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Alternative approaches to treatment of Central Sleep Apnea

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Synopsis

Divergent approaches to treatment of hypocapnic central sleep apnea syndromes reflect the difficulties in taming a hyperactive respiratory chemoreflex. As both sleep fragmentation and a narrow CO_2 reserve or increased loop gain drive the disease, sedatives (to induce longer periods of stable non-rapid eye movement (NREM) sleep and reduce the destabilizing effects of arousals in NREM sleep) and CO_2-based stabilization approaches are logical. Adaptive ventilation reduces mean hyperventilation yet can induce ventilator-patient dyssynchrony, while enhanced expiratory rebreathing space (EERS, dead space during positive pressure therapy) and CO_2 manipulation directly stabilize respiratory control by moving CO_2 above the apnea threshold. Carbonic anhydrase inhibition can provide further adjunctive benefits. Provent and Winx may be less likely to trigger central apneas or periodic breathing in those with a narrow CO_2 reserve. An oral appliance can meaningfully reduce positive pressure requirements and thus enable treatment of complex apnea. Novel pharmacological approaches may target mediators of carotid body glomus cell excitation, such as the balance between gas neurotransmitters. In complex apnea patients, single mode therapy is not always successful, and multi-modality therapy might need to be considered. Phenotyping of sleep apnea beyond conventional scoring approaches is the key to optimal management.

Keywords

carbon dioxide; oxygen rebreathing; acetazolamide Provent; Winx; multimodal complex; central apnea; periodic breathing

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Disclosures

Dr. Thomas is 1) co-inventor of the ECG-spectrogram technique to phenotype sleep and sleep apnea. This technology is licensed by the Beth Israel Deaconess Medical Center to MyCardio, LLC; 2) co-inventor of the Positive Airway Pressure Gas Modulator, a device that treats central/complex apnea with low concentration CO_2 added to positive pressure therapy. He consults for DeVilbiss in the development of a new generation auto-CPAP.

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INTRODUCTION

The treatment of central sleep apnea syndromes, especially the hypocapnic type characterized by a hyperactive respiratory chemoreflex, is challenging. The adaptive servo-ventilators target respiratory rhythm besides providing upper airway support, and are described in other chapters in this volume. Here alternative approaches to management are described, which in some instances may be used as adjunctive to positive airway pressure. As the hypocapnic central sleep apnea syndromes are characterized by specific pathological rhythms of respiration, accurate polysomnographic recognition of driving chemoreflex influences is critical to "dose" primary and adjunctive/alternative therapies. Phenotyping sleep apnea contributory components are central to phenotype-driven therapy. The phenotypes that have current treatment options are upper airway collapsibility, chemoreflex activation level, and sleep fragmentation propensity.

POLYSOMNOGRAPHIC RECOGNITION OF A HEIGHTENED RESPIRATORY CHEMOREFLEX

Scoring of respiratory events in sleep apnea patients have traditionally been biased to an obstructive phenotype, though the recent update of the 2007 American Academy of Sleep Medicine (AASM) guidelines has criteria for scoring central hypopneas and short sequences of periodic breathing/Cheyne-Stokes respiration.[1] The guidelines state that central hypopneas should not be scored in the presence of flow-limitation, but obstruction is a common feature of central events,[2] even at simulated altitude,[3] the latter being a relatively pure model of chemoreflex-driven sleep apnea. Direct visualization of the upper airway shows collapse at the nadir of the cycle to be common even in polysomnographic "central" disease. [4] Expiratory pharyngeal narrowing occurs during central hypocapnic hypopnea, [5] directly supporting the concept that the presence of flow-limitation alone cannot be used to distinguish obstructive and central hypopneas. [3] Complex sleep apnea as currently "defined" requires a central apnea-hypopnea index ≥ 5/hour of sleep with centrally mediated respiratory events constituting ≥ 50% of all respiratory events during CPAP titration, in those who do not fulfill criteria for primary central sleep apnea or periodic breathing on the diagnostic polysomnogram. However, publications of complex apnea did not score central hypopneas or periodic breathing. D*escriptions of low (< 5%) persistence of "complex apnea" may be inaccurate and reflect reliance solely on scoring classic central apneas.* [6, 7] The guideline for recognition of "Cheyne-Stokes respiration" also require a cycle duration of at least 40 seconds, but we have shown that even shorter cycle times in the range of 20–25 seconds is typical of NREM-dominant sleep apnea,[8] reminiscent of high altitude periodic breathing. *The most characteristic feature of chemoreflex drivenevents is not the morphology of individual events but NREM-dominance and timing/morphology of sequential events (nearly identical) in a consecutive series of events*.[9]

A related dimension is the criteria used for estimating success of therapies. For example, if 4% oxygen desaturation is used to score hypopneas (in most treatment reports and which continues to be the recommendation of the AASM), significant degrees of baseline and residual disease can be missed. Moreover, adaptive servo-ventilators distort the conventional polysomnogram signals and unless the pressure output of the devices are used to score

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events, inappropriate success may be declared. When periodic breathing is not adequately controlled, the primary marker on the polysomnogram is pressure cycling associated with arousals. Scoring respiratory events during adaptive servo-ventilation needs to use the pressure output signal from the ventilator, which is roughly equal and opposite to the patient's abnormality. When pressure cycling persists, sleep fragmentation is usually severe even if respiration is "improved" by conventional criteria.

ADVANCED PHENOTYPING OF CHEMOREFLEX INFLUENCES ON SLEEP RESPIRATION

The NREM sleep CO_2 reserve can be exposed inadvertently during bilevel positive pressure titration in the sleep laboratory, when central apneas or periodic breathing may emerge though continuous positive pressure was well tolerated and efficacious. An experimentally precise version of this approach uses bilevel ventilation with measurement of end-tidal CO_2 – the difference between stable breathing and the level just before bilevel-induced periodic breathing or central apneas. This is the CO_2 reserve, and is smaller, 2–3 mm Hg, in those with heart failure and predominantly central sleep apnea.[10] Proportional assist ventilation may also be used to estimate the "ease of induction" of central apnea and periodic breathing, and thus quantify the contribution of enhanced respiratory chemoreflexes to sleep apnea severity.[11–15] This technique requires considerable expertise and is not readily applicable to a clinical laboratory environment.

Time series analysis of the electrocardiogram (using heart rate variability and heart rate/respiratory coupling) can provide a map of sleep state oscillations, with the spectral dispersion providing phenotyping information regarding chemoreflex influences [9]. The technique, the ECG-spectrogram, maps coupled oscillations of heart rate variability and respiratory R-wave ECG amplitude modulation. The ECG-derived sleep spectrogram can detect low frequency coupled oscillations with two primary patterns: broad band and narrow band. Elevated narrow band coupling which detects sequences of central apneas and periodic breathing is noted in patients with complex sleep apnea. Those with the ECG-spectrogram biomarker of strong chemoreflex modulation of sleep respiration also have more severe sleep apnea and greater degrees of sleep fragmentation [16]. A wearable device (FDA approved, M1, www.sleepimage.com) is currently available for clinical and research use.

Determination of multiple phenotypic traits can be accomplished by assessing the dynamic flow and pressure responses to positive pressure dial down.[17] In a follow-up study, [18] 75 men and women with and without OSA aged 20–65y were studied on 3 separate nights. The following were determined - anatomical collapsibility (Pcrit), and non-anatomical factors (genioglossus muscle responsiveness, arousal threshold, and respiratory control stability/loop gain). The key findings, of which formal publication is awaited, varied substantially between participants. In brief, 36% of OSA patients had minimal genioglossus muscle responsiveness during sleep, 37% had a low arousal threshold, 36% had high loop gain; 28% had multiple non-anatomical features. Nineteen percent had a relatively non-collapsible upper-airway similar to controls, and in these patients, loop gain was almost twice as high as patients with a collapsible airway, despite comparable apnea-hypopnea indices.

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Experimental elegance does not readily translate to clinical utility. However, review of the data tables of virtually all publications on central and complex sleep apnea, regardless of exact criteria and comorbid diseases such as congestive heart failure, and when available in description of sleep apnea phenotyping approaches, show one common theme – NREM sleep dominance of sleep apnea. Table 1 describes the features of an activated respiratory chemoreflex on polysomnographic and polygraphic (home sleep studies, for example) assessments. These features are valid on diagnostic assessments and during therapeutic interventions. Figures 1 and 2 are an overall schema of integration of various therapeutic modalities with and without positive airway pressure, respectively.

NON-POSITIVE AIRWAY PRESSURE TREATMENTS FOR CENTRAL SLEEP APNEA SYNDROMES

Minimization of hypocapnia

The use of supplemental CO_2 for hypocapnic central sleep apnea syndromes is old news. That CO_2 can stabilize respiration has been known for decades, but high concentrations fragment sleeps by inducing arousals secondary to respiratory stimulation and sympathoexcitation.[19, 20] The key challenge has been delivery of CO_2 in a clinically adequate, tolerated, and precise manner. Prevention of hypocapnia is a critical stabilizing factor in sleep respiratory control. “Minimization of hypocapnia” is also physiologically a more appropriate phrase than “induction of hypercapnia” as the latter is utterly unnecessary. The key is holding the CO_2 steady and just above the NREM sleep CO_2 threshold – protecting the CO_2 reserve.

A recent study by Xie et al is one of the best demonstrations of the power of CO_2 modulation in treating sleep apnea syndromes.[21] Twenty-six patients with obstructive sleep apnea (AHI 42±5 events/hour with 92% of apnea were obstructive) were treated with O_2 supplementation, an isocapnic rebreathing system in which CO_2 was added only during hyperpnea to prevent transient hypocapnia, using a continuous rebreathing system. Each patient’s controller gain below eupnea was measured, as was CO_2 reserve, plant gain, and passive upper airway closing pressure. With isocapnic rebreathing, 14/26 reduced their apnea-hypopnea index (AHI) to 31±6% of control ($p<0.01$) (responders); 12/26 did not show significant change (non-responder). The responders vs. non-responders had a greater controller gain, a smaller CO_2 reserve but no differences in Pcrit. Hypercapnic rebreathing (+4.2±1 mmHg $PETCO_2$) reduced AHI to 15±4% of control ($P<0.001$) in 17/21 subjects with a wide range of CO_2 reserve. Hyperoxia (SaO_2 ~95–98%) reduced AHI to 36±11% of control in 7/19 OSA patients tested.

Thus, there is strong evidence from multiple studies over the years that manipulation of arterial CO_2 levels might provide an alternative treatment strategy. Addition of a closed volume (space) to exhalation increases rebreathing of the exhaled air and results in a quick increase in CO_2 levels and an increased tidal volume and respiratory rate. This is similar to breathing into a plastic bag when trying to treat anxiety-induced hyperventilation. Increased amounts (>300 mL) manifestly feel uncomfortable from both CO_2 retention and volume effects. The concept has been used in mechanical ventilation to reduce hypocapnia for

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several years and more recently has been successfully used to treat central sleep apnea and Cheyne-Stokes respiration in heart failure. None of these uses combine it with positive airway pressure.

We have shown that keeping CO_2 above the apnea threshold with the use of Enhanced Expiratory Rebreathing Space (EERS) is an effective adjunct to PAP therapy [22]. Enhanced expiratory rebreathing space (EERS) is the dead space concept applied to pressure ventilation. Positive airway pressure therapy usually induces mild relative (to pretreatment) hypocapnia. Central apneas and periodic breathing can be generated when the arterial PCO_2 level falls below that required to stimulate respiration. This level is referred to as the *apnea threshold*. Hypocapnia at or near the apnea or CO_2 control threshold destabilizes sleep-breathing control, resulting in periodic breathing patterns of various severities and morphological characteristics. Preventing hypocapnia is a powerful stabilizing influence on sleep-breathing control, regardless of the presence of hypoxia. Atmospheric CO_2 levels are near zero, therefore the CO_2 levels in the blood are the result of the balance between metabolism in the patient and blow-off during breathing.

The clinical effect of using EERS is consistently positive (Figures 3a–3e) and this approach is now routinely available in our sleep laboratory to use with CPAP or adaptive servo-ventilation, as requested by the physician. We described in our original report improved clinical tolerance, compliance and sustained clinical improvement monitored over a period of several months by adding EERS [22]. This was achieved in a subgroup of patients who had stopped using CPAP, and whom we were able to salvage with the use of EERS. Sub-tidal volume dead space is adequate when the upper airway is also supported, and is well tolerated physiologically. Control of respiratory abnormality is achieved with minimal increase in CO_2 (2–3 mmHg) which we speculate judging by the beneficial effects seen within 20–30 seconds is due to the effect on carotid chemoreceptors.

There is strictly no true dead space when this concept is used with pressure ventilation. Mixing, turbulence, and leaks ensure variable degrees of effective rebreathing (thus the suggested term *enhanced expiratory rebreathing space*). There is, however, a reduction in ventilatory blow-off, with remarkable clinical effectiveness. There is no/minimal increase in inspiratory CO_2 because of the positive pressure-induced washout. One important practical effect of using positive airway pressure with enhanced expiratory rebreathing space is that the respiratory rate seems unchanged, and the subject does not notice any significant discomfort. This is not surprising, given the known effects of positive pressure support on relieving shortness of breath in mechanically ventilated patients. Such symptom minimization is obviously important when considering use in patients who are already short of breath, such as in heart failure.

The physiological target for titrations with enhanced expiratory rebreathing space is to maintain $ETCO_2$ at the low normal range for sleep. Normal sleep results in an increase of 2 to 8 mm Hg in $ETCO_2$. With this technique the target is to keep the $ETCO_2$ in the high 30s to low 40s, the lower end of normal. Those with central and mixed sleep-disordered breathing show a prominent tendency to hypocapnia during sleep. The primary monitoring is that of $ETCO_2$ with a mainstream CO_2 sensor at the mask. Transcutaneous CO_2 may

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usefully complement end-tidal measures but is not critical for treatment of hypocapnic central/complex sleep apnea. Transcutaneous measurements can have a role in hypercapnic central apnea management. A biocalibration of $ETCO_2$ may be done before the sleep study (1 to 2 minutes rested steady breathing, average final 10 breaths), with a nonvented (NV) mask and 50, 100, and 150 mL added dead space. This biocalibration may be used to determine the starting EERS volume or flag those with too high a $ETCO_2$ to use a NV mask approach. The CO_2 targets are to keep the $ETCO_2$ below 50 mm Hg during sleep and not greater than 5 mm Hg increase from wake. If transcutaneous CO_2 is monitored, keep at less than 50 mm Hg or limit increases to 5 mm Hg from baseline. The latter approach is somewhat approximate, because sleep baseline $ETCO_2$ without an NV mask in the patient will probably not be known and it is unclear how much time is required for equilibration after sleep onset.

The mask-fitting clinic at the Beth Israel Deaconess Medical Center has modified a large number of masks. Specific masks, methods to convert to NV, and appropriate connectors are available on request (contact the author at rthomas1@bidmc.harvard.edu) and are tabulated with mask-specific PowerPoint files. The nonvented configuration, including the safety valve, adds 60 to 100 mL of dead space (including the intra-mask space), and this “NV alone” usually means about 60 to 100 mL of dead space/EERS compared to a vented mask. What this means in practical terms is that adding further EERS is often not necessary any more.

There are two approaches to titration of EERS, “forward” and “backward.” In the forward approach, incremental options are considered with positive airway pressure first with a vented mask, then converting to a nonvented mask, then adding rebreathing space (e.g., 50 mL, then 100 mL, etc.), O_2. In the backward approach, maximal stabilization is provided at the outset, starting at 50 mL “dead space” (which seem to be adequate for most) and 2 L/min O_2. After obtaining control in REM/stable and unstable NREM sleep, the O_2 and CO_2 modulations can be progressively withdrawn to assess the minimum requirement. Typically with successful dead space, O_2 is not critical but can be a useful backup, because consistent good seals at home are hard to maintain. Obtaining a plateau on the $ETCO_2$ signal ensures effectiveness (that the seal is adequate) and accuracy of the reading. An alternate approach is to simply start with an NV mask and no added EERS and titrate as required.

CO_2 manipulation can also be done by bleeding CO_2 in to the circuit by a more precisely controlled flow-independent method. Successful treatment of mixed obstructive and central sleep apnea using a proprietary device has been reported, the positive airway pressure gas modulator (PAPGAM), which delivers precisely controlled concentrations of CO_2. In a small case series, 6 patients with average AHI of 43/h on CPAP improved with reduction of AHI to 4.5/h with addition of 0.5–1% using PAPGAM [23]. However, this requires experienced technologists and the development of a clinically safe device. It is unclear if dynamic CO_2 manipulation (delivery restricted to a specific phase of the respiratory cycle) will improve upon the stabilizing effects of CO_2, but if a medical grade CO_2 source (cylinder) is needed, improved efficiency and duration of a single refill may be achieved.[24]

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Oxygen

Nasal O_2 has a long history of use to treat central sleep apnea and periodic breathing.[25, 26] Effectiveness is partial and residual sleep apnea and sleep fragmentation are typical. Adding oxygen to CPAP may result in better control of central/complex apnea, with a reduction in responsiveness of peripheral chemoreceptors and the loop gain [27]. The limitations include the long term cost and difficulty with reimbursement in 'non hypoxic' patients. A recent study in a Veteran's population showed that O_2 has beneficial effects, but the polysomnographic changes were delayed by as much as an hour or more.[28] One change to be aware is that of respiratory event cycle length – which can lengthen with the use of O_2. Such a change may "reduce" the respiratory event index but not imply a true stabilization of respiration. Use of O_2 also negates use of desaturation link to score hypopneas. It should be noted that hypoxia levels used to initiate O_2 therapy are not the threshold for evaluating supplemental O_2 - moving saturations from the mid to the high 90's can be beneficial. Use of O_2 is off-label for central apnea syndromes. Supplemental O_2 can thus usefully be a component of a multi-modal multi-step approach to management of central sleep apnea syndromes. Figure 4a–4c is an example of use of supplemental O_2 during positive pressure therapy, along with EERS – the treatment response also provides information about the phenotype.

Sleep stabilization

Most patients, including older individuals or those on benzodiazepines/sedative drugs, exhibit periods of sleep that are not scored as N3 by conventional criteria (or any modification thereof) but clearly have ample low amplitude delta frequency waves. Respiration is usually quite stable during this period (functionally, think of it as slow wave sleep), and if recognized, the same precautions as during conventionally scored slow wave sleep apply. Those who study the cyclic alternating pattern (CAP) will recognize this type of "stable" NREM sleep as predominantly non-CAP.[29] In fact, for the purpose of titration, dividing sleep into stable and unstable NREM sleep (or non-CAP/CAP) and REM works well, better than N1 to N3 and REM sleep. It may be easier to recognize stable and unstable NREM sleep from non-electroencephalographic signals, such as respiration, heart rate variability, and respiratory amplitude modulation of the electrocardiogram.[30] The stability of this non-CAP or slow wave-like (frequency but not amplitude) sleep can cause a false sense of security (of treatment efficacy); it is also important not to change pressures if this state is recognized (unless obstructions and flow limitation are quite overt). Flow can look absolutely normal in this state, and then rather abruptly (often within a minute) a switch to being quite abnormal may occur. Such switches of stable/unstable state are spontaneous, and disease or treatment needs to deal with this dynamic.

The sleep fragmentation phenotype can be suggested by several polysomnographic features. There may be prolonged (more than 5–10 minutes) sleep-wake transitional instability. The same pattern can be seen if the laboratory bedtime is before the internal biological night (a phase delayed person trying to sleep hours before natural bedtime). The sleep efficiency may be low (less than 70%) and stage N1 remaining increased (greater than 15%) during the positive pressure titration study. There may be prolonged post-arousal instability (1–2 minutes of periodic breathing after individual arousals). Slow waves may evolve poorly

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across the night with a low density of the waves of the < 1Hz slow oscillation - this may be more readily visualized than quantitatively estimated in the sleep laboratory as conventional slow-wave sleep is only a fraction of stable NREM sleep. However, relative paucity of non-CAP EEG morphology during titration (less than 30%) is a marker I have found useful. If the fragmentation phenotype is recognized, the following are options: 1) reduce pressure (watch for evidence of increased obstruction) or change mode; 2) allow the patient to take a break, until subjective sleepiness is noted, to allow better expression of homeostatic sleep drive; 3) trigger the physician-directed drug option if ordered.

The core concept then is to use sedatives that can induce stable NREM sleep. While the conventional approach avoids sedatives in “obstructive sleep apnea”, these drugs can be used safely in NREM-dominant apnea as here arousals further destabilize sleep and worsen sleep apnea severity. In fact eszopiclone can improve sleep apnea in those with a low arousal threshold.[31] Arousals from sleep and frequent sleep stage transitions can both induce and increase the severity of central and complex sleep apnea. The proposed mechanisms are arousal induced hypocapnia, reduction of upper airway resistance upon arousal and increased neural output to respiratory centers in wake. Triazolam, temazepam, zolpidem, and clonazepam have all been shown to reduce central apnea pathology. [32–35] We selectively use hypnotics with good clinical results with patients with the sleep fragmentation phenotype. Short-acting sedatives can be part of a “lab pharmacology protocol” (Figure 1, 2) or the patient can take the drug at bedtime.

Opioid dose reduction

Opioid use is a risk factor for development of ataxic breathing and central sleep apneas.[36–38] Decreasing the dose of opiates may help reduce central apneas [39]. In most patients stopping opiates entirely is not possible. The pathophysiology involves modulation of hypoxic and hypercapnic ventilatory responses,[40] but opiate receptors are seen all over the respiratory control pathways. Opiate-induced ataxic breathing is quite sensitive to CO_2 levels – with ready induction of central apnea and worsening of dysrhythmic breathing with continuous or non-adaptive bilevel positive pressure ventilation. Though these patients tend to show mild hypercapnia, with end-tidal CO_2’s in the high 40’s to low 50’s, using a NV mask and EERS as needed to hold CO_2 in the mid-40’s can be useful. We have found the use of acetazolamide to be of consistent benefit. Adaptive servo-ventilation is a double-edged sword in these patients – being able to both enable stable breathing and markedly destabilize breathing.

Carbonic anhydrase inhibition

Acetazolamide, a diuretic and carbonic anhydrase inhibitor diminishes the ventilator response of the peripheral chemoreceptors to hypoxia, decreases loop gain, and reduces the ventilatory response to arousals.[41–44] In animal models, it has been shown to lower the $PETCO_2$ apnea threshold and widen the difference between the eupneic and $PETCO_2$ thresholds [45]. Acetazolamide has been used in treating central apneas and Cheyne-Stokes breathing in patients with and without CHF.[46] While the results may be statistically significant, the degree of residual sleep apnea is unacceptable as sole long-term therapy. The drug can convert those with mixed obstructive and central sleep apnea to mostly obstructive

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(the reverse of CPAP-induced central sleep apnea). The drug is now part of our algorithm for management of central sleep apnea and periodic breathing. Those with short-cycle (30 seconds or less) periodic breathing not responding to EERS are the best candidates, as in this subset, the time constant of the adaptive servo-ventilators seems too long to optimally entrain and stabilize respiration. Carbonic anhydrase inhibition with acetazolamide or topiramate can be part of a “lab pharmacology protocol”, and can be used with a non-vented mask/EERS (Figure 5a, 5b). Acetazolamide has been successfully used as CPAP adjuncts at high-altitude.[47, 48] Zonisamide[49] and topiramate[50] have carbonic anhydrase inhibitory effects, and could in theory be used in the place of acetazolamide. It is not known if the neuronal effects would have an impact on respiratory control integration.

Clonidine

One report describes a potential role for clonidine as adjunctive therapy for hypocapnic central sleep apnea syndromes.[51] In a study of 10 healthy subjects (4 females) (age 22.3 +/− 3.0 years; BMI 25.5 +/− 3.4 kg/m^2), subjects were randomized to receive placebo or 0.1 mg/45 kg of clonidine on 2 separate nights. Ventilation and upper airway resistance were monitored during wakefulness and sleep. Two separate experiments were performed. In one (8 subjects), CO_2 reserve, hypocapnic apneic threshold and hypocapnic ventilatory responses were determined using non-invasive hyperventilation to induce hypocapnia. In a second protocol, peripheral hypocapnic ventilatory response was determined by non-invasive ventilation using short (3 breaths) hyperventilation. Clonidine decreased the systolic blood pressure by 12 +/− 10 mmHg but did not affect baseline ventilation or upper airway resistance during wakefulness or sleep. Clonidine was associated with a decreased hypocapnic apneic threshold relative to placebo (37.3 +/− 3.3 mmHg vs. 39.7 +/− 3.4 mmHg, increased CO_2 reserve (−3.8 +/− 1.3 mmHg vs. −2.8 +/− 1.2 mmHg), and decreased hypocapnic ventilatory responses (1.6 +/− 0.6 L/min/mmHg vs. 2.5 +/− 1.3 L/min/mmHg). Administration of clonidine did not decrease peripheral ventilatory responses. The hypotensive effect will likely reduce enthusiasm for clinical use, but the concept has merit.

Nasal expiratory positive pressure

Nasal expiratory positive airway pressure (Provent, Ventus Medical), another device with a simple design marketed for use in patients with mild OSA may also be useful in treating central and complex apnea. This device helps generate auto PEEP and increased tracheal tug via increased lung volumes, which may relieve obstructive sleep apnea; efficacy is variable and unpredictable [52]; in our center, about 25% show acceptable benefits when evaluated during polysomnography, including central sleep apnea and periodic breathing (Figure 6a–6c). This effect of Provent can be enhanced by acetazolamide, similar to the use of the drug with CPAP [48]. We speculate that Provent, while providing increased nasal expiratory resistance also gently increases the end tidal CO_2 which may stabilize the chemo-reflex driven breathing instability [52].

Oral appliances

In patients who chose oral appliances as first line treatment, it is important to be aware that central apneas can also emerge in these settings.[53] At our center we have used these devices in PAP intolerant complex apnea patients with reasonable success. Residual sleep apnea is

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typical, and requires adjunctive therapy. Oral appliances are less likely, it seems, to induce hypocapnia, but treatment of obstruction is less precise. “Cocktails” that are currently being used by our patients include oral appliance + acetazolamide, or a benzodiazepine, or supplemental oxygen. One specific use of oral appliance is use with positive pressure, to reduce pressure requirements.[54, 55]

Weight reduction

Major weight reduction, for example, through gastric bypass procedures can have profound effects on sleep apnea, though true cures are rare. In my personal experience, a small subset of post-bypass patients has conversion of predominantly REM-dominant obstructive apnea to predominantly NREM-dominant central apnea/periodic breathing after major weight loss.

Nerve stimulation

There is no data on the effect of hypoglossal nerve stimulation in patient with mixed apnea. Though speculative, it is plausible that acetazolamide could convert a mixed apnea picture to predominantly obstructive, which is then amenable to treatment with stimulation. Residual sleep fragmentation could also benefit from NREM sleep stabilization. Transvenous phrenic nerve stimulation can lower the central apnea index but more data is required to establish a clinical role.[56] Sleep efficiency in this study of 19 subjects remained unchanged, raising the possibility that improving respiration comes as the cost of inducing arousals or at least not treating disease well enough to result in sleep quality improvements.

Maxillomandibular advancement

Intuitively, maxillomandibular advancement should be reserved for obstructive sleep apnea. However, in our center we have treated over 10 patients with mixed obstructive and central sleep apnea, with the expectation of needing adjunctive therapy with nasal O_2, acetazolamide or a sedative, singly or in combination, for optimal benefit. This has indeed been the case, for requiring these alternatives.

Winx/Oral (negative) pressure therapy

This new approach uses a mouth piece to apply gentle negative intraoral suction that moves the tongue and soft palate anteriorly, opening and stabilizing the airway.[57] As positive pressure is not applied, perhaps there is less hypocapnia induction. There is no reason why Winx could not be used with, for example, acetazolamide, to provide complementary and synergistic effects on sleep-breathing, or Winx + nasal oxygen, or Winx + Provent, or indeed Winx + dead space. I have tried all these options in the sleep laboratory and they seem to have potential for benefit in individual patients (Figure 7a–7c).

Body position manipulation

A subset of central and complex apnea appears to very position dependent. These patients are “unfixable” while supine and “angels when non-supine”. The reasons include upper airway and lung volume effects, the latter perhaps altering plant gain unfavorably when supine. Positional effects in central apnea syndromes have been reported in patients with classic Cheyne-Stokes respiration in the setting of heart failure.[58, 59] Sleeping on the side is

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also an important adjunctive treatment to reduce positive pressure requirements which may cause less CO_2 blow off and respiratory instability.

A second effect of body position is on fluid redistribution from the caudal to cranial parts of the body.[60–64] The effect is rapid, associated with increased neck circumference, and hypocapnia from increased lung water in those with central apnea. Therapeutic manipulation is currently clunky but a wedge pillow or pillows are options.

Summary

Enhanced or dysregulated respiratory chemoreflexes have a profound impact on sleep-breathing and the polygraphic patterns that emerge. There is an increasing array of treatment options, on and off-label, singly or in combination, that can be used to enhance system stability. Three major components need to be adequately phenotyped and targeted – upper airway, respiratory control, and sleep fragmentation/consolidation. Alternative options for treating central sleep apnea syndromes need testing in randomized prospective trials to determine optimal roles in disease management. Until then, case-by-case trials of effectiveness will be required.

References

1. 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; 8:597–619. [PubMed: 23066376]
2. Jobin V, Rigau J, Beauregard J, et al. Evaluation of upper airway patency during Cheyne-Stokes breathing in heart failure patients. Eur Respir J. 2012; 40:1523–30. [PubMed: 22599358]
3. Thomas RJ, Tamisier R, Boucher J, et al. Nocturnal hypoxia exposure with simulated altitude for 14 days does not significantly alter working memory or vigilance in humans. Sleep. 2007; 30:1195–1203. [PubMed: 17910391]
4. Badr MS, Toiber F, Skatrud JB, et al. Pharyngeal narrowing/occlusion during central sleep apnea. J Appl Physiol. 1995; 78:1806–15. [PubMed: 7649916]
5. Sankri-Tarbichi AG, Rowley JA, Badr MS. Expiratory pharyngeal narrowing during central hypocapnic hypopnea. Am J Respir Crit Care Med. 2009; 179:313–19. [PubMed: 19201929]
6. Westhoff M, Arzt M, Litterst P. Prevalence and treatment of central sleep apnoea emerging after initiation of continuous positive airway pressure in patients with obstructive sleep apnoea without evidence of heart failure. Sleep Breath. 2012; 16:71–8. [PubMed: 21347650]
7. Javaheri S, Smith J, Chung E. The prevalence and natural history of complex sleep apnea. Journal of clinical sleep medicine : J Clin Sleep Med. 2009; 5:205–11.
8. Thomas RJ, Terzano MG, Parrino L, et al. Obstructive sleep-disordered breathing with a dominant cyclic alternating pattern--a recognizable polysomnographic variant with practical clinical implications. Sleep. 2004; 27:229–34. [PubMed: 15124715]
9. Thomas RJ, Mietus JE, Peng CK, et al. Differentiating obstructive from central and complex sleep apnea using an automated electrocardiogram-based method. Sleep. 2007; 30:1756–69. [PubMed: 18246985]
10. Xie A, Bedekar A, Skatrud JB, et al. The heterogeneity of obstructive sleep apnea (predominant obstructive vs pure obstructive apnea). Sleep. 2011; 34:745–50. [PubMed: 21629362]
11. Loewen A, Ostrowski M, Laprairie J, et al. Determinants of ventilatory instability in obstructive sleep apnea: inherent or acquired? Sleep. 2009; 32:1355–65. [PubMed: 19848364]
12. Meza S, Mendez M, Ostrowski M, et al. Susceptibility to periodic breathing with assisted ventilation during sleep in normal subjects. J Appl Physiol. 1998; 85:1929–40. [PubMed: 9804601]

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13. Younes M. Role of respiratory control mechanisms in the pathogenesis of obstructive sleep disorders. J Appl Physiol. 2008; 105:1389–1405. [PubMed: 18787092]
14. Younes M, Ostrowski M, Atkar R, et al. Mechanisms of breathing instability in patients with obstructive sleep apnea. J Appl Physiol. 2007; 103:1929–41. [PubMed: 17823298]
15. Younes M, Ostrowski M, Thompson W, et al. Chemical control stability in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2001; 163:1181–90. [PubMed: 11316657]
16. Thomas RJ. Strong chemoreflex modulation of sleep-breathing: some answers but even more questions. J Clin Sleep Med. 2009; 5:212–14. [PubMed: 19960640]
17. Wellman A, Edwards BA, Sands SA, et al. A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. J Appl Physiol. 2013; 114:911–22. [PubMed: 23349453]
18. Eckert DJ, White DP, Jordan AS, et al. Defining Phenotypic Causes of Obstructive Sleep Apnea: Identification of Novel Therapeutic Targets. Am J Respir Crit Care Med. 2013 (In Press).
19. Szollosi I, Jones M, Morrell MJ, et al. Effect of CO2 inhalation on central sleep apnea and arousals from sleep. Respiration. 2004; 71:493–98. [PubMed: 15467327]
20. Khayat RN, Xie A, Patel AK, et al. Cardiorespiratory effects of added dead space in patients with heart failure and central sleep apnea. Chest. 2003; 123:1551–60. [PubMed: 12740273]
21. Xie A, Teodorescu M, Pegelow DF, et al. Effects of stabilizing or increasing respiratory motor outputs on obstructive sleep apnea. J Appl Physiol. 2013; 115:22–33. [PubMed: 23599393]
22. Gilmartin G, McGeehan B, Vigneault K, et al. Treatment of positive airway pressure treatment-associated respiratory instability with enhanced expiratory rebreathing space (EERS). J Clin Sleep Med. 2010; 6:529–38. [PubMed: 21206741]
23. Thomas RJ, Daly RW, Weiss JW. Low-concentration carbon dioxide is an effective adjunct to positive airway pressure in the treatment of refractory mixed central and obstructive sleep-disordered breathing. Sleep. 2005; 28:69–77. [PubMed: 15700722]
24. Giannoni A, Baruah R, Willson K, et al. Real-time dynamic carbon dioxide administration: a novel treatment strategy for stabilization of periodic breathing with potential application to central sleep apnea. J Am Coll Cardiol. 2010; 56:1832–37. [PubMed: 21087712]
25. Sakakibara M, Sakata Y, Usui K, et al. Effectiveness of short-term treatment with nocturnal oxygen therapy for central sleep apnea in patients with congestive heart failure. J Cardiol. 2005; 46:53–61. [PubMed: 16127894]
26. Gold AR, Bleecker ER, Smith PL. A shift from central and mixed sleep apnea to obstructive sleep apnea resulting from low-flow oxygen. Am Rev Respir Dis. 1985; 132:220–23. [PubMed: 4026046]
27. Allam JS, Olson EJ, Gay PC, et al. Efficacy of adaptive servoventilation in treatment of complex and central sleep apnea syndromes. Chest. 2007; 132:1839–46. [PubMed: 18079219]
28. Chowdhuri S, Ghabsha A, Sinha P, et al. Treatment of central sleep apnea in U.S. veterans. J Clin Sleep Med. 2012; 8:555–63. [PubMed: 23066368]
29. Parrino L, Ferri R, Bruni O, et al. Cyclic alternating pattern (CAP): the marker of sleep instability. Sleep Med Rev. 2012; 16:27–45. [PubMed: 21616693]
30. Thomas RJ, Mietus JE, Peng CK, et al. An electrocardiogram-based technique to assess cardiopulmonary coupling during sleep. Sleep. 2005; 28:1151–61. [PubMed: 16268385]
31. Eckert DJ, Owens RL, Kehlmann GB, et al. Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. Clin Sci (Lond). 2011; 120:505–14. [PubMed: 21269278]
32. Quadri S, Drake C, Hudgel DW. Improvement of idiopathic central sleep apnea with zolpidem. J Clin Sleep Med. 2009; 5:122–29. [PubMed: 19968044]
33. Bonnet MH, Dexter JR, Arand DL. The effect of triazolam on arousal and respiration in central sleep apnea patients. Sleep. 1990; 13:31–41. [PubMed: 2406849]
34. Guilleminault C, Crowe C, Quera-Salva MA, et al. Periodic leg movement, sleep fragmentation and central sleep apnoea in two cases: reduction with Clonazepam. Eur Respir J. 1988; 1:762–65. [PubMed: 3234522]

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35. Nickol AH, Leverment J, Richards P, et al. Temazepam at high altitude reduces periodic breathing without impairing next-day performance: a randomized cross-over double-blind study. J Sleep Res. 2006; 15:445–54. [PubMed: 17118102]
36. Wang D, Teichtahl H, Drummer O, et al. Central sleep apnea in stable methadone maintenance treatment patients. Chest. 2005; 128:1348–56. [PubMed: 16162728]
37. Sharkey KM, Kurth ME, Anderson BJ, et al. Obstructive sleep apnea is more common than central sleep apnea in methadone maintenance patients with subjective sleep complaints. Drug Alcohol Depend. 2010; 108:77–83. [PubMed: 20079978]
38. Charpentier A, Bisac S, Poirot I, et al. Sleep quality and apnea in stable methadone maintenance treatment. Subst Use Mis. 2010; 45:1431–34.
39. Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. J Clin Sleep Med. 2007; 3:455–61. [PubMed: 17803007]
40. Teichtahl H, Wang D, Cunnington D, et al. Ventilatory responses to hypoxia and hypercapnia in stable methadone maintenance treatment patients. Chest. 2005; 128:1339–47. [PubMed: 16162727]
41. Shore ET, Millman RP. Central sleep apnea and acetazolamide therapy. Arch Intern Med. 1983; 143:1278–80. [PubMed: 6860061]
42. Inoue Y, Takata K, Sakamoto I, et al. Clinical efficacy and indication of acetazolamide treatment on sleep apnea syndrome. Psyc Clin Neurosci. 1999; 53:321–22.
43. Edwards BA, Sands SA, Eckert DJ, et al. Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. J Appl Physiol. 2012; 590:1199–1211.
44. Edwards BA, Connolly JG, Campana LM, et al. Acetazolamide attenuates the ventilatory response to arousal in patients with obstructive sleep apnea. Sleep. 2013; 36:281–85. [PubMed: 23372276]
45. Nakayama H, Smith CA, Rodman JR, et al. Effect of ventilatory drive on carbon dioxide sensitivity below eupnea during sleep. Am J Respir Crit Care Med. 2002; 165:1251–60. [PubMed: 11991874]
46. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. Am J respir Crit Care Med. 2006; 173:234–37. [PubMed: 16239622]
47. Latshang TD, Nussbaumer-Ochsner Y, Henn RM, et al. Effect of acetazolamide and autoCPAP therapy on breathing disturbances among patients with obstructive sleep apnea syndrome who travel to altitude: a randomized controlled trial. J Am Med Assoc. 2012; 308:2390–98.
48. Glidewell RN, Orr WC, Imes N. Acetazolamide as an adjunct to CPAP treatment: a case of complex sleep apnea in a patient on long-acting opioid therapy. J Clin Sleep Med. 2009; 5:63–4. [PubMed: 19317383]
49. De Simone G, Di Fiore A, Menchise V, et al. Carbonic anhydrase inhibitors. Zonisamide is an effective inhibitor of the cytosolic isozyme II and mitochondrial isozyme V: solution and X-ray crystallographic studies. Bio Med Chem Lett. 2005; 15:2315–20.
50. Westwood AJ, Vendrame M, Montouris G, et al. Pearls & Oy-sters: treatment of central sleep apnea with topiramate. Neurology. 2012; 78:e97–9. [PubMed: 22508854]
51. Sankri-Tarbichi AG, Grullon K, Badr MS. Effects of clonidine on breathing during sleep and susceptibility to central apnoea. Respir Physiol Neurobiol. 2013; 185:356–61. [PubMed: 23017329]
52. Patel AV, Hwang D, Masdeu MJ, et al. Predictors of response to a nasal expiratory resistor device and its potential mechanisms of action for treatment of obstructive sleep apnea. Journal of clinical sleep medicine : J Clin Sleep Med. 2011; 7:13–22.
53. Avidan AY. The development of central sleep apnea with an oral appliance. Sleep Med. 2006; 7:85–6. [PubMed: 16194621]
54. Denbar MA. A case study involving the combination treatment of an oral appliance and auto-titrating CPAP unit. Sleep Breath. 2002; 6:125–8. [PubMed: 12244492]
55. El-Solh AA, Moitheennazima B, Akinnusi ME, et al. Combined oral appliance and positive airway pressure therapy for obstructive sleep apnea: a pilot study. Sleep Breath. 2011; 15:203–8. [PubMed: 21063793]

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56. Zhang XL, Ding N, Wang H, et al. Transvenous phrenic nerve stimulation in patients with Cheyne-Stokes respiration and congestive heart failure: a safety and proof-of-concept study. Chest. 2012; 142:927–34. [PubMed: 22302299]
57. Colrain IM, Black J, Siegel LC, et al. A multicenter evaluation of oral pressure therapy for the treatment of obstructive sleep apnea. Sleep Med. 2013; 14:830–7. [PubMed: 23871259]
58. Szollosi I, Roebuck T, Thompson B, et al. Lateral sleeping position reduces severity of central sleep apnea/Cheyne-Stokes respiration. Sleep. 2006; 29:1045–51. [PubMed: 16944673]
59. Joho S, Oda Y, Hirai T, et al. Impact of sleeping position on central sleep apnea/Cheyne-Stokes respiration in patients with heart failure. Sleep Med. 2010; 11:143–8. [PubMed: 20093078]
60. White LH, Bradley TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnoea. J Physiol. 2013; 591:1179–93. [PubMed: 23230237]
61. Redolfi S, Yumino D, Ruttanaumpawan P, et al. Relationship between overnight rostral fluid shift and Obstructive Sleep Apnea in nonobese men. Am J Respir Crit Care Med. 2009; 179:241–6. [PubMed: 19011149]
62. Kasai T, Motwani SS, Yumino D, et al. Differing relationship of nocturnal fluid shifts to sleep apnea in men and women with heart failure. Circ Heart Fail. 2012; 5:467–74. [PubMed: 22679060]
63. Friedman O, Bradley TD, Chan CT, et al. Relationship between overnight rostral fluid shift and obstructive sleep apnea in drug-resistant hypertension. Hypertension. 2010; 56:1077–82. [PubMed: 21060007]
64. Elias RM, Bradley TD, Kasai T, et al. Rostral overnight fluid shift in end-stage renal disease: relationship with obstructive sleep apnea. Nephrol Dial Transplant. 2012; 27:1569–73. [PubMed: 22058175]

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Key Points

- The phenotype that reflects heightened respiratory chemoreflex activation is NREM-dominant sleep apnea. Conventional scoring may categorize many of these patients as “obstructive”.
- Targeting respiratory chemoreflex sensitivity or effects, and sleep fragmentation, can provide useful alternative or adjunctive therapy for central sleep apnea syndromes
- CO_2 is the dominant driver of sleep-respiration, and manipulation of CO_2 has the greatest potential for clinical effects. The primary challenges are simultaneously technical and biological: how to keep the CO_2 levels just above the NREM sleep CO_2 threshold. As these levels are not hypercapnic, sympathoexcitation would not occur.
- Treatments for obstructive components of sleep apnea that may be less prone to destabilize respiratory control include Provent, oral appliances, and Winx. However, residual disease is common and requires adjunctive therapies.
- Reducing the impact of arousals and inducing a stable form of NREM sleep may be achieved by sedatives, including the classic benzodiazepines and the non-benzodiazepines such as zolpidem.
- Multi-modality approaches to treatment of sleep apnea are especially important for central sleep apnea syndromes.

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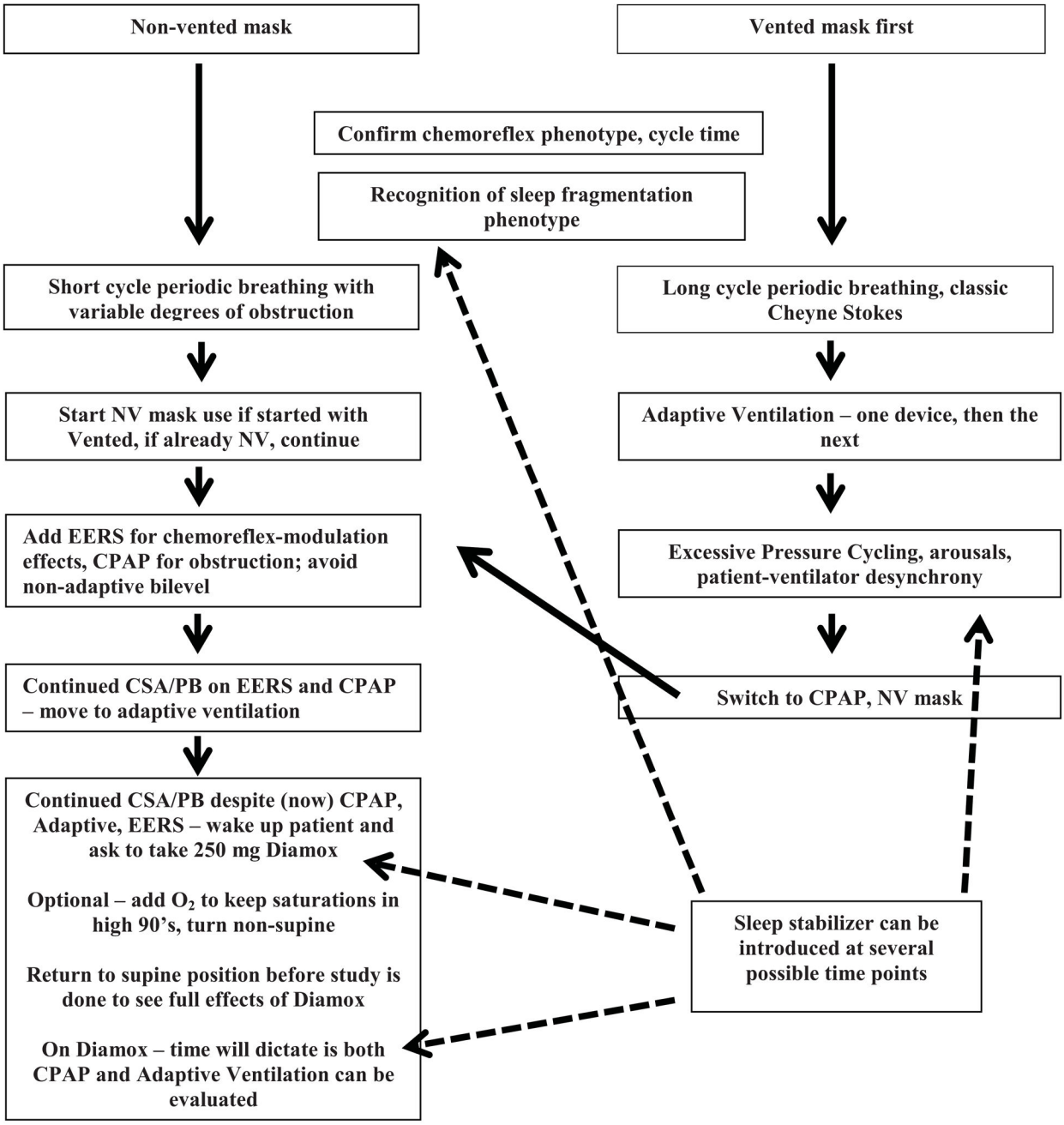

Figure 1.

How to use alternative and adjunctive therapies for central sleep apnea – positive airway pressure based approaches

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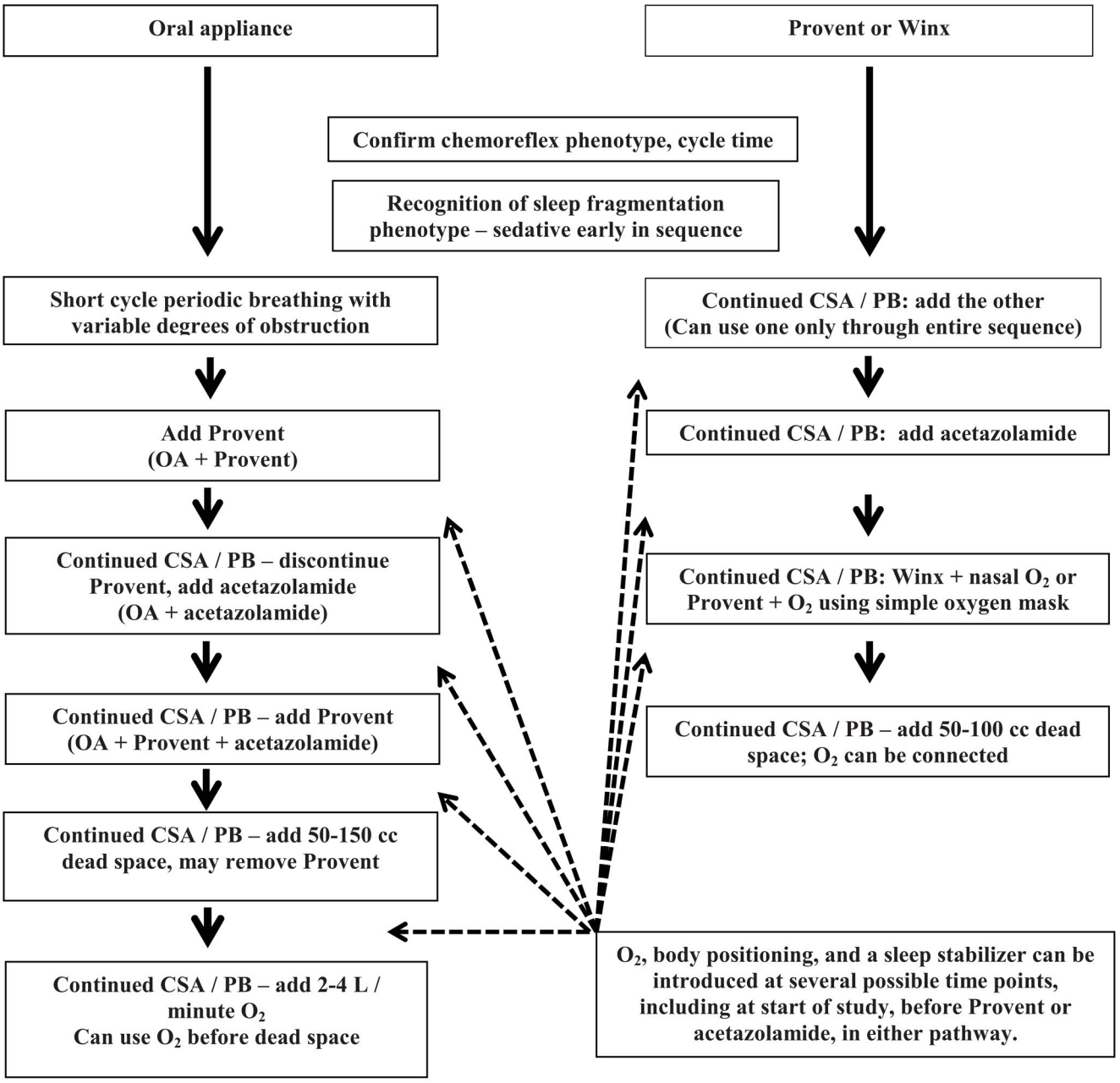
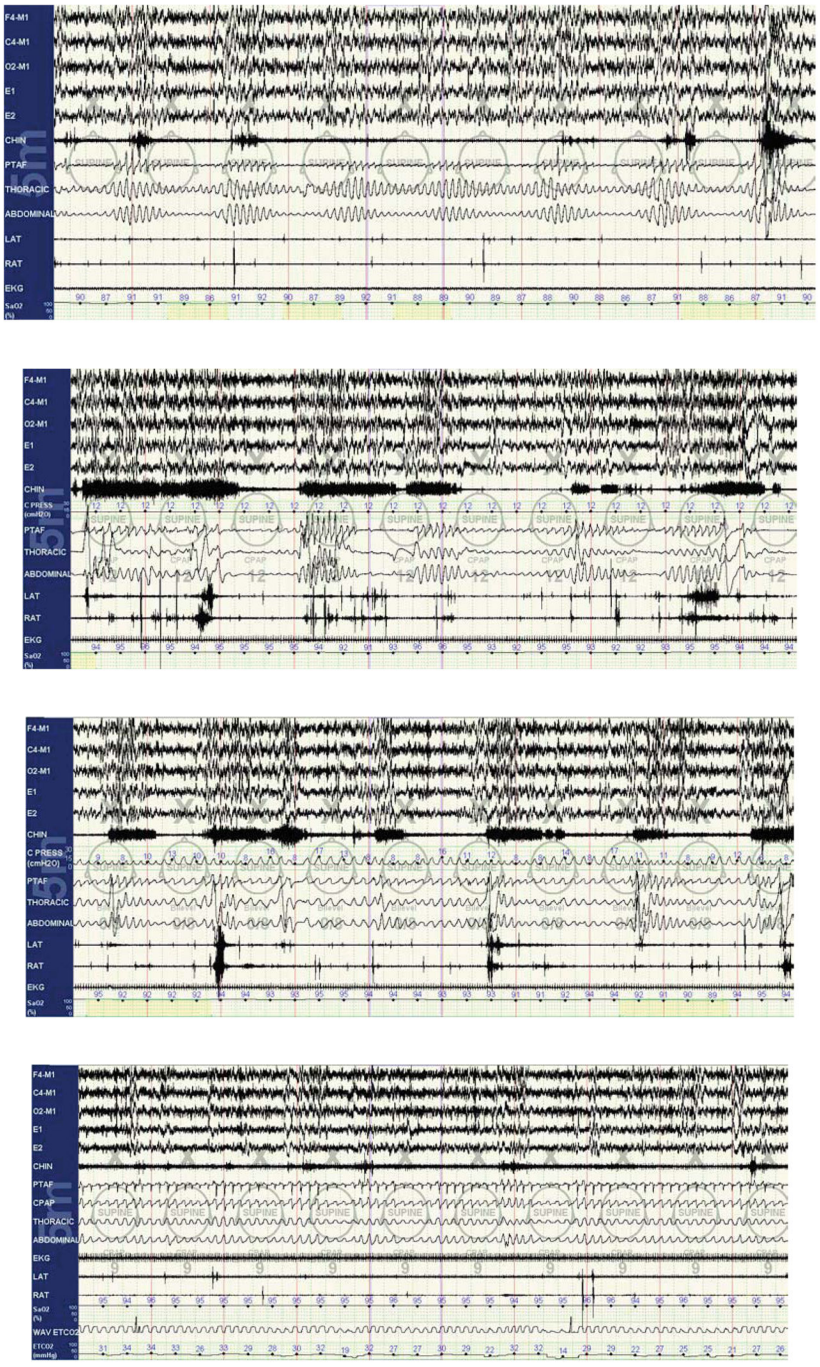


Figure 2.

How to use alternative and adjunctive therapies for central sleep apnea – without positive airway pressure



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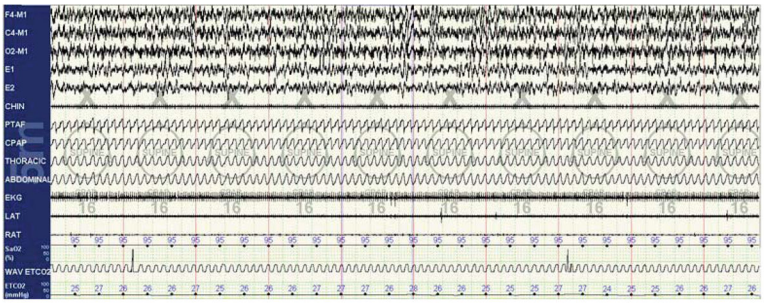

Figure 3.

Figure 3a: Classic periodic breathing/Cheyne-Stokes respiration (CSR).

A 72-year old with congestive heart failure. Note the typical waxing-waning respiratory pattern. All figure 3 subsets are from the same patient.

Figure 3b: CSR with CPAP failure. Note continuing CSR.

Figure 3c: CSR with adaptive servo-ventilation failure. Note excessive cycling of pressure (the CPRESS channel) and the associated arousals.

Figure 3d: CSR with 50 cc Enhanced Expiratory Rebreathing Space. Note stabilization of respiratory rhythm but residual flow limitation and mild residual periodic breathing.

Figure 3e: CSR with 100 cc EERS. Note normalization of sleep and respiration. The $ETCO_2$ signal plateau is slightly blunted and thus the CO2 measured is falsely low. However, the resting wake $ETCO_2$ of this patient was 30 mm Hg, a level that can be readily seen in patients with congestive heart failure.

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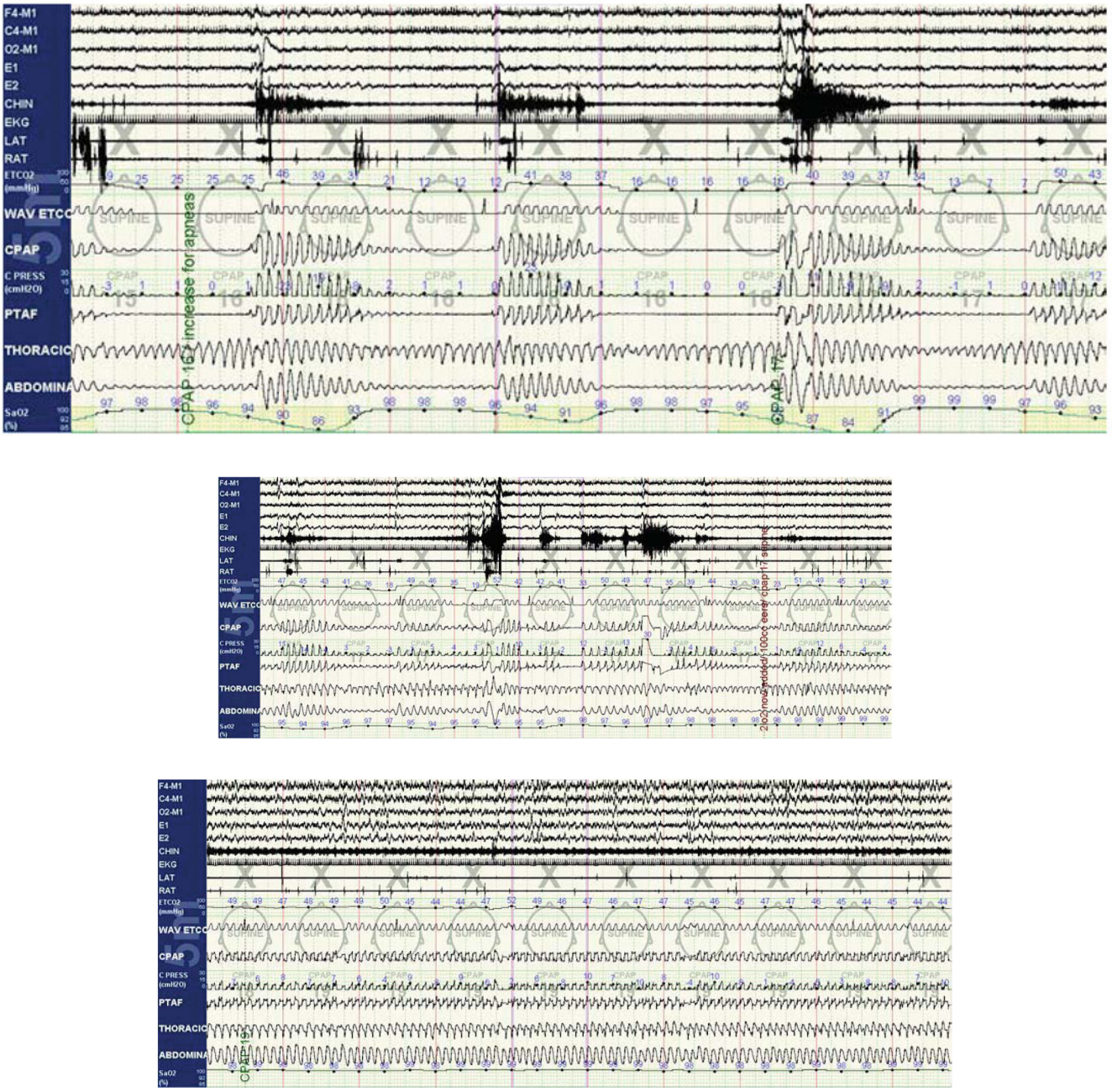

Figure 4.

Figure 4a: CPAP refractory mixed apnea: obstruction and periodic breathing.

Note periodic breathing pattern of respiratory effort, unresponsiveness to CPAP of 16–17 cms H_2O, while on a non-vented mask alone without EERS.

Figure 4b: CPAP refractory mixed apnea: CO_2 **effects.** The same patient as in 4a, but now with 100 cc EERS. Note improved respiratory stabilization, but periodic breathing and obstructive features (flow-limitation) coexist and contribute to ongoing sleep fragmentation.

Figure 4c: CPAP refractory mixed apnea: adjunctive O_2 **effects.** The same patient as in 4a, now with 4 L/minute of supplemental oxygen. Note complete stabilization of respiratory rhythm but residual obstruction – which ultimately required 22 cm H_2O to eliminate.

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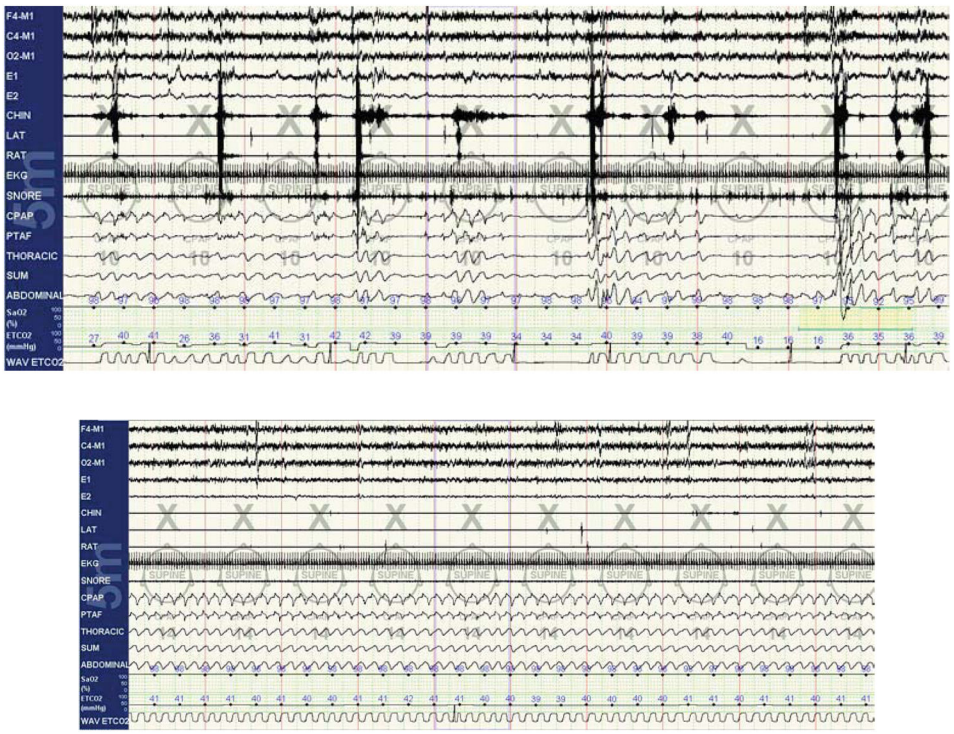

Figure 5.

Figure 5a. Pre-acetazolamide treatment resistant sleep apnea.

At the start of this polysomnogram, the patient was failing CPAP, 150 cc ERRS and supplemental O_2.

Figure 5b. Post-acetazolamide effects, one hour later. The patient received a single dose of 250 mg acetazolamide about 2 hours before this snapshot. Note complete resolution of central sleep apnea, which was maintained for the rest of the night. 50 cc of ERRS was continued.

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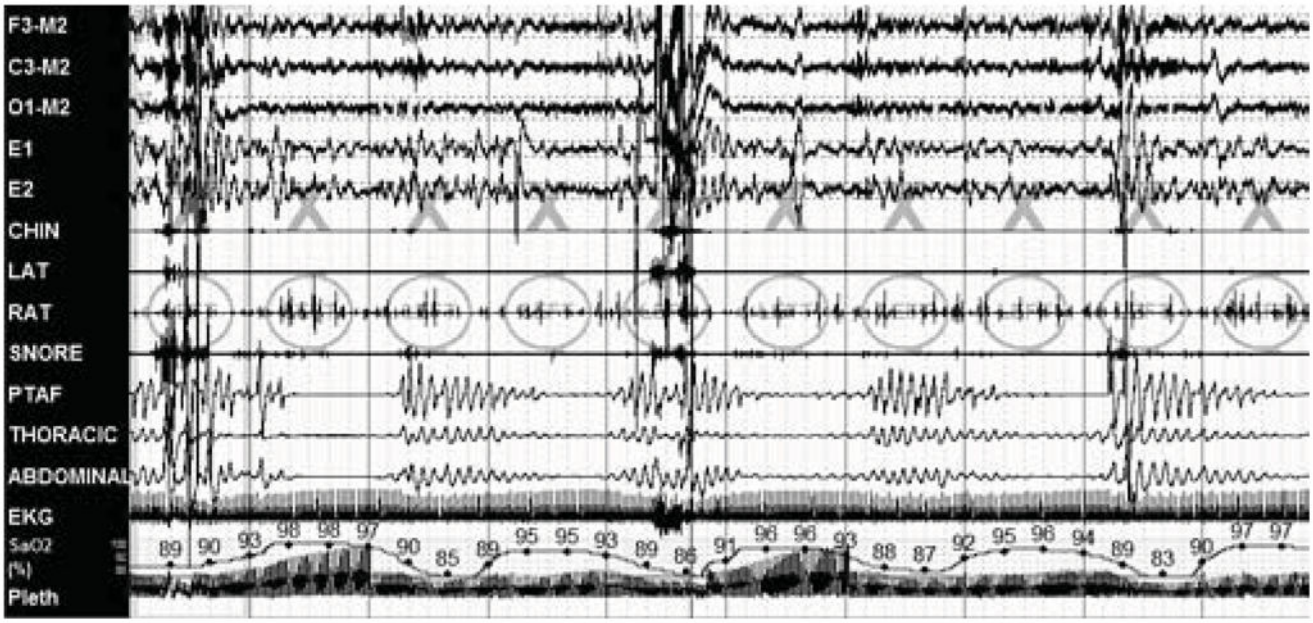

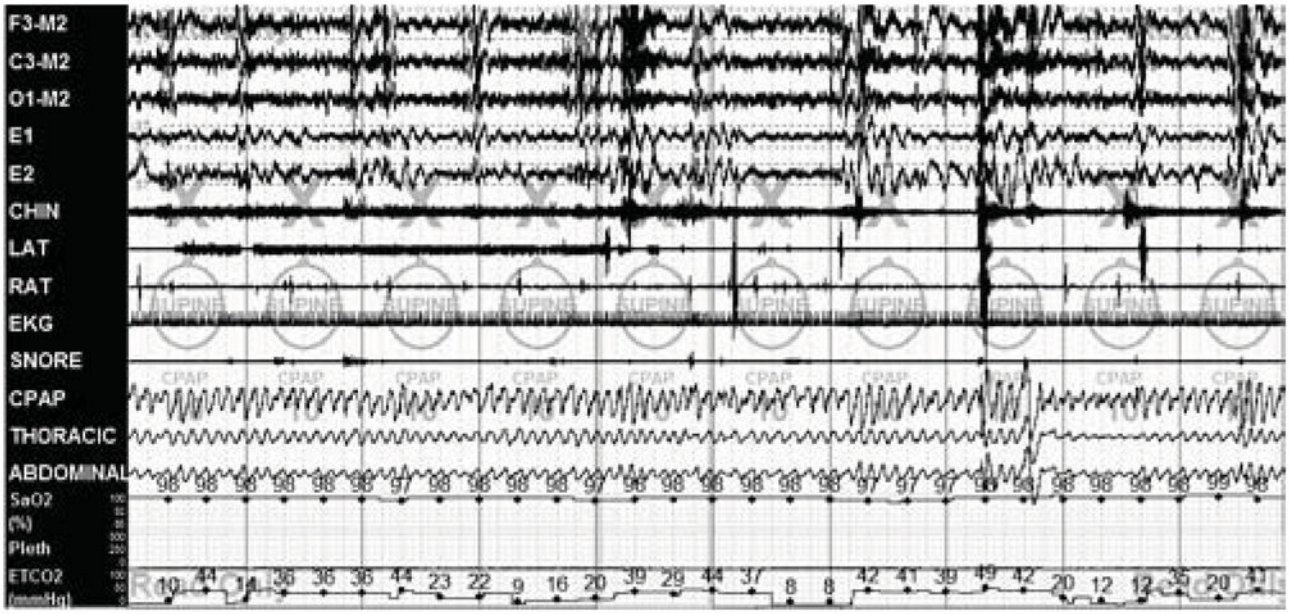

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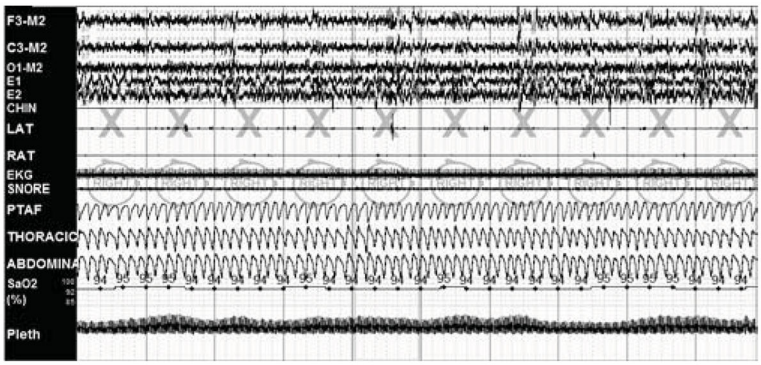

Figure 6.

Figure 6a: Periodic breathing, pre CPAP or Provent.

Note severe periodic breathing with some mild obstructive features.

Figure 6b: Periodic breathing on CPAP. Same patient as in Figure 6a. Though there is significant improvement of respiration, treatment was not tolerated for home use and there is ongoing clear evidence of sleep fragmentation/arousals.

Figure 6c: Periodic breathing resolved on Provent. The same patient as in Figure 6a and 6b. Note complete resolution of sleep apnea and absence of arousals.

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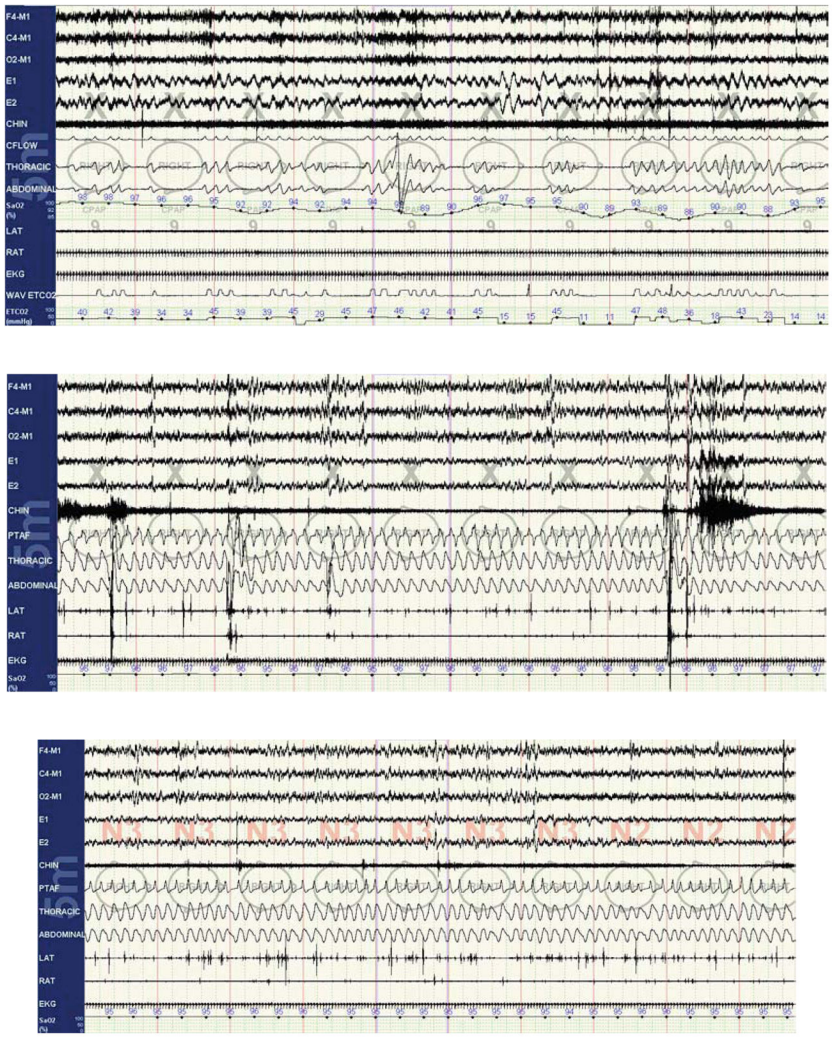

Figure 7.

Figure 7a: CPAP failure, central sleep apnea.

The patient was pretreated with acetazolamide and clonazepam as there were multiple past failures of positive pressure titration due to both periodic breathing and severe sleep fragmentation which was considered disproportionate to the severity of sleep apnea.

Figure 7b. CPAP failure, improved on Winx. Same patient as in Figure 7a. Note a marked improvement of sleep apnea on Winx, with the residual abnormality seemingly flow-limitation and arousals. The relative efficacy of Winx vs. CPAP may reflect the tendency of CPAP to worsen hypocapnia.

Figure 7c. CPAP failure, resolved with Winx + Provent. Same patient as in Figures 7a and 7b. As a final step, Provent was added, with complete resolution of sleep apnea and sleep fragmentation; the treatment “cocktail” here is acetazolamide, clonazepam, Winx + Provent.

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Table 1

Recognition of Strong Chemoreflex Modulation of Sleep Breathing

Polysomnographic Characteristic	Relatively Pure Obstructive Sleep Apnea	Chemoreflex-Modulated Sleep Apnea
Obstructive apneas	Dominant.	Less common.
Central apneas	Rare.	Dominant form of apneas.
Progressive flow limitation	Typical; long variable- length segments of limited breaths are typical.	Commonly seen with mixed apneas except for in the purest form (e.g., in classic Cheyne-Stokes respiration).
Periodic breathing/Cheyne-Stokes pattern	Rare; may be seen at sleep onset or around sleep-wake transitions.	Typical (often short cycle, ≤ 30 seconds, in the absence of congestive heart failure).
Relative severity in NREM versus REM sleep	Greater severity in REM sleep.	Minimal severity in REM sleep; this may be best evident during CPAP titrations.
Positive pressure therapy	Generally good response with improvement in flow limitation and AHI	Response variable- may worsen with positive pressure therapy.
Central apneas before elimination of flow limitation during titration	Rare.	Typical.
Respiratory event cycle durations	Variable.	Short cycle (25–35 seconds) is highly suggestive, but long cycle forms also occur.
Respiratory event symmetry in NREM sleep including a mirror-imaging pattern	Minimal symmetry.	Very symmetrical, and mirror imaging is typical (one half of an event is the mirror image of the other).
Effort signal morphology	Well maintained during obstructed breath.	Complete or partial loss between recovery breaths clusters.
Flow-effort relationships	Discordant: flow is reduced disproportionately to reduction in effort signals.	Concordant: flow and effort follow each other in amplitude.
Arousal timing	Early part of event termination, often first recovery breath related.	“Crests” event, often in the center of a sequence of recovery breaths that progressively increase in amplitude and decrease.
Oxygen desaturation profile	Irregular, progressive drops, sharp contour (‘V’ shape).	Smooth, symmetrical, progressive drops rare. Rarely < 80%. (‘band pattern’)
CO_2	If CO_2 is affected, generally eupnic or hypercapnic	Usually hypocapnic
Nonadaptive bilevel PAP - induced instability	Less common, usually with excessive pressure support or severe mask leak only.	Typical.

CPAP: continuous positive airway pressure; *NREM*: non-rapid eye movement; *PAP:* positive airway pressure; *REM*: rapid eye movement.