Respiratory system loop gain in normal men and women measured with proportional-assist ventilation

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Wellman, Andrew, Atul Malhotra, Robert B. Fogel, Jill K. Edwards, Karen Schory, and David P. White. Respiratory system loop gain in normal men and women measured with proportional-assist ventilation. J Appl Physiol 94: 205–212, 2003. First published September 20, 2002; 10.1152/japplphysiol.00585.2002.—We hypothesized that increased chemical control instability (CCI) in men could partially explain the male predominance in obstructive sleep apnea (OSA). CCI was assessed by sequentially increasing respiratory control system loop gain (LG) with proportional-assist ventilation (PAV) in 10 men (age 24–48 yr) and 9 women (age 22–36 yr) until periodic breathing or awakening occurred. Women were studied in both the follicular and luteal phases of the menstrual cycle. The amount by which PAV amplified LG was quantified from the tidal volume amplification factor (VTAF) assisted tidal volume/unassisted tidal volume. LG was calculated as the inverse of the VTAF occurring at the assist level immediately preceding the emergence of periodic breathing (when LG × VTAF = 1). Only 1 of 10 men and 2 of 9 women developed periodic breathing with PAV. The rest were resistant to periodic breathing despite moderately high levels of PAV amplification. We conclude that LG is low in the majority of normal men and women and that higher volume amplification factors are needed to determine whether gender differences exist in this low range.

ventilatory stability; gender; sleep apnea; control of breathing

SLEEP APNEA IS TWO TO THREE TIMES more common in men than in women (5, 27, 41). This may be due to gender differences in pharyngeal structure and/or function or ventilatory control stability.

The female pharynx, despite some evidence of greater upper airway muscle activity (25), is anatomically smaller (6, 19, 28) or of similar size (7, 16) to the male airway during both wakefulness and sleep. Because a small airway generally predisposes one to sleep apnea, the smaller female airway is unlikely to be protective. Furthermore, pharyngeal collapsibility, as well as the sleep-related increase in upper airway resistance, are not systematically different between the sexes, as conflicting results have been reported (26, 28–31). Thus, it is difficult to conclude that structural and/or functional differences alone are responsible for the male predominance in obstructive sleep apnea (OSA).

On the other hand, differences in respiratory control system stability may be a contributing factor. First, sleep apnea in women, unlike in men, is almost exclusively related to obesity (5), suggesting that factors such as chemical control instability (CCI) may play a greater role in male sleep apnea. Second, some evidence suggests that males have greater awake hypoxic and hypercapnic ventilatory responses (HVR and HCVR, respectively) (36), although a subsequent study failed to reproduce this (1). Third, men are more susceptible to hypocapnic ventilatory inhibition during sleep (higher apnea threshold) (42). However, interpretation of these traditional control of breathing tests is limited because they do not assess the dynamic aspects of chemical control, nor do they assess the plant or feedback gains, which are major components of stability (Fig. 1). Consequently, it is still unclear whether gender differences in CCI exist.

Recently, a technique for measuring CCI during sleep has been developed that encompasses all components of the chemical feedback loop, including the dynamic response characteristics (40). This technique measures loop gain (LG) at the frequency of periodic breathing and takes advantage of the ability of proportional-assist ventilation (PAV) to enhance respiratory controller gain (Fig. 1). LG is a term well known to control engineers and is a measurement of the propensity for a system governed by feedback loops to develop unstable behavior (for a review of LG, see Ref. 13). It has both a magnitude and a dynamic component. The magnitude of LG is determined by the ratio of the corrective response to a disturbance (which is also the product of the controller, plant, and feedback gains). The dynamic component consists of the circulatory delay and the time constants of the three loop components. Instability occurs when the corrective response, $180^\circ$ out of phase with the disturbance, is equal to or greater than the disturbance. Consequently, by incor...
porating the gain of all loop components as well as the phase angle, LG is a more complete metric of stability than traditional steady-state (or progressive) gain tests (e.g., HVR, HCVR) and apneic threshold measurements.

We hypothesized that men have intrinsically higher LG than women and that this may partially explain the gender discrepancy in sleep apnea. We tested this hypothesis by incrementally increasing LG magnitude with PAV in both genders until periodic breathing or awakening occurred. This ability to manipulate LG tells us how close a subject is to spontaneous oscillation; individuals requiring less ventilatory augmentation with PAV to induce periodic breathing have greater CCI and vice versa.

METHODS

Subjects. Normal, healthy volunteers were recruited from the community for this study. Women were required to have normal menses and not be pregnant or taking oral contraceptive pills. Subjects were excluded if they had a chronic medical condition (except for treated hypertension) or complained of snoring or daytime sleepiness. Twenty-six individuals gave informed written consent to participate in the study. However, 7 developed claustrophobia or were unable to sleep on PAV, leaving 19 participants (10 men, 9 women) who completed the study. Women were studied in both the follicular (days 5–11, with day 1 being the final day of menses) and luteal (days 17–22) phases of the menstrual cycle. The study was approved by the human subjects committee at Brigham and Women’s Hospital.

Equipment. Electroencephalography (EEG; C3/A2, O2/A1), electrooculography, and submental electromyography were assessed for sleep staging. Oxygen saturation was monitored by using a pulse oximeter attached to the index finger (BCI Cappnograph Series 9000, Waukesha, WI), and Pco2 was sampled at the mask by using a calibrated infrared CO2 analyzer (BCI). Airflow was measured using a pneumotachometer (Hans-Rudolph, Kansas City, MO) placed between the mask and the intentional leak port, and the airflow signal was integrated for tidal volume (VT). Airway pressure was measured at the mask using a pressure transducer (Vadynex, Northridge, CA). All data were displayed on a Grass model 78E Polygraph (West Warwick, RI) as well as a computer (Spike 2, Cambridge Electronic Design, Cambridge, UK). LG measurements were made by using a BiPAP Vision (Respironics, Murraysville, PA) mechanical ventilator capable of delivering CPAP alone or in varying combinations with PAV.

PAV is a mode of ventilatory support that works by generating pressure at the airway in proportion to a person’s instantaneous respiratory effort (38). It does this by using a flowmeter to detect movement of air from the ventilator to the patient at multiple points within each breath, resulting in a flow and a VT (by integrating flow) signal. These signals are then amplified by two separate gain controls called flow assist (FA) and volume assist (VA). The amplified flow and VT signals dictate ventilator pressure output. To ensure that ventilatory assistance is given in proportion to the subject’s respiratory mechanics, FA and VA are set to equal the subject’s estimated resistance and elastance, respectively (see Protocol). Finally, a percent-assist dial can be set to determine the percentage of FA and VA gains used to amplify the flow and VT signals. For example, if the percent assist is set at 50%, then 50% of the pressure needed to overcome the resistance and elastance of the respiratory system is supplied by the ventilator.

Protocol. Subjects reported to the sleep laboratory at about 9:30 PM. Sleep staging equipment was attached to each subject, and PAV was connected by using a nasal mask held in place with straps. Before application of the mask, each nostril was decongested with one application of oxymetazoline HCl. Once all of the equipment was attached and the nostril was decongested with one application of oxymetazoline HCl. Once all of the equipment was attached and the nostril was decongested with one application of oxymetazoline HCl. Once all of the equipment was attached and the nostril was decongested with one application of oxymetazoline HCl.
flow) on the pneumotachometer tracing disappeared. Because these were normal, nonsnoring subjects, CPAP ranged from 4 to 6 cmH₂O (with 4 cmH₂O CPAP being the minimal setting allowed by the ventilator).

PAV titration was then initiated. This began by first estimating respiratory system elastance and resistance. Elastance was estimated by using the "runaway" method (40). First, the percent-assist dial was set to 100%, and the VA and FA were both set to zero. With the subject asleep (when exhalation is passive), VA was slowly increased until runaway breathing occurred. Runaway occurs when the pressure given by the ventilator is greater than the resistive and elastic recoil pressures of the respiratory system. As a result, at the point of runaway, VA approximates elastance. Respiratory system resistance was estimated in a similar manner by turning the percent-assist dial to 100% and the VA dial to 80% of elastance. FA was then increased from zero until runaway breathing again occurred. The FA level needed to produce runaway was thus a rough estimate of resistance. Although this measurement of resistance has not been validated, the low levels obtained in our study (4.21 ± 1.58 cmH₂O/liter) were consistent with the low resistive work of breathing on CPAP.

Once elastance and resistance were estimated and entered into the computer as VA and FA, respectively, we began increasing percent assist in 5 or 10% increments beginning with 30% assist. Subjects were maintained at each level for 3 min to establish a steady state and to see whether periodic breathing developed. If at any time during this procedure the variable leak (e.g., a leak around the mask) exceeded 5 l/min, as shown on the ventilator display screen, the variable leak (e.g., a leak around the mask) was decreased by turning the percent-assist dial to 100% and the VA dial to 1–3 cmH₂O/liter. As VA was decreased, the low resistive work of breathing on CPAP was decreased to zero for one breath (single-breath reloading test) to measure the Vs amplification factor (VtAF). VtAF, which is the ratio of assisted VT to unassisted VT (VtAF = assisted Vt/unassisted Vt), quantifies the amount by which PAV amplifies controller gain. VTAF was measured on three to five occasions ≈30 s apart for each level. If periodic breathing occurred, the assist level was maintained constant until the subject awoke. If awakening occurred before periodic breathing, then the percent assist was decreased back to zero until sleep resumed. After establishment of NREM sleep, the sequence was reinitiated starting with the last steady-state level achieved before to awakening.

If 100% assist was attained without runaway breathing (due to changes in respiratory system mechanics during the course of the night), VA was increased in steps of 1 cmH₂O/liter until periodic breathing or runaway occurred. Again, at each successive level, steady state was established and VtAF was measured three to five times as previously described. The titration procedure ended when periodic breathing or runaway occurred.

Data analysis. Sleep staging and arousals were scored using standard criteria (26). Arousals were defined as an abrupt increase in EEG frequency to 8 Hz or greater for at least 3 s. Data were analyzed from NREM sleep only, with the majority coming from stage 3/4 sleep because subjects tended to arouse easily at high levels of assist in stage 2 sleep. Because Vs tended to vary, particularly at high levels of assist, the three Vs values before the unassisted breath were averaged and used for the numerator of VtAF. The VtAFs for each assist level were then averaged. The average VtAF at the level immediately preceding the development of periodic breathing or runaway was used for LG calculation.

LG was calculated as follows. As stated earlier, periodic breathing occurs when LG equals or just exceeds 1. Thus, at the point when periodic breathing began to emerge, we knew that LG on PAV (LGpav) was equal to 1. Because LGpav = LG inherent (the subject’s inherent LG) × VTAF, then we calculated LG inherent as the reciprocal of the VTAF from the preceding percent-assist level (40). If LG could not be brought to 1 due to runaway (LG × VTAF < 1), then LG was reported as a "less than" value on the basis of the highest amplification achievable.

We defined periodic breathing as a crescendo-decrescendo pattern of flow and Vt with a period of 20–100 s, because this covers the range of cycle lengths generally observed in periodic breathing (13). We did not require that central apnea occur, but the nadir Vt had to be <50% of peak Vt. Furthermore, arousal could not occur during or before cycling. Occasionally, subjects would take large breaths followed by decayed oscillations, particularly when percent assist was high. Therefore, for cycling to represent a LG of 1, we required that periodic breathing be sustained for at least four cycles. VtAF was compared between men and follicular-phase women using an unpaired t-test and between follicular and luteal-phase women using a paired t-test. We also compared LG in the men with LG in follicular-phase women by using a log-rank test. Statistical significance was accepted when $P < 0.05$.

RESULTS

Ten men (age 24–48 yr) and nine women (age 22–36 yr) completed the study. The average body mass index was 23.2 for the men and 22.6 for the women. With the exception of one woman, data were collected in both the follicular and luteal phases of all women.

A representative example of periodic breathing in female subject 7 is shown in Fig. 2. When the assist was increased to 75%, sustained periodic breathing at a frequency of 0.92 Hz appeared. Cyclic breathing usually began within 30–60 s of the PAV increase. Vt (0.60 liter) and PCO₂ (38 Torr), just before cycling, were not substantially different from baseline even at 70% assist, signifying both a compensatory reduction in respiratory muscle pressure and an intact chemical control system.

Figure 3 shows data from female subject 6, who was resistant to periodic breathing. An increase in the percent-assist level led to a failure to transition into expiration at end-neural inspiration (i.e., runaway breathing). In this instance, runaway occurred before LG could be brought to 1 with PAV. VtAF at the preceding percent-assist level was 1.82, meaning the subject’s underlying LG had to be <0.55.

Men. Of the 10 men, 1 developed periodic breathing at a VtAF of 1.50 (LG = 0.67) (Table 1). All others experienced runaway breathing that precluded further increases in controller gain and consequently LG quantification. We were able to demonstrate, however, that LG was at most <0.46 in 7 of 10 men, 4 of whom had LGs of <0.37. The average of the highest VtAF achieved in each man was 2.49, which was not significantly different from the follicular-phase female value of 2.06 ($P = 0.22$). LG between men and follicular-phase women was not statistically different either ($P = 0.38$).
Women. For women in the follicular phase, two of nine experienced periodic breathing at a VTAF of 1.28 (LG = 0.78) and 2.26 (LG = 0.44) (Table 1). LG was <0.52 in five follicular-phase women, three of whom were <0.45. When studied in the luteal phase, the same two women who developed periodic breathing in the follicular phase did so again in the luteal phase at VTAF levels of 1.79 (LG = 0.56) and 2.06 (LG = 0.48). Five of eight luteal-phase women had LGs of <0.55, two of whom were <0.44. The average of the highest VTAF achieved in each follicular-phase woman was 2.06, which was not significantly different compared with the luteal-phase value of 1.98 (P = 0.68).

DISCUSSION

The purpose of this study was to determine whether gender differences in CCI exist. We utilized a recently described technique for quantifying the LG of the respiratory control system with PAV. Our data indicate that LG is low in normal men and women, because most subjects from both gender groups were resistant to periodic breathing despite levels of PAV high enough to induce runaway. These results, however, do not definitively answer the question of whether gender differences in LG exist in these lower ranges. To do so would require higher volume amplification factors than we were able to achieve in this study. Potential reasons for this are discussed below. Nonetheless, previous data, in which PAV induced periodic breathing in only 5 of 24 normal people (17, 18), as well as our results suggest that LG is low in the majority of normal healthy individuals, regardless of gender. Our data also suggest that LG is not considerably increased by circulating progesterone, because LG during the luteal phase was similar to or less than LG during the follicular phase (in the 2 women in whom LG could be quantified). Although our results do not exclude LG as a component contributing to the male predominance in...
OSA, they suggest that other factors, like pharyngeal structure and/or tissue characteristics or state-dependent muscle function, may be more important.

There are two possible explanations for why we were unable to find a gender difference in LG. First, the combination of physiological variables known to affect LG magnitude (15, 37, 40) and phase angle (e.g., circulatory delay) must yield a sufficiently stable respiratory control system in both sexes such that “large” amplifications of controller gain (to the point that runaway breathing occurs) do not produce instability. Thus there may be no actual difference in CCI between the genders. On the other hand, we may have failed to demonstrate a difference because we could not measure LG in the lower ranges. When LG was less than −0.50, it was difficult to quantify chemical control instability with PAV. Therefore, differences in the lower ranges could still exist.

Role of LG in OSA. There appears to be an anatomic continuum for the risk of CCI-induced upper airway obstruction. It is known that individuals with moderately compromised upper airway anatomy and/or physiology (e.g., snorers) develop repetitive pharyngeal obstruction to a greater degree than nonsnorers at the nadir of hypoxia-induced periodic breathing (10, 20, 32). Indeed, Cheyne-Stokes respiration is often associated with upper airway occlusion (2). This occurs because the pharyngeal dilator muscles, like the diaphragm, receive input from medullary respiratory neurons (21, 32). During periods of increased respiratory drive, when output from these neurons is high, pharyngeal dilator muscles are activated (4, 22) and help maintain upper airway patency. During low drive, however, these muscles relax (3), making the pharynx more collapsible and prone to occlusion, particularly in the setting of deficient upper airway anatomy (20). Thus the oscillating respiratory drive during periodic breathing provides an ideal milieu for recurrent collapse of the upper airway. Consequently, depending on the anatomic substrate, a LG in the moderate range (e.g., 0.4–0.5) may produce enough oscillation in respiratory drive to “tip” a snorer over into the OSA category or worsen existing OSA (40).

Gender differences in chemoresponsiveness. Components of the ventilatory control system (HVR and HCVR) have been compared between men and women both awake and asleep. During wakefulness, White et al. (34, 35) found HVR to be greater in men, although a subsequent study showed the opposite (awake HVR greater in women) (1). Nevertheless, HVR appears to be similar in men and women during sleep (34). When HCVR is measured during wakefulness, men appear to have greater chemoresponsiveness than women (1, 9, 34). During sleep, however, HCVR is either similar (34) or substantially greater in men (42), depending on the study.

It is difficult to relate these chemoresponsiveness findings to our LG data for the following reasons. First, when HVR and HCVR were measured during sleep (the period of time in which we are most interested), the sleep-induced increase in upper airway resistance, which blunts ventilatory responsiveness, was not addressed. Second, as stated previously, HVR and HCVR give information about only one component of ventilatory control (the controller gain), without regard to the plant or feedback gains. Third, chemoresponsiveness tests, unlike LG, are steady-state or progressive measurements. Periodic breathing, however, represents a highly unsteady state. Therefore, dynamic (as opposed to steady-state or progressive) chemoresponsiveness is a more relevant marker of stability as it accounts for the timing component of ventilatory responsiveness. Nonetheless, most of the chemoresponsiveness data would support our findings that ventilatory stability is not substantially different between the genders during sleep, inasmuch as both genders were found to have low LGs.

Gender differences in apnea threshold. There is recent evidence of a gender difference in apnea threshold, with men being more susceptible to hypocapnic-induced ventilatory inhibition than women (42). This could have important effects on LG for the following

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Mean ± SD 2.49 ± 0.88* 2.06 ± 0.52† 1.98 ± 0.26‡

VtAF, tidal volume amplification factor. *P = 0.22 for men different from follicular-phase women. †P = 0.68 for differences between menstrual phases in women. ‡P = 0.38 by using log-rank test to compare loop gain between men and follicular-phase women.
reason. A high apnea threshold (small difference between eupneic and apneic $P_{\text{CO}_2}$) would tend to amplify the ventilatory undershoot that occurs in response to a preceding hyperpnea, which would increase LG (by increasing the response-to-disturbance ratio). Importantly, the PAV technique incorporates this apnea threshold into its LG measurement. Thus, if men have a higher apnea threshold than women (and all other factors that influence LG are equal), one would predict that cycling would be easier to induce (and thus LG would be higher) in men. Because the men in our study were as resistant to periodic breathing as the women, we would conclude that gender differences in apnea threshold are not substantial enough to translate into gender differences in LG, at least within the range that we could measure it.

LG in normal subjects. Our findings agree with previous PAV studies in normal people. In the first study to introduce PAV as a tool for measuring ventilatory stability, Meza and Younes (18) attempted to induce periodic breathing in 12 normal subjects (7 nonsnorers, 5 snorers). None of the 12 developed sustained periodic breathing on PAV either spontaneously or after a ventilatory perturbation (percent assist was turned to 0 for 3–4 breaths). Baseline LG in these subjects was reported to be $<0.3$. According to Meza et al (17), however, this study used an inaccurate amplification factor to calculate LG. In a follow-up study that used a different amplification factor (but not VTAF), 5 of 12 normal sleep-deprived subjects (2 of whom received 0.5 mg lorazepam) developed periodic breathing on PAV, and LG was reported to be on average $<0.28$ (17). Because VTAF was not used to calculate LG in either of these two studies, and because some subjects were sleep deprived or taking benzodiazepines, direct comparisons with our data are difficult.

Technical considerations. There are two potential reasons why we did not achieve as high a VTAF as desired in each subject. First, we did not set pressure or $V_t$ limits on the ventilator, because we reasoned that this may have blunted ventilatory responsiveness. However, this made it difficult to distinguish true runaway (runaway occurs with almost every breath) from spontaneously large $V_t$ values, which occur singly. Because it was necessary to turn down the assist after a large breath (as a result of subject awakening), we could not confirm that true runaway had occurred. However, we were careful not to call a large $V_t$ breath runaway unless it had a typical “saddle-shaped” flow pattern (Fig. 3) (39). Furthermore, we achieved runaway on several occasions before terminating the study. Nonetheless, it is likely that we could have maintained subjects on a higher level of assist for a longer period of time, and possibly have achieved higher volume amplification, if pressure and volume limits were set at 25 cmH$_2$O and 1.5 liters, respectively (M. Younes, personal communication).

Limitations. First, we measured LG in a group of relatively young men and women without comorbidities, a population that has a low incidence of OSA.

Second, we found it very difficult to measure LG during the light stages of NREM sleep. Because stages of consciousness and sleep can affect airway collapsibility (31) and chemoresponsiveness (34) differently in men and women, it is possible that gender differences in LG may exist in stage 2 but not in stage 3/4 sleep. It is also possible that LG may be different depending on the stage of sleep. This is suggested by the tendency for periodic breathing to occur more frequently in light sleep (8, 33), a phenomenon that can be interpreted in one of two ways: 1) the chemical control system is more unstable in light sleep, or 2) the fluctuations between sleep and arousal (which occur more frequently in light sleep) are driving an otherwise stable control system into an unstable state. The first interpretation is supported by the classic study of Bulow (8), which showed a gradual decrease in progressive CO$_2$ controller gain as sleep state deepened. Whether this translates into changes in overall LG, however, is not clear. The second explanation is best supported by the tight correlation between EEG oscillations and ventilatory oscillations during sleep (23). Which mechanism, chemical instability or state instability, is primarily responsible for the ventilatory variability of light sleep is a perplexing question, one that could be partially answered by measuring LG in the various stages of sleep. This possibility was not tested in this protocol, although gender comparisons in LG were made across the same sleep state.

Third, to facilitate sleep, subjects were allowed to sleep in the supine or lateral position, which could have affected LG via changes in lung volume, etc.

Fourth, CPAP may have affected lung volume as well as other variables that influence CCI (14, 40). However, the CPAP levels used in this study were low (men 4.6 ± 1.26 cmH$_2$O, women 4.2 ± 0.66 cmH$_2$O; $P = 0.43$), and respiratory elastance (men 11.2 ± 2.57 l/cmH$_2$O, women 13.6 ± 2.40 l/cmH$_2$O; $P = 0.06$) was not statistically different between the genders. Thus it is not likely that CPAP affected one gender more than the other.

Finally, by applying CPAP, we eliminated the contribution of fluctuating upper airway resistance to ventilatory stability (11, 12). Thus there exists the possibility that gender differences in ventilatory stability exist that were not assessed by our PAV study. However, we believe that this possibility is small for the following three reasons. First, we studied nonsnorers individuals in whom changes in muscle activity are unlikely to have produced sizable changes in upper airway resistance. Second, state-related changes in upper airway muscle activity are not significantly different between men and women in both tonic and phasic components (24) (A. S. Jordan, personal communication). Therefore, to the extent that the prevailing fluctuations in upper airway resistance are due to state-related changes in muscle activity, it is not likely that this mechanism plays a contributing role. Third, upper airway muscle activity (and thus airway caliber) is influenced by output from the central pattern generator (3, 4, 10, 20–22, 32), which functions under the
authority of the chemoreflex control system during NREM sleep. Thus the low loop gains found in our study would tend to indicate that upper airway resistance does not fluctuate substantially in normal individuals during NREM sleep.

Conclusions. We found that, insofar as LG was low in the majority of our subjects, CCI was not substantially different between the genders. Therefore, CCI may not play as large a role in male OSA as we originally hypothesized. Higher VtAfS than were achieved in this study, however, would be necessary to determine whether gender differences exist in this lower range.

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