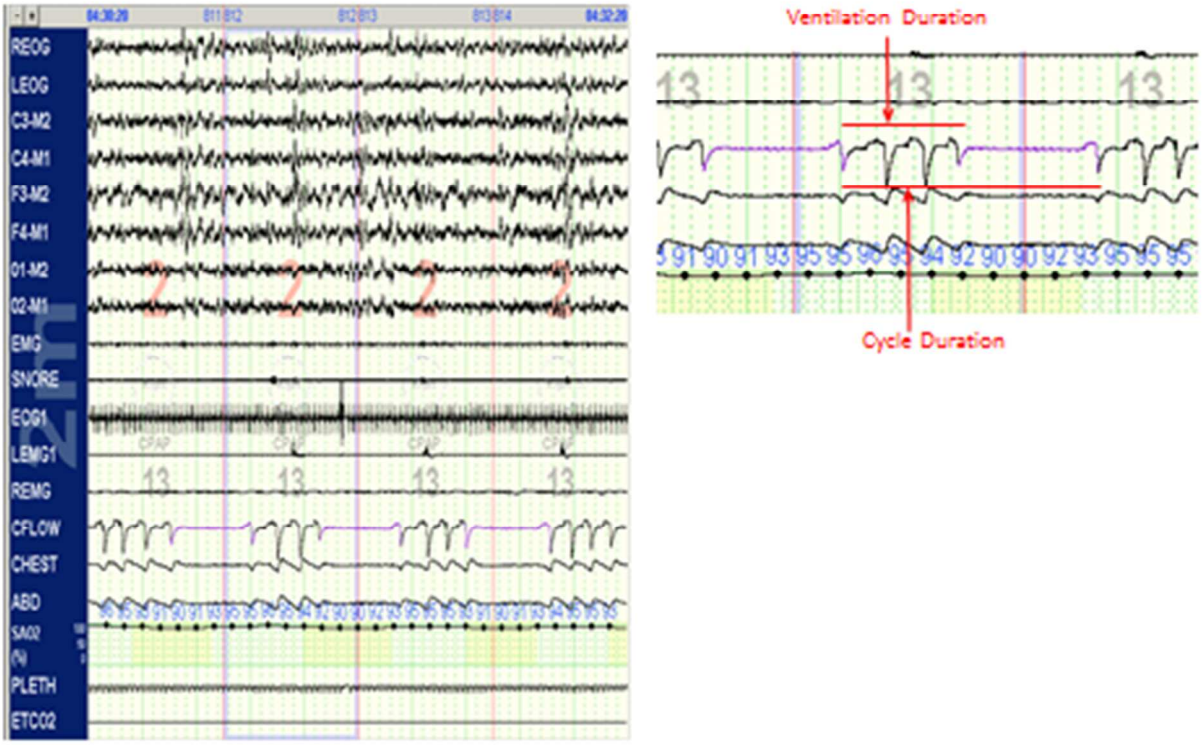

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FIGURE 3

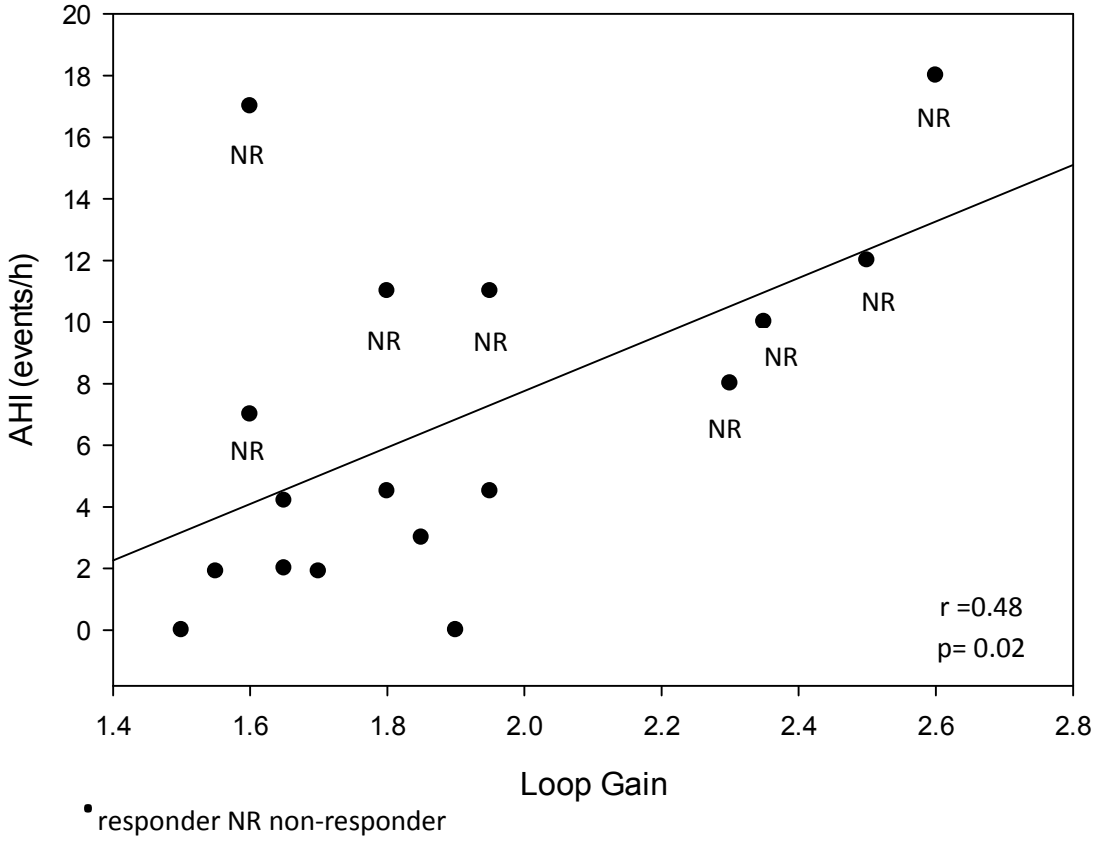

FIGURE 4