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Quantifying the ventilatory control contribution to sleep apnoea using polysomnography

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Abstract

Elevated loop gain, consequent to hypersensitive ventilatory control, is a primary nonanatomical cause of obstructive sleep apnoea (OSA) but it is not possible to quantify this in the clinic. Here we provide a novel method to estimate loop gain in OSA patients using routine clinical polysomnography alone. We use the concept that spontaneous ventilatory fluctuations due to apnoeas/hypopnoeas (disturbance) result in opposing changes in ventilatory drive (response) as determined by loop gain (response/disturbance). Fitting a simple ventilatory control model (including chemical and arousal contributions to ventilatory drive) to the ventilatory pattern of OSA reveals the underlying loop gain.

Following mathematical-model validation, we critically tested our method in patients with OSA by comparison with a standard (continuous positive airway pressure (CPAP) drop method), and by assessing its ability to detect the known reduction in loop gain with oxygen and acetazolamide.

Our method quantified loop gain from baseline polysomnography (correlation *versus* CPAP-estimated loop gain: n=28; r=0.63, p<0.001), detected the known reduction in loop gain with oxygen (n=11; mean±SEM change in loop gain (ΔLG) −0.23±0.08, p=0.02) and acetazolamide (n=11; ΔLG −0.20±0.06, p=0.005), and predicted the OSA response to loop gain-lowering therapy.

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We validated a means to quantify the ventilatory control contribution to OSA pathogenesis using clinical polysomnography, enabling identification of likely responders to therapies targeting ventilatory control.

Introduction

Obstructive sleep apnoea (OSA) is prevalent affliction with major health consequences, but its treatment is largely limited to continuous positive airway pressure (CPAP), which has an adherence rate as low as 50% [1]. As alternative treatments that target either anatomical or neurophysiological compromise have variable success rates [2–8], methods to determine who will respond to these therapies are clearly needed [9].

In recent years, investigators have shown that OSA severity is only modestly determined by a patient's upper airway anatomy [10, 11], leading to the view that OSA is more than just an anatomical problem. Accumulating evidence demonstrates that a hypersensitive chemoreflex feedback loop (*i.e.* a high loop gain) is a key modifiable factor contributing to OSA in around a third of patients [2, 4, 12–14]. Among patients with OSA but only mild anatomical deficiency, loop gain is elevated [10, 12] and is an important determinant of apnoea severity [12, 15]. As a therapeutic target, loop gain can be lowered with oxygen, acetazolamide and carbon dioxide [2–4], an approach that is particularly effective in the subset of patients with a high loop gain but not in those with a low loop gain [2, 3]. Likewise, anatomical treatments for sleep apnoea may be ineffective in those with excessively high loop gain [16]. Hence, measurement of the underlying loop gain could enable clinicians to provide judiciously alternative therapies to patients for whom CPAP is intolerable or ineffective.

Our objective is to bridge the gap between scientific knowledge of OSA pathophysiology and clinical practice to allow nonanatomical causes of OSA to be targeted for treatment. To achieve this objective, the current study provides an innovative, noninvasive method to quantify loop gain in patients with OSA from standard clinical sleep recordings (polysomnography). Here, we measured loop gain by fitting a simplified control system model incorporating a chemoreflex response (gain, time constant and delay) [17] and ventilatory response to arousal to the pattern of ventilation during spontaneous OSA. First, we validated our noninvasive method using mathematical simulations in a ventilatory control model [4, 17–19]. Second, we applied our method to measure loop gain from the baseline polysomnography of OSA patients and compared our values against an invasively measured standard. Finally, we tested whether our method can detect the known reduction in loop gain with oxygen [2] and acetazolamide [4], and sought to predict successful responses to such therapies.

Theory

Loop gain is the input-output function of the feedback loop controlling ventilation, which determines the magnitude and time course of the ventilatory "response" (increased ventilatory effort or "drive") that follows a ventilatory "disturbance" (reduced ventilation with apnoea/hypopnoea). The magnitude of loop gain (response/disturbance) represents the sensitivity of the ventilatory control system.

Estimating loop gain during obstructive apnoea—The key to our method lies in the recognition that obstructive apnoeas/hypopnoeas provide a disturbance of the ventilatory control system, which alters arterial blood gases and, in turn, raises ventilatory drive (V_{drive}). This rise in V_{drive} is then revealed as the degree of hyperventilation seen when the airway reopens at apnoea/hypopnoea termination. In principle, the spontaneous disturbances and responses of OSA provide the necessary information to quantify loop gain (online supplementary material).

Briefly, we model V_{drive} as the sum of "chemical drive" (V_{chem}) as a response to elevated carbon dioxide and decreased oxygen, and a nonchemical or "wakefulness" drive to breathe that accompanies arousal ($V_{arousal}$) (fig. 1a) [20, 21]:

$$V_{\text{drive}}=V_{\text{chem}}+V_{\text{arousal}} \quad (1)$$

The time-course of V_{chem} itself is determined by previous levels of ventilation (V_E) and a standard three-parameter, first-order model [17, 19, 20]:

$$\tau\frac{\mathrm{d}V_{\text{chem}}}{\mathrm{d}t}=-V_{\text{chem}}-\mathrm{LG}_0\times V_{\mathrm{E}}(t-\delta) \quad (2)$$

where δ is the delay time (principally the circulation time between the lung and chemoreceptors), τ is the characteristic time constant (*e.g.* due to time course of the buffering of carbon dioxide in the lung and tissues) and LG_0 is the steady state loop gain (fig. 1b). $V_{arousal}$ is modelled as a constant increase in ventilatory drive (γ) that accompanies a scored electroencephalogram (EEG) arousal [20, 21]. Specifically, during arousal, $V_{arousal}=\gamma$, otherwise, $V_{arousal}=0$.

This model outputs an estimated V_{drive} signal that depends on the observed changes in V_E and the presence or absence of an arousal (model inputs). To characterise the system, the parameters (δ, τ, LG_0 and γ) are adjusted until V_{drive} best fits the observed V_E during unobstructed breaths (when V_E reflects V_{drive}). These parameters are then used to calculate the magnitude of loop gain at any frequency (*f*) using:

$$|\mathrm{LG}_f|=\frac{\mathrm{LG}_0}{\sqrt{1+(2\pi\tau f)^2}} \quad (3)$$

Note that loop gain depends on the timing (frequency) of the disturbance (online supplementary fig. S1). For consistency with the dynamics of OSA [4], our primary measure of loop gain was taken at f=1 cycle·min^{-1} (LG1). To assess the overall timing properties of the feedback response, we quantified the natural cycling period *T*n (*T*n manifests as the cycle duration of periodic breathing if the system is unstable and is defined as the period of sinusoidal disturbance that results in an "in phase" feedback response). In essence, a higher *T*n denotes a slower chemical response to ventilatory stimuli.

Methods

Computational model verification

As a first validation step, we simulated OSA by imposing obstructive events and arousals on our mathematical model (equations 1 and 2). Using just the ventilation and arousal signals, we applied our method to recover the underlying loop gain. Agreement between the estimated and true loop gain was taken as initial validation of our methodology. Details are provided in the online supplementary material.

Loop gain quantification in OSA: comparison to published standard

We then compared our measure of loop gain against a published standard (CPAP drops). We examined 28 patients, who were a subset of a larger physiological investigation [10, 22]. All patients with apnoea-hypopnoea index (AHI) ≥15 events·h^{-1} during supine non-REM, and who were studied at our affiliated clinical laboratory (former Sleep Health Centers, Massachusetts, USA) were included in our analysis (online supplementary fig. S2). Full clinical polysomnography was performed, including EEG and nasal pressure airflow, and was scored according to standard criteria [23]. The published standard measure of loop gain (and other physiological traits including anatomy/collapsibility) was performed on additional nights by manipulating CPAP levels [4, 17] and fitting the three-parameter model (equation 2) to the ventilatory overshoot following the switch from subtherapeutic to therapeutic mask pressure.

Detecting reduced loop gain with oxygen and acetazolamide

Finally, we tested whether our method could detect a known reduction in loop gain with intervention, again, using only arousal and ventilation signals. To achieve this goal, we applied our new method to the polysomnographic recordings of OSA patients [2, 4] at baseline and while treated with oxygen (original polysomnography data from three out of 12 patients in the published study were unable to be retrieved, but unpublished data from two additional patients who did not complete the full protocol were able to be included; n=11) or acetazolamide (all data from the published study was used in this analysis; n=12).

Data analysis

Our loop gain estimates were made using routine polysomnographic signals from spontaneously breathing OSA patients. Briefly, 7-min periods of supine non-REM sleep that contained one or more scored obstructive apnoeas/hypopnoeas were automatically identified using a software routine. The 7-min duration was chosen to provide time for ~10 cyclic obstructive events (based on the average inter-event interval of ~40 s), which was considered sufficient for separating V_{chem} and arousal contributions to total ventilatory output. Importantly, the use of similar window lengths did not alter the significance of the results presented in this study (online supplementary fig. S6). Nasal pressure (square-root transformed) was taken as a surrogate of ventilatory flow [24], and was integrated (uncalibrated tidal volume × respiratory rate) and normalised by the mean to provide V_E data for subsequent analysis. We created a categorical breath-to-breath time-series of scored EEG arousals (1=arousal, 0=no arousal) and scored obstructed breaths (1=unobstructed,

0=obstructed). Using these data, our model (equations 1 and 2) was fit to determine the best set of system parameters (and hence loop gain) for each epoch; median values are reported for each patient.

For comparison with loop gain measured from CPAP drops (taken primarily over the first 4–5 h of sleep), we used the first 50% of the available polysomnographic data to control for expected time-of-night effects. Otherwise, loop gain determined over the whole night was used to describe effects of treatment and associations with clinical parameters.

Statistical analysis

Correlation analysis was used to assess relationships between our measure of loop gain and the published standard (CPAP drops), and to assess relationships between multiple additional variables. Student's t-tests were used to compare our measurement of loop gain on and off oxygen and acetazolamide, and to assess changes in other variables on and off these agents. $p<0.05$ was considered statistically significant.

Results

Computational model verification

Our measure of loop gain from each epoch of simulated OSA data matched the known loop gain within a 95% confidence interval of ±0.09 with negligible bias (fig. 2a–b).

Loop gain quantification in OSA: comparison to published standard

Subject characteristics are detailed in table 1. Example traces illustrating loop gain estimation in patients with low and high loop gain are presented in figure 3. Group data demonstrated that our measure closely matched the values of loop gain estimated using CPAP drops (fig. 4 and online supplementary fig. S3).

We also observed a significant association between loop gain and OSA severity (LG1 *versus* AHI; $r=0.72$, $p<0.001$), the relative predominance of non-REM *versus* REM OSA (LG1 *versus* REM AHI minus non-REM AHI; $r=-0.46$, $p=0.02$) and the median duration from one adjacent apnoea/hypopnoea to the next (LG1 *versus* inter-event interval; $r=-0.47$, $p=0.01$). We observed no link indicative of a confounding relationship between measured loop gain and anatomy/collapsibility (online supplementary fig. S5).

Detecting reduced loop gain with oxygen and acetazolamide

As expected, our estimate of loop gain fell with oxygen treatment compared with baseline (fig. 5a). Other changes with oxygen included a reduced γ (fig. 5b) and an increased T_n (fig. 5c). Likewise, loop gain fell with acetazolamide (fig. 6a); there was also a trend towards a reduced γ (fig. 6b) and a significantly longer T_n (fig. 6c) *versus* baseline.

The reduction in loop gain with oxygen and acetazolamide was strongly linked to the degree of improvement in OSA severity (fig. 7a) as described previously [2, 4]. Patients who had a higher LG1 (fig. 7b) and a faster T_n (fig. 7c) at baseline exhibited a greater reduction in AHI with loop gain-lowering therapy.

Discussion

Our study demonstrates that loop gain can be quantified from routine clinical polysomnography using the spontaneous ventilatory patterns of patients with OSA. We confirmed the validity of our measure using several independent approaches. First, in a mathematical model of OSA, our measure of loop gain estimated from ventilatory pattern precisely matched the known underlying loop gain. Second, in patients with OSA, our measure closely matched the experimentally measured loop gain using CPAP drops. Finally, our method tracks the reduction in loop gain achieved with both oxygen and acetazolamide treatment, and provides predictions from baseline polysomnography of likely responders to loop gain-lowering therapy. Hence, we have comprehensively tested a clinically feasible means to quantify the ventilatory control contribution to OSA. This novel method opens the door for clinicians to target treatments at nonanatomical mechanisms responsible for OSA in selected individuals.

Consistency with the available literature

Several methods have been employed previously to characterise ventilatory control from spontaneous breathing but have been limited to using invasive measurement of ventilatory drive [25] or situations when the airway can be assumed to be open [16, 26–28]. In patients with central sleep apnoea (Cheyne–Stokes respiration), we recently demonstrated that the ventilatory pattern (apnoea duration/cycle duration) is uniquely linked to the underlying loop gain and provides important clues as to likely responders to treatment [16]. Our method combines previously employed concepts to measure loop gain from spontaneous OSA patterns: our approach is “autoregressive” in that the model output (V_{drive}) depends on its own previous values (V_E) 26; it handles intermittent airflow obstruction (nonrandom disturbances) by comparison of the predicted V_{drive} output to the observed ventilation only when the airway is unobstructed (through weighted least squares) [17] and incorporates arousals by “subtracting out” their additive nonchemical influence on V_{drive} [21, 29].

Our method determined values for ventilatory control variables that are consistent with the literature. On average, our loop gain values were similar in magnitude to those estimated from CPAP drops across a range of *f* (fig. 4). Furthermore, chemoreflex delays were estimated to be 7–16 s (mean±SEM 10.4±0.4 s), consistent with the lung–chemoreceptor delay time [30]. The time constant of the chemoreflex (~2 min) is similar to values reported for the chemoreflex response to carbon dioxide [31]. In addition, our measure of loop gain fell with both oxygen and acetazolamide treatment, as expected from the known stabilising effects of these therapies *via* reduced chemosensitivity [32] and plant gain [4], respectively. Our observation of a ~50% reduction in the ventilatory response to arousal is also consistent with physiological data [20]. The typical baseline value for the *T*n of ~38 s in our study (figs 5c and 6c, and online supplementary table S1) closely matches the ~37-s *T*n seen in patients with idiopathic central sleep apnoea [30]. Moreover, our findings of an increased *T*n with acetazolamide and oxygen is in concordance with the increased cycle duration of periodic breathing caused by both of these therapies [16, 33].

We additionally compared our loop gain values with the published standards taken from the oxygen [2] and acetazolamide [4] data. Our loop gain estimates closely matched the values

obtained using both “proportional assist ventilation” (pooled pre- and post-oxygen data) and the CPAP drop method (pooled pre- and post-acetazolamide data) (online supplementary fig. S7). This agreement provides further validity to our technique.

Clinical implications

OSA remains markedly undertreated due largely to the lack of effective therapies beyond CPAP. This major issue has inspired investigation into simple ways to characterise the pathophysiological contributions to OSA. Methods to assess noninvasively the anatomical contribution to sleep apnoea (*e.g.* neck circumference, acoustic pharyngometry, Kushida index and forced oscillations) have been promising [34–36]. Yet noninvasively assessing the ventilatory control contribution to OSA in the clinic has remained elusive. Available methods require patient intervention [3, 17, 37], additional measurements (*e.g.* end-tidal gases or intrathoracic pressure) [25, 26] and all disrupt the pattern of OSA under investigation (*e.g.* requiring CPAP or wakefulness). Our method to measure loop gain can be applied to routine polysomnogram data recorded using standard sleep software and does not require manual analysis beyond scoring of respiratory events and arousals; hence, negligible additional cost is accrued. The method can be applied to a variety of clinically observed manifestations of sleep apnoea (obstructive and, in principle, central and mixed events; online supplementary fig. S8) and enables ventilatory stability to be determined in individual OSA patients *in situ* when it is most relevant. Computations for this method take ~10 min per patient on a standard personal computer and could therefore be integrated within the typical overnight polysomnography workflow. Our current software (online supplementary material) requires polysomnography data (scored using standard criteria) to be exported from clinical sleep software and then imported into a format for analysis using MATLAB (MathWorks, Natick, MA, USA). Interested clinicians/investigators can contact the authors for technical assistance.

Our approach seeks to enable clinical identification of patients with a ventilatory control phenotype (high loop gain) whose affliction is expected to respond relatively well to therapies that stabilise ventilator control [2, 3, 10]. We demonstrated that a high loop gain and a fast *T*n at baseline (implying fast-acting carotid-body involvement) predict a greater suppression of OSA when loop gain is lowered medically. A higher loop gain (LG1 >0.7) predicted a reduction in AHI of ≥20 events·h^{-1} with 80% sensitivity and 67% specificity; and a faster *T*n (<40 s) predicted this response with 80% sensitivity and 75% specificity (fig. 7b and c) (chosen cut-offs maximised sensitivity and specificity). With a pre-test probability for such response of ~40% (fig. 7), targeting therapies on the basis of our technique would roughly double the positive predictive value (approximately two-thirds of patients treated based on a high loop gain would now exhibit a successful response). Similarly, trial of treatment that is likely to be ineffective in most patients with low loop gain would be avoided (negative predictive value of 83%). To further advance our approach, it is necessary to examine: 1) whether incorporating additional OSA traits, including anatomical measures (anatomy/collapsibility and critical airway closing pressure), can further enhance the predictive value; and 2) the utility of our method in predicting successful resolution of OSA and downstream sequelae with loop gain-lowering therapy (*e.g.* supplemental oxygen) in a randomised, controlled investigation.

Methodological considerations

Our method has several limitations. First, our study analysed data from retrospective physiological studies that required participants to be CPAP compliant. These participants are likely to be more accustomed to sleep instrumentation and it is expected that polysomnogram signal quality is higher in this group than may be expected in people attending a clinic for an initial diagnostic study. Criteria may need to be developed to automatically exclude periods of poor signal quality in such patients. Second, our measure requires the existence of spontaneous disturbances in ventilation. While our method may theoretically apply to the subtle disturbances observed in controls (as in our previous work 26) and mild OSA, we chose first to validate the method in patients with moderate-to-severe OSA who exhibit substantial disturbances, and in whom treatment can greatly impact health outcomes. Third, our method does not determine the mechanism of elevated loop gain (increased chemoreflex sensitivity *versus* increased plant gain), although inclusion of end-tidal carbon dioxide measurement would make such determination feasible [26]. Notably, it is loop gain that determines whether oscillatory behaviour will ensue and, thus, in principle, loop gain is the variable that determines whether the feedback control of ventilation is a likely targetable trait for OSA suppression. Fourth, given the close relationship between loop gain and OSA severity (AHI) in the current study, we were concerned that the severity of airflow obstruction (due to airway collapsibility) may have affected loop gain estimation. Yet we found no confounding relationship between gold standard measures of airway collapsibility and loop gain in the patients studied (online supplementary fig. S5). Finally, we used linearised nasal pressure rather than a pneumotachograph to measure ventilation. Nasal pressure provides an uncalibrated ventilation signal, the sensitivity of which can vary overnight with movement of the cannula relative to the nares or with varied mouth breathing. However, loop gain is a unitless measurement that does not require calibration, and the use of relatively short epochs (7 min, up to ~10 events) means that sensitivity is mostly preserved within each epoch. A requirement for pneumotachograph flow would rule out widespread use of our method in the clinical setting, a major goal of this research. Despite this practical concern, the current study assessed data from a typical in-laboratory clinical environment, and was able to determine loop gain effectively and predict therapeutic responses.

Further applications

Our method provides a measure of V_{drive} during events, and therefore paves the way to noninvasively quantify other key neurophysiological phenotypic traits (*e.g.* arousal threshold and muscle responses) contributing to OSA. For example, a low arousal threshold may present as a low ventilatory drive preceding arousal and may predict responsiveness to sedatives [5]. Likewise, an improvement in ventilation as V_{drive} rises and recruits upper airway muscles will reflect the compensatory response to obstruction [17, 38]; agents to reduce loop gain or raise the arousal threshold may be most effective in such patients with scope to recruit muscle activity and achieve stable breathing on their own.

Conclusions

Sleep medicine has been greatly hampered by the lack of means to assess the pathophysiological mechanisms of OSA in the clinical setting. Our study provides a novel, validated method to quantify the ventilatory control contribution to OSA from standard polysomnography. This clinically feasible method to quantify loop gain requires no patient intervention or specialised measurements. We envisage that knowledge of the mechanisms responsible for OSA in individuals will enable rescue therapies to be directed to selected patients with the highest likelihood of a positive response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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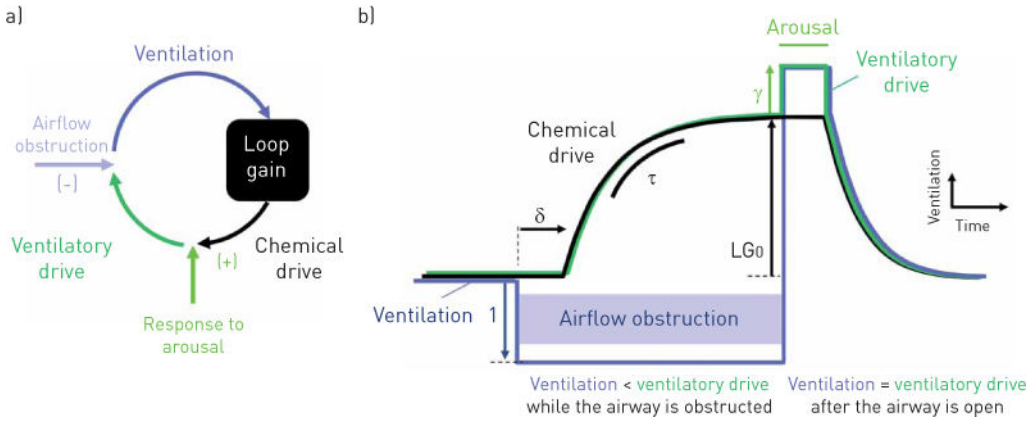

FIGURE 1.

Mathematical basis of the method. a) Schematic of the feedback loop controlling ventilation showing the influence of arousal and airflow obstruction. Ventilatory drive is the sum of chemical drive and the response to arousal (γ) (equation 1 in the main text). Airflow obstruction provides a disturbance that reduces ventilation from the intended level (*i.e.* ventilatory drive). In response, chemical drive rises as determined by the chemical control system (loop gain). b) Time course of chemical drive during a step reduction in ventilation (*e.g.* obstructive hypopnoea). The rise in chemical drive is governed by and the parameters that determine its gain (LG_0), time constant (τ) and delay (δ) (equation 2 in the main text); these system characteristics are revealed in the time course of ventilation when the airway is reopened.

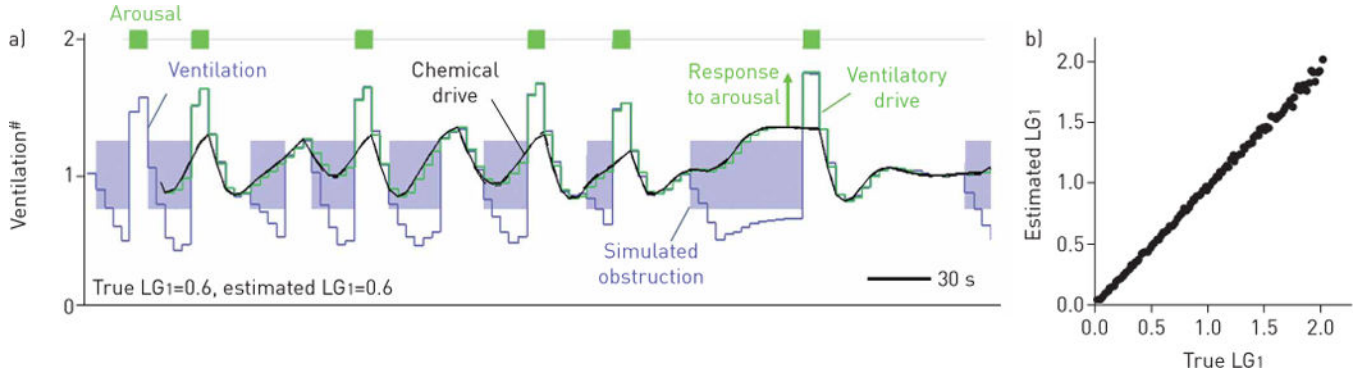

FIGURE 2.

Mathematical model validation. a) Example simulation showing that loop gain is accurately recovered from ventilation in a model of obstructive sleep apnoea (loop gain, LG1 is the response to a 1-cycle·min^{-1} disturbance). Shaded regions denote periods of obstruction. The estimated chemical drive (solid smooth black line) is precisely superimposed on true chemical drive (dashed black line is not visible due to near-perfect overlap); likewise, estimated ventilatory drive (green staircased line) is closely overlaid upon the observed ventilation (blue staircase line) in the absence of obstruction. b) Group simulation data show that the method accurately reveals the true loop gain given to the model. Model parameters: delay 12 s, time constant 12.5 s and response to arousal 0.4 (40% eupnoeic ventilation). Obstructive events were imposed by halving the controller gain (doubling resistance) for three or more breaths at random times in a graduated manner. Arousals were imposed for two breaths at the termination of 80% of obstructive events and on 1% of unobstructed breaths. #: normalised such that 1=eupnoea.

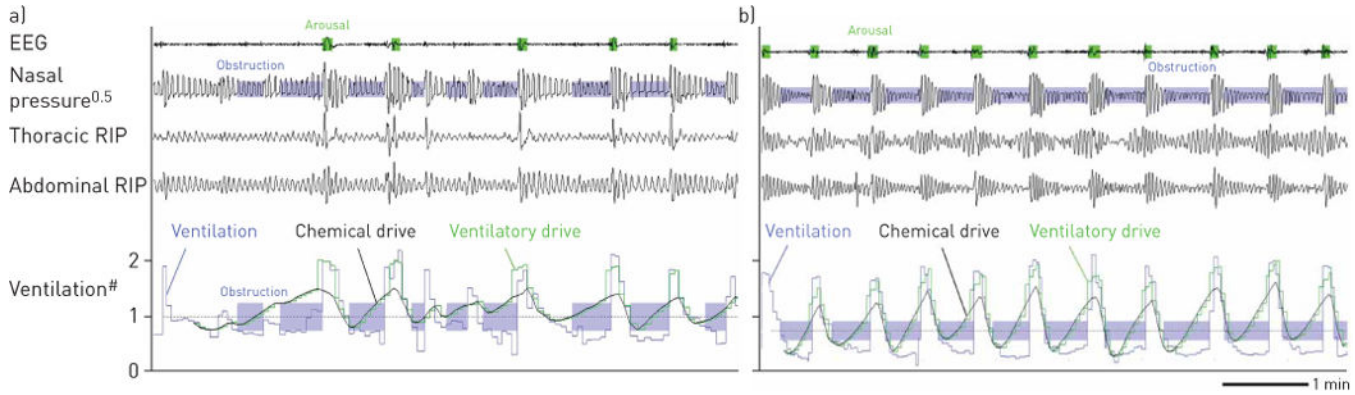

FIGURE 3.

Estimating loop gain using diagnostic polysomnography. Example traces illustrate epochs with a) relatively low loop gain (response to a 1-cycle·min^{-1} disturbance (LG1)=0.6) and b) relatively high loop gain (LG1=1.1). Note that ventilatory drive (chemical drive + response to arousal) closely fits ventilation during periods of unobstructed airflow. Loop gain determines the increase in chemical drive in response to the reduction in ventilation. EEG: electroencephalogram; RIP: respiratory inductance plethysmography. #: normalised.

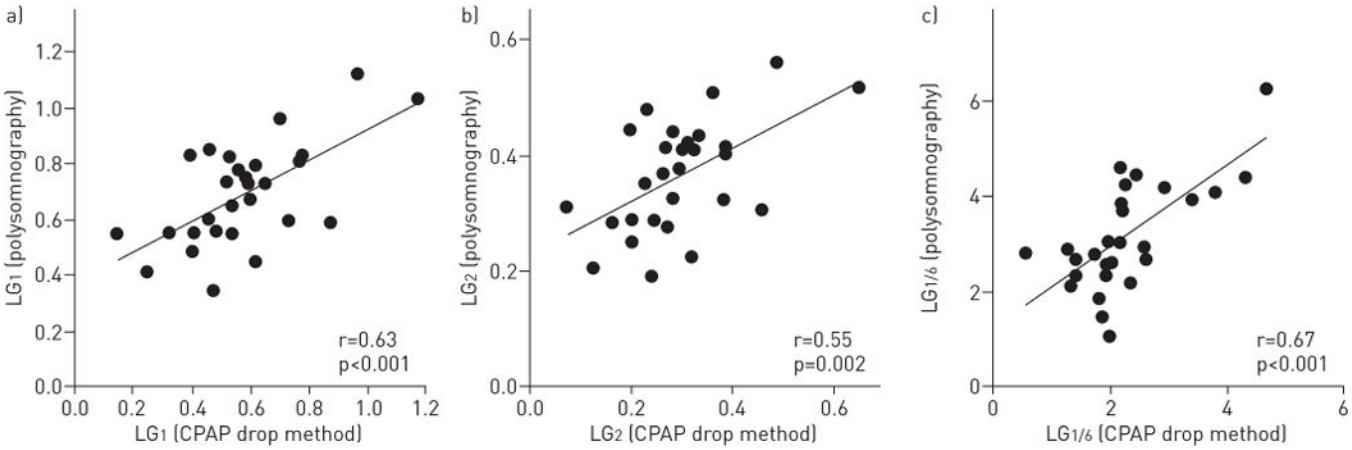

FIGURE 4.

Comparison of our method and the continuous positive airway pressure (CPAP) drop method for measuring loop gain. Agreement was observed across a range of frequencies including a) "mid-frequency" (1 cycle·min^{-1} (LG1)), b) "high frequency" (LG2) and c) "low frequency" ($LG_{1/6}$; 6-min period). Note that loop gain (the chemical drive response to a reduction in ventilation) is a function of the frequency (*e.g.* timing) of the disturbance in ventilation.

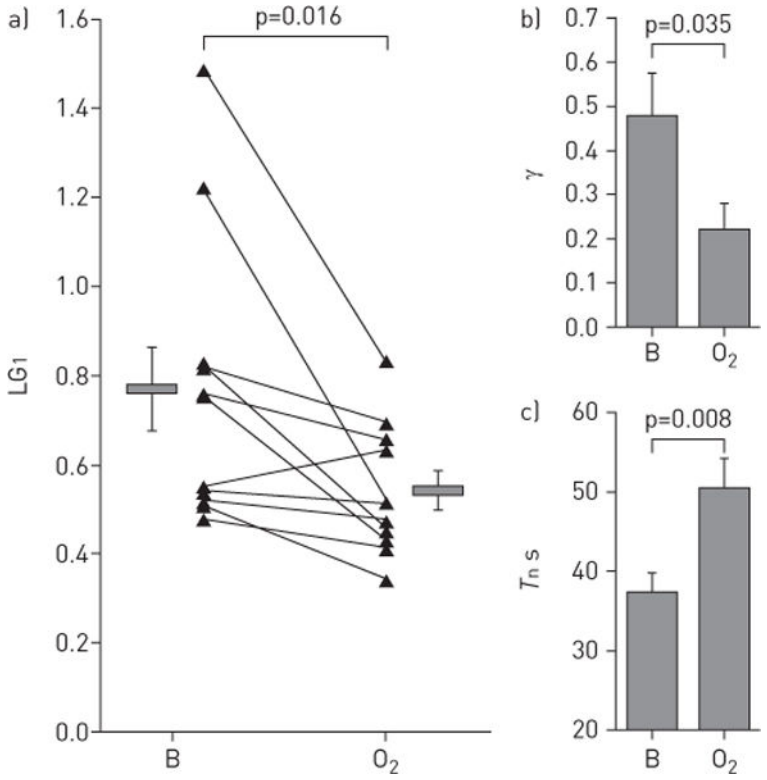

FIGURE 5.

Detecting the reduction in loop gain with oxygen. a) Reduction in loop gain (response to a 1-cycle·min^{-1} disturbance (LG1)) with oxygen *versus* baseline (B). b) Reduced ventilatory response to arousal (γ), as a fraction of mean ventilation, with oxygen. c) The feedback system's natural cycling period (*T*n) rose with oxygen (*i.e.* feedback was more sluggish). Data are presented as mean±SEM.

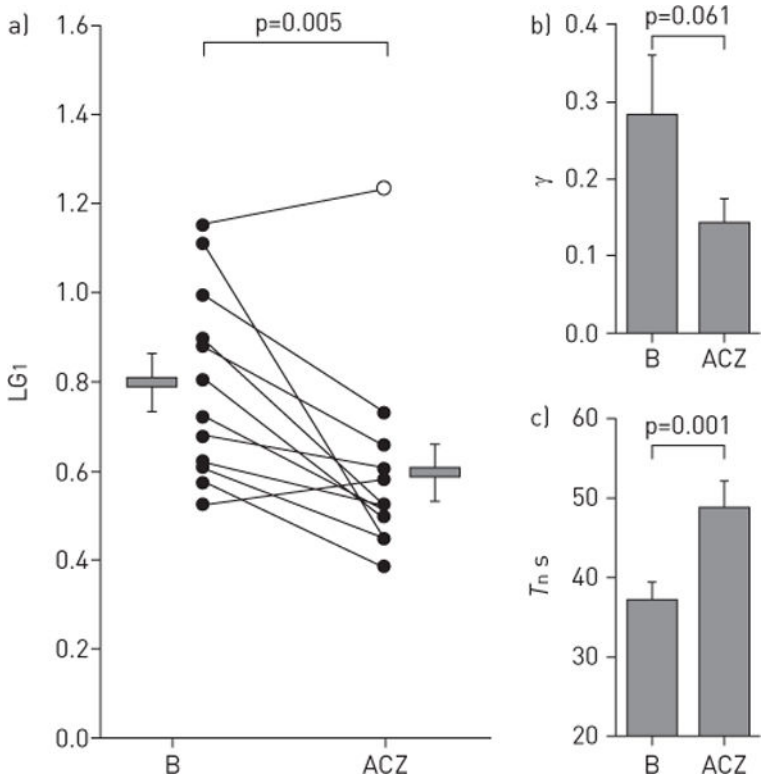

FIGURE 6.

Detecting the reduction in loop gain with acetazolamide (ACZ). a) Reduction in loop gain (response to a 1-cycle·min^{-1} disturbance (LG1)) with ACZ *versus* baseline (B). b) Reduced ventilatory response to arousal (γ), as a fraction of mean ventilation, with ACZ. c) The feedback system's natural cycling period (*T*n) rose with ACZ (*i.e*. feedback was more sluggish). Note that in one subject, LG1 and other variables were not measured from the obstructive sleep apnoea pattern on ACZ due to insufficient obstructive events. The open circle represents a patient whose loop gain unexpectedly rose with ACZ as confirmed with the continuous positive airway pressure drop method. Data are presented as mean±SEM.

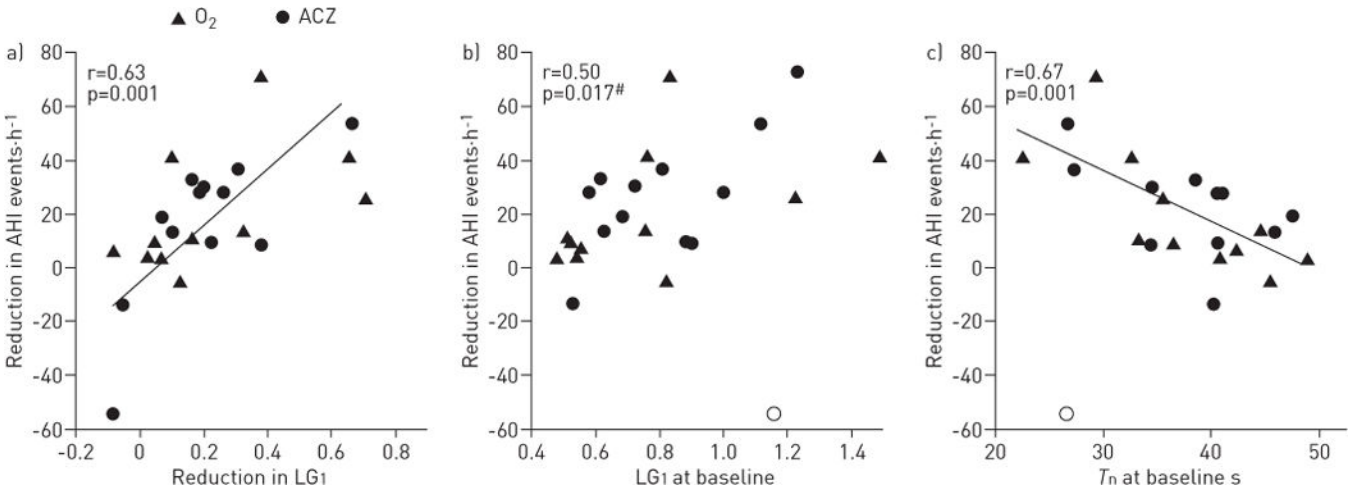

FIGURE 7.

Predicting responses to lowering loop gain with oxygen and acetazolamide (ACZ). a) A larger reduction in sleep apnoea severity with oxygen or ACZ was seen when treatment induced a greater fall in loop gain in response to a 1-cycle·min^{-1} disturbance (LG1). b) The reduction in aponea–hypopnoea index (AHI) could be predicted *a priori* by a high baseline LG1 and c) a low baseline cycling period (*T*n); that is, responders have a more sensitive and brisk feedback response than nonresponders. The outlier (open circle) whose LG1 rose greatly and unexpectedly (confirmed by the continuous positive airway pressure drop method) was excluded from associations in (b) and (c) because the intention was to examine the effectiveness of lowering loop gain on AHI. AHI: apnoea–hypopnoea index. #: Spearman rank correlation.

TABLE 1

Patient characteristics

Characteristics	Comparative dataset	Effect of O_2		Effect of ACZ	
		Baseline	O_2	Baseline	ACZ
Demographics					
Males/females n/n	19/9	9/2		7/5	
Age years	48±10	49±10		48±7	
Body mass index $kg \cdot m^{-2}$	35±6	34±7		34±7	
CPAP cmH_2O	10.9±2.9	10.6±2.4		10.5±2.0	
Sleep					
Time in bed min	416±37	403±41	402±30	428±40	413±39
TST min	321±51	325±55	299±57	340±42	338±44
Supine non-REM	261±63	273±60	243±65*	285±68	296±52
Supine REM	28±17	37±24	35±30	32±14	30±11
Respiratory event characteristics					
AHI $events \cdot h^{-1}$	33 (32)	58 (56)	42 (38)*	48 (17)	25 (20)
Supine non-REM	33 (37)	56 (55)	42 (43)*	50 (19)	24 (22)*
REM/non-REM	1.18±0.83	1.09±0.84	1.38±0.92	0.94±0.38	1.30±1.10
Obstructive apnoea index# $events \cdot h^{-1}$	2.1 (12.6)	31 (29)	16 (43)	4.86 (7.28)	0.63 (6.21)
Mixed apnoea index# $events \cdot h^{-1}$	0.00 (0.53)	0.37 (4.55)	0.22 (0.60)	0.00 (0.65)	0.00 (0.04)
Central apnoea index# $events \cdot h^{-1}$	0.00 (0.50)	0.39 (5.32)	0.00 (0.27)*	0.00 (0.16)	0.00 (0.00)
Hypopnoea index# $events \cdot h^{-1}$	33 (22)	12 (14)	11 (11)	39 (24)	18 (15)
Arousal index# $events \cdot h^{-1}$	41 (24)	60 (44)	51 (35)	39 (10)	32 (7)
Mean O_2 saturation# %	94±2	93±3	97±1*	94±1	95±2*
Minimum O_2 saturation# %	83±6	78±7	89±4*	82±4	85±5
Stable breathing#,¶ %	18±18	14±17	14±16	10±12	20±17
Event duration s	26±6	23±4	27±5*	30±10	36±10*
Inter-event interval s	44±10	38±8	49±8*	49±13	61±14*
Ventilatory control					

Characteristics	Comparative dataset	Effect of O_2		Effect of ACZ	
		Baseline	O_2	Baseline	ACZ
Standard loop gain[+]	0.57±0.21	0.46±0.26[§]	0.32±0.06[f]	0.60±0.33	0.35±0.21[*]

Data are presented as mean±SDor median (interquartile range), unless otherwise stated. ACZ: acetazolamide; CPAP: continuous positive airway pressure; TST: total sleep time; REM: rapid eye movement; AHI: apnoea–hypopnoea index.

[#] measured in supine non-REM sleep

[¶] stable breathing (no events or arousals for ≥5 min)

[+] ratio of feedback response to a 1-cycle·min^{-1} oscillatory disturbance as measured using CPAP drops except for in the O_2 study, when proportional ventilation was used in some individuals

[§] proportional assist ventilation used in nine individuals

[f] proportional assist ventilation used in seven individuals.

[*] p<0.05 *versus* baseline.