EVALUATION OF UPPER AIRWAY PATENCY DURING CHEYNE-STOKES BREATHING IN HEART FAILURE PATIENTS.

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ABSTRACT

Little is known about changes in upper airway caliber in Cheyne-Stokes Respiration (CSR) during sleep in patients with congestive heart failure. This study aimed to test the hypothesis that upper airway closure occurs during central CSR events, by assessing upper airway caliber during sleep using the forced oscillation technique (FOT).

Nine males with compensated heart failure (mean left ventricular ejection fraction 27.9 ± 5.1 (SEM) %) and predominant central CSR (apnea-hypopnea index = 43.9 ± 4.2 events/h) were studied during overnight polysomnography, which included pneumotachography, inductance plethysmography or esophageal pressure, and a FOT-derived impedance signal (|Z|).

Baseline |Z| values during stable breathing in stage 2 sleep were 11.0 ± 1.3 cm H₂O*s/L. Mean |Z| increased to 31.9 ± 6.7 cm H₂O*s/L during obstructive apneas (7% of events, n=46). Increases in |Z| consistent with upper airway narrowing (> 2-fold baseline) were common during central apneas (50 ± 12% of events) occurring in the middle or end of apneas and occurred during some (16 ± 10% of events) central hypopneas, typically in the expiratory phase.

These findings indicate that in heart failure patients, reductions in upper airway caliber are common during CSR apneas, and may also occur during central hypopneas.

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INTRODUCTION
Cheyne-Stokes Respiration (CSR) during sleep is prevalent among patients with congestive heart failure (CSR-CHF) [1] and is associated with increased mortality. [2, 3] The pathophysiology of CSR remains incompletely understood. A key factor triggering central apneas is a reduction in PCO$_2$ below the apnea threshold [1], that is related to sleep-wake instability, altered ventilatory and cerebrovascular CO$_2$ chemosensitivity, prolonged circulation time and stimulation from pulmonary irritant receptors [1, 4-6]. However, the observation that there may be a shift between obstructive and central apneas in CSR-CHF [7, 8], that CSR can be affected by posture, [9, 10] and may be suppressed by continuous positive airway pressure (CPAP) in some patients [11] suggests that upper airway instability may also play a role in this disorder. Dynamic changes in upper airway caliber might therefore be a further factor contributing to ventilatory instability in CSR-CHF.

Upper airway (UA) closure has previously been reported to occur in some forms of both spontaneous and experimentally induced central apnea [7] [12-14] [15]. However, upper airway patency during central apneas and hypopneas has not been systematically investigated in patients with congestive heart failure.

The Forced Oscillation Technique (FOT) is a non-invasive method for instantaneous measurement of respiratory system mechanics which has been shown to be reliable in assessing upper airway caliber during sleep in patients with obstructive sleep apnea (OSA)[16] [17, 18]. FOT systems have been developed which measure impedance ($|Z|\text{in cm H}_2\text{O}*\text{s/l}$) of the respiratory system during sleep in a continuous fashion without disturbing sleep architecture or altering upper airway muscle tone[19]. FOT has been shown to be a sensitive indicator of dynamic changes in upper airway caliber during obstructive events[17] and can be used to both detect respiratory events and guide CPAP titration[16, 20, 21].

In the present study, we hypothesized that in CHF patients with CSR, upper airway closure would occur during central apneas and hypopneas. The objective of the study was to evaluate changes in upper airway caliber during CSR using FOT.
METHODS

Subjects:
Patients with stable chronic CHF being screened for the CANPAP study [11] were recruited from the Sleep Disorders and Cardiac Function Clinics of the McGill University Health Centre. The Research Ethics Board approved the study protocol.

Eligibility requirements have been described in full elsewhere [22]. Briefly, subjects were adults with stable CHF due to ischemic, idiopathic or hypertensive cardiomyopathy with left ventricular ejection fraction < 40% (by radionuclide angiography) and ≥15 apneas and hypopneas per hour of sleep (apnea-hypopnea index, AHI), of which > 50% were central at screening polysomnography. We recruited eligible subjects who either declined participation in the main study or were studied before randomization within CANPAP.

Experimental Protocol:
After initial screening polysomnography to determine eligibility, each subject underwent a subsequent overnight (n = 8) or daytime (n = 1) conventional polysomnogram with the addition of esophageal pressure (Pes) monitoring when tolerated by the subject, and a sealed face mask connected to the FOT circuit for measurement of respiratory system impedance (|Z|).

Each polysomnogram was first scored in a standard manner (sleep and respiratory events) [11] by a trained polysomnographic technologist. Afterwards, FOT-derived impedance values during respiratory events in non-REM sleep were assessed as described below.

Measurements:
A. Polysomnography
Signals included: electroencephalogram (EEG) (C4A1, C3A2) chin electromyogram (EMG), electrocardiogram (ECG) and electrooculogram (EOC) that were recorded and scored for sleep stages and arousals according to standard criteria [23, 24]; Noctural arterial oxyhemoglobin saturation (SpO₂) measured with a finger probe (Ohmeda Biox 3700, Mississauga ON); rib cage and abdominal movements by inductance plethysmography (Respirace, Ambulatory monitoring}
inc., Ardsely NY); esophageal pressure (Pes) (balloon-tipped catheter attached to a differential pressure transducer: Validyne, Northridge CA) and airflow and oscillatory impedance using the FOT device as described below. These variables were simultaneously recorded using a standard polysomnography system (Sandman, Ottawa ON) and a second computerized system (CODAS, Dataq instruments, AkronOH) for subsequent respiratory signal processing. At least 3 hours of sleep were necessary in order for PSG data to be included in the final analysis.

B. Oscillatory impedance measured using the forced oscillation technique (FOT)
FOT was applied as previously described[17, 18][25]. A full-face mask was connected to a mesh-wire based pneumotachograph (resistance = 0.522 L/s) connected to a T-piece (T). One arm of the T-piece was connected (Tb1) to a chamber with a loudspeaker (LS. 8 BR40, Beyma, Valencia SPAIN) and the other arm to a tube (Tb2) acting as a pneumatic low-pass filter. A continuous bias flow (0.4 L/s) through all the tubing was applied to the system in order to avoid rebreathing. A small amplitude (1 cmH2O peak-to-peak) pressure oscillation of 5Hz was generated with the loudspeaker and applied on the mask while the patient breathed spontaneously. Mask pressure (Pm) and flow (V') signals were measured with differential pressure transducers (range +/- 9 and 2 cmH2O, respectively, Validyne P300D, Northridge California). The frequency responses at 5 Hz of the flow and pressure transducers were matched within 1% in gain and 1° in phase. Special attention was paid in avoiding leaks by carefully fitting the full-face mask. The raw flow and pressure signals were analogically low-pass filtered (Butterworth 8-poles, 32 Hz) and introduced in a microprocessor-based system for digital on-line computation of $|Z|$
[26]. This signal was recorded on the polygraph as well as in the CODAS acquisition system as an additional channel.

Data analysis:
A. Scoring of respiratory events:
Scoring criteria for respiratory events were identical to those used in the CANPAP study [11], although with substitution in the present study of the pneumotachograph airflow signal for nasal pressure, and the availability of additional information concerning respiratory effort in subjects with esophageal pressure catheters in place. CSR was defined as repetitive cycles of apneas and/or hypopneas alternating with hyperpneas having a crescendo-decrescendo pattern of tidal volume, occurring at a rate of more then 15 events per hour of sleep. Central apneas (CA) were
defined as the absence of tidal volume for 10 or more seconds without thoracoabdominal motion and central hypopneas (CH) as a reduction of 50 percent or more in tidal volume from baseline for 10 or more seconds with flow paralleling esophageal pressure and/or thoraco-abdominal displacement, and without clear inspiratory airflow limitation on the pneumotachograph signal. Apneas and hypopneas were classified as obstructive if there was out-of-phase motion of the rib cage and abdomen, incremental respiratory effort disproportionate to flow on esophageal pressure tracing or clear inspiratory airflow limitation on the pneumotachograph signal.

B. Measurements of impedance values $|Z|$ during apneas and hypopneas:

We analyzed impedance in 1 out of 5 CSR events in each patient, with the first event randomly selected then every $5^{th}$ consecutive event analyzed. For obstructive events, due to the small number, all events observed were analyzed.

Impedance was measured during the apneic or hypopneic period of the CSR cycle. For apneas, measurements of impedance were done by computing the mean $|Z|$ value of a 2 sec window at the beginning, middle and end of the apnea. For hypopneas, to determine the beginning and end of the measurement period, we defined a threshold flow as 50% of the mean of the 10 peak values of inspiratory flow during stable respiration (without CSR or OSA) in supine stage 2 sleep. A hypopnea began with the first cycle that included a peak inspiratory flow below the threshold flow and it ended with the last cycle that contained a peak inspiratory flow below the threshold flow. To measure $|Z|$ values during hypopnea, first, the mean mid-inspiratory $|Z|$ value (window: 0.4 s at the middle of inspiration) for 10 consecutive breathing cycles of spontaneous normal breathing was averaged in order to obtain a normalized inspiratory value (stage 2 supine or awake if not available during sleep). The same analysis was performed with the corresponding expiratory cycle phases in order to obtain a normalized mid-expiratory value. Then, inspiratory degree of occlusion was calculated by averaging the mid inspiratory value (window: 0.4 s) for each respiratory cycle during the event and expiratory degree of occlusion was calculated by averaging the mid expiratory value (window: 0.4 s) for each respiratory cycle during the event.
Previous studies in patients with OSA have indicated that major UA narrowing or collapse can be reliably identified when the impedance value increases to levels greater than 2 times baseline values during tidal breathing\cite{16, 27}. Therefore, for the various categories of respiratory events, we determined the proportion of events for which $|Z|$ exceeded this value.

**Statistical analysis:**

FOT - derived impedance $|Z|$ values were expressed as absolute values or as percentage of baseline $|Z|$ value during stable breathing. $|Z|$ values during stable breathing, central and obstructive apneas and hypopneas were normally distributed and mean values were compared using t-test. Correlations between anthropometric or clinical measures and $|Z|$ values were assessed using Pearson's product-moment coefficient. Data are expressed as mean $\pm$ SEM unless otherwise specified. A threshold of $p < 0.05$ was used for statistical significance.

**RESULTS**

Subject characteristics are presented in Table 1. On the original diagnostic polysomnograms, the Apnea index was $30.5 \pm 3.6$ events/h, total sleep time $5.2 \pm 0.8$ h and $66.3 \pm 3.6\%$ of events were central. CHF etiology was ischemic in 6 subjects and idiopathic in 3. NYHA Class was II 4 subjects and III in 5. Placement of an oesophageal catheter was attempted in all subjects but was unsuccessful due to discomfort in 4. Subject characteristics were not significantly different between those with vs. without oesophageal catheters.

Representative tracings of typical respiratory events are shown in Figures 1 - 3. Figure 1a illustrates the impedance signal during central apneas during the CSR cycle in which the impedance value remained low throughout. In contrast, figure 1b shows central apneas during which the impedance signal increased substantially during the course of the events, followed by a rapid fall to baseline as soon as respiratory effort was initiated.

Figure 2 illustrates central hypopneas as evidenced by the changes in airflow paralleling changes in respiratory effort. Impedance values during hypopneas were often increased above baseline values during stable breathing, most often during the hypopneic phase of the CSR cycle (Fig 2a)
but in some cases across the CSR cycle (Fig 2b). $|Z|$ values tended to be higher during expiration and fall during inspiration. This pattern was observed in 5 of the 8 subjects with central hypopneas. Overall, however, mean $|Z|$ values during the expiratory phase were not significantly higher than during the inspiratory phase (15.7 ± 0.8 vs 14.9 ± 1.1 cm H$_2$O*s/L $p=0.81$).

We observed a small number of obstructive events in this patient group. One example is shown in figure 3 with the typical CSR pattern of effort during absent airflow, followed by a sudden resumption of airflow with airway re-opening. The impedance signal increases progressively during the obstructive event, with initially, impedance increasing during inspiratory effort and decreasing during the expiratory phase, followed by consistently high values indicative of persistent airway closure, followed by a rapid fall in impedance at airway re-opening.

A total of 647 events were analyzed, the majority of which were central (Table 1). As noted above, for central events, every fifth event was analyzed, while all obstructive events observed were analyzed. All 9 subjects demonstrated central apneas (40 ± 10 events analyzed per subject), 8 of 9 demonstrated central hypopneas (27 ± 11 events analyzed per subject), while 4 subjects demonstrated obstructive events (18 ± 3 analyzed per subject).

The mean baseline FOT-derived impedance value during stable breathing in non-REM sleep was 11.0 ± 1.3 cm H$_2$O*s/L. For the different categories of respiratory events, mean $|Z|$ values were, respectively: 15.3 ± 1.7 cm H$_2$O*s/L for central hypopneas (34% of total events analyzed); 27.3 ± 5.9 cm H$_2$O*s/L for central apneas (55% of events); 30.6 ± 11.5 cm H$_2$O*s/L for obstructive hypopneas (4% of events) and 31.9 ± 6.7 cm H$_2$O*s/L for obstructive apneas (7% of events). All of these values were significantly greater than baseline ($p<0.005$).

Figure 4 shows mean values for $|Z|$ during the first, middle and latter third of apneas for central versus obstructive apneas. While values during obstructive events tended to be higher, there were substantial increases in mean $|Z|$ during central events indicating prominent degrees of upper airway closure.
Figure 5 illustrates the proportion of respiratory events during which UA closure occurred as defined by a criterion of $|Z|$ reaching twice the baseline value during stable breathing. Given the small number of obstructive events, apneas and hypopneas were pooled for this analysis. For central hypopneas, 5 subjects demonstrated varying degrees of UA closure. For central apneas, the frequency of UA closure during events also varied between subjects, with UA closure occurring rarely or not at all in some subjects but in a majority of events in others. The upper airway was more likely to be occluded during central apneas than hypopneas as shown by the significantly higher proportion of events with $|Z|$ values exceeding twice baseline values for central apneas compared with hypopneas ($0.50 \pm 0.12$ vs $0.16 \pm 0.1$, $p = 0.03$).

There were no systematic differences in subject characteristics including age, BMI, LVEF, AHI or other measures of apnea severity between subjects with frequent vs. rare or absent upper airway closure during central events (Table 1). Airway closure during central events was not consistently related to the occurrence of obstructive events in the same subjects. There was a trend to a positive correlation between BMI and baseline pre-event $|Z|$ value ($r= 0.64$, $p=0.06$). No significant correlations were identified between anthropometric measures and the proportions shown in Figure 5. For the subjects (n = 4) who demonstrated occasional obstructive events, $|Z|$ values during central apneas were high in 2 and low in 2 others).

**DISCUSSION**

In this study, we applied the forced oscillation technique to assess upper airway patency during predominantly central sleep apneas and hypopneas in subjects with compensated chronic congestive heart failure. We found that airway closure occurred to a variable extent during central apneas, with some patients frequently demonstrating airway closure, and others rarely demonstrating evidence of upper airway collapse. Upper airway narrowing was less common during CSR hypopneas than apneas, and during hypopneas, UA impedance tended to be higher during expiration than inspiration.

The FOT-derived impedance $|Z|$ signal has previously been used to identify UA obstruction during sleep in OSA [17] UA closure is a dynamic process in OSA associated with an
instantaneous large increase in respiratory resistance, which cannot be accounted for by other changes within the respiratory system. One limitation of our study is that we did not directly visualize the upper airway. However, invasive techniques such as videoendoscopy would likely be poorly tolerated in CHF patients whose sleep quality is generally poor. The values of the impedance signal observed during obstructive events in the present study were comparable with those previously described in severe OSA \(|Z| = 36 \pm 8 \text{ cmH}_2\text{O/ls-1}|\) [12] supporting the conclusion that high impedance values observed during central events were indeed indicative of substantial upper airway narrowing.

Another potential limitation of the study was the inability of 4 of 9 subjects to tolerate an oesophageal catheter, which can be useful in distinguishing central from obstructive hypopneas. Only central apneas were observed in one of the 4 subjects without esophageal pressure, and in the other 3 subjects, the number of central apneas sampled/analyzed outnumbered central hypopneas two-fold. Nonetheless in the latter subjects, we were confident of the central nature of the events so designated, based on the pneumotachography and inductance plethysmography signals, as well as the characteristic pattern of \(|Z|\) changes during these events (cf. Fig 2 vs. Fig 3). Another potential limitation of the study was the relatively small number of subjects which may have restricted our ability to identify anthropometric and other clinical factors in contributing to upper airway collapse.

The findings of the present study are in accordance with previous studies providing direct evidence of UA collapse during spontaneous or induced central apneas/hypopneas using acoustic or video-endoscopic techniques [13, 15]. More recently, Vanderveken and colleagues applied FOT in 8 patients with predominantly obstructive sleep apnea and demonstrated variable increases in \(|Z|\) during a small number of central apneas [12]. However, to our knowledge, ours is the first study to assess UA caliber with FOT in a group consisting of exclusively stable CHF patients with predominantly central events.

FOT alone does not permit determination of the specific site of UA obstruction, or whether airway closure is passive or active. Reductions in pharyngeal cross-sectional area level have been observed by videoendoscopy during spontaneous idiopathic central apneas [13], [15]. In one
study [13] EMG recordings demonstrated that pharyngeal constrictors were inactive, suggesting passive airway closure. As well, Badr and colleagues observed diminished pharyngeal cross-sectional area on videoendoscopy associated with increased UA resistance during induced central hypocapnic hypopnea [15] [14]. Of note, retropalatal narrowing under these low drive/hypotonic conditions occurred predominantly during the expiratory phase [14]. In our study, the development of UA closure during the course of central apneas, with immediate airway re-opening associated with the onset of inspiratory effort and airflow (Figs. 1b, 4) could be consistent with passive pharyngeal collapse during the apnea phase followed by active re-opening of the airway as inspiratory drive resumes.

During CSR hypopneas, some subjects demonstrated substantial increases in $|Z|$ values compared with stable breathing periods, at similar lung volumes as judged from respiratory inductance plethysmography signals, consistent with upper airway narrowing. This was most prominent during the hypopneic phase of the cycle (Fig 2), and impedance tended to be higher in expiration and fall during inspiration. Lung volume changes could potentially have contributed to the inspiratory decrease in $|Z|$, and the increased expiratory impedance during the hypopneic phase could reflect dynamic narrowing of intrathoracic large airways although this seems unlikely in the context of reduced drive. It seems more likely that the expiratory increase in $|Z|$ is reflective of passive upper airway narrowing during the period of reduced drive. The inspiratory fall in $|Z|$ could also represent active inspiratory airway opening. Our observations during both CSR apneas and hypopneas are therefore consistent with passive upper airway narrowing due to withdrawal of inspiratory drive to the pharyngeal dilators.

However UA caliber could also be actively diminished at the laryngeal level since it has been shown that vocal cord adductors are activated and abductors suppressed during induced hypocapnia in animals [28] as well as humans [29]. While this seems somewhat less likely in the context of CSR, the mechanisms and site of UA closure in CSA-CSR may differ between individuals, depending upon UA anatomy, CO$_2$ responsiveness and other factors [15] [14]. Ideally, innovative non-invasive imaging techniques should be combined with electromyographic studies to further characterize UA narrowing in CHF-CSR.
The observation of supine-dependence of central CSA-CSR [9, 10] and responses to fixed CPAP in some patients [11] suggest that UA narrowing during CSR events may contribute to the pathogenesis of this condition. This could be mediated through reflex inhibitory effects of UA closure, which may precipitate or prolong central apneas [30]. Variations in UA caliber could be a contributing factor to ventilatory instability, promoting ventilatory overshoot with abrupt decreases in UA resistance or dampening compensatory responses in the context of high resistance [31]. The frequent occurrence of reduced airway caliber during central CSR events in some subjects with central CSR also sheds light on the previously reported overlap between CSR and OSA [7, 8]. When airway caliber is reduced, conceivably only small changes in airway dimensions related to respiratory drive, tissue fluid shifts or changes in lung volume would be required to either promote or alleviate an inspiratory obstructive component to periodic breathing.

The findings of this study also suggest potential clinical applications for FOT in CHF-CSR patients. For diagnostic purposes, FOT-derived impedance during CSR hypopneas could assess inspiratory UA obstruction. Increased impedance could potentially be a marker for a response of CSR to fixed CPAP[11] although this remains to be tested. As well, FOT-driven auto-CPAP has been used successfully in OSA[32]. Conceivably, FOT-derived impedance could be incorporated into servo-ventilation algorithms to adjust end-expiratory pressure levels to assure upper airway patency during treatment of CSR.

In conclusion, our findings support the hypothesis that in CHF patients with CSR, UA closure occurs commonly during CSR apneas, and may also occur during central hypopneas in non-REM sleep. Further studies are needed to identify the specific site and mechanism of occlusion and the possible contribution of upper airway closure to the pathophysiology of CSR.
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REFERENCES


FIGURE LEGENDS:

Figure 1:
Examples of central CSR apneas with absence of airflow and respiratory effort from the same patient in which (1a) the FOT-derived impedance signal (|Z|) remains low throughout the event, and (1b) |Z| increases during the course of the event.
Other abbreviations: V': Flow (positive values indicates inspiration); Pes : Esophageal pressure.
Figure 2:
Representative tracings of central CSR hypopneas with the variation in airflow paralleling respiratory effort. Fig. 2a **Left panel:** the FOT-derived impedance signal increases in expiration during the hypopneic phase of the CSR cycle. **Right panel:** Magnified view of the segment indicated by the arrow in the left panel illustrating the increase in $|Z|$ during the expiratory phase of the respiratory cycle. Fig 2b shows tracings from another subject in whom expiratory $|Z|$ values remain elevated across the CSR cycle with discrete reductions in $|Z|$ during inspiration. Arrow indicates the magnified segment. Other abbreviations as in Figure 1.
Figure 3:
Representative tracings of an obstructive hypopnea with a CSR pattern of respiratory effort. **Left panel:** the FOT-derived impedance increases in concert with increasing respiratory effort, followed by an abrupt fall signaling airway re-opening at the end of the obstructive event. **Right panel:** Magnified view of the segment indicated by the arrow in the left panel. The marked increases in impedance are occurring during the inspiratory phase consistent with dynamic inspiratory airway collapse. Other abbreviations as in Figure 1.
Figure 4:
Group mean values (± SE) for FOT-derived $|Z|$ during apneas during the first, middle and latter third of CSR central apneas (open circles) compared with obstructive apneas (closed circles).
Figure 5:
Proportion of respiratory events with $|Z|$ increases consistent with upper airway closure, by event type. Smaller symbols indicate individual patient values, while group mean values (± SE) are indicated by symbols with error bars. *p<0.05 vs central events (hypopneas or apneas). # p<0.05 vs central hypopneas.
Table 1

Subject Characteristics and Proportion of Respiratory Events with Increased $|Z|$

| Subject | Age (y) | BMI (kg/m²) | LVEF (%) | AHI (l/h) | n   | $|Z| > 2X$ (proportion) | CH n | $|Z| > 2X$ (proportion) | OAH n |
|---------|---------|-------------|-----------|------------|-----|------------------------|------|------------------------|-------|
| 1       | 47      | 24.3        | 5         | 40.8       | 29  | 0.34                   | 14   | 0.00                   | 6     |
| 2       | 68      | 25.7        | 20        | 57.2       | 110 | 0.72                   | 97   | 0.40                   | 18    |
| 3       | 76      | 32.4        | 39        | 62.9       | 34  | 0.62                   | 45   | 0.38                   | -     |
| 4       | 84      | 31.2        | 33        | 48.9       | 60  | 0.20                   | 29   | 0.07                   | -     |
| 5       | 59      | 48.7        | 29        | 24.2       | 37  | 1.00                   | -    | -                      | -     |
| 6       | 70      | 24.3        | 38        | 28.0       | 16  | 0.00                   | 2    | 0.00                   | -     |
| 7       | 60      | 23.0        | 23        | 44.8       | 10  | 1.00                   | 2    | 0.00                   | 22    |
| 8       | 70      | 31.0        | 40        | 58.0       | 12  | 0.08                   | 14   | 0.14                   | 13    |
| 9       | 63      | 24.5        | 23        | 50.0       | 48  | 0.56                   | 16   | 0.31                   | -     |
| Mean±SE | 66.3 ± 3.4 | 29.5 ± 2.7 | 27.9 ± 3.8 | 46.1 ± 4.4 | 0.50 ± 0.12 | 0.16 ± 0.10 |

Abbreviations: BMI: body mass index; LVEF: left ventricular ejection fraction; AHI: apnea-hypopnea index from original diagnostic polysomnogram; CA, CH: Central apneas, hypopneas from study night (every 5th event analyzed); OAH: obstructive apneas & hypopneas from study night (all events analyzed); n: number of events; $|Z| > 2X$: proportion of events with $|Z|$ greater than 2-fold baseline values (see Methods for details).